RENAL DYSFUNCTION ASSOCIATED WITH INFRARENAL CROSS CLAMPING OF THE AORTA DURING MAJOR VASCULAR SURGERY

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DECLARATION

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

WL van der Merwe

ABSTRACT

Acute renal failure still is, with the exception of cardiac deaths, the most important pathological process associated with perioperative mortality in patients operated for abdominal aortic aneurysms. The intraoperative change in renal blood flow (RBF) and glomerular function have been investigated in human and animal models, particularly over the past 15 years. Despite large variation in study populations, measurement techniques and study designs in general, a significant body of evidence has developed which suggests infrarenal aortic clamp-induced renal ischemia to be the cause of postoperative acute renal failure when this complication does occur.

It is rather surprizing then that, despite some recent studies which have reported on various pharmacological interventions to prevent intraoperative renal ischemia (with variable success), very little has apparently been done to unravel the pathogenesis and exact pathophysiology of this potentially lethal complication. Although a number of investigators suggest the possibility of hormonal involvement (particularly renin-angiotensin, antidiuretic hormone (ADH) and catecholamines) in the process, the exact role of these mediators have not been explored (or reported) in a structured fashion.

In an initial human study, renal hemodynamics and function were measured from the preoperative period, during the intraoperative phase and at least until 4 hours after aortic unclamping. To investigate the possibility of a temporal relationship between renal changes and fluctuations in hormonal concentrations, plasma concentrations of relevant hormones were determined at every sampling period where renal parameters were measured.

The decrease in RBF and glomerular filtration rate (GFR) which we demonstrated to coincide with infrarenal aortic cross clamping, is consistent with results previously published. We demonstrated persistence of the impairment of these parameters as long as 4 hours into the postoperative phase; which has previously only been reported for the period until immediately after aortic unclamping with the abdomen still open. The persistence of a depressed GFR until the time of discharge of patients is cause for concern, particularly in patients with compromised renal function prior to surgery.

Of the measured hormones with a potential influence on RBF and nephron function, renin was the only mediator where changes in plasma concentrations coincided with the depression of RBF and GFR after aortic cross clamping. The design of our study did not allow us to conclude whether the concomitant increase in angiotensin II was primarily responsible for the change in renal hemodynamics, or whether the raised renin (and angiotensin) levels were stimulated by the decrease in RBF induced by another mechanism.

In another patient group, we demonstrated that the combination of mannitol and dopamine provided no protection against the deleterious effects of aortic cross clamping. In fact, the high urine volumes produced under the influence of these agents (which did not correlate with RBF at the corresponding periods), is likely to prompt a false sense of security. Given the lack of any objective benefit afforded by these agents, their use in these clinical circumstances should be discouraged.

The animal studies were aimed at elucidation of the exact role of angiotensin in the pathogenesis and pathophysiology of the renal changes associated with infrarenal aortic clamping, as well as the interaction of angiotensin with other modulators for which an interactive relationship had been described previously under other experimental and/or clinical circumstances.

The first study showed that, although renin (and thus angiotensin) concentrations were high **after aortic unclamping,** the hormone had no pathogenic or pathophysiological role of significance in the observed renal changes **during this period** (since blocking angiotensin II activation by the prevention of renin release, or by inhibiting the conversion enzyme, did not prevent a substantial decrease in RBF or GFR during that period). Preventing angiotensin II activation did, however, **prevent renal changes during aortic clamping.** This beneficial effect did **not** establish a **primary** role for angiotensin during that period, since the favourable influence could also (at least partially) be explained by prevention of the permissive influence of angiotensin on other vasoconstrictors and/or other vasodilatory influences of ACE inhibition and ß-blockade which are unrelated to angiotensin. This study did indicate that (at least partially) different mechanisms are responsible for the renal changes seen **during aortic clamping**, and **after aortic unclamping.**

The second study explored the role of calcium in the renal pathophysiological changes **during aortic clamping** and **after unclamping.** The protective influence effected by the administration of a Ca^{2+}-blocker suggest the dependence of the renal vasoconstrictive and glomerular pathophysiological process(es) on the cellular influx of Ca^{2+} through voltage-gated channels. It unfortunately provides no definitive insight into the primary instigators of these processes. However, it does offer a clinically useful method of preventing these changes and protecting the kidney against ischemic injury during abdominal aortic surgery.

The third component of the animal studies demonstrates the importance of the protective effect of renal prostaglandins during the specific experimental (and probably also the clinical) circumstances. Again, it does not provide definitive information on the mediators responsible for the renal changes, since the deleterious effects of numerous endogenous substances have previously been shown to be counterbalanced by intrarenal synthesis of prostaglandins under various experimental and clinical circumstances. The extent of the pathophysiological and ultrastructural changes which occurred under the influence of a NSAID does, however, suggest that these drugs should not be used under these clinical circumstances.

The last component of the study provides evidence that angiotensin only plays a **secondary/supplementary role** in the renal pathophysiological process **even during aortic clamping.** This may explain the contradictory evidence regarding the potential beneficial effect of ACE inhibition (on renal hemodynamics and glomerular function) during abdominal aortic surgery (Licker et al. 1996, Colson et al. 1992a). Based on our studies, ACE inhibition can not be supported for this purpose.

ABSTRAK

Akute nierversaking is met die uitsondering van kardiale sterftes, steeds die belangrikste patologiese proses wat geassosieer is met perioperatiewe mortaliteit in pasiënte wat opereer word vir abdominale aorta aneurismes. Die intraoperatiewe veranderinge in renale bloedvloei (NBV) en glomerulêre funksie is die afgelope 15 jaar ondersoek en gerapporteer in pasiënte- sowel as diere-modelle. Ten spyte van groot variasies in studie-populasies, meettegnieke en ontwerp van studies in die algemeen, dui 'n wesenlike hoeveelheid getuienis daarop dat infrarenale klemming van die aorta renale isgemie induseer, wat die oorsaak is van postoperatiewe akute nierversaking wanneer hierdie komplikasie voorkom.

Dit is verbasend dat, ten spyte van sommige onlangse studies wat rapporteer oor 'n verskeidenheid farmakologiese ingrepe om intraoperatiewe renale isgemie te voorkom (met wisselende sukses), baie min oënskynlik gedoen is om die patogenese en die presiese patofisiologie van hierdie potensieel dodelike komplikasie te ontrafel. Hoewel verskeie outeurs die moontlikheid van hormonale betrokkenheid (veral renien-angiotensien, antidiuretiese hormoon en katekolamiene) in hierdie proses suggereer, is die presiese rol van hierdie mediators nog nie op 'n gestruktureerde wyse ondersoek (of rapporteer) nie.

In ons aanvanklike pasiënte-studie is renale hemodinamika en –funksie gemeet vanaf die preoperatiewe periode, gedurende die intra-operatiewe fase en tot minstens vier uur na ontklemming van die aorta. Serumkonsentrasies van relevante hormone is bepaal tydens elke metingsperiode waar renale parameters gemeet is, ten einde die moontlikheid van 'n temporale verwantskap tussen renale veranderinge en variasies in hormoonkonsentrasies te ondersoek.

Die vermindering in NBV en glomerulêre filtrasiespoed (GFS) wat ons aangetoon het om saam te val met infrarenale aortaklemming, stem ooreen met resultate wat tevore deur ander navorsers publiseer is. Ons het aangetoon dat die inkorting van hierdie parameters voortduur tot minstens vier uur na aorta-ontklemming. Hierdie veranderinge is tevore slegs rapporteer vir periodes tot kort na aorta-ontklemming voor sluiting van die buikwond. Die feit dat die GFS steeds verlaag is met ontslag van

hierdie pasiënte, skep rede tot kommer, veral in pasiënte wat alreeds ingekorte nierfunksie het voor die chirurgiese prosedure.

Van die gemete hormone wat moontlik 'n invloed sou kon uitoefen op NBV en nefronfunksie, was renien die enigste waarvan verandering in plasmakonsentrasies saamgeval het met die onderdrukking van NBV en GFS na aortaklemming. Die ontwerp van ons studie het ons nie toegelaat om 'n besliste uitspraak te maak of die geassosieerde verhoging in angiotensien II primêr verantwoordelik was vir die verandering in renale hemodinamika, of dat die verhoogde renien (en angiotensien) bloedvlakke moontlik sekondêr stimuleer is deur die verandering in NBV wat deur 'n ander meganisme induseer is.

In 'n ander pasiëntegroep het ons aangetoon dat die kombinasie van mannitol en dopamien geen beskerming verleen het teen die nadelige effekte van aorta-klemming nie. Die groot volumes uriene wat uitgeskei is onder die invloed van hierdie middels (wat nie korreleer het met NBV tydens ooreenstemmende periodes nie), het inderwaarheid 'n ontoepaslike gerustheid uitgelok. Weens die ooglopende gebrek aan objektiewe voordeel wat verleen word deur hierdie middels, behoort hulle gebruik tydens hierdie kliniese omstandighede ontmoedig te word.

Die doel van die diere studies was die identifisering van die presiese rol van angiotensien in die patogenese en patofisiologie van die renale veranderinge geassosieer met infrarenale aortaklemming, sowel as die interaksie van angiotensien met ander modulators waarvoor 'n interaktiewe verwantskap voorheen beskryf is onder eksperimentele en/of kliniese omstandighede.

Die eerste studie het getoon dat alhoewel renien (en dus angiotensien) konsentrasies hoog was **na aorta-ontklemming,** die hormone geen betekenisvolle patogenetiese of patofisiologiese rol in die waargenome renale veranderinge **gedurende hierdie periode** het nie (aangesien blokkade van angiotensien aktivering deur voorkoming van renien vrystelling, of deur inhibisie van angiotensien omsettingsensiem (AOE), nie 'n daling in NBV of GFS kon voorkom nie). Voorkoming van angiotensien II aktivering het egter wel **renale verandering voorkom gedurende aortaklemming.** Diè voordelige effek het nie 'n primêre rol vir angiotensien gedurende die periode bevestig nie, aangesien die gunstige invloed ook (ten minste gedeeltelik) verduidelik kon word deur die voorkoming van die fassiliterende invloed van angiotensien op ander

vasokonstriktore en/of ander vasodilator-invloede van die onderdrukking van AOE en ß-blokkers (wat geen verband het met angiotensien of die blokkade daarvan nie) . Die studie het aangetoon dat (ten minste gedeeltelik) verskillende meganismes verantwoordelik is vir renale veranderinge wat gesien is **gedurende aortaklemming** en **na -ontklemming.**

Die tweede studie het die rol van kalsium in die renale patofisiologiese veranderinge **gedurende aortaklemming** en **na ontklemming** ondersoek. Die beskermende invloed wat deur die toediening van Ca^{2+}-blokkers bewerkstellig is, het bevestig dat die renale vasokonstriktoriese en glomerulêre patofisiologiese prosesse afhanklik is van sellulêre influks van kalsium deur spannings-afhanklike kannale. Dit het ongelukkig geen definitiewe insig verleen ten opsigte van die primêre inisieerders van die proses nie. Dit verskaf nogtans 'n bruikbare kliniese metode om daardie veranderinge te voorkom en die niere teen isgemiese besering gedurende abdominale aorta-chirurgie te beskerm.

Die derde komponent van die diere-studies demonstreer die belangrikheid van die beskermende effek van renale prostaglandiene tydens die spesifieke eksperimentele (en waarskynlik ook die kliniese) omstandighede. Weereens gee dit nie definitiewe inligting oor die bemiddelaars wat verantwoordelik is vir die renale veranderinge nie, aangesien die skadelike effekte van verskeie endogene stowwe voorheen aangetoon is om beperk of voorkom te word deur die intrarenale vrystelling van prostaglandiene. Die omvang van die patofisiologiese en ultrastrukturele veranderinge wat ontstaan het onder die invloed van nie-steroïed anti-inflammatoriese middels (wat gebruik is om prostaglandien sintese te inhibeer), dui aan dat hierdie middels vermy moet word onder soortelyke kliniese omstandighede.

Die laaste komponent van die studie verskaf 'n sterk aanduiding dat angiotensien slegs 'n **sekondêre/aanvullende** rol speel in die renale patofisiologiese proses, **selfs gedurende aortaklemming.** Dit mag die weersprekende getuienis oor die potensiële voordeel van AOE onderdrukking (op renale hemodinamika en glomerulêre funksie) gedurende abdominale aortachirurgie (Licker et al. 1996, Colson et al. 1992a) verklaar. Gebaseer op ons studies, kan AOE onderdrukking nie ondersteun word vir hierdie doel nie.

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CONTENTS

1. LITERATURE REVIEW AND HYPOTHESIS

1.1 **RENAL DYSFUNCTION AND/OR FAILURE ASSOCIATED WITH INFRARENAL CROSS CLAMPING OF THE AORTA DURING ABDOMINAL AORTIC SURGERY**

With the exception of cardiac deaths, acute renal failure (ARF) remains the most important pathological process associated with mortality in the immediate postoperative period subsequent to abdominal aortic surgery since Dubost et al. (1952) described the first successful resection and graft replacement of an atherosclerotic abdominal aortic aneurysm (Wantz et al. 1964; Hicks et al. 1975; Crawford et al. 1981; Fielding et al. 1984; Szilagi et al. 1986; Breckwoldt et al. 1992). When renal failure occurs postoperatively, it carries a poor prognosis with a mortality in excess of 50% which has not improved over the past decades (Wantz et al. 1964; Abbott et al. 1971; Chawla et al. 1975; McCombs et al. 1979; Wakefield et al. 1982; Nachbur et al. 1987; Johnston et al. 1988; Sullivan et al. 1990).

The incidence of renal failure after abdominal aortic surgery has not changed substantially with reported figures varying between 7% and 27% in the 1960's (Wantz et al. 1964; Porter et al. 1966; Graham et al. 1968), 4% and 39% in the 1970's (Van Heeckeren 1970, Couch et al. 1970; Thompson et al. 1975; Powis et al. 1975; Hicks et al. 1975; Chawla et al. 1975; Young et al. 1977; Baird et al. 1978; McCombs et al. 1979; Lawrie et al. 1979) and 7% and 45% in the 1980's (Whittemore et al. 1980; Wakefield et al. 1982; Diehl et al. 1983; Alpert et al. 1984; Fielding et al. 1984; Serrano-Hernando et al. 1985; Ostri et al. 1986; Cohen et al. 1986; Szilagi et al. 1986; Nachbur et al. 1987; Johnston et al. 1988). These figures are dependent on the population studied, with groups with ruptured aortic aneurysms demonstrating a much higher incidence of renal failure than patients operated electively.

It is uncertain why neither a reduction in the incidence of renal failure or an improvement in outcome, has been recorded when renal failure does occur. It is conceivable that this could be due partly to the fact that improved monitoring, management technology and regimen has allowed more critically ill and older patients to be accepted for surgery (Lazarus 1986). However, this speculation has not been explored in the literature in this population group. Critical analysis of the literature indicates that population groups, with the associated risk factors for the development of ARF, vary significantly between studies. It is not possible to ascertain to what extent this contributes to a lack of improvement in the

reported incidence of ARF and adverse outcome. A vast variation in definition of renal insufficiency and/or ARF compromises interpretation of the literature and the comparison of studies. The fact that stricter criteria that defined renal dysfunction at a lesser degree of renal insufficiency had been applied in studies published more recently may contribute to the apparent continued high incidence of renal insufficiency (Porter et al. 1966; Sturm et al. 1987). Strict and appropriate criteria recently applied does, however, not explain the continued high mortality associated with renal dysfunction and ARF. On the contrary, similar mortality rates in association with stricter criteria for renal dysfunction would indicate deterioration in outcome.

Initial studies suggesting that early dialysis improved prognosis in patients with ARF, have not been confirmed (Brady et al. 1996). There is, however, some evidence that the maintenance phase of acute tubular necrosis in a diverse population of patients is significantly shorter with the use of biocompatable dialysis membranes (Hakin et al. 1994). Very little information is available on the influence of dialysis in patients with ARF after aortic surgery. Early hemodialysis was suggested to improve outcome in patients who develop ARF after abdominal aortic surgery (Chawla et al. 1975). This recommendation is based on a 66% survival in 9 patients who developed ARF perioperatively versus a 100% mortality rate in 5 other patients with ARF who were not dialised because it was either considered to be too late to be effective or was thought to be contraindicated in the face of other complications. Clearly the design of this study, including the patient numbers, is inadequate to make such a suggestion. In a similar population of patients without prior renal disease who developed ARF after ruptured aortic aneurysms, Abbot et al. (1975) employed an intravenous nutritional program plus aggressive early dialysis. They could only achieve a 12,5% survival in 32 patients. In another study by Cohen et al. (1986), from a group of 6 patients with preoperative serum creatinine values in excess of 4mg.dl^{-1} (353 µmol.l^{-1}) 4 patients showed increased renal dysfunction postoperatively, which was treated with early hemodialysis. Although only one of the four patients died within 30 days of surgery, the mean duration of hospital stay was 30 days and the one year survival of the group was only 33%. Other studies (Wakefield et al. 1982) also failed to show benefit in terms of survival with employment of hemodialysis and reported a 68% mortality in patients with a blood urea nitrogen in excess of 50mg.dl^{-1} (17,85 mmol.l^{-1}).

If one accepts that ARF is still a major predictor of morbidity and mortality in abdominal aortic aneurysm (AAA) repair despite significant improvements in perioperative care of

patients, it should be clear that an approach aimed at the prevention of renal dysfunction and ARF may prove to be of benefit in improving (renal) outcome. Such an approach could include the following:

1.   Defining preoperative, intraoperative and postoperative risk factors.

1.1   Preoperative risk factors: The delineation of preoperative risk factors that would predict postoperative renal dysfunction and subsequent identification of such risk factor(s) in an individual patient, could result in one of two major management approaches. If quantitative information from the literature indicates that the degree of risk for the development of ARF is such that is exceeds the risk of adopting a conservative non-surgical approach with regular assessment of increase in aneurysm size (Christenson et al. 1977), the latter method could be adopted. If, on the other hand, the preoperative risk factor(s) is quantitatively of a lesser magnitude or cannot be quantified from the literature, an approach of optimizing those parameters perioperatively would be more appropriate (Pollock and Johnson 1973; Bush et al. 1981).

1.2   Intraoperative and postoperative risk factors: The occurrence of unforeseen intraoperative and postoperative incidents (such as hypotension, long cross clamp time and significant blood loss) which the literature may define as risk factors are less easily predicted in any individual patient. Awareness of such risk factors demands an approach of constant optimalisation of these variables (Wakefield et al. 1982; Ostri et al. 1986).

2.   Defining the major cause(s) of ARF associated with abdominal aortic surgery.

The most common renal causes of ARF reported in earlier studies of major vascular surgery were nephrotoxins (particularly radiographic contrast dyes and aminoglycoside antibiotics) and atheromatous emboli or thrombosis of the renal arteries (Thurlbeck and Castleman 1957; Hardin 1964; Wantz et al. 1964). Delaying surgery for at least 24 hours after the use of radiographic contrast media and specific surgical precautions including renal artery bypass grafting in patients at risk of thromboembolic occlusion of the renal arteries have minimized the risk of ARF due to renal causes (Novick et al. 1977).

Prerenal ARF is by far the most common cause of perioperative renal failure in the broad

4

surgical population, with renal ischemia almost invariably the underlying etiology (Wilkes and Mailloux 1986). Although disputed by some investigators (Mowlem et al. 1960), there was already a growing body of evidence in the early 1960's to support renal ischemia as the most significant cause of ARF subsequent to abdominal aortic surgery. This conclusion was based on collateral facts such as the histological changes in the kidneys (Nanson et al. 1959), the benefit of renal neural blockade (Porter et al. 1966) and adequate intravascular volume replacement (Beall et al. 1963), as well as direct evidence provided by renographic investigations (Whitley et al. 1961). Renal ischemia is now generally accepted to be the major cause of both temporary renal dysfunction (Gamulin et al. 1984; Gelman 1995) and ARF (McCombs et al. 1979) after infrarenal cross clamping of the aorta. The exact pathogenic and pathophysiological mechanisms involved in the decrease in renal blood flow remain elusive (Myers et al. 1996).

3.   The cause of reduced renal blood flow associated with AAA surgery.

Despite the knowledge of the importance of renal ischemia in the pathophysiology of ARF and attempts at manipulating RBF perioperatively, renal dysfunction continues to be a frequent complication of abdominal aortic surgery (Szilagi et al. 1986, Breckwoldt et al. 1992). Theoretically, at least, elucidation of the mechanism(s) or cause(s) of the reduction in RBF will provide therapeutic option(s), which, by addressing the primary cause of the problem, may have a distinct chance of preventing renal ischemia and adverse outcome.

Although a number of possible mechanisms such as renin release (Berkowitz and Shetty 1974), angiotensin II (Colson et al. 1992a; Licker et al. 1996) calcium flux (Colson et al. 1992a) and renal prostanoids (Myers et al. 1996) have been manipulated pharmacologically with varying degrees of success, the primary mechanism(s) remains to be established. In addition, the relative degree of success in manipulating potential causative factors remains in dispute (Colson et al. 1992a; Licker et al. 1996; Myers et al. 1996), largely because of the lack of a common experimental or clinical model in the various studies. Possible interaction of various potential causative factors in a sequence of pathophysiological events also remains to be explored.

1.2 CHANGES IN RBF AND KIDNEY FUNCTION ASSOCIATED WITH INFRA-RENAL CROSS CLAMPING OF THE AORTA

1.2.1 Human studies

Human studies of significance where RBF was measured perioperatively together with some form of assessment of nephron function at the same measurement times, were only reported since 1984 (Gamulin et al. 1984; Myers et al. 1984; Gamulin et al. 1986; Colson et al. 1992a; Colson et al. 1992b; Licker et al. 1996) (Table 1.1). Although attempts were made to influence RBF pharmacologically in some studies (Gamulin et al. 1986; Colson et al. 1992a; Licker et al. 1996), these attempts were either unsuccessful (Gamulin et al. 1986) or a control group (where no manipulation was attempted) was not included so that comparison of RBF and nephron function at various measurement times is not possible between these studies.

All these studies, with the exception of the reports by Myers et al. (1984) and Colson et al. (1992b), demonstrated a significant decrease in RBF subsequent to infrarenal cross clamping of the aorta when compared to intraoperative preclamp values. Colson et al. (1992a) and Licker et al. (1996) reported a return of RBF towards preclamp values after release of the cross clamp, while Gamulin et al. (1984 and 1986) demonstrated a continued reduction in RBF after clamp removal in the intraoperative period. It is unclear why Colson et al. (1992a) showed a reduction in RBF with an associated decrease in GFR during aortic cross clamping, while the same investigators (Colson et al. 1992b) were unable to show similar changes in a subgroup where the anaesthetic technique and experimental method were comparable to the former study. Small numbers (n = 8) and the fact that some patients received drugs such as angiotensin converting enzyme inhibitors (ACE inhibitors) and calcium entry blockers preoperatively, may have had an influence in the latter study (Colson et al. 1992b).

Gamulin et al. (1984 and 1986) demonstrated an increase in the I^{131}-hippuran extraction fraction subsequent to aortic cross clamping, which is suggestive of a redistribution of RBF towards the renal cortex. This is contrary to studies of ARF in humans (Hollenberg et al. 1968) and experimental animals (Parekh and Veith 1981) where renal ischemia was associated with a redistribution of RBF towards the deeper cortical and medullary regions.

Table 1.1 Human studies where both renal blood flow and nephron function were measured in infrarenal abdominal aortic surgery

Authors Publication Year	RBF preop	RBF preclamp (measurement method)	RBF perclamp	RBF post unclamp	RBF postop	Change in RBF distribution	RVR	FF	GFR preop	GFR preclamp	GFR perclamp	GFR post unclamp	GFR postop	Prox tub preclamp	Prox tub perclamp	Prox tub post unclamp	Prox + Dist tub preop	Prox + Dist tub preclamp	Prox + Dist tub perclamp	Prox + Dist tub post unclamp	Comments
Myers et al. 1984	⊗	C (PAH)	±	±	⊗	⊗	⊗	⊗	C	↓ (20-35%)	⊗	⊗	± (24 hours)	⊗	⊗	⊗	⊗	⊗	⊗	⊗	
Gamulin et al. 1984	⊗	C (^{125}I-hippuran)	↓	↓	⊗	Towards cortex	↑	± during study	⊗	C	±	±	⊗	C	±	±	⊗	C	±	±	• Mannitol used; might have influenced results, particularly distribution of RBF and GFR
Gamulin et al. 1986	⊗	C (^{125}I-hippuran)	↓	↓	⊗	Towards cortex	↑	↑ perclamp + post unclamp	⊗	C	↓	↓	⊗	C	±	±	⊗	C	±	±	• Renal sympathetics blocked with epidural • Mannitol used
Colson et al. 1992 a	⊗	C (^{131}I-hippuran)	↓	±	⊗	⊗	⊗	⊗	⊗	C	↓	↓	⊗	⊗	⊗	⊗	⊗	C	±	↓	• Just results of control group given (authors also reported on groups where Ca^{2+}-blockers and ACE-inhibitors were given)
Colson et al. 1992 b	⊗	C (^{131}I-hippuran)	±	±	⊗	⊗	⊗	⊗	⊗	C	±	±	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	• Group where fentanyl/droperidol maintenance of anaesthesia was used, do not show same changes in RBF and GFR as in 1992a study -? reason
Licker et al. 1996	⊗	C (PAH)	↓	±	⊗	No change measured	↑ (perclamp)	⊗	C	±	↓	↓	↓ (12 hours)	⊗	⊗	⊗	C	↓	↓	↓	• Mannitol not used (see RBF distribution in studies by Gamulin et al. 1984, 1986)

RBF = renal blood flow; RVR = renal vascular resistance; FF = filtration fraction; GFR = glomerular filtration rate; Prox tub = proximal tubular function; Prox + Dist tub = proximal and distal tubular function (measured with fractional excretion of sodium or free water clearance); perclamp = during clamp; C = control measurement; ± = no change from control; ↓ = decreased relative to control; ↑ = increased relative to control; ⊗ = not measured/reported

However, Gamulin et al. (1984 and 1986) used a constant infusion of mannitol intra-operatively in an attempt to maintain adequate volumes of urine production for accurate clearance measurements, which may have been responsible for the increase in cortical blood flow (Velasques et al. 1973; Abbott et al. 1974). Licker et al. (1996) were unable to demonstrate redistribution of RBF after aortic cross clamping.

All four studies where aortic cross clamping was shown to induce a reduction in RBF, also demonstrated a concomitant decrease in GFR which persisted after clamp removal. In the studies by Colson et al. (1992a) and Licker et al. (1996), this occurred despite normalisation of RBF. In the Myers et al. study (1984) a reduction of between 20% and 35% in GFR was demonstrated, but intragroup statistical analysis was not reported as this study primarily compared a group where the cross clamp was applied infrarenally with another group where clamping was done above the renal arteries.

Only Gamulin et al. (1984 and 1986) investigated the possibility of proximal tubular damage, which, together with the thick ascending limb of the loop of Henle in the medullary region (mTAL), is the most vulnerable part of the kidney during ischemic injury (Brezis et al. 1984). They were unable to demonstrate liganduria or lysozymuria, which would have been indicative of ischemic dysfunction of the proximal tubules.

Gamulin et al. (1984 and 1986) were unable to demonstrate distal nephron dysfunction by sequential measurement of free water clearance (C_{H2O}), a sensitive index of early ischaemic functional impairment (Baek et al. 1973). Colson et al. (1992a) and Licker et al. (1996) measured fractional excretion of sodium (FE_{Na}) for the same purpose (Steiner 1984). Both groups demonstrated increased FE_{Na} after aortic cross clamping with extension into the postoperative period in the latter study, suggesting distal nephron dysfunction. However, this change could also be due to an increased sodium load through intravascular fluid loading, volume depletion with pre-existing chronic renal disease, or osmotic or chemical diuresis (Steiner 1984).

In summary, these studies suggest a reduction in RBF after infrarenal cross clamping of the aorta with a concomitant decrease in GFR which remains depressed even after recovery of RBF. The integrity of tubular function apparently remains intact. A few important issues remain unanswered by these studies. Firstly, because renal venous samples could only be obtained directly from the renal vein after laparotomy, none of the

studies could measure preoperative awake control values of RBF or GFR. The effect of anaesthesia and surgery (prior to cross clamping of the aorta) on these parameters in this particular population group remains unclear, although Colson et al. (1992c) showed lower **intraoperative** control values for RBF and GFR in a halothane subgroup in comparison to an isoflurane group, suggesting a detrimental effect of the former drug. Secondly, although GFR remained decreased in comparison to preclamp values after release of the clamp intraoperatively, only one study where intraoperative reduction in RBF and GFR was demonstrated also reported postoperative GFR measurements (Licker et al. 1996). This group reported creatinine clearances (C_{creat}) 12 hours postoperatively that were less than preoperative and intraoperative preclamp measurements. Subsequent follow up was not reported.

A number of studies report perioperative changes in renal function without measurement of RBF in abdominal aortic surgery (Table 1.2). These studies are almost invariably retrospective and the majority suffers from other design defects which compromise interpretation of results. Powis et al. (1975) is the only group to report on both glomerular and tubular function. They report lysozymuria indicative of proximal tubular dysfunction in 65% (n=34) of aortic surgery patients in the postoperative period while stating that C_{creat} was decreased postoperatively in 21 patients (62% of their sample). The extent and duration of this abnormality is not reported. Cohn et al. (1970) and Pollock et al. (1973) also report on perioperative changes in C_{creat}. In a patient group where relatively small volumes of intravenous fluids were given, postoperative C_{creat} was shown to be depressed in a graph, but statistical analysis was not reported (Pollock et al. 1973). Cohn et al. (1970) showed C_{creat} to be increased one hour postoperatively with a return to control values on the seventh postoperative day, but again no statistical analysis was given. Bush et al. (1981), Wakefield et al. (1982), Ostri et al. (1986) and Breckwoldt et al. (1992) reported increases in peak serum creatinine levels in the postoperative period when compared with preoperative controls. Ostri et al. (1986) and Breckwoldt et al. (1992) claimed a return to control values at the time of discharge. Wakefield et al. (1982) did not report on discharge creatine levels and Bush et al. (1981) indicated that creatinine levels were still more than $0,5mg.dl^{-1}$ ($44\mu mol.l^{-1}$) above preoperative control values in 4 out of 9 patients where intraoperative fluid administration was titrated against central venous pressure measurements. Alpert et al. (1984) claimed that serum creatinine levels did not increase perioperatively in aortic surgery patients who became oliguric, but no data or

Table 1.2 **Human studies where preoperative renal function were reported without measurement of renal blood flow in infrarenal aortic surgery**

Authors Publication year	C_{creat} preop	C_{creat} intraop	C_{creat} postop	[Creat] preop	[Creat] postop	[Creat] postop	Periop change in BUN	Lysozymuria	Comments
Porter et al. 1966	⊗	⊗	⊗	⊗	⊗	⊗	↑ in 47% postop	⊗	• ↑ BUN when more than 20mg% increase • No statistics given
Cohn et al. 1970	C	⊗	± (7 Days)	⊗	⊗	⊗	⊗	⊗	• Immediate postop C_{creat} increased on graph, no statistics given • C_{creat} 7 days postop reported to be unchanged from preop values
Pollock et al. 1973	C	↓IV:↓ ↑IV:±	↓IV:↓ ↑IV:±	⊗	⊗	⊗	⊗	⊗	• Study design makes interpretation difficult • Retrospective allocation to high (↑IV) and low (↓IV) intravenous fluid volume groups
Powis et al. 1975	C	⊗	n=21:↓ n=9:↑ n=3:±	⊗	⊗	⊗	⊗	↑ in 76% (elective) ↑ in 72% (ruptured)	• No statistics on postop C_{creat} values • No indication of C_{creat} values at discharge • Lysozymuria is indicative of proximal tubular dysfunction
Bush et al. 1981	⊗	⊗	⊗	C	↑ (CVP fluid control)	? ↑ (CVP fluid control)	⊗	⊗	• 4 (out of 9) CVP control patients creatinine still >0.5mg.dl⁻¹ above preop values at discharge • Mean creatinine still increased at discharge, no statistics
Wakefield et al. 1982	⊗	⊗	⊗	⊗	⊗	↑ in 62% of patients	Same as [Creat]	⊗	• Increased incidence of renal dysfunction in ruptured aneurysm patients • No indication of creatinine levels at discharge
Alpert et al. 1984	⊗	⊗	⊗	C	⊗	± in patients with intraop oliguria	Same as [Creat]	⊗	
Cohen et al. 1986	⊗	⊗	⊗	C	⊗	?	⊗	⊗	• Patients with preoperative renal dysfunction • ? = 4 out of 6 patients with preop creatinine 2-4mg.dl⁻¹ required postop dialysis
Ostri et al. 1986	⊗	⊗	⊗	C	⊗	↑ in 30% (elective) ↑ in 62% (ruptured)	⊗	⊗	• Retrospective study • Dysfunction diagnosed when [Creat] increased > 20% and minimum level of 168µmol.l⁻¹ per day on 2 consecutive days
Breckwoldt et al. 1992	⊗	⊗	⊗	C	⊗	↑ at peak ± at discharge	⊗	⊗	• Retrospective study • Dysfunction diagnosed when [Creat] increased >20% and minimum level of 168µmol.l⁻¹

C_{creat} = creatinine clearance; [Creat] = creatinine concentration; BUN = blood urea nitrogen; C = control measurement; ⊗ = not measured/reported; ± = no change from control; ↑ = increased relative to control; ↓ = decreased relative to control

statistics were given to support this claim. All studies reporting on serum creatinine levels must be evaluated with the knowledge that serum creatinine levels demonstrate a poor correlation with changes in glomerular or renal function (Kim et al. 1969), with elevation of serum creatinine only becoming evident when 60% of the functional renal mass has been (irreversibly) injured (Tobias et al. 1962). Clearly, the human studies reporting only on perioperative changes in kidney function with abdominal aortic surgery, provides inconclusive information on the change in function. In addition, it suffers from the disadvantage that absence of concurrent RBF data makes it impossible to ascertain to which extent renal ischemia contributed to whatever functional changes were shown.

1.2.2 Animal studies

Early studies, using a number of different measurement techniques, demonstrated a decrease in total RBF when the aorta was clamped infrarenally in various dog models (Gagnon et al. 1960; Whitley et al. 1961; Stein et al. 1972). Gagnon et al. (1960) reported a gradual improvement during a 2-hour clamping period with restoration of normal renal blood flow within the first hour after release of the clamp, while RBF was still significantly reduced after clamp removal in the study by Stein et al. (1972). Nanson et al. (1959) injected India ink into the renal artery after infrarenal cross clamping and demonstrated redistribution of blood flow away from the cortex towards the medulla. They also demonstrated proximal and distal tubular necrosis consistent with severe ischemic injury.

More recently Abbot et al. (1973) and Berkowitz et al. (1974), using Xenon 133 washout techniques and Gelman et al. (1984a), measuring regional blood flow with labeled microspheres, were unable to demonstrate a decrease in total RBF after infrarenal aortic clamping. However, all three studies reported a redistribution of blood flow away from the superficial cortex to the deeper corticomedullary region that was maintained in the two studies that continued measurement after unclamping (Abbot et al. 1973; Berkowitz et al. 1974). These changes are similar to the response described in other models of early renal ischemia (Hollenberg et al. 1968; Parekh and Veith 1981).

Although the decrease in RBF towards the end of a 60 minute clamping period was statistically insignificant, it decreased further subsequent to clamp removal to be significantly reduced 60 minutes after unclamping in the most recent report where mean transmittable doppler flowmeters were used to measure RBF in a rat model

(Myers et al. 1996).

Animal studies (Table 1.3) contrast sharply with those done in humans where a reduction in total RBF associated with decreased GFR after infrarenal aortic cross clamping is reported in the majority of publications. No clear tendency emerges from animal studies however, with reports ranging from decreases in total RBF (Stein et al. 1972); redistribution of RBF without reduction of total RBF (Gelman et al. 1984a) and studies reporting no change (Cronenwett and Lindenauer 1977). Reasons for both the difference between conclusions in human and animal studies, as well as the widely divergent findings between various animal studies, could possibly be elucidated further if a clinically relevant animal model is used and subjected to similar pharmacological manipulation as occurs in humans.

Species differences could be a contributing factor for different results, although mongrel dogs were used in the majority of animal studies. However, even within the same species, differences in size of the animals (frequently not specified) and particularly age (invariably not specified) could have contributed to divergent outcomes. Differences in experimental design and particularly the lack of universal technique of RBF measurement with the reported use of microspheres (Gelman et al. 1984a), xenon washout (Abbot et al. 1973), electromagnetic flow probe (Stein et al. 1972), external renograms (Whitley et al. 1961), PAH clearance (Gagnon et al. 1960) and doppler flowmeters (Myers et al. 1996) could also have contributed.

More important, however, are the differences in outcome between human and animal studies. Clearly, species differences could again play a role. Differences in measurement techniques could also have had an influence with radio-isotope labeled hippuran or PAH clearance almost invariably used in human studies. Less obvious, but perhaps much more important, are two other differences:

1.   The age of animals used in experimental studies is never mentioned (and probably not known to the investigators) except for referring to them as "adult" (Abbot et al. 1974). One may speculate that these animals were probably not old and therefore not subject to the physiological and sometimes pathophysiological changes of ageing. This contrasts with human studies where patients presenting for abdominal aortic surgery are almost invariably from the elderly age group (Cohen et al. 1986; Colson et al. 1992a, 1992b; Licker et al. 1996). The fact that advanced

Table 1.3 Measurement of renal blood flow and glomerular function in experimental animals subjected to infrarenal aortic cross clamping

Authors Publication Year	Animals used	Method RBF measurement	RBF perclamp	RBF during clamp	RBF post-unclamp	Change in RBF distribution	GFR pre-clamp	GFR perclamp, after unclamp	Comments
Nanson et al. 1959	Dogs	Not given; Distribution: India ink in renal artery	C	±	⊗	Redistribution to medulla	⊗	⊗	
Gagnon et al. 1960	Dogs	PAH	C	↓	± (1 hour after unclamp)	⊗	C(C_{creat})	↑ perclamp ± after unclamp	
Whilley et al. 1961	Dogs	External renogram (Orthoiodohippuric acid I^{131})	C	↓	"recover over hours"	⊗	⊗	↑ perclamp + post unclamp	
Stein et al. 1972	Dogs	Electromagnetic flow probe	C	↓	↓	⊗	⊗	⊗	
Abbott et al. 1973	Dogs	Xenon 133 washout	C	±	±	Redistribution to deeper cortico-medullary area	⊗	⊗	• RBF decrease with 16% during clamp; not statistically significant • Redistribution still present 60 minutes after unclamp
Berkowitz et al. 1974	Dogs	Xenon 133 washout	C	±	±	Redistribution to deeper cortico-medullary area	⊗	⊗	
Cronenwett et al. 1984	Dogs	Electromagnetic flow probe and microspheres	C	±	±	⊗	C	±	• GFR measured with creatinine clearance
Gelman et al. 1984	Dogs	Microspheres	C	±	⊗	Redistribution to deeper cortico-medullary area	⊗	⊗	• "tendency toward a decrease in (cortical) flow" with 9mm microspheres; statistically not significant (n = 7)
Frank et al. 1988	Dogs	Doppler flow meter	C	±	↓	⊗	⊗	⊗	
Myers et al. 1996	Rats	Doppler flow meter	C	Initially ± later ↓	↓ (1 hour after unclamp)	⊗	⊗	⊗	

RBF = renal blood flow; GFR = glomerular filtration rate; C = control measurement; ± = no change relative to control; ↓ = decreased relative to control; ↑ = increased relative to control; ⊗ = not measured/reported

12

age was demonstrated to be predictive of adverse renal outcomes in some studies on vascular surgery patients (Svensson et al. 1989; Bergqvist et al. 1983), is probably related to the fact that preoperative renal dysfunction is much more common in this population group (Novis et al. 1994). Indeed, 74% to 84% of patients with abdominal aortic aneurysms have other pre-existing disease (Thompson et al. 1975; Scobie et al. 1977, Crawford et al. 1981) with hypertension, general atherosclerosis and diabetes mellitus being extremely prevalent; all of which cause pathological changes in the kidney. Porter et al. (1966) demonstrated a preponderance of severe chronic renal disease in all patients who died subsequent to aortic surgery, irrespective of whether renal failure contributed to the mortality. Renal vascular changes, particularly arteriolosclerosis (McLachlan 1978) and progressive histopathological abnormalities of the nephron (reduction in the number of glomeruli (Kaplan et al. 1975) and thickening of the glomerular and tubular basement membrane (McLachlan 1978)) occurs with ageing even in the absence of disease. This explains the functional changes in the kidney, which occurs with age. These changes are not reflected by the usual preoperative measurements such as serum creatinine and blood urea nitrogen (BUN) (Kim et al. 1969). The structural changes are also accompanied by altered tubular responses to hormones (Epstein and Hollenberg 1976) and a variable degree of dependence on renal prostaglandins for the maintenance of renal blood flow (Gurwitz et al. 1990) which is absent in normal adults (Donker et al. 1976). Although it may be difficult to find an animal model with comparable preoperative renal changes, it should be clear that published differences between human and animal models in response to aortic cross clamping may at least partially be contributed to this fact.

2. Although stabilization (no surgical stimuli) during perclamp measurement times is only mentioned in some animal studies (Gagnon et al. 1960; Berkowitz and Shetty 1974), it is clear from the description of methodology in the other studies that surgical stimulation was minimal after initial preparation of the models. This contrasts with human studies where significant intra-abdominal surgical stimulation associated with resection and bypass grafting of abdominal aortic aneurysms were invariably present at the times of perclamp measurement of renal hemodynamics. The hormonal changes associated with such surgical stimulation alone (Kataja et al. 1989), could quite conceivably have contributed to any changes in RBF and

kidney function which occurred during aortic cross clamping. Simulating such surgical stimulation in animal models is likely to influence the results.

1.3 ETIOLOGY OF CHANGES IN RBF AND KIDNEY FUNCTION WITH ABDOMINAL AORTIC SURGERY

There is probably general agreement that the renal failure and, less dramatically, the more frequent changes in renal function associated with infrarenal cross clamping of the aorta during abdominal aortic surgery, is of ischemic origin (Stein et al. 1972; Bush et al. 1983; Gamulin et al. 1984, 1986; Myers et al. 1996). An understanding of the etiology and pathophysiology involved in this particular population may help to identify beneficial pharmacological manipulation(s) that could be applied prophylactically, since the use of pharmacologic agents is of questionable benefit in patients with established or early ARF (Lazarus 1986). A number of potential endocrine and autonomic nervous system mediators have been reported in the literature; to date without exact clarification of the pathogenic role of any of these factors.

1.3.1. Renal sympathetic nerves and circulating catecholamines

1.3.1.1 Relevant physiology

The kidney demonstrates the ability to autoregulate its blood flow independent of extrinsic modulation (Waugh et al. 1960), primarily through varying resistance of the preglomerular afferent arteriole. However, unlike the cardiac and cerebral circulations, sympathomimetic effects may override the intrinsic control of RBF (Hermansson et al. 1981). Although the exact physiological role of the renal adrenergic nerves is still unclear, the renal sympathetics, as well as circulating catecholamines, have been demonstrated to influence RBF significantly under pathological conditions. Under conditions of stress, renal sympathetic mediated release of noradrenaline causes renal vasoconstriction through an alpha-adrenergic receptor mechanism (Schrier 1974). Circulating catecholamines have a similar effect (Rector et al. 1972). Although both renal nerve stimulation and circulating catecholamines exert a significant direct effect on renal vascular tone, a considerable portion of vascular resistance changes seems to be mediated additionally via angiotensin II production through renin release (Pelayo et al. 1984). Despite the fact that both afferent and efferent arterioles have adrenergic innervation and receptors (Ljungqvist and Wagermark 1970), adrenergic effects are much more prominent on the efferent arteriole

(Pelayo et al. 1984). This is probably due to adrenergically mediated angiotensin II production, the effect of the latter hormone being more prominent on the efferent than on the afferent arteriole. This leads to an increased glomerular ultrafiltration fraction (Hermansson et al. 1981) which can be blocked by angiotensin converting enzyme (ACE) inhibition (Anderson RJ et al. 1975; Anderson WP et al. 1981).

1.3.1.2 The role of the renal sympathetic nerves and circulating catecholamines in renal changes with aortic surgery

The involvement of the renal sympathetic nerves in the changed renal hemodynamics with infrarenal aortic clamping has been explored in a number of animal and human studies. In animal studies in which the aortic cross clamp was applied, infiltration of the renal vascular pedicle with a local anaesthetic agent or the administration of ganglion blockers have been successful in preventing the change in renal hemodynamics (Nanson et al. 1959; Whitley et al. 1961) and reduced the extent of histological change in the kidney (Nanson et al. 1959). However, other studies have been unable to demonstrate similar benefit with ganglion blockade (Stein et al. 1972). While Powers et al. (1957) found both infiltration of the renal pedicle and ganglion blockade to be capable of preventing oliguria in patients, Porter et al. (1966) were unable to show prevention of postoperative changes in BUN with pedicle infiltration in a similar population. Neither of these groups measured changes in RBF. Gamulin et al. (1986) failed to show any improvement in changed renal hemodynamics with aortic clamping when blocking the renal sympathetic outflow with thoracolumbar epidural block in patients. All the above studies, other than being inconclusive in terms of the possible etiological role of the renal sympathetic nerves, fail to examine the potential contribution of increased plasma concentrations of catecholamines during aortic surgery (Kataja et al. 1989) in the changed renal hemodynamics.

Both stimulation of the renal sympathetic nerves and increased levels of circulating catecholamines may stimulate renin release from the kidney (Schrier 1974) through an agonist effect on β_1-receptors (Osborn et al. 1981). The release of renin leads to an increase in angiotensin II levels in the presence of angiotensin converting enzyme (Margolis and Stein 1984). Increased levels of circulating catecholamines and stimulation of the renal sympathetic nerves could therefore influence renal hemodynamics indirectly by increasing systemic and renal concentrations of angiotensin II, a potent renal vasoconstrictor (Pelayo et al. 1984). Renin release that has been shown to occur in

abdominal aortic surgery (Berkowitz and Shetty 1974; Grindlinger et al. 1981; Grant et al. 1983), can be prevented by the administration of ß-blockers to humans (Grant et al. 1983) and to experimental animals (Berkowitz and Shetty 1974). RBF was only measured in the study by Berkowitz and Shetty (1974), who showed prevention of the redistribution of blood flow to the corticomedullary region (which occurred in animals not treated with ß-blockade). Because intra-abdominal surgical stimulation probably did not occur during measurement of RBF in the Berkowitz study, the potential direct effects of increased renal sympathetic tone (Schrier 1974) and circulating catecholamines (Kataja et al. 1989) are again obscured, which limits the conclusions, which could be drawn from this study.

The exact nature of the interaction between catecholamine blood levels and the changes in RBF during abdominal aortic surgery remains to be established.

1.3.2. The renin angiotensin system

1.3.2.1 Relevant physiology

Although a comprehensive review of the physiology of the renin-angiotensin system is beyond the scope of this thesis, the most relevant aspects of its physiology in the context of the clinical and experimental studies presented in this thesis will be discussed briefly.

The renal as well as systemic effects of renin are almost exclusively a consequence of angiotensin II (Gillies and Morgan 1982) which is produced by the effect of converting enzyme on angiotensin I (Margolis and Stein 1984). Renin release is controlled by a number of factors which can be classified as intrarenal (including the renal vascular receptor and the macula densa), sympathetic (including the renal nerves and circulating catecholamines) and humoral factors (including ADH, angiotensin II, prostaglandins and electrolytes) (Davis and Freeman 1976). The inhibitory effect of angiotensin II on renin release establishes a homeostatic regulatory loop for the system (Haber 1976).

Angiotensin II has significant effects on RBF and GFR. Through a vasoconstrictor effect on both the afferent (Mitchell and Navar 1987) and the efferent (Edwards 1983) arterioles, it can cause a variable, concentration dependant reduction in RBF (Edwards 1983; Blantz et al. 1976). Because the effect of angiotensin II on the efferent arteriole usually predominates (Edwards 1983), intraglomerular capillary hydrostatic pressure is increased, with maintenance or even an increase in GFR despite a decrease in RBF

(Kastner et al. 1984). Filtration fraction is therefore increased. However, angiotensin II also causes contraction of the mesangial cells in the glomerulus, which reduces the ultrafiltration coefficient (Blantz et al. 1976) and would tend to decrease GFR despite the increase in intraglomerular capillary hydrostatic pressure. Although the latter effect is probably of lesser importance in physiologic conditions, it may contribute significantly to regulation of GFR in pathologic conditions (Ichikawa and Harris 1991). Because of these variable effects of angiotensin II, blockade of angiotensin II action has been demonstrated to lead to an increase (Ichikawa and Brenner 1984; Navar et al. 1982), a decrease (Hall et al. 1979) or to an unchanged GFR (Clappison et al. 1981; Yoshioka et al. 1986).

Angiotensin II also exerts effects on the renal tubular system where it increases the reabsorption of sodium and water in the proximal tubule (Hall et al. 1977) independent of its stimulatory effect on the secretion of aldosterone, which increases sodium reabsorption largely in the distal tubule and collecting duct (Biron et al. 1961). Despite the identification of a substantial number of additional transport systems in the renal tubule, the renin-angiotensin-aldosterone system is still considered to be the most important regulator of sodium transport in this part of the nephron (Berry et al. 1996). The importance of the direct effect of angiotensin II is illustrated by the fact that ACE inhibition produces sodium loss even when aldosterone is infused concomitantly (Hall et al. 1979).

Several studies have shown angiotensin II to also be a local regulatory hormone in the kidney (Hall et al. 1977; Mendelsohn 1982) and many other tissues (Dzau 1987). The local production of angiotensin II has been identified in all regions of the kidney where physiological effects of the hormone have been demonstrated (Mendelsohn 1982; Blantz and Gabbai 1987). Consequently, measurement of plasma renin or angiotensin levels may not give an accurate indication of the extent of tissue angiotensin effects at any specific time (Waeber et al. 1989). Similarly, indication of complete systemic blockade of angiotensin II production may not necessarily reflect adequate blockade at tissue level (Dzau 1987). This may explain why larger doses of ACE inhibitors exert more significant clinical effects than what is possible to achieve with doses that provide complete suppression of systemic renin or angiotensin II levels (Dzau 1987; Brunner et al. 1987).

Finally, angiotensin interacts with other mediators and ions that may influence its effects, particularly in the kidney. The effect of angiotensin II is markedly increased in the presence of physiological concentrations of calcium in both the rat (Douglas et al. 1982)

and human (Chansel et al. 1982) kidney. Angiotensin II increases the prejunctional release of noradrenaline when the sympathetic nervous system is stimulated (Zimmerman 1978) and will therefore enhance vascular and other effects of increased sympathetic tone. This interaction explains the reduction in circulating noradrenaline concentrations observed during ACE inhibition (Maslowski et al. 1981). Angiotensin II activates phospholipase A in the vascular smooth muscle and mesangial cells in the kidney (Zusman et al. 1977; Ardaillou et al. 1987). Prostaglandins, resulting from phospholipase A activation, modulate the renal effects of angiotensin II significantly (Zusman and Keiser 1977; Schnerman et al. 1984). Although this interaction is probably unimportant in normal physiological conditions, it is of great significance under pathophysiological circumstances (Henrich et al. 1978a, 1978b).

1.3.2.2 The role of angiotensin II in ischemic ARF

From the physiological background it is clear that angiotensin II has the potential to produce significant decreases in RBF with concomitant changes in nephron function.

Impaired RBF may initiate ARF firstly by reducing glomerular capillary pressure to a level at which filtration is severely impaired or ceases and secondly by causing ischemic damage to the functional components of the nephron (De Torrente, 1984). Reduced RBF has also been demonstrated during the maintenance phase of postischemic ARF after termination of the initiating event (intrarenal noradrenaline or clamping of the renal artery) in animal models (Cronin et al. 1978a, 1978b; Venkatachalam et al. 1978) and humans (Reubi 1974). Extreme elevation of plasma renin levels during this phase and its subsequent fall in the recovery phase (Brown et al. 1970; Moran and Myers 1985) have led to suggestions that angiotensin II may be the mediator responsible for the reduction in RBF. Indeed, blocking the effect of angiotensin II has been shown to be of prophylactic benefit in some models of ARF (Falk et al. 1980). However, a number of studies have failed to establish such a pathogenic role for angiotensin II (Arendshorst et al. 1976; Mason et al. 1979; Bidani et al. 1979) although some of this evidence is circumstantial and the possible role of local intrarenal angiotensin II has not been adequately explored in various models of ischemic ARF. Based on current evidence it is suggested that hyperangiotensinemia during ARF is more likely a result of postischemic tubular injury than a primary pathogenic phenomenon (Myers and Moran 1986). The same authors and others (Badr and Ichikawa 1988) conclude however, that high angiotensin II concen-

trations do contribute to the pathophysiological and biochemical changes and that normalization of angiotensin blood levels could be important in facilitating the onset of recovery.

1.3.2.3 The role of the renin-angiotensin system in renal changes with aortic surgery

There is a lack of consistency with regard to changes demonstrated in renin concentration subsequent to aortic cross clamping in experimental models (Table 1.4), with some studies showing an increase (Berkowitz and Shetty 1974) and others no significant change (Cronenwett and Lindenauer 1977).

A number of studies have reported on changes in plasma renin concentrations during abdominal aortic surgery in humans (Table 1.5). Gal et al. (1974) observed increased intraoperative renin concentrations, even before aortic clamping, when compared with preoperative control values. In other studies preclamp intraoperative renin concentrations were not significantly increased when compared with preoperative controls (Grindlinger et al. 1981; Grant et al. 1983; Kataja et al. 1989). All of the above studies demonstrated an increase in plasma renin concentrations after infrarenal cross clamping the aorta. In studies by Gal et al. (1974) and Grant et al. (1983) plasma renin levels continued to rise after unclamping the aorta, reaching a peak 30 minutes after unclamping in the former study while peaking only 30 minutes after arrival in the recovery ward in the latter study. In the studies by Grindlinger et al. (1981) and Kataja et al. (1989) renin levels after unclamping were similar to values during the clamping period. Salem et al. (1988) observed increased renin concentrations after infrarenal aortic cross clamping compared with intraoperative preclamp controls in patients receiving intravenous dopamine in a dose of $2\mu g.kg^{-1}.min^{-1}$. In a non-dopamine control group, increased renin concentrations did not reach statistical significance because of wide scatter, despite a mean renin level which was even higher than in the dopamine group. Renin concentrations were not determined after unclamping of the aorta in this study.

While patients receiving ß-blockers preoperatively (for various indications) did not demonstrate an increase in perioperative renin levels in the study by Grant et al. (1983), there was no difference in renin concentration-change between patients on ß-blockers preoperatively and those not receiving ß-blockers in the Grindlinger et al. (1981) study.

Table 1.4 Studies in animals (dogs) in which plasma renin levels were measured with infrarenal cross clamping of the aorta

Authors Publication Year	Renin pre-induction	Renin pre-clamp	Renin post-clamp	Renin pre-unclamp	Renin post-unclamp	Renal blood flow	Comments
Stein et al. 1972	⊗	C	?	?	?	⊕ (see comments)	• Poor study; no measurement results given; comments that "renin varied from animal to animal and showed no consistent pattern that could be related to changes in any other parameter"
Berkowitz et al. 1974	⊗	C	↑	↑↑	± (60 min after unclamp)	⊕ (see comments)	• ß-blockade prevented renin increase • ß-blockade also prevented redistribution of renal blood flow away from cortex
Cronenwett et al. 1977	⊗	C	±	⊗	±	⊕ (see comments)	• Mean renin levels doubled after clamp, but statistically not significant (n=6) • No change in renal blood flow

C = control measurement; ± = no change relative to control; ↑ = increased relative to control; ↑↑ = highest levels measured; ⊗ = not measured/reported; ⊕ = measured; ? = unclear whether measured/no results given

Table 1.5 Human studies in which plasma renin was measured in abdominal aorta surgery

Authors Publication Year	Renin pre-induction	Renin pre-clamp	Renin post-clamp	Renin pre-unclamp	Renin post-unclamp	Renal blood flow	Comments
Gal et al. 1974	C	↑	↑	⊗	↑↑	⊗	• Renin levels in patients with renal (lumbar) sympathectomy not different from those without sympathectomy
Grindlinger et al. 1981	C	Renin ± angiotensin ↑	Renin and angiotensin ↑	⊗	Renin and angiotensin ↑	⊗	• Renin levels also increased in patients on ß-blockers preoperatively • No correlation between postop hypertension and renin levels
Grant et al. 1983	C	±	±	↑	↑↑	⊗	• Highest levels 30 minutes after arrival in recovery ward • Renin not increased in patients on ß-blockers preoperatively
Salem et al. 1988	⊗	C	↑	⊗	⊗	⊗	• Renin levels increased irrespective of whether dopamine ($2\mu g.kg^{-1}.min^{-1}$) was administered or not
Kataja et al. 1989	C	±	±	↑	↑	⊗	• No correlation between postop hypertension and renin levels

C = control measurement; ± = no change relative to control; ↑ = increased relative to control; ↑↑ = highest levels measured; ⊗ = not measured/reported

The reason for this difference between the two study outcomes is unclear, but may relate to different doses of ß-blockers received or to the possibility that patients in the latter study did not receive ß-blockers in the immediate preoperative period (not specified). RBF was not measured in any of the above human studies, despite reference to the possibility of involvement of the renin-angiotensin mechanism in the etiology of reduced RBF during abdominal aortic surgery (Gal et al. 1974; Grant et al. 1983; Salem et al. 1988; Kataja et al. 1989). The relationship, if any, between renal hemodynamics and increases in renin or angiotensin concentrations in aortic surgery are consequently not elucidated by the above studies.

The existence of such a relationship could also be shown indirectly by demonstrating prevention of changes in renal hemodynamics subsequent to blockade of angiotensin receptors or inhibiting the synthesis of angiotensin by the administration of ACE inhibitors. A beneficial effect of ACE inhibition on RBF may not necessarily resolve the question whether increases of renin or angiotensin concentrations (if shown to be correlated with reduced RBF during abdominal aortic surgery), is in fact the cause or the result of decreases in RBF. A decrease in RBF due to other mechanisms has been shown to induce secondary release of renin and therefore also increased angiotensin II concentrations (Badr and Ichikawa 1988). This secondary increase in angiotensin II concentrations does however contribute to the maintenance of increased renal vascular resistance (Hostetter and Brenner 1988). Only two recently published studies have explored this therapeutic option (Colson et al. 1992a; Licker et al. 1996). Colson et al. (1992a) demonstrated a reduction in RBF after infrarenal aortic clamping in patients despite the administration of enalapril 10mg orally twice daily for two days prior to surgery. A similar reduction in RBF and GFR in a placebo group suggests no benefit derived from the administration of the ACE inhibitor. In contrast, Licker et al. (1996) reported maintenance of RBF after aortic clamping in patients who received a single intravenous dose of enalapril ($50\mu g.kg^{-1}$) preoperatively, while clamping induced a significant decrease in RBF in a saline control group. They suggest differences in dose regimen, anaesthetic management and measurement methods as possible reasons for the contradictory results. No reference could be found to assist in comparing the two dose regimen in terms of possible plasma concentrations or biological efficacy. The two preparations used for the measurement of RBF, I^{131}-hippuran and para-aminohippuric acid respectively, have been shown to be handled identically by the kidney with a direct correlation between the

clearances (correlation coefficient = 0.993) of the two substances (Ram et al. 1967). This makes divergent results due to different measurement techniques unlikely. The fact that 5 of the 11 enalapril patients in the Licker study received calcium channel blockers as part of their preoperative therapy, could have influenced their results. Patients on preoperative calcium blockers were excluded from the Colson (1992a) study. The latter group of investigators also demonstrated that the intraoperative administration of the calcium channel blocker, nicardipine, prevented changes in RBF after aortic clamping in one of the subgroups of their study.

Kataja et al. (1989) in a study of patients during abdominal aortic surgery where RBF was unfortunately not measured, reports intraoperative urine output in patients receiving preoperative captopril to be almost twice the volume achieved in a non-captopril control group. It is possible, but not yet proven that the ACE inhibitor may have been responsible for the improved urine flow, although no further parameters of renal function were assessed.

The indirect evidence to suggest an etiological role for the renin-angiotensin system in the reduction of RBF induced by infrarenal aortic cross clamping in humans is therefore also inconclusive.

Conclusions from studies performed during other surgical procedures suggest a role for the renin-angiotensin system in the pathophysiology of reduced RBF and therefore potential benefit from interrupting the angiotensin activation pathway. Plasma renin levels were shown to be increased with suprarenal cross clamping of the aorta (Symbas et al. 1983; Joob et al. 1986), even when adjuncts (shunt or bypass) were used to increase RBF during clamping (Symbas et al. 1983). While RBF remained depressed 30 minutes after release of the suprarenal cross clamp (± 50% of preclamp control values) in control animals, RBF returned to preclamp control levels after release of the clamp in animals pretreated with an ACE inhibitor (Joob et al. 1986). Angiotensin was also suggested to play a significant role in the hypertension associated with suprarenal cross clamping of the aorta (Hong et al. 1992). While Taylor et al. (1977) observed a substantial increase in plasma angiotensin concentrations during cardiopulmonary bypass (CPB) which remained elevated for several hours, Colson et al. (1990) reported prevention of the decrease in RBF during CPB with the preoperative administration of an ACE inhibitor.

The indiscriminate use of ACE inhibitors in patients scheduled for abdominal aortic surgery without proof of benefit in terms of renal hemodynamics or improved clinical outcome cannot be recommended. Recovery of blood pressure and renal perfusion after hemorrhagic hypotension, which is relatively common during aortic surgery, is significantly impaired in the presence of ACE inhibition (Yamashita et al. 1977; Zerbe et al. 1981). Patients with renal artery stenosis, which occurs not infrequently in the presence of aortic aneurysms (Novick et al. 1977), and especially bilateral stenosis, may suffer a dramatic decrease in GFR and renal function subsequent to ACE inhibitor therapy (Hricik et al. 1983; Lakhani et al. 1985). The absence of renal artery stenosis on angiography was a noted exclusion criterion in the studies of Colson et al. (1992a) and Licker et al. (1996).

1.3.3. Arginine vasopressin (AVP)/antidiuretic hormone (ADH)

1.3.3.1 Relevant physiology

Factors responsible for the release of ADH during anaesthesia and surgery (Ishihara et al. 1978) are stimulation of hypothalamic osmoreceptors by increased serum osmolality (Schrier et al. 1979), stimulation of carotid baroreceptors by decreased arterial blood pressure (Woods et al. 1983) and of volume receptors located in the left atrium, which are sensitive to reduced circulating blood volume (Yared et al. 1985). Surgical (visceral) stimulation and stress (Knight et al. 1986) and increased concentrations of catecholamines and angiotensin II (Schrier et al. 1975; Stella and Zanchetti 1987) also contribute significantly to stimulation of ADH secretion.

ADH is a potent systemic vasoconstrictor (McNeil et al. 1970; Boyle et al. 1983), but its effect on vascular smooth muscle is probably unimportant under normal physiological conditions (Padfield et al. 1981).

ADH has been shown to exert vasoconstrictive effects in the kidneys of experimental animals (Yared et al. 1985), reducing glomerular perfusion. ADH also evokes the release of vasodilatory prostaglandin E (Zipser et al. 1981), balancing the renal vasoconstrictive effects of ADH and other vasoactive substances under pathophysiological conditions (Patrono and Dunn 1987). Glomerular function is further modulated by ADH through stimulation of mesangial cell contraction (Schor et al. 1981) which decreases the glomerular ultrafiltration coefficient and GFR independent of a pathway involving angiotensin II. This effect of ADH is also attenuated by prostaglandin E_2, which is

synthetized by mesangial cells (Scharschmidt et al. 1983). The prostaglandin stimulatory effect of ADH is suggested to be dependent on the pressor, not the antidiuretic, activity of this hormone (Sawyer et al. 1977).

ADH exerts its tubular effects mainly on the distal tubule and collecting duct where it promotes water reabsorption, as well as on the thick ascending limb of the loop of Henle where it stimulates active reabsorption of sodium (Amiel et al. 1987). Because of predominance of the former effect, varying degrees of hyponatremia are a common feature of high plasma concentrations of ADH. In addition, particularly in the presence of normovolemia, high ADH concentrations would lead to oliguria and a high urinary sodium concentration (Zaloga and Hughes 1990). Such circumstances would obviate the use of urinary sodium concentration or FE_{Na} in the diagnosis of ARF.

1.3.3.2   The role of ADH in ischemic ARF

The presence of ADH has been suggested to be necessary for the full nephrotoxic effect of cyclosporine in the rat kidney (Barros et al. 1987). The pathophysiological role of ADH is postulated to be either its renal vasoconstrictor effect or its action on mesangial cells leading to reduced glomerular ultrafiltration independent of angiotensin II (Schor et al. 1981).

Elevated concentrations of angiotensin II and ADH often circulate in all forms of ARF, including renal failure of ischemic origin (Hostetter and Brenner 1988). It is suggested that under such circumstances the reductions in ultrafiltration coefficient may be brought about, at least in part, through the actions of these agents rather than by direct glomerular injury. Although ADH is therefore not suggested to be a primary pathogenic instigator of injury in ischemic ARF, it does participate in the pathophysiological process.

1.3.3.3   The role of ADH in renal changes with aortic surgery

Plasma ADH concentrations are not increased by anaesthesia as such or by anaesthetic agents such as fentanyl or halothane (Ishihara et al. 1978). Morphine has been reported to stimulate (Lightman and Forsling 1980) and inhibit (Woods et al. 1983) the release of ADH. Changes in ADH concentrations seen with intravenous morphine administration are likely to be induced by its effect on vascular smooth muscle leading to a state of relative

hypovolemia, a known stimulus for ADH release (Yared et al. 1985), rather than a direct effect of the drug.

The trauma and stress of surgery causes dramatic increases in ADH secretion (Sinnatamby et al. 1974), the magnitude and duration of the hormonal response being in proportion with the severity of the surgical procedure (Haas and Glick 1978). ADH concentrations consistently rise far in excess of levels necessary for maximum antidiuresis (Fieldman et al. 1985) and are therefore responsible for the significantly negative free water clearance (C_{H2O}) seen in the perioperative period. Excessive ADH levels are also responsible for the high FE_{Na} seen after major surgery and in critically ill patients in the absence of ARF (Zaloga and Hughes 1990).

Although ADH contributes to changes in systemic vascular resistance during surgery (Boyle et al. 1983), its potential effect on the renal vasculature has not been studied under these circumstances. In the only study of abdominal aortic surgery to report on changes in ADH concentrations perioperatively, Kataja et al. (1989) report concentrations to be increased even before cross clamping of the aorta, reaching a peak in the recovery ward and remaining increased on the first postoperative morning. Changes in RBF and renal function were not reported in this study.

The presence or absence of a temporal relationship between ADH concentrations and altered kidney function and RBF in aortic surgery therefore remains to be elucidated.

1.3.4. The role of other substances in altered renal hemodynamics and function in ischemic ARF and during aortic surgery

A number of other non-hormonal substances have been suggested to play a role in the changes in RBF and kidney function associated with abdominal aortic surgery (Gamulin et al. 1986). A few studies where the potential benefit of blocking the release or the biological effect of these substances were investigated in clinical or experimental models during infrarenal clamping of the aorta, have been published recently. These studies, as well as the possible pathogenic role of these substances in inducing the changes seen in aortic surgery, will be briefly reviewed.

1.3.4.1   Calcium (Ca^{2+})

The effects of Ca^{2+} on renal hemodynamics and kidney function have been investigated predominantly by using calcium channel blockers or physiological antagonists of Ca^{2+} in various clinical and experimental models.

Ca^{2+} does not influence RBF (Wallia et al. 1985) or GFR (Leonetti et al. 1982; Wallia et al. 1985) in normal humans indicating minimal effect of Ca^{2+} on resting renal vascular tone. In contrast to the lack of effect in normal subjects, hypertensive patients exhibit a significant renal hemodynamic effect with sustained increases in RBF and GFR under the influence of calcium channel blockers (Ca^{2+}-blockers) (Reams and Bauer 1990).

Although Ca^{2+}-blockers do not affect renal hemodynamics under normal resting conditions, they dramatically alter the response of the kidney to vasoconstrictor agents. The renal vasoconstrictive effects of noradrenaline (Loutzenhiser and Epstein 1987), angiotensin II (Ichikawa et al. 1979), thromboxane (Loutzenhiser et al. 1986) and endothelin (Loutzenhiser et al. 1990) are significantly attenuated by Ca^{2+}-blockers. The predominant effect of Ca^{2+}-channel blockade is on the afferent arteriole (Flemming et al. 1987), thereby decreasing preglomerular vascular tone. The nett result is an increase in intracapillary hydrostatic pressure in the glomerulus with a modest improvement in renal blood flow, but a marked augmentation of GFR when Ca^{2+}-blockers are administered in the presence of renal vasoconstrictors (Loutzenhiser et al. 1985).

1.3.4.1.1   The role of Ca^{2+} in ARF

Although Ca^{2+} has been demonstrated to play a specific role in renal tubular damage in ARF (Wilson et al. 1984; Arnold et al. 1986), this brief review will, in the context of this thesis, focus predominantly on the effect of Ca^{2+} in changed renal hemodynamics and glomerular function as well as its interaction with other vasoactive substances in ischemic ARF.

Ca^{2+}-blockers protect the kidney more effectively against noradrenaline induced ischemia than against ARF induced by total renal artery clamping (Malis et al. 1983). This is proposed to be due to verapamil preventing total cessation of RBF during intrarenal noradrenaline infusion. Moreover, Ca^{2+}-blockers have been shown to inhibit the renal vasoconstrictive effects of noradrenaline, angiotensin II, thromboxane, ADH and

endothelin (Ichikawa et al. 1979; Loutzenhiser et al. 1986; Loutzenhiser and Epstein 1987; Loutzenhiser et al. 1990), and the plasma concentrations of these vasoconstrictors are generally increased during ischemic episodes associated with clinical ARF. Use of in vitro cell culture techniques has also demonstrated that vasoconstrictors most probably mediate their effects on vascular smooth muscle and the mesangial cells in the glomerulus by increasing intracellular Ca^{2+} (Takeda et al. 1986; 1988; Bonventre et al. 1986). The initial increase in cytosolic Ca^{2+} occurs secondary to intracellular Ca^{2+}-mobilisation as it occurs even in the presence of Ca^{2+}-free media or a Ca^{2+}-blocker (Takeda et al. 1986; 1988). However, the sustained (minutes) vascular effects of ADH on vascular smooth muscle (Takeda et al. 1988) and of angiotensin II on glomerular mesangial cells (Takeda et al. 1986) involve replenishment of intracellular Ca^{2+} stores by enhanced Ca^{2+} influx, an effect which can be partially blocked by Ca^{2+}-blockers (Takeda et al. 1986; 1988).

It is well known that autoregulation of RBF is abolished for days to weeks after an ischemic insult known to cause ARF (Adams et al. 1980). This effect is detrimental as it predisposes the kidney to subsequent ischemic damage if fluctuation in renal perfusion pressure occurs. Verapamil and diltiazem have been shown to prevent this loss of autoregulation of RBF subsequent to an intrarenal noradrenaline insult known to cause reversible ischemic ARF (Robinette et al. 1987), this despite the fact that Ca^{2+}-blockers have been demonstrated to block the renal autoregulatory capability in a non-ischemic kidney model in vitro (Cohen and Fray 1982).

Inhibition of the physiological and pathophysiological role of Ca^{2+} in glomerular function may also be beneficial in ARF. The reduction of glomerular filtration coefficient mediated at least partly by vasoactive substances is blocked by the administration of verapamil (Ichikawa et al. 1979). Indeed, filtration fraction has been demonstrated to be increased or unchanged under the influence of Ca^{2+}-blockers (Dietz et al. 1983; Roy et al. 1983; Bell and Lindner 1984). This maintenance of glomerular capillary permeability is suggested to be secondary to the prevention of mesangial cell contraction. Ca^{2+}-blockers also predominantly reduce the vascular tone of preglomerular blood vessels (Flemming et al. 1987), thus assisting the maintenance of intracapillary hydrostatic pressure in the presence of a decrease in renal artery perfusion pressure.

The combination of maintenance of glomerular permeability and capillary hydrostatic pressure is responsible for the increase in GFR subsequent to the administration of Ca^{2+}-

blockers in ARF (Wait et al. 1983; Woolley et al. 1988). Maintenance of GFR may be beneficial in ARF by assisting in the washout of necrotic cellular debris and thus preventing or attenuating tubular obstruction, the primary maintenance factor in ARF (Burke et al. 1980). Maintenance of GFR may not be universally beneficial, as a decrease in GFR may be associated with a decrease in tubular reabsorption, thereby decreasing renal energy and oxygen requirements (Brezis et al. 1984a, 1989).

The detrimental effects of cellular and mitochondrial Ca^{2+} overload as well as the potential beneficial effects of Ca^{2+}-blockers have been well described and reviewed (Schrier et al. 1987; Weinberg 1991). It will not be described here as it falls out of the scope of this thesis.

1.3.4.1.2 The role of Ca^{2+} in renal changes with aortic surgery

Only one published study (Colson et al. 1992a) has explored the possible role of Ca^{2+} in the changed renal hemodynamics and glomerular function indirectly by investigating the potential benefit of prophylactic administration of a Ca^{2+}-blocker. They reported maintenance of RBF and GFR in patients who received nicardipine, while RBF and GFR were decreased after aortic cross clamping in both a control group and in another group of patients who received an ACE inhibitor. The calculated filtration fraction was significantly higher in the nicardipine group than in any of the other groups, which is consistent with the predominantly preglomerular vascular effect and maintenance of glomerular filtration coefficient described for Ca^{2+}-blockade (Ichikawa et al. 1979; Flemming et al. 1987).

A beneficial effect of Ca^{2+}-blockade does not establish a primary pathogenic role for Ca^{2+} in the renal changes, which occur with infrarenal aortic cross clamping. In fact, it is much more likely that the benefit is derived from blocking the effect of Ca^{2+} much lower down the pathophysiological pathway induced by other mediators known to exert their effects through a Ca^{2+}-modulated mechanism (Ichikawa et al. 1979; Loutzenhiser et al. 1986, Loutzenhiser and Epstein 1987, Loutzenhiser et al. 1990).

1.3.4.2 Endothelin

Endothelin has been postulated to play a local regulatory role in renal function, particularly in respect of the control of RBF and glomerular function, together with other vasoactive substances (Lüscher et al. 1991). Endothelin has been shown to be synthetised in

mesangial cells (Zoja et al. 1991), glomerular epithelial cells (Kasinath et al. 1992) and endothelial cells of the renal microvasculature (Marsden et al. 1991). Endothelin (receptor) binding sites have been shown to be distributed through the kidney, with higher densities in the glomeruli, inner medulla and vasa recta (Power et al. 1989). The effects of endothelin on the renal vasculature produces significant decreases in RBF and GFR in association with a decrease in sodium excretion and an increase in plasma renin activity (Miller et al. 1989) in concentrations low enough not to elicit changes in arterial blood pressure (Badr et al. 1989). Endothelin produces a renovascular effect of long duration, with renal vasoconstriction persisting up to 40 minutes after cessation of an intravenous infusion of endothelin (Goetz et al. 1989).

A wide range of interactions have been described between endothelin and other vasoactive substances, which modulate the actions of endothelin and may even be responsible for a major part of its primary actions in vivo. The renal actions of endothelin are associated with activation of the renin-angiotensin system, suggesting that the renal vasoconstrictor response to endothelin may involve a contribution from angiotensin II (Miller et al. 1989). In addition, endothelin has been shown to promote angiotensin II production by enhancing the activity of the ACE (Kawaguchi et al. 1990). Angiotensin II on the other hand, enhances the effect of endothelin by stimulating endothelin synthesis and release (Kohno et al. 1991), as well as increasing vascular responsiveness to endothelin (Dohi et al. 1992). The biological significance of the above interactions is demonstrated by the marked inhibition of the renal effects of endothelin when angiotensin II synthesis is blocked by the administration of an ACE inhibitor (Chan et al. 1994).

Calcium and calcium ionophores also play a role in the synthesis and release of endothelin (Boulanger and Lüscher 1990; Lüscher et al. 1991). Through binding with its receptor on vascular smooth muscle, endothelin increases intracellular Ca^{2+} via activation of phospholipase C and phosphoinositol metabolism (Simonson et al. 1989). The resultant increase in renal vascular tone can be inhibited by Ca^{2+}-blockers (Loutzenhiser et al. 1990). Endothelin enhancement of the effect of other vasoconstrictors such as noradrenaline also involves activation of voltage-operated Ca^{2+}-channels, which can be inhibited by Ca^{2+}-blockade (Yang et al. 1990).

Endothelin also interacts intrarenally with two important vasodilatory substances. Similar to other vasoconstrictors, endothelin stimulates the release of the vasodilatory

31

prostaglandins E_2 and I_2 from the kidney (Rae et al. 1989; Chou et al. 1990). Endothelium-derived relaxing factor (or nitric oxide) has effects opposing those of endothelin in the kidney (Tollins et al. 1990) and also inhibits the angiotensin II induced contraction of mesangial cells (Shultz et al. 1990). Renal vasoconstriction induced by low concentrations of endothelin is also markedly potentiated in the presence of an inhibitor of nitric oxide production (Lerman et al. 1992). The above findings thus demonstrate the importance of a balance between endothelium derived vasoconstricting and vasodilating substances as a local regulatory system of kidney function and suggest that this balance may be important in disease states in which these factors are excessively stimulated or absent.

1.3.4.2.1   The role of endothelin in ischemic acute renal failure

In patients with ARF, plasma endothelin levels are elevated and they decline during recovery from the disease (Tomita et al. 1989). It is suggested that ischemia may stimulate endothelin production (Yanagisawa et al. 1988) although decreased clearance may also be partly responsible for the increased concentration. In ischemic ARF of the rat, infusion of an antibody against endothelin ameliorates the vasoconstriction characteristics of postischemic nephrons and markedly increases renal plasma flow and single nephron GFR (Kon et al. 1989). In another model of ischemic ARF, endothelin antibodies protected the kidney from acute tubular necrosis after renal artery occlusion (Shibouta et al. 1990), suggesting that endothelin may be one of the important deleterious mediators in the pathogenesis of ischemic ARF.

Endothelin is also suggested to play a pathogenic role in ARF induced by cyclosporin. Similar to the ischemic ARF model, increased systemic concentrations of endothelin have been observed in patients treated with cyclosporin (Deray et al. 1991) and treatment with endothelin antibody was found to improve the immunosuppressant-induced decrease in RBF and GFR (Kon et al. 1990).

1.3.4.2.2   The role of endothelin in renal changes with aortic surgery

Changes in endothelin concentrations with infrarenal aortic cross clamping have only been investigated in one study (Antonucci et al. 1990). This group reported a significant increase in endothelin plasma levels after aortic clamping. They suggested that infusion of nifedipine was responsible for the maintenance of GFR demonstrated in the presence of increased endothelin levels. Unfortunately, RBF was not measured and a non-nifedipine

control group was not included in the study to substantiate their claim for the beneficial effect of the Ca^{2+}-blocker.

Based on evidence from other studies where changed renal hemodynamics induced by endothelin was reversed by the administration of an ACE inhibitor (Chan et al. 1994), ACE inhibition may also be expected to be of benefit with aortic cross clamping if endothelin does prove to be an important pathogenic factor in the renal dysfunction associated with this procedure.

1.3.4.3. Adenosine

Adenosine has been postulated to link control of RBF and GFR with changes in renal metabolism (Osswald et al. 1980; Spielman and Thompson 1982). However, it is questionable whether renal blood flow has a metabolic control component since complete renal autoregulation is retained in the non-filtering kidney (Ofstad and Aukland 1985). The quantitative importance of adenosine as a physiological regulator of renal hemodynamics is still poorly understood.

Acute administration of adenosine causes significant renal vasoconstriction with concomitant decreases in filtration fraction and GFR (Hester et al. 1983; Hall et al. 1985). It appears that adenosine needs a functioning angiotensin II receptor system for its renal vasoconstrictor action (Dietrich et al. 1991). The combined renal vasoconstrictive effect of adenosine and angiotensin II is predominantly on preglomerular vessels (Tagawa and Vander 1970; Hall et al. 1985), which is in contrast with the more prominent influence of angiotensin II alone on the efferent arteriolar tone (Edwards 1983). With continued infusion of adenosine, renal vascular resistance and RBF return toward normal (Tagawa and Vander 1970; Hall et al. 1985). This is at least partly due to the suppression of renin secretion (and subsequent reduced angiotensin II production) caused by adenosine (Tagawa and Vander 1970). If renin or angiotensin II levels remain increased despite the suppressive effect of adenosine on renin secretion, the secondary renal vasodilation will be attenuated (Hall et al. 1985). Increased sodium intake also decreases the renal vasoconstrictive effect of adenosine probably due to its inhibitory effect on the renin-angiotensin system, but it may also be in response to other effects of increased sodium.

Even when the renal vasoconstrictive effect of adenosine is inhibited by the administration of an ACE inhibitor, GFR still decreases (Hall et al. 1985). This is at least partly due to the

vasodilator effect of adenosine on efferent arterioles through the A_2-adenosine receptor, which is independent of the presence of angiotensin II (Holz and Steinhausen 1987). GFR also remains decreased despite recovery of RBF with continued (chronic) administration of adenosine (Hall et al. 1985). The cause of the continued reduction in GFR is partly due to the efferent vasodilator effect of adenosine and partly because adenosine-induced reduction of renin and angiotensin concentrations would also reduce efferent arteriolar tone which decreases intraglomerular hydrostatic pressure and filtration fraction. An increase in renal prostaglandin synthesis (Hall et al. 1985) and a decrease in noradrenaline sensitivity (Hashimoto and Kokobun 1971) may also play a contributory role.

1.3.4.3.1.   The role of adenosine in ischemic acute renal failure

It is possible that the adenosine-angiotensin II interaction may play a role in causing renal vasoconstriction and ischemic renal failure during certain pathological conditions such as severe renal artery stenosis or hypoxia since tissue, urine and blood concentrations of adenosine have been shown to increase markedly during renal artery occlusion (Miller et al. 1978). In such circumstances angiotensin II levels have also been demonstrated to be elevated (Brown et al. 1970; Moran and Myers 1985) and adenosine has been demonstrated to cause sustained renal vasoconstriction of preglomerular vessels when angiotensin II is maintained at high concentrations (Hall et al. 1985). The magnitude and time course of adenosine-induced renal vasoconstriction is nevertheless such that is it unlikely to be the primary pathogenic mediator responsible for acute renal failure (Firth et al. 1988).

1.3.4.3.2.   The role of adenosine in renal changes with aortic surgery

Adenosine has been suggested as the mediator of changes in renal hemodynamics with infrarenal aortic cross clamping in a study on dogs (Frank et al. 1988). In this study RBF decreased and renal vascular resistance increased only after release of the aortic cross clamp and was associated with an increase in adenosine levels in the systemic circulation. The increase in adenosine concentrations is suggested to be due to tissue ischemia distal to the aortic cross clamp. If adenosine is the only or primary mediator involved in renal hemodynamic changes with aortic surgery, it would be difficult to explain the renal changes, which occur immediately after clamping of the aorta (Gamulin et al. 1984, 1986; Colson et al. 1992a). Patients with well developed collateral circulation such as individuals with occlusive arterial disease would then also be unlikely to suffer the same renal

hemodynamic upsets as patients without adequate collateral blood flow. Patients with aorto-iliac occlusive disease were included in renal hemodynamic studies during aortic surgery and were not reported to behave differently in terms of reported renal changes (Gamulin et al. 1984, 1986; Colson et al. 1992a; Licker et al. 1996).

If adenosine does play a role in renal hemodynamic changes with aortic surgery, ACE inhibition is likely to be beneficial in preventing these changes based on the evidence of the adenosine-angiotensin interaction in the renal circulation (Hall et al. 1985; Dietrich et al. 1991).

1.4   HYPOTHESIS

From the preceding literature survey, it is clear that a number of important aspects relating to renal changes with infrarenal cross clamping of the aorta still need to be elucidated.

Although the majority of human studies suggest a decrease in RBF and GFR associated with infrarenal aortic cross clamping, the exact duration of these changes, particularly the decreased GFR, is still unclear. A significant decrease in GFR would introduce a significant risk and would, by decreasing functional renal reserve, increase the possibility of frank renal failure with subsequent (future) ischemic (or other) insults, or even through the progressive deterioration of renal function with ageing (Kaplan et al. 1975; McLachlan 1978).

Published human studies also employ intraoperative preclamp measurement of RBF as control against which subsequent changes are compared for significance. Such an approach ignores the possibility that anaesthesia and surgery may decrease RBF from awake values, hence obscuring decreases in RBF, which may be even more significant in a statistical and clinical context.

Hormones involved in the normal physiological control of RBF and kidney function are known to be present in higher concentrations in ischemic ARF (Badr and Ichikawa 1988). Although their roles in the pathogenesis of ischemic ARF is in dispute, it is accepted that they play a role in the pathophysiology of this condition (Myers and Moran 1986; Badr and Ichikawa 1988).

With the exception of renin measurements, plasma levels of the above hormones have only rarely been determined in abdominal aortic surgery. None of the human studies

where renin (or any other hormone) levels were measured, report on concomitant measurement of RBF. The association between increased levels of hormones and changes in renal hemodynamics therefore also remains to be explored.

There is significant interaction between hormonal vasoconstrictors. In addition, the final intracellular vasocontrictive mechanisms invariably overlap. Inhibition of one vasoactive mediator could therefore attenuate the vasoconstrictive response induced by another. This is supported by the apparent success of different pharmacological agents in maintaining RBF and GFR with infrarenal aortic cross clamping (Colson et al. 1992a; Licker et al. 1996). Although results are conflicting, it may be argued that any agent that increases RBF during aortic surgery would suffice. However, different substances influence some intrarenal vascular beds more than others, so that improved global renal blood flow may not reflect adequate regional perfusion and function. In addition, specific vasoconstrictive substances initiate specific homeostatic and pathophysiological sequences (Margolis and Stein 1984) so that non-selective vasodilatation may not necessarily inhibit other concurrent harmful pathophysiological effects.

If hormones therefore play a pathophysiological, if not pathogenic, role in altered renal hemodynamics and function with abdominal aortic surgery, identification of those substances would assist in the selection of the most appropriate pharmacological agents to maintain renal homeostasis for the duration of the renal insult.

ARF remains an important cause of morbidity and contributes to mortality after abdominal aortic surgery (Nachbur et al. 1987; Johnston et al. 1988) and renal ischemia is suggested to be the cause (Gamulin et al. 1984; Gelman 1995). Since pharmacological treatment of early and established ARF is notoriously unsuccessful (Lazarus 1986), a preventative approach aimed at inhibition of endogenous agents involved in the etiology of ARF in this particular population, may be expected to be more successful in improving outcome.

Based on the above, the hypothesis for this thesis is that infrarenal aortic cross clamping induces a reduction in RBF and kidney function, which is associated with changes in plasma hormone concentrations that play a pathogenic or pathophysiological role in the changed renal hemodynamics.

The aim of this thesis is therefore to:

1.   **Confirm or reject this hypothesis;**

2.   **Demonstrate whether pharmacological manipulation of pathophysiological hormonal factors inhibits the adverse renal effects of aortic cross clamping.**

2. METHODS

2.1   HUMAN STUDY

The human study was approved by the Ethics Committee of the Faculty of Medicine, University of Stellenbosch (Project number 88/036).

Patients scheduled for elective abdominal aortic grafting surgery were used for this study. Thirty-three patients were operated electively for non-ruptured aortic aneurysms and twelve for atherosclerotic aortoiliac occlusive disease. Informed consent was obtained from all patients. Preoperative assessment included measurement of serum urea, creatinine, electrolytes, glucose, full blood count, blood gasses, and clotting profile. A twelve lead ECG and erect antero-posterior chest X-ray was performed. Creatinine clearance was done preoperatively, using a 24-hour urine collection period. Creatinine clearance was repeated postoperatively on day 6 or 7. Twenty four hour urine samples for the measurement of creatinine clearance 1 day peroperatively and 7 days postoperatively were collected under strict supervision with the patients voiding voluntarily. Patients emptied their bladders immediately before the commencement of the sampling period and again at the end of 24 hours. The latter sample and others voided in the course of the sampling period were kept in a refrigerator until a collective sample was taken for measurement of creatinine concentration. Adequacy of urine collection was assessed with the measurement of 24 hour total creatinine excretion. Additional cardiac assessment included a stress ECG and an assessment of ventricular function (echo-cardiography or radio-isotope cardiography), the latter in cases with a clinical history indicative of compromised ventricular function. Patients with a positive stress ECG were considered for coronary angiography by a cardiologist and aortic surgery postponed if considered necessary.

Patients with preoperative renal dysfunction (creatinine clearance less than 50 ml.minute^{-1} and/or serum creatinine in excess of 120μmol/liter), cardiac failure, or renal artery stenosis detected on the preoperative aortic angiogram, were not included in the study. Patients on ACE inhibitor therapy were also excluded from the study and in patients receiving diuretics, therapy was stopped three days prior to surgery. Other preoperative therapy (methyldopa, n = 9; digoxin, n = 5; nifedipine, n = 2; ß-adrenergic receptor blockers, n = 7; nitrates, n = 11) was maintained up to and including the morning of surgery.

On the morning of surgery patients were premedicated with diazepam 10 mg orally one hour before transportation to the radiology theatre. A radio-opaque catheter was

advanced into the renal vein under x-ray screening control and its tip positioned as close as possible to the renal pelvis. Placement was done under local anaesthesia (lignocaine 2%) from the right femoral vein (n = 37) except in cases where the preoperative angiogram indicated the probability of distal anastomoses of a bifurcation graft on the femoral arteries. In these patients (n = 8) the renal venous catheter was placed from the right internal jugular vein. Where technically possible the catheter tip was placed in the right renal vein (n = 38), with the others advanced into the left renal vein (n = 7). Correct placement of the catheter was confirmed with a hard copy x-ray and the catheter secured in position with a skin suture. All renal venous catheter placements were performed by the same radiologist.

After securing the renal venous catheter, the patients were taken directly to the anaesthetic induction room. In the induction room a peripheral venous cannula, a radial arterial and a thermodilution pulmonary artery catheter (Edwards labs. Size 7F) were placed under local anaesthesia (lignocaine 2%). A Foley (12g) urinary bladder catheter was inserted under cover of local anaesthetic jelly (lignocaine 0.02%). During placement of the intravascular lines and urinary catheter, midazolam was administered if deemed necessary for additional anxiolysis in 1mg increments (maximum dose = 7mg). A lumbar epidural catheter was placed via the L2-L3 or L3-L4 interspace. After returning the patient to the prone position, a test dose of 3ml 0.5% bupivacaine with 1:200 000 adrenaline was injected through the catheter. Ringers lactate was given intravenously according to a regimen of 1.5ml per kilogram bodyweight for each hour the patient had been nil per mouth prior to induction of anaesthesia. This volume was supplemented when necessary to obtain a left ventricular filling pressure of at least 6 mmHg at the time of induction.

Anaesthesia was induced after a 3 minute period of preoxygenation with 100% oxygen. Alfentanil was infused at a rate of $10\mu g.kg^{-1}.min^{-1}$ for ten minutes, followed by a continuous infusion of $1\mu g.kg^{-1}.min^{-1}$ for the duration of the procedure and terminated 30 minutes prior to the expected completion of surgery. After 4 minutes of the priming infusion of alfentanil, thiopentone ($2-4mg.kg^{-1}$) was administered until loss of eyelid reflex. Endotracheal intubation was facilitated with the injection of pancuronium $0.1mg.kg^{-1}$. Muscle relaxation was maintained with additional bolus administration of pancuronium ($0.01mg.kg^{-1}$) whenever the fourth twitch returned clinically with train of four ulnar nerve stimulation. After intubation, patients were ventilated (Ohmeda 7000, BOC) with oxygen in air ($FiO_2 = 0.5$). Minute volume of ventilation was adjusted to maintain the end-expired partial pressure of carbon dioxide ($P_{ET}CO_2$) at 4 - 4.5kPa as

measured with a capnograph (Datex Cardiocap CCI 104-23-01, Finland). Concurrence between expiratory CO_2 values and blood gasses were verified and ventilation adjusted in accordance with arterial carbon dioxide partial pressures ($PaCO_2$) if a gradient existed. Anaesthesia was maintained with halothane (0.8-1.0%) from a calibrated vaporizer and the alfentanil infusion ($1\mu g.kg^{-1}.min^{-1}$), supplemented with additional bolusses of $10\mu g.kg^{-1}$ if deemed necessary. No patient received more than two additional bolusses during the procedure. Preservative free morphine (3 - 5mg) was administered epidurally as soon as the patient stabilized after induction to provide postoperative analgesia and facilitate extubation as soon as possible after completion of surgery.

Mean arterial blood pressure (MAP) was maintained within 20% of resting preoperative control values throughout the procedure. An intravenous infusion of nitroglycerine (Tridil[R], Boots Pharmaceuticals) was instituted after induction of anaesthesia and the dosage adjusted to maintain the blood pressure within the above limits throughout the procedure. Nitroglycerine was continued in the postoperative period at a dose of $0.5\mu g.kg^{-1}$. The maximum dosages during each of the measurement periods were noted. Intravenous fluid (isotonic crystalloid, colloid or packed red cells) was infused to maintain pulmonary artery wedge pressure (PAWP) above 9 mmHg, hematocrit above 29% and MAP within the designated limits. Total volumes of each fluid type for the immediate preoperative period and the duration of the surgical procedure was noted for each patient. Body temperature as measured with the pulmonary artery thermistor was maintained above 35°C with the use of a warm water humidifier (Fisher & Paegel MR300, Fisher & Paegel, New Zealand) attached to the inspiratory limb of the anaesthetic circle system, by employing an under-table warming blanket, by warming all intravenous fluids with an in-line warming device (Fenwall, Model 4R4303, Fenwall, USA) and by warming all fluids used for intra-abdominal lavage as well as wet swabs to 37°C.

The aorta was approached by means of a median laparotomy in all patients. Depending on the vascular pathology, a tube or bifurcation graft was used. The aorta was clamped 2 - 3cm below the renal arteries and the proximal clamp was maintained in position until completion of the distal anastomoses. Total aortic clamping time was noted.

Heart rate (HR) (recorded from standard lead II), systolic and diastolic arterial pressure, central venous pressure (CVP) and PAWP were recorded. The filling pressures were

recorded at end-expiration from a monitor hard copy printout (Datex DR-104-23-00, Datex, The Netherlands) using the mid-axillary line as zero reference point. Standard pressure transducers were used (Statham P23, Statham, Puerto Rico) and transducers were calibrated before each recording. MAP was calculated and recorded from the area under the radial artery pressure recording. Cardiac output was determined in triplicate with the thermodilution method by injection of 5ml of a 5% dextrose solution at 4°C into the proximal port of the pulmonary artery catheter over a 5 seconds period. The injections were spaced throughout the respiratory cycle and the mean of the three computed values (Spectramed Starcom, Spectramed, USA) was calculated and recorded for this study. Systemic vascular resistance was calculated with the following formula:

$$SVR \ (dynes.sec.cm^{-5}) = (MAP - CVP). \ 80/CO$$

All hemodynamic parameters were measured in the middle and at the end of each measurement period and the mean of the two measurements was calculated and noted as the value for that particular measurement period.

Renal plasma flow and glomerular filtration rate were measured using clearances of I^{125} hippuran (C_{HIP}) and Cr^{51} EDTA (C_{EDTA}) respectively (Gamulin et al. 1984; Mimran et al. 1983). The labeled compounds were injected as soon as intravenous access was established in the awake patient in the induction room as a bolus of 1,1MBq I^{125} hippuran and 2,2MBq Cr^{51} EDTA. In addition, a continuous infusion of 2,7MBq I^{125} hippuran and 5,3MBq Cr^{51} EDTA in 1 litre 0.9% sodium chloride was initiated and continued throughout the study to maintain stable blood levels of the labeled compounds. The infusion rate was started at 150ml.hr^{-1} and decreased by 10ml.hr^{-1} every 5 minutes down to 100ml.hr^{-1}, which was continued as the maintenance infusion rate. The first clearance measurements were started 60 - 70 minutes after initiating the infusion of labeled compounds. Cr^{51} EDTA was supplied by Amersham (UK) and I^{125} hippuran by the National Accelleration Centre (Faure, RSA). For clearance measurements urine was collected through the indwelling intravesical Foleys catheter for periods of either 20 or 30 minutes and arterial blood samples were taken in the middle and at the end of each sampling period. To ensure that the bladder was properly emptied at the commencement and at the end of each measurement period, 200ml air was injected into the bladder just before the beginning, and again at the end of each sampling period. Activity of the marker isotopes were measured in a counter (Canberra Well) linked to a multichannel analyzer (Canberra Series 20). Arterial activity was expressed as the mean of the two samples taken during each

measurement period and the percentage difference between these two measurements was also calculated. In order to calculate the extraction fraction of I^{125} hippuran (E_{HIP}) across the kidney, renal venous blood was sampled with a mechanical pump for the 5 minutes preceding the middle, as well as the 5 minutes preceding the end of the measurement period at a rate of $1ml.min^{-1}$. Renal venous isotope activity was calculated in the same manner as arterial activity. C_{HIP}, C_{EDTA}, E_{HIP}, filtration fraction (FF), RBF and renal vascular resistance (RVR) were calculated by using the following equations:

$C_{HIP}(ml.min^{-1}) = U_{HIP} \times Uvol/a_{HIP}$

(where U_{HIP} = urinary concentration of I^{125} hippuran; Uvol = urinary volume in $ml.min^{-1}$; and a_{HIP} = arterial plasma concentration of I^{125} hippuran)

$C_{EDTA}(ml.min^{-1}) = U_{EDTA} \times Uvol/a_{EDTA}$

(where U_{EDTA} = urinary concentration of Cr^{51} EDTA; and a_{EDTA} = arterial plasma concentration of Cr^{51} EDTA

$E_{HIP} = (a_{HIP} - RV_{HIP})/a_{HIP}$

(where RV_{HIP} = renal venous plasma concentration of I^{125} hippuran)

$FF = C_{EDTA}/C_{HIP}$

$RBF (ml.min^{-1}) = C_{HIP}/E_{HIP} \times 100/(100-Hct)$

(where Hct = hematocrit)

$RVR (dyne.sec.cm^{-5}) = 80 \times (MAP-CVP)/RBF$

In order to calculate creatinine clearance (C_{creat}) and the two indices of renal tubular function, fractional excretion of sodium (FE_{Na}) and free water clearance (C_{H2O}), the following measurements were made on arterial blood samples taken in the middle of each sampling period, as well as a sample from the urine collected during the whole sampling period:

1.   Plasma and urine sodium (Na^+) concentrations were determined with a Technikon SMAC automated analyzer (Technikon, New York, USA) by use of an ion-selective glass electrode.

2. Plasma and urine creatinine concentrations were determined with the Technikon SMAC automated analyzer (Technikon, New York, USA), using the colorimetric measurement of the reaction between creatinine and saturated pipric acid as automated by Chasson et al. (1961).

3. Serum and urine osmolality were determined using the freezing point method (Ganotec Osmomat 030, Ganotec).

The calculated indices were determined with the following equations:

$$C_{creat}(ml.min^{-1}) = U_{creat} \times Uvol/P_{creat}$$

(where U_{creat} = urine creatinine concentration; P_{creat} = plasma creatinine concentration; Uvol = urine volume)

$$TU_{Na} (mEq.min) = U_{Na}/_{1000} \times Uvol$$

(where TU_{Na} = total urinary Na^+; U_{Na} = urinary sodium concentration; Uvol = urine volume per minute)

$$FE_{Na} = U_{Na}/P_{Na} \times P_{creat}/U_{creat}$$

(where U_{Na} = urinary Na^+ concentration; P_{Na} = plasma Na^+ concentration)

$$C_{H2O} (ml.min^{-1}) = Uvol - (Uvol \times U_{osm}/P_{osm})$$

(where U_{osm} = urine osmolality; P_{osm} = plasma osmolality).

Functional integrity of proximal tubular cells was tested with the measurement of urinary ß$_2$-microglobulin (Schardijn and Van Eps, 1987). Urine samples were taken during every measurement period and kept at 4°C before and after pH adjustment to values of 6-8 with 1 M NaOH. Quantitative determinations of ß$_2$-microglobulin levels were done the day after surgery, using a double antibody radioimmunoassay technique (Pharmacia ß$_2$-micro RIA, Pharmacia Diagnostics AB).

A range of hormone levels were measured in arterial blood samples taken at the midpoint of each measurement period. Arginine vasopressin was measured with a double disequilibrium radioimmunoassay technique (Robertson et al. 1970; Robertson et al. 1973) after extraction with bonded phase (C2 Ethyl) solid phase collumns (Anatech Instruments). Plasma renin activity on arterial and

renal venous blood samples taken at the midpoint of each measurement period were determined by radioimmunoassay of generated Angiotensin I with a Gamma Coat (I^{125}) technique (Incstar, USA). Aldosterone concentrations of arterial blood samples were measured using a "no extraction" Coat-a-Count radioimmunoassay test kit (Diagnostic Products Corporation, USA). An immunoradiometric assay (Incstar, USA) was used to determine ACTH concentrations in arterial blood samples taken at the middle of each sampling period. Plasma catecholamine (adrenaline, noradrenaline and dopamine) concentrations were measured on arterial blood samples taken only at two occasions per patient; the first after induction of anaesthesia and commencement of surgery but before mannitol and dopamine administration was started and the second immediately after aortic cross clamping. The catecholamine concentrations were determined (after acidic extraction) by injection of a plasma extract into a high performance liquid chromatograph-electrochemical detection system (Model LC-304, Bioanalytical Systems) as previously described by Russell et al. (1985).

Patients were randomly allocated to one of two study groups:

1.   Control (n = 22)

These patients were managed as described above and no additional pharmacological manipulation was done.

2.   Mannitol + dopamine (n = 23)

These patients received the same basic anaesthetic regimen as previously described. They also received mannitol as a single dose of 0.5g.kg^{-1} over a 10 minute period, which was completed 5 minutes before application of the aortic cross clamp. A constant infusion of dopamine (2μg.kg^{-1}.min^{-1}) was initiated immediately after completion of the preclamp measurement period and continued until 24 hours postoperatively.

Co-workers responsible for conducting the anaesthetic, taking blood and urine samples, as well as those responsible for analysis of those samples were blinded to the group allocation of patients.

Measurements were taken at the following times:

1.   Before induction of anaesthesia with the patient breathing room air.

2.   After induction of anaesthesia with surgery in progress before cross clamping of the aorta (this measurement period ended within 10 minutes of aortic cross clamping in all patients).

3.   Immediately after cross clamping of the aorta.

4.   Just before unclamping of the aorta.

5.   Immediately after unclamping of the aorta.

6.   Four hours after unclamping of the aorta.

7.   Twenty four hours after unclamping of the aorta (only β_2-microglobulin).

On completion of surgery, patients were ventilated until they were adequately awake; had a core temperature of at least 36°C; were hemodynamically stable and had a hematocrit of at least 30%; and had an oximeter saturation in excess of 95% with an FiO_2 of 0.4, before they were extubated. Nine patients were still being ventilated at the time of the sixth measurement period 4 hours after aortic unclamping (control group n = 5; mannitol + dopamine group n = 4).

2.2   ANIMAL STUDIES

The animal studies were approved by the Ethics Committee of the Faculty of Medicine of the University of Stellenbosch (Project number 88/036).

2.2.1 The influence of the renin-angiotensin system on changes in renal hemodynamics and kidney function with infrarenal cross clamping of the aorta

Twenty four pigs were used in this part of the study. All animals received food and water ad libitum until experimentation. Their weights varied between 19kg and 29kg. The animals were initially sedated with ketamine 10mg.kg^{-1} intramuscularly and brought to the operating theatre where intravenous access was secured with a 18g cannula into a vein of the pinna. Anaesthesia was subsequently induced with thiopentone (5 mg.kg^{-1}). A tracheostomy was performed and the trachea intubated with a cuffed tracheostomy tube. On initiation of intermittent positive pressure ventilation, muscle paralysis was obtained by injecting a bolus of pancuronium (0,1mg.kg^{-1}), followed by a constant infusion of 0,1mg.kg^{-1}.hr^{-1}. Animals were ventilated with oxygen and nitrogen with an inspiratory oxygen concentration of 50%. A ventilation frequency of 14 breaths

per minute was used and tidal volume was adjusted to maintain the end expiratory CO_2 concentration between 4 and 5 volumes percent, using a circle system with CO_2 absorption. If subsequent blood gas analysis showed a $PaCO_2$ value in excess of 5kPa or below 4kPa, ventilation was adjusted to obtain $PaCO_2$ levels between those limits. Anaesthesia was maintained with halothane 1,2%, vaporized from a calibrated vaporizer (Drägerwerk, Germany).

An under-table-heating device and an in-line intravenous fluid warmer was used to maintain blood temperature of the animals above 35°C. The laparotomy incision and bowels of the animals were covered with plastic and surgical drapes as far as possible during and after the surgical preparation, for the same purpose. Blood temperature was measured with the pulmonary artery catheter and recorded at each measurement period. Normal saline was infused at a variable rate to maintain left ventricular filling pressure (PAWP) between 10 and 15 mmHg.

Cr^{51} EDTA (Amersham, UK) and I^{123} hippuran (National Acceleration Centre, Faure, RSA) were used for the determination of GFR and RBF respectively. Bolus doses of 1,1 M Bq (Cr^{51} EDTA) and 0,55 M Bq (I^{123} hippuran) were administered intravenously immediately after placement of the intravenous cannula. This was followed by a continuous infusion of the isotopes; 2,65 M Bq Cr^{51} EDTA and 1,35 M Bq I^{123} hippuran in 200ml saline given at a rate of $1ml.kg^{-1}.hr^{-1}$ (13,25 K Bq and 6,75 K Bq per kilogram per hour respectively) for the duration of the study protocol. Arterial and renal venous plasma as well as urinary isotope activity was counted in a Canberra Well (Canberra) counter linked to a multichannel analyzer (Canberra Series 20, Canberra). C_{EDTA}, C_{HIP}, E_{HIP}, FF and RBF were calculated for each measurement period, using the same formulae as applied in the human study.

Arterial pressure was transduced (Statham P23, Statham) from a cannula inserted into the left carotid artery. Mean arterial pressure (MAP) was computed from the area under the arterial pressure recording. A pulmonary artery catheter (Edwards Labs. Size 5F) was inserted from the left internal jugular vein to obtain PAWP recordings and for thermodilution cardiac output (CO) determination with a CO computer (Mansfield 9530, Mansfield). Pressure transducers were calibrated before each recording. CO determinations were done in triplicate at each measurement time and the means of these values are reported. Measurements of CO were done by injecting 5ml of 5% dextrose and water at 4°C by hand into the proximal injection port, spacing injections throughout the respiratory cycle.

A laparotomy was performed through a median incision. The retroperitoneal space was opened and both ureters identified. The ureters were sequentially tied off approximately 5cm proximal to the bladder, the ureteral lumen opened and a thin bore catheter with total internal volume of 0.8ml advanced proximally to between 2 and 3cm from the renal calyx. A ligature was tied around the ureter and catheter to secure the catheter position and to ensure free drainage of all urine produced by each kidney through its ureteral catheter for accurate urine volume measurements.

The retroperitoneal space was opened over the left renal pelvis and carefully dissected onto the renal vein without disturbing the renal nerves. A 20 gauge cannula was then inserted into the renal vein approximately 3cm from the renal pelvis with its tip directed towards the kidney and secured with a suture.

The aorta was dissected 2cm distal to the origin of the renal arteries to allow for placement of an aortic cross clamp. Circumferential dissection invariably led to drainage of lymphatic fluid from the para-aortic tissue, the loss of which was compensated with intravenous saline as already described.

All sampling periods were of 20 minutes duration. Hemodynamic measurements (MAP, PAWP, heart rate, CO) were taken in the middle of each renal venous blood sampling described below (i.e. 5 and 15 minutes into each sampling period). Hemodynamic results are given as the mean of these two measurements for each period.

Plasma renin activity on renal venous and arterial blood samples were determined by radioimmunoassay of generated angiotensin I with a I^{125} Gamma Coat technique (Incstar, USA) for each measurement period. Arterial blood samples were taken to enable calculation of FE_{Na} and C_{H2O} with the same formulae as given in the human studies. Renal venous blood samples were taken manually from a 3-way tap on an extension tube (dead space volume = 1ml) attached to the renal venous cannula. Two samples of 5ml each were taken for the isotope studies after discarding the saline withdrawn from the extension tube. Each sample was drawn over a 5 minute period (starting from the end of the third and twelfth minute of the measurement period respectively) to ensure a sample representative of renal venous isotope concentrations for the 20 minute sampling period and to prevent contamination with inferior vena cava blood. Arterial blood samples for isotope measurements were taken at the middle of the two renal venous sampling periods. Arterial and renal venous isotope activities were expressed as the mean of the counts done on the two samples per measurement

period. The percentage difference in counts done on arterial samples were calculated and noted for each measurement period. Extensions and cannulae were flushed with a heparin/saline solution (500 IU heparin/100ml saline) after sampling, to prevent clotting.

All urine investigations were done on samples taken from the combined urine production of both kidneys over the full 20 minute sampling period (differences in urine volumes between kidneys were always less than 10% for all sampling periods in all animals).

Animals were randomly allocated to one of three study groups:

1.   Animals where only the radio-isotopes were administered as a constant infusion (n = 8).

2.   Animals where esmolol was infused at a dose of $300\mu g.kg^{-1}.min^{-1}$ together with the radio-isotopes from the time of securing the intravenous infusion (n = 8).

3.   Animals where enalaprilat was infused at $15\mu g.kg.^{-1}.hr^{-1}$ with the radio-isotopes, together with an initial bolus of 1,25mg over 10 minutes immediately after establishing intravenous access (n = 8). The enalaprilat dose was established in a dose finding study in two pigs. The aim of this study was to identify a dose which would not induce decreases in MAP below 80% of pre-enalaprilat control values for the full experimental period, and at or above the dose recommended for comprehensive ACE inhibition (Rutledge et al. 1988).

Assistants and co-workers who were responsible for sampling and measurement of any parameter were blinded to the group allocation of individual animals. A minimum of 90 minutes from initiation of radio-isotope and study drug infusion was allowed before any sampling or other measurements were commenced. After surgical preparation of the animals, infrarenal para-aortic manual pinching of tissues at a rate of 5 pinches per minute were continued during the experimental period to simulate clinical conditions during aortic aneurysm surgery.

Sampling and measurements were done over 20 minute periods at the following times:

1.   **Control preclamp:** After completion of surgical preparation with a minimum of 90 minutes from commencing the isotope infusion, ± study drug.

2. **Postclamp:** Immediately after cross-clamping the aorta 2cm below the renal arteries.

3. **Pre-unclamp:** The last 20 minutes of an one hour clamping period.

4. **Post-unclamp:** This period commenced 30 minutes after release of the aortic cross clamp.

After completion of the last sampling period, the capsule of the left kidney was opened, the kidney extricated from the capsule and the renal pedicle was clamped. The kidney was immediately removed, a full length sagittal incision made and full thickness (cortex and medulla) biopsies were taken for light and electron microscopy and fixed in 10% formaline and 2,5% phosphate buffered glutharaldehyde respectively. Removal and biopsies of the right kidney were done in a similar fashion. Total time elapsed between unclamping of the aorta and nephrectomy/biopsies varied between 55 and 60 minute for all animals.

Standard Light Microscopy:

After fixation of the specimens overnight at 4°C in 2.5% phosphate buffered glutaraldehyde or 10% formalin, sections thereof preferably representing both cortex and medulla were imbedded in wax (paraffin). Microtome sections three microns thick were cut from the wax blocks, dewaxed in xylol and rehydrated in decreasing concentrations ethanol down to water. Staining with Mayer's haematoxylin for 10 minutes was followed by thorough rinsing in running water and thereafter 5 to 10 seconds of differentiation in 1% acid-alcohol (1% HCl in 70% ethanol). The sections were rinsed again in water followed by staining in 1% eosine Y for 3 minutes, sequential dehydration in increasing concentrations of ethanol and clarification with xylol. The stained sections were then mounted on glass slides under a cover slip with DPX.

Electron Microscopy:

Following fixation overnight in 2.5% phosphate buffered glutaraldehyde (pH7.4) the specimens were further dissected with the aid of a dissecting microscope in order to obtain areas of cortex as near as possible to the cortico-medullary junction. The samples thus obtained were rinsed in phosphate buffer followed by 60 minutes of post fixation in 1.5% buffered osmium tetroxide. After double rinsing in distilled water the tissue was placed in 2% uranyl acetate in 70% ethanol for 20 minutes. The specimens were sequentially dehydrated for 5 minutes in each of 70% and 96% ethanol and then

placed in 2% uranyl nitrate in 96% ethanol for 10 minutes. After thrice placing the specimens in 100% ethanol/sodium sulphate for a total of 45 minutes it was embedded in Spurr's epoxy resin and left overnight at 60°C. Sections were then cut with a glass knife using a LKB Bromma Ultratome. One micron thick sections were stained with 1% toluidine blue and used for light microscopic orientation and selection of deep cortical areas containing proximal convoluted tubules (pars convoluta), the proximal straight tubule (pars recta) and the cortical thick ascending limb of the distal tubule. Ultrathin sections of 80-100 nm representative of these 3 nephron segments were mounted on copper grids and stained with 2% uranyl acetate in 50% ethanol followed by lead citrate staining. The sections were then examined with a Hitachi-H600 transmission electron microscope at a voltage of 50kV.

The presence and extent of morphologic change indicative of cellular injury was assessed in blinded fashion. Reliable parameters were identified after comparison with a control group of 5 animals where kidney biopsies were taken after induction of anaesthesia and without surgical stimulation other than surgical exposure of the kidney through a laparotomy similar to the procedure for the experimental animals. The four ultrastructural parameters assessed in this manner were changes in brush border microvilli, the granular endoplasmic reticulum, the structure (and particularly swelling) of the mitochondria, and changes in nuclear chromatin. Each of these parameters were further graded, a score of 0 representing absence of change and a score of 3 the most extreme degree of alteration. After grading for each of the above parameters were done for a particular animal, such an animal was designated to one of two possible groups in accordance with the assessment and grading. Those with at least 2 parameters with change (regardless of the grading ≥ 1) or 1 parameter given a grading of 3 were designated "clearly abnormal", whereas those falling short of these criteria were regarded as "minimally altered to normal".

After the bilateral nephrectomies and biopsies, the animals were killed with the administration of potassium chloride intravenously while still under anaesthesia.

One of the animals in the enalaprilat group developed malignant hyperpyrexia during the experiment and had to be excluded from the group.

2.2.2 The comparative influences of angiotensin converting enzyme (ACE) inhibition and Ca^{2+}-blockade on renal hemodynamics and function with infrarenal aortic cross clamping

Animals were randomly assigned to one of two groups:

1. A group of pigs where verapamil was administered in a dose of 0.25mg.kg^{-1} over 10 minutes after placement of the intravenous cannula, followed by a continuous intravenous infusion of verapamil at a dose of 2μg.kg^{-1}.min^{-1} for the duration of the experiment (n = 8).

2. A group of animals where enalaprilat was administered intravenously in the same manner as described in group 3 of 2.2.1 (n = 8). This group was included mainly for three reasons. Firstly, it prevented the possibility of bias, which would have been relevant if only a verapamil group of pigs were studied on their own in this part of the study. Secondly, if comparisons between results in this group and the enalaprilat group of the first part of the study (2.2.1) demonstrated no significant differences between the groups, it would indicate lack of methodological and other differences between these two studies. This would provide justification for inclusion of the control group of pigs of the **first** part of the study (2.2.1), into comparative analysis of animal groups in **this** section of the study. Thirdly, it provides the opportunity of comparing the potential benefits of ACE-inhibition and Ca^{2+}-channel blockade in these experimental circumstances.

The general preparation and experimental design was as described in section 2.2.1. Two animals in the enalaprilat group and one in the verapamil group developed malignant hyperpyrexia in the course of the experiment and had to be excluded from the study.

Statistical analysis includes comparisons between the above two groups and control animals from section 2.2.1. This was considered to be justifiable due to the fact that the experimental design was exactly the same and because statistical comparisons between the two enalaprilat groups from section 2.2.1 and 2.2.2 demonstrated no differences in any of the measured or calculated parameters at any of the measurement periods.

2.2.3 The influence of prostaglandins in the changed renal hemodynamics and glomerular function associated with infrarenal cross clamping of the aorta and the effect of prostaglandin inhibition on the potential beneficial influence of ACE inhibition

Animals were randomly assigned to one of two groups:

1. A group of pigs where diclofenac was administered in a dose of 2mg.kg^{-1} together with the radio-isotope bolus immediately after establishing the intravenous infusion (n = 8). This was to investigate (through an indirect method) the role of renal prostaglandins in balancing the effect of vasoconstrictors previously described for **different** experimental conditions (Henrich et al. 1978a, Schnermann et al. 1984, Rae et al. 1989, Chou et al. 1990), under our experimental and clinical circumstances.

2. A group of pigs where diclofenac (2mg.kg^{-1}) was administered together with the radio-isotope bolus after establishing the intravenous infusion. In addition, enalaprilat was administered as described in group 3 of section 2.2.1 (n = 8).

The general preparation and experimental design was as described in section 2.2.1. One animal in the diclofenac plus enalaprilat group developed malignant hyperthermia in the course of the experiment. In one pig in the diclofenac group it was discovered after 20 minutes of aortic clamping that sterile water rather than normal saline had been administered as intravenous fluid. A further two pigs in the diclofenac group developed persistent anuria soon after application of the aortic cross clamp so that clearance measurements for the calculation of RBF and GFR could no longer be performed. The above animals (one in the diclofenac plus enalaprilat group and three in the diclofenac group) were therefore excluded from the study.

Separate statistical analyses were done **firstly** between the diclofenac and control groups, and **secondly** between the diclofenac plus enalaprilat and the enalaprilat (from section 2.2.2) groups. This was considered justifiable as argued in section 2.2.2.

2.3.1 Statistical analysis

Statistical analysis was performed in collaboration with Dr. S. Maritz of the Institute for Biomedical Statistics of the Medical Research Council.

For the analysis of all data in the human study and for the analysis of intragroup changes in the animal studies, a standard computer software package (Sigmastat version 5.0 for DOS; Jandel Scientific Software, San Rafael, California, USA) was used. Within-group measurements were evaluated using analysis of variance

(ANOVA) for repeated measurements and between-group comparisons were made using one-way ANOVA. If the data were not normally distributed (Kolmogorov-Smirnov test, $p < 0.05$) and/or did not have equal variances (Levene Median test, $p < 0.05$), equivalent non parametric tests were performed. These were the Friedman two-way repeated measures ANOVA on ranks and the Kruskal-Wallis ANOVA on ranks (Siegel 1953a). Post-hoc multiple comparison procedures were performed using the Student-Newman-Keuls test. Paired and unpaired t-tests were done as appropriate when comparing two groups and if these did not meet the criteria for normality of distribution and equality of variances, the equivalent non-parametric tests were performed (Wilcoxon signed rank test and rank sum test [Mann-Whitney]) (Siegel 1953b). Nominal and proportional data were analysed using Chi-squared tests and Fisher's exact test where expected values were less than five (Siegel 1953c). An alpha value equal to or less than 0.05 was regarded as indicating a significant result.

For comparisons of intergroup data in the animal studies, analyses of **changes** from one measurement period to the next were performed between the relevant animal groups for reasons discussed in section 4.4. The MINITAB computer software package (MINITAB Inc., State College, Pennsylvania, USA) was used for this purpose. Comparisons between groups were made using one-way ANOVA. In cases of non-homogeneous standard deviations, and where p-values were marginally close to the 0.05 cut-of for statistical significance, the Welch test (the approach of the MINITAB program to the Behrens-Fisher problem) was performed to confirm the conclusions suggested by the p-values. In the cases where the test on single variables did not demonstrate significant differences, a global test of equality of the profiles of the relevant animal groups were performed for confirmation. The Wilks statistic (MANOVA) was used for this purpose.

3. RESULTS

3.1 PATIENT STUDY

3.1.1 Intra-group changes at various measurement times in humans

3.1.1.1 Intra-group changes in 22 control patients

Timing of measurement steps:

Step 1: awake control

Step 2: post-induction before aortic clamping

Step 3: immediately after aortic clamping ⎫
Step 4: just before unclamping of aorta ⎬ perclamp

Step 5: immediately after aortic unclamping

Step 6: 4 hours after unclamping of aorta

Step 7: 24 hours after aortic unclamping (only $ß_2$-microglobulin)

RBF and the $^{RBF}/_{CO}$ ratio were not influenced by the induction of anaesthesia and surgery prior to aortic cross clamping (steps 1-2; Table 3.1). RBF decreased significantly relative to awake control and intraoperative preclamp values subsequent to application of the aortic cross clamp (50.4% and 48.2% reduction respectively). RBF remained depressed throughout the period of clamping and immediately after release of the clamp, relative to the two preclamp measurements. Four hours after unclamping RBF was still decreased in comparison with the two preclamp measurements although it had improved relative to the perclamp (during clamping: steps 3 and 4) and initial postclamp values (Table 3.1). The $^{RBF}/_{CO}$ ratio demonstrated the same patterns of change as RBF, except that $^{RBF}/_{CO}$ had not recovered relative to the two preclamp measurements even 4 hours after aortic unclamping (Table 3.1).

Considering the changes in RBF, RVR predictably increased upon aortic cross clamping and remained raised until after unclamping (Table 3.1). However, 4 hours after unclamping RVR returned to values similar to the two sets of preclamp calculations.

Hippuran extraction 4 hours after unclamping was lower than the 2 sets of preclamp values, but the maximum change was less than 9% (Table 3.1).

GFR as measured by Cr^{51} EDTA clearance was not influenced by the induction and maintenance of anaesthesia and surgery prior to clamping the aorta (Table 3.2). GFR

decreased significantly after infrarenal cross clamping (54% lower that the preclamp measurement) and remained low throughout the clamping period. It improved relative to the two perclamp measurements subsequent to release of the clamp, but was still significantly reduced in comparison with the two preclamp measurements. GFR measurement 4 hours after unclamping demonstrated a further improvement relative to the first measurement after unclamping, but was still significantly less than the preclamp values. When using calculated C_{creat} as a measure of GFR, mean values and changes concurred with Cr^{51} EDTA clearances, except that improvement in C_{creat} was delayed until 4 hours after aortic unclamping relative to perclamp and immediate post-unclamp values (Table 3.2). FF remained unchanged throughout the experimental period (Table 3.2).

Urine production decreased significantly after application of the aortic cross clamp (Table 3.4) and remained depressed relative to preclamp urine volumes throughout the experimental period. Although mean urine volume 4 hours after unclamping was more than double volumes measured immediately after aortic cross clamping (statistically non-significant), it was still significantly less than mean volumes measured during the two preclamp measurement periods.

Fractional excretion of sodium (FE_{Na}) was significantly greater during the awake control measurement period than any of the subsequent measurement periods (Table 3.4). Total urinary sodium excretion (TU_{Na}) demonstrated the same pattern, while the post-induction measurement was also greater than the two perclamp measurements (Table 3.4). Free water clearance (C_{H2O}) became more positive during the two perclamp (during application of the cross clamp) measurement periods relative to the awake control value (Table 3.4). Subsequent to release of the aortic cross clamp, urinary concentration of ß$_2$-microglobulin increased relative to all previous measurements. The mean values continued to rise in the urine samples collected 4 hours and 24 hours after aortic unclamping respectively, although these increases were not significantly different from the measurements immediately after unclamping (Table 3.4).

Systemic hemodynamic parameters remained relatively stable throughout the experimental period. Heart rate remained unchanged until after unclamping, when it increased relative to the two perclamp measurements (Table 3.3). Four hours after unclamping the heart rate was greater than any of the previous measurement periods. The two CVP measurements after unclamping were greater than the awake control value (Table 3.3). CO and PAWP were unchanged throughout the experimental period

(Table 3.3). Calculated SVR was greater in the awake control period than any of the other measurement times (Table 3.3). Immediately before unclamping the aorta, SVR was increased relative to the values in the two measurement periods after aortic unclamping.

Both arterial and renal venous renin activity were uninfluenced by anaesthesia and the initial surgical stimulus prior to aortic clamping, but increased significantly immediately after clamping and remained elevated (relative to the first two measurements) throughout the experimental period (Table 3.5). The serum aldosterone concentrations remained unchanged until the second perclamp measurement. Thereafter they increased relative to the two preclamp concentrations whence they continued to rise so that the 4 hour post-unclamp measurement was higher than the first four measurement periods (Table 3.5). ACTH concentrations only increased relative to awake control values at the pre-unclamp (step 4) measurement period (Table 3.5). The highest concentrations were obtained after unclamping with values immediately after unclamping greater than all previous measurement periods and the 4 hour post-unclamp concentrations higher than both preclamp measurements and the first measurement after aortic clamping. ADH concentrations increased significantly on commencement of surgery relative to the awake values (Table 3.5). A further increase occurred after aortic unclamping, with both post-unclamp concentrations (steps 5 and 6) being greater than all measurement steps prior to unclamping.

All intraoperative and the 4 hours post-unclamp measurements of hematocrit were lower than the preoperative control value (Table 3.6). The 4 hours post-unclamp mean value was significantly greater than the postclamp (step 3) mean.

Body core temperature decreased intraoperatively relative to awake control measurement, but recovered relative to intraoperative temperatures at 4 hours after unclamping (Table 3.6).

All intraoperative nitroglycerine infusion rates were greater than the dose administered 4 hours postoperatively (Table 3.6). The preclamp and postclamp (steps 2 and 3) infusion rates were also significantly greater than the dose immediately after unclamping.

Cr^{51} EDTA and I^{125} hippuran concentrations were relatively constant within measurement periods with no significant differences between the measurement steps (Table 3.7).

Table 3.1   **Renal hemodynamic variables in 22 control patients**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
RBF	1	22	1258.3	342.1	72.9				c,d,e,f
$(ml.min^{-1})$	2	19	1204.5	349.8	80.2				c,d,e,f
	3	18	623.4	158.2	37.3				a,b,f
	4	19	687.2	269.4	61.8				a,b,f
	5	19	727.2	315.1	72.3				a,b,f
	6	15	994.9	316.5	81.7				a,b,c,d,e
$^{RBF}/_{CO}$	1	22	0.244	0.067	0.014				c,d,e,f
	2	19	0.206	0.113	0.024				c,d,e,f
	3	18	0.112	0.071	0.015				a,b
	4	19	0.132	0.081	0.017				a,b
	5	19	0.112	0.067	0.014				a,b
	6	15	0.124	0.099	0.021				a,b
RVR	1	22	6.69	1.78	0.38	6.52	5.38	7.66	c,d,e
$(dyn.s.cm^{-5})$	2	19	5.75	1.92	0.44	5.39	4.88	7.03	c,d,e
	3	18	10.28	2.94	0.69	9.43	7.74	13.01	a,b,f
	4	19	10.38	4.41	1.01	9.74	7.56	11.94	a,b,f
	5	19	10.59	5.50	1.26	9.56	6.88	12.22	a,b,f
	6	15	6.65	1.85	0.48	6.82	5.33	7.38	c,d,e
E_{HIP}	1	22	0.67	0.102	0.022				f
	2	19	0.66	0.090	0.021				f
	3	18	0.64	0.062	0.014				
	4	19	0.65	0.072	0.016				
	5	19	0.63	0.071	0.016				
	6	15	0.61	0.050	0.013				a,b

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$);
c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$);
e = significantly different from step 5 ($p < 0.05$); f = significantly different from step 6 ($p < 0.05$).

ANOVA; Student-Newman-Keuls (RBF, $^{RBF}/_{CO}$, E_{HIP}).
Friedman ANOVA on ranks; Student-Newman-Keuls (RVR).

RBF = renal blood flow; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output; RVR = renal vascular resistance;
E_{HIP} = Hippuran extraction fraction.

57

Table 3.2 **Glomerular function variables in 22 control patients**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
GFR	1	22	97.8	22.82	4.87				c,d,e,f
(ml.min.$^{-1}$)	2	22	98.5	31.88	6.8				c,d,e,f
	3	22	45.3	13.64	2.98				a,b,e,f
	4	22	50.7	27.74	5.91				a,b,e,f
	5	22	61.7	24.5	5.22				a,b,e,f
	6	22	76.1	21.73	4.63				a,b,c,d,e
C $_{creat}$	1	22	92.2	17.05	3.63	89.6	77	110.4	c,d,e,f
(ml.min.$^{-1}$)	2	22	90.7	17.66	3.77	92.5	74.8	105	c,d,e,f
	3	22	48.9	21.12	4.5	46.4	38.8	53.1	a,b,f
	4	22	48.7	18.9	4.03	44.3	36	59	a,b,f
	5	22	57.7	20.04	4.27	54	43.9	64.8	a,b,f
	6	22	72.3	17.26	3.68	59.8	48	84.3	a,b,c,d,e
FF	1	22	0.2	0.039	0.008				
	2	22	0.21	0.057	0.012				
	3	22	0.19	0.063	0.014				
	4	22	0.18	0.067	0.014				
	5	22	0.22	0.063	0.013				
	6	22	0.22	0.06	0.013				

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$); e = significantly different from step 5 ($p < 0.05$); f = significantly different from step 6 ($p < 0.05$).

ANOVA; Student-Newman-Keuls (GFR, FF).
Friedman ANOVA on ranks; Student-Newman-Keuls (C_{creat}).

GFR = glomerular filtration rate (measured by clearance of Cr^{51} EDTA); C_{creat} = calculated creatinine clearance; FF = filtration fraction.

Table 3.3   **Systemic hemodynamic variables in 22 control patients**

Variable	Step	N	Mean	SD	SE	Interstep differences
HR	1	22	74.45	12.48	2.66	f
(beats.min^{-1})	2	22	75.82	14.85	3.17	f
	3	22	69.41	16.05	3.42	e,f
	4	22	71.32	17.03	3.63	e,f
	5	22	80.41	16.30	3.48	c,d,f
	6	22	92.36	19.71	4.20	a,b,c,d,e
MAP	1	22	107	14.89	3.17	b,c,d,e,f
(mmHg)	2	22	91.23	15.03	3.20	a
	3	22	85.79	10.38	2.21	a
	4	22	88.76	15.54	3.31	a
	5	22	91.23	12.97	2.76	a
	6	22	88.86	13.95	2.98	a
CVP	1	22	7.14	2.21	0.47	e,f
(mmHg)	2	22	9.36	3.51	0.75	
	3	22	9.73	3.62	0.77	
	4	22	9.82	3.53	0.75	
	5	22	10.18	2.36	0.50	a
	6	22	10.82	4.44	0.95	a
PAWP	1	22	11.27	3.77	0.80	
(mmHg)	2	22	11.00	3.30	0.70	
	3	22	12.41	4.06	0.87	
	4	22	12.23	2.89	0.62	
	5	22	12.05	3.87	0.83	
	6	22	13.36	4.72	1.01	
CO	1	22	5.27	0.97	0.21	
(l.min^{-1})	2	22	5.42	1.37	0.29	
	3	22	5.02	1.32	0.28	
	4	22	4.80	1.24	0.27	
	5	22	5.78	1.43	0.31	
	6	22	5.97	1.45	0.31	
SVR	1	22	1540.3	280.6	59.6	b,c,d,e,f
(dyn.s.cm^{-5})	2	22	1242.6	262.5	55.6	a
	3	22	1255.6	249.4	52.8	a
	4	22	1360.2	322.1	68.1	a,e,f
	5	22	1160.2	254.5	53.9	a,d
	6	22	1098.8	316.4	69.8	a,d

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$); e = significantly different from step 5 ($p < 0.05$); f = significantly different from step 6 ($p < 0.05$).

ANOVA; Student-Newman-Keuls.

HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; PAWP = pulmonary artery occlusion pressure; CO = cardiac output; SVR = systemic vascular resistance.

Table 3.4   Parameters of renal tubular function in 22 control patients

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
Uvol	1	22	5.32	4.12	0.88	3.75	2.95	6.25	c,d,e,f
(ml.min^{-1})	2	22	4.24	2.29	0.49	4.14	2.03	5.40	c,d,e,f
	3	22	1.54	0.76	0.16	1.68	0.87	2.25	a,b
	4	22	1.69	0.85	0.18	1.53	1.00	2.25	a,b
	5	22	2.19	1.11	0.24	2.48	1.10	3.0	a,b
	6	22	3.17	3.00	0.64	2.20	1.17	3.3	a,b
FE$_{Na}$	1	22	0.04	0.019	0.004	0.030	0.03	0.05	b,c,d,e,f
	2	22	0.03	0.020	0.004	0.030	0.014	0.04	a
	3	22	0.02	0.013	0.003	0.012	0.01	0.03	a
	4	22	0.02	0.019	0.004	0.015	0.01	0.04	a
	5	22	0.03	0.020	0.004	0.020	0.01	0.04	a
	6	22	0.03	0.039	0.008	0.020	0.01	0.03	a
TU$_{Na}$	1	22	0.544	0.227	0.048	0.512	0.392	0.641	b,c,d,e,f
(mEq.min^{-1})	2	22	0.353	0.200	0.042	0.317	0.197	0.486	a,c,d
	3	22	0.116	0.072	0.015	0.097	0.066	0.178	a,b
	4	22	0.138	0.096	0.020	0.106	0.065	0.186	a,b
	5	22	0.201	0.143	0.030	0.176	0.101	0.321	a
	6	22	0.338	0.395	0.084	0.203	0.115	0.360	a
C$_{H2O}$	1	22	-0.82	3.04	0.65	-1.62	-0.87	-2.69	
(ml.min^{-1})	2	22	-0.53	1.88	0.40	-0.99	-0.38	-1.63	
	3	22	-0.52	0.43	0.09	-0.45	-0.32	-0.77	
	4	22	-0.63	0.58	0.13	-0.61	-0.38	-0.95	
	5	22	-0.70	0.61	0.13	-0.79	-0.54	-1.00	
	6	22	-1.24	1.74	0.37	-0.81	-0.55	-1.27	
ß$_2$-micro	1	22	0.35	0.51	0.11	0.2	0.16	0.35	e,f,g
(ng.ml^{-1})	2	22	0.28	0.24	0.05	0.2	0.20	0.36	e,f,g
	3	22	0.65	1.26	0.27	0.2	0.13	0.40	e,f,g
	4	22	0.87	1.30	0.28	0.31	0.28	0.90	e,f,g
	5	22	2.10	2.03	0.43	1.63	0.70	2.81	a,b,c,d
	6	22	6.37	5.64	1.20	5.18	1.80	10.40	a,b,c,d
	7	21	10.28	8.92	1.95	9.0	1.93	15.59	a,b,c,d

a = significantly different from step 1 (p < 0.05); b = significantly different from step 2 (p < 0.05); c = significantly different from step 3 (p < 0.05); d = significantly different from step 4 (p < 0.05); e = significantly different from step 5 (p< 0.05); f = significantly different from step 6 (p < 0.05); g = significantly different from step 7 (p < 0.05).

Friedman ANOVA on ranks; Student-Newman-Keuls.

Uvol = urine volume; FE$_{Na}$ = fractional excretion of sodium; TU$_{Na}$ = total urinary excretion of sodium; C$_{H2O}$ = free water clearance; ß$_2$-micro = ß$_2$-microglobulin.

Table 3.5   Hormonal changes in 22 control patients

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
P_{ren}	1	22	1.45	1.45	0.31	0.90	0.5	2.1	c,d,e,f
$(\mu g.l^{-1}.hr^{-1})$	2	22	1.80	1.40	0.30	1.34	0.77	2.6	c,d,e,f
	3	22	4.47	3.33	0.71	3.41	2.4	5.84	a,b
	4	22	5.82	10.04	2.14	3.62	2.5	5.0	a,b
	5	22	3.86	2.80	0.60	2.51	2.1	4.37	a,b
	6	22	5.93	10.37	2.21	2.90	2.28	4.9	a,b
RV_{ren}	1	22	1.94	1.59	0.34	1.84	0.6	2.4	c,d,e,f
$(\mu g.l^{-1}.hr^{-1})$	2	22	2.14	1.58	0.34	1.71	1.02	3.2	c,d,e,f
	3	22	7.09	5.11	1.09	5.23	3.6	8.56	a,b
	4	22	8.44	9.34	1.99	5.61	3.5	7.74	a,b
	5	22	5.97	3.84	0.82	4.51	3.39	8.6	a,b
	6	22	7.39	10.15	2.16	4.16	2.9	7.52	a,b
ACTH	1	21	13.41	8.05	1.76	13.1	7.6	15.63	d,e,f
$(mg.l^{-1})$	2	22	95.14	163.79	34.92	12.2	7.3	99.60	e,f
	3	22	76.27	105.32	22.46	21.3	5.0	79.70	e,f
	4	22	141.72	199.88	42.61	19.5	7.2	204.7	a,e
	5	22	250.80	263.96	56.28	145.05	8.9	526.7	a,b,c,d
	6	22	222.68	214.08	45.64	156.75	27.7	405.9	a,b,c
Aldosterone	1	21	107.09	77.99	17.02	138.0	41.9	139.0	d,e,f
$(pmol.l^{-1})$	2	22	112	66.00	14.07	138.5	41.6	139.0	d,e,f
	3	22	168.8	122.66	26.15	139.0	115.0	191.0	e,f
	4	22	248.64	129.98	27.71	226.5	164.0	308.0	a,b
	5	22	343.86	251.96	53.72	282.5	161.0	476.0	a,b,c
	6	22	400.68	308.74	65.82	304.0	192.0	511.0	a,b,c,d
ADH	1	21	1.30	0.93	0.20	1.15	0.7	1.83	b,c,d,e,f
$(pg.ml^{-1})$	2	22	9.77	9.12	1.94	6.43	1.7	19.24	a,e,f
	3	22	9.66	8.76	1.87	8.62	1.32	14.06	a,e,f
	4	22	10.23	8.99	1.92	9.65	1.2	18.5	a,e,f
	5	22	15.23	9.78	2.08	18.34	5.26	24.5	a,b,c,d
	6	22	17.42	8.16	1.74	20.55	11.21	24.5	a,b,c,d

a = significantly different from step 1 (p < 0.05); b = significantly different from step 2 (p < 0.05); c = significantly different from step 3 (p < 0.05); d = significantly different from step 4 (p < 0.05); e = significantly different from step 5 (p < 0.05); f = significantly different from step 6 (p < 0.05).

Friedman ANOVA on ranks; Student-Newman-Keuls.

P_{ren} = arterial renin activity; RV_{ren} = renal venous renin activity; ACTH = adrenocorticotrophic hormone; DH = antidiuretic hormone

Table 3.6   **Diverse parameters, which may influence renal hemodynamics in 22 control patients**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
Hct	1	22	38.8	4.00	0.85				b,c,d,e,f
(%)	2	22	33.3	5.05	1.08				a
	3	22	32.8	4.26	0.91				a,f
	4	22	34.4	4.86	1.04				a
	5	22	35.3	4.76	1.02				a
	6	22	35.9	4.22	0.90				a,c
Temp	1	22	36.2	0.60	0.13	36.2	35.8	36.7	b,c,d,e
(°C)	2	22	35.6	0.35	0.08	35.6	35.3	35.8	a,f
	3	22	35.3	0.48	0.10	35.4	34.9	35.6	a,f
	4	22	35.4	0.58	0.12	35.3	34.9	35.7	a,f
	5	22	35.4	0.56	0.12	35.3	35.0	35.8	a,f
	6	22	36.9	1.12	0.24	36.5	36.0	37.8	b,c,d,e
TNT	1	22	0						
$(\mu g.kg^{-1}.min^{-1})$	2	22	1.55	0.64	0.14				e,f
	3	22	1.55	0.80	0.17				e,f
	4	22	1.32	0.57	0.12				f
	5	22	1.07	0.44	0.10				b,c,f
	6	22	0.52	0.11	0.02				b,c,d,e

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$); e = significantly different from step 5 ($p < 0.05$); f = significantly different from step 6 ($p < 0.05$).

ANOVA; Student-Newman-Keuls (Hct, TNT).
Friedman ANOVA on ranks; Student-Newman-Keuls (Temp).

Hct = hematocrit; Temp = blood temperature; TNT = maximum intravenous infusion rate of nitroclycerine.

Table 3.7   **Differences in arterial isotope counts between two samples per measurement time in 22 control patients**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
% Cr^{51}	1	22	3.87	3.08	0.66	3.5	1.3	5.6
	2	22	4.15	3.55	0.76	3.7	1.3	6.4
	3	22	4.85	3.50	0.75	4.05	1.9	6.6
	4	22	4.65	4.02	0.86	2.95	1.7	7.1
	5	22	3.14	2.96	0.63	2.75	0.9	4.5
	6	21	2.98	3.03	0.66	1.5	0.93	4.45
% I^{125}	1	22	8.86	5.15	1.10	9.35	4.9	10.8
	2	22	7.07	5.79	1.23	5.50	2.4	9.6
	3	22	6.18	4.35	0.93	5.20	3.7	8.3
	4	22	5.95	6.48	1.38	3.95	1.2	7.9
	5	22	5.40	5.29	1.13	4.65	1.1	6.7
	6	21	6.55	6.55	1.43	3.20	1.88	11.1

No interstep differences

ANOVA; Student-Newman-Keuls

% Cr^{51} = % difference in arterial Cr^{51} concentrations between 1st and 2nd blood sample per measurement step;
% I^{125} = % difference in arterial I^{125} concentrations between 1st and 2nd blood sample per measurement step.

3.1.1.2 Intra-group changes in 23 patients who received mannitol and dopamine

Timing of measurement steps:
Step 1: awake control
Step 2: post-induction before aortic clamping
Step 3: immediately after aortic clamping ⎫
Step 4: just before unclamping of aorta ⎬ perclamp
Step 5: immediately after aortic unclamping
Step 6: 4 hours after unclamping of aorta
Step 7: 24 hours after aortic unclamping (only ß$_2$-microglobulin)

RBF and the $^{RBF}/_{CO}$ ratio were uninfluenced by anaesthesia and surgery prior to infrarenal aortic cross clamping (steps 1-2; Table 3.8). Both parameters decreased significantly immediately after application of the cross clamp (49.5% and 40.8% respectively, relative to the preclamp values). RBF and $^{RBF}/_{CO}$ remained depressed throughout the rest of the experimental period relative to the two preclamp measurements. Four hours after unclamping, both parameters were still significantly depressed relative to preclamp values (34% reduction in RBF and 45.2% decrease in $^{RBF}/_{CO}$ ratio).

All calculated RVR values after aortic cross clamping were significantly greater than the preclamp value (Table 3.8). The two perclamp and immediately post-unclamp RVR calculations were also increased relative to the awake control RVR, but 4 hours after unclamping RVR had returned to values similar to the awake control calculations.

Although the hippuran extraction 4 hours after aortic unclamping was only 12% less than the awake control measurement, this difference was nevertheless statistically significant due to little scatter of the data (Table 3.8).

GFR as measured by Cr^{51} EDTA clearance decreased subsequent to induction of anaesthesia and commencement of surgery relative to the awake control measure-ment, (Table 3.9). The two perclamp measurements and immediately post-unclamp value were significantly less than the two preclamp measurements. Although GFR 4 hours after unclamping had increased relative to the perclamp and immediately post-unclamp measurements, it was still significantly less than the awake control value (28.6% difference). When using calculated C_{creat} as a measure of GFR, mean values and changes concurred with Cr^{51} EDTA clearances except that the 4 hour post-unclamp value was still decreased relative to both preclamp measurement times (Table 3.9).

FF during the perclamp period decreased significantly relative to awake controls, but was again comparable to control values subsequent to release of the aortic cross clamp (Table 3.9).

Although urine production immediately after aortic cross clamping decreased relative to both preclamp measurements, none of the subsequent volumes differed significantly from any of the preclamp measurements (Table 3.11). FE_{Na} and TU_{Na} remained unchanged throughout the experimental period (Table 3.11). C_{H2O} was more negative 4 hours after unclamping than any of the calculated values in earlier measurement periods (Table 3.11). Subsequent to release of the aortic cross clamp, urinary ß$_2$-microglobulin concentration increased relative to all previous measurements (Table 3.11). Mean ß$_2$-microglobulin concentrations continued to rise in urine samples collected 4 hours and 24 hours after unclamping, although these values were not significantly different from the measurement immediately after unclamping due to large scatter of data.

Systemic hemodynamic parameters were relatively stable throughout the experimental period. Heart rate increased after induction of anaesthesia during the initial surgical phase, but returned to awake control values after aortic clamping (Table 3.10). Four hours after unclamping, heart rate was increased relative to all previous measurement periods. MAP decreased after induction of anaesthesia and after aortic cross clamping it decreased further, to values less than both preclamp measurements (steps 1 and 2) as well as both post-unclamp measurements (steps 5 and 6) (Table 3.10). The measurement immediately prior to unclamping increased to the extent that it did not differ from other measurements except for being lower than awake control and 4 hours post-unclamp measurements. Awake control CVP measurement was less than the value just before aortic unclamping and the two post-unclamp measurements (Table 3.10). The first postclamp PAWP measurement was statistically significantly lower than the measurements in the subsequent three measurement periods (Table 3.10). Cardiac output decreased upon aortic cross clamping in comparison to the measurement immediately prior to clamping (Table 3.10). The first CO after aortic clamping was also significantly less than the two post-unclamp measurements. Induction of anaesthesia and aortic unclamping (steps 2 and 5 respectively) produced a reduction in SVR relative to the awake control calculation (Table 3.10).

Arterial and renal venous renin activity were uninfluenced by anaesthesia and the initial surgical period, but increased significantly immediately after aortic clamping and remained elevated relative to the two preclamp measurements throughout the rest of

the experimental period (Table 3.12). The serum aldosterone concentrations demonstrated the same trends (Table 3.12). Serum ADH concentrations increased subsequent to anaesthetic induction and commencement of surgery and showed no additional response to aortic clamping, but both measurements after unclamping were increased relative to all previous concentrations (Table 3.12). All post-induction ACTH concentrations were greater than awake the control concentrations (Table 3.12). The two post-unclamp measurements were also raised in comparison with the two preclamp and first postclamp concentrations.

All intra-operative hematocrit values were less than awake control measurements, with return to control values 4 hours post-unclamp (Table 3.13). The 4 hours post-unclamp measurement was also greater than the two perclamp measurements and the immediate post-unclamp value already showed an improvement on the first perclamp concentration.

Body core temperature decreased intraoperatively relative to awake control measurement, but recovered relative to intraoperative temperatures at 4 hours after unclamping (Table 3.13). The first perclamp measurement was also significantly lower than the intraoperative preclamp temperature, but mean temperatures never decreased below 35°C.

All intraoperative nitroglycerine infusion rates were comparable and greater than the dose administered 4 hours after unclamping (Table 3.13).

Cr^{51} EDTA and I^{125} hippuran concentrations were relatively constant within measurement periods throughout the experimental period with only the awake control and first postclamp measurements of I^{125} hippuran demonstrating differences of significance (Table 3.14).

Table 3.8　　　**Renal hemodynamic variables in 23 patients who received mannitol and dopamine.**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
RBF	1	19	1255.4	271.3	62.2				c,d,e,f
(ml.min⁻¹)	2	19	1404.8	436.2	100.1				c,d,e,f
	3	19	709.8	313.9	76.1				a,b
	4	17	831.3	289.7	66.5				a,b
	5	16	781.9	267.9	71.6				a,b
	6	12	925.6	247.2	87.4				a,b
$^{RBF}/_{CO}$	1	19	0.239	0.066	0.015				c,d,e,f
	2	19	0.250	0.108	0.024				c,d,e,f
	3	19	0.148	0.058	0.014				a,b
	4	17	0.160	0.071	0.016				a,b
	5	16	0.132	0.058	0.016				a,b
	6	12	0.137	0.064	0.021				a,b
RVR	1	19	6.67	2.05	0.47				c,d,e
(dyn.s.cm⁻⁵)	2	19	5.57	2.16	0.50				c,d,e,f
	3	19	11.04	5.22	1.27				a,b
	4	17	9.31	4.13	0.95				a,b
	5	16	10.25	4.10	1.10				a,b
	6	12	8.72	3.07	1.09				b
E_{HIP}	1	19	0.72	0.073	0.017	0.74	0.68	0.76	f
	2	19	0.66	0.076	0.017	0.66	0.61	0.71	
	3	19	0.67	0.072	0.018	0.68	0.61	0.71	
	4	17	0.64	0.076	0.017	0.63	0.58	0.68	
	5	16	0.63	0.073	0.019	0.61	0.59	0.67	
	6	12	0.63	0.080	0.028	0.62	0.57	0.67	a

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$); e = significantly different from step 5 ($p < 0.05$); f = significantly different from step 6 ($p < 0.05$).

ANOVA, Student-Newman-Keuls (RBF, $^{RBF}/_{CO}$, RVR).
Friedman ANOVA on ranks; Student-Newman-Keuls (E_{HIP}).

RBF = renal blood flow; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output; RVR = renal vascular resistance; E_{HIP} = hippuran extraction fraction.

Table 3.9　　　**Glomerular function variables in 23 patients who received mannitol and dopamine**

Variable	Step	N	Mean	SD	SE	Interstep differences
GFR	1	23	103.4	31.6	6.59	b,c,d,e,f
(ml.min⁻¹)	2	23	86.2	22.29	4.65	a,c,d,e
	3	23	40.5	15.49	3.23	a,b,f
	4	23	48.4	20.56	4.29	a,b,f
	5	23	48.1	24.93	5.2	a,b,f
	6	19	73.5	26.63	6.11	a,c,d,e
C_{creat}	1	23	97.7	16.36	3.41	c,d,e,f
(ml.min⁻¹)	2	22	93.7	17.51	3.73	c,d,e,f
	3	22	43.7	13.20	2.81	a,b,f
	4	22	50.9	15.91	3.39	a,b,f
	5	22	50.2	19.12	4.08	a,b,f
	6	22	72.5	20.09	4.28	a,b,c,d,e
FF	1	23	0.20	0.04	0.009	c,d
	2	23	0.17	0.06	0.012	
	3	23	0.16	0.04	0.009	a,e,f
	4	23	0.15	0.04	0.009	a,e,f
	5	23	0.19	0.06	0.013	c,d
	6	19	0.20	0.06	0.014	c,d

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$); e = significantly different from step 5 ($p < 0.05$); f = significantly different from step 6 ($p < 0.05$).

ANOVA; Student-Newman-Keuls.

GFR = glomerular filtration rate (measured by clearance of Cr^{51} EDTA); C_{creat} = calculated creatinine clearance; FF = filtration fraction.

Table 3.10   **Systemic hemodynamic variables in 23 patients who received mannitol and dopamine**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
HR	1	23	75.96	14.4	3.0				b,f
(beats.min⁻¹)	2	23	84.09	16.65	3.47				a,c,d,f
	3	23	74.78	15.77	3.29				b,f
	4	23	73.96	15.86	3.31				b,f
	5	23	81.04	12.31	2.57				f
	6	23	91.43	16.42	3.42				a,b,c,d,e
MAP	1	23	107.48	16.76	3.49	109.0	101.0	117.5	b,c,d
(mmHg)	2	23	95.65	17.61	3.67	94.5	82.0	106.0	a,c
	3	23	88.39	12.78	2.66	87.5	79.5	94.75	a,b,e,f
	4	23	92.87	13.66	2.85	92.0	81.25	98.75	a,f
	5	23	99.26	15.71	3.28	100.0	89.0	112.0	c
	6	23	103.22	17.81	3.71	102.5	88.25	119.25	c,f
CVP	1	23	6.52	4.23	0.88	6.0	3.0	10.0	d,e,f
(mmHg)	2	23	7.83	3.82	0.80	8.0	4.0	10.5	
	3	23	7.96	3.52	0.73	8.0	4.5	10.75	
	4	23	8.54	3.38	0.71	9.0	5.5	10.75	a
	5	23	9.09	4.16	0.87	9.0	6.0	11.75	a
	6	23	9.22	3.45	0.72	9.0	7.0	11.0	a
PAWP	1	23	9.61	5.23	1.09	9.0	6.0	13.25	
(mmHg)	2	23	10.43	5.16	1.08	10.0	6.5	13.50	
	3	23	9.65	5.39	1.24	8.5	6.0	13.50	d,e,f
	4	23	11.26	5.06	1.05	10.0	8.0	14.00	c
	5	23	12.13	5.14	1.07	11.0	8.25	14.75	c
	6	23	12.43	4.73	0.99	12.0	10.0	14.75	c
CO	1	23	5.54	1.17	0.25				
(l.min⁻¹)	2	23	5.93	1.46	0.30				c
	3	23	4.97	1.10	0.23				b,e,f
	4	23	5.37	1.55	0.32				
	5	23	6.25	1.32	0.28				c
	6	23	5.95	2.09	0.44				c
SVR	1	23	1508.5	455.6	94.8				b,e
(dyn.s.cm⁻⁵)	2	23	1214.2	322.1	67.0				a
	3	23	1351.7	453.4	94.3				
	4	23	1313.6	378.9	78.9				
	5	23	1205.6	408.5	85.2				a
	6	23	1404.5	601.7	125.0				

a = signigicantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$);
c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$);
e = significantly different from step 5 ($p < 0.05$); f = significantly different from step 6 ($p < 0.05$).

ANOVA; Student-Newman-Keuls (CO, HR, SVR).
Friedman ANOVA on ranks; Student-Newman-Keuls (PAWP, MAP, CVP).

CO = cardiac output; HR = heart rate; PAWP = pulmonary artery occlusion pressure; MAP = mean arterial pressure;
CVP = central venous pressure; SVR = systemic vascular resistance.

Table 3.11   **Parameters of renal tubular function in 23 patients who received mannitol and dopamine**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
Uvol	1	23	6.51	3.64	0.76	6.5	3.68	9.34	c
(ml.min^{-1})	2	23	7.01	4.25	0.89	7.0	2.75	9.94	c
	3	23	4.07	2.41	0.5	3.53	2.81	4.19	a,b
	4	23	4.85	3.07	0.64	3.9	3.00	6.21	
	5	23	4.34	2.42	0.50	4.25	2.78	5.86	
	6	23	5.35	3.10	0.65	5.5	2.33	7.60	
FE$_{Na}$	1	23	0.05	0.035	0.007				
	2	22	0.06	0.039	0.008				
	3	22	0.09	0.061	0.013				
	4	22	0.08	0.053	0.011				
	5	22	0.08	0.038	0.008				
	6	22	0.08	0.044	0.009				
TU$_{Na}$	1	23	0.671	0.401	0.083				
(mEq.min^{-1})	2	22	0.778	0.443	0.094				
	3	22	0.487	0.367	0.078				
	4	22	0.516	0.328	0.070				
	5	22	0.530	0.295	0.063				
	6	22	0.718	0.455	0.097				
C$_{H2O}$	1	23	-0.13	2.32	0.48	-0.36	1.20	-1.79	f
(ml.min^{-1})	2	22	-0.70	1.78	0.38	-1.13	-0.48	-1.55	f
	3	22	-0.88	1.38	0.30	-0.50	-0.35	-0.89	f
	4	22	-0.73	0.87	0.19	-0.55	-0.29	-1.18	f
	5	22	-0.78	0.69	0.15	-0.71	-0.32	-1.25	f
	6	22	-1.82	1.43	0.3	-1.67	-0.8	-2.38	a,b,c,d,e
ß$_2$-micro	1	23	0.33	0.49	0.10	0.20	0.16	0.22	e,f,g
(ng.ml^{-1})	2	23	0.44	0.42	0.09	0.26	0.2	0.48	e,f,g
	3	23	0.93	1.81	0.38	0.31	0.2	0.87	e,f,g
	4	23	1.97	3.99	0.83	1.00	0.21	1.69	e,f,g
	5	22	3.38	3.47	0.74	2.11	1.37	3.33	a,b,c,d
	6	23	9.92	13.92	2.90	5.00	1.3	10.5	a,b,c,d
	7	21	16.26	12.08	2.64	15.95	6.5	26.9	a,b,c,d

a = significantly different from step 1 (p < 0.05); b = significantly different from step 2 (p < 0.05); c = significantly different from step 3 (p < 0.05); d = significantly different from step 4 (p < 0.05); e = significantly different from step 5 (p < 0.05); f = significantly different from step 6 (p < 0.05); g = significantly different from step 7 (p < 0.05).

ANOVA; Student-Newman-Keuls (FE$_{Na}$, TU$_{Na}$).
Friedman ANOVA on ranks; Student-Newman-Keuls (Uvol, C$_{H2O}$, ß$_2$-micro)

Uvol = urine volume; FE$_{Na}$ = fractional excretion of sodium; TU$_{Na}$ = total urinary excretion of sodium; C$_{H2O}$ = free water clearance; ß$_2$-micro = ß$_2$-microglobulin.

Table 3.12   **Hormonal changes in 23 patients who received mannitol and dopamine**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
P_{ren}	1	23	1.11	0.75	0.16				c,d,e,f
$(\mu g.l^{-1}.hr^{-1})$	2	22	1.43	1.33	0.28				c,d,e,f
	3	23	6.60	11.15	2.33				a,b
	4	23	7.10	10.83	2.26				a,b
	5	23	7.24	9.86	2.06				a,b
	6	23	6.00	11.52	2.40				a,b
RV_{ren}	1	23	1.39	11.15	0.24				c,d,e,f
$(\mu g.l^{-1}.hr^{-1})$	2	22	2.05	2.02	0.43				c,d,e,f
	3	23	8.06	11.45	2.39				a,b
	4	23	8.83	10.78	2.25				a,b
	5	23	10.8	11.49	2.40				a,b
	6	23	7.20	11.90	2.48				a,b
ACTH	1	22	15.31	20.60	4.39	8.00	5.0	15.8	b,c,d,e,f
$(mg.l^{-1})$	2	22	52.36	85.77	18.29	21.55	8.3	65.8	a,e,f
	3	22	55.77	81.4	17.35	27.05	10.8	50.7	a,e,f
	4	22	79.52	97.19	20.72	39.6	11.1	107.2	a
	5	22	190.32	222.83	47.51	88.8	17.3	380.2	a,b,c
	6	22	220.55	216.65	46.19	167.5	19.7	360.6	a,b,c
Aldosterone	1	22	112.5	114.81	24.47	139.0	50.0	139.0	c,d,e,f
$(pmol.l^{-1})$	2	22	102.53	97.92	20.88	139.0	40.2	124.0	c,d,e,f
	3	22	163.18	57.22	12.02	139.0	108.0	188.0	a,b
	4	22	230.7	138.22	29.43	182.5	139.0	294.0	a,b
	5	22	240.97	140.92	30.04	179.0	139.0	334.0	a,b
	6	22	274.48	263.74	56.23	227.5	143.0	441.0	a,b
ADH	1	22	1.36	1.17	0.25				b,c,d,e,f
$(pg.ml^{-1})$	2	22	12.45	8.71	1.86				a,e,f
	3	22	10.23	8.29	1.77				a,e,f
	4	22	10.47	8.58	1.83				a,e,f
	5	22	16.92	8.97	1.91				a,b,c,d
	6	22	17.51	8.56	1.83				a,b,c,d

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$);
c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$);
e = significantly different from step 5 ($p < 0.05$); f = significantly different from step 6 ($p < 0.05$).

ANOVA; Student-Newman-Keuls (P_{ren}, RV_{ren}, ADH).
Friedman ANOVA on ranks; Student-Newman-Keuls (ACTH, Aldosterone).

P_{ren} = arterial renin activity; RV_{ren} = renal venous renin activity; ACTH = adrenocorticotrophic hormone; ADH = antidiuretic hormone.

Table 3.13 Diverse variables which may influence renal hemodynamics in 23 patients who received mannitol and dopamine

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
Hct	1	23	39.91	4.48	0.93				b,c,d,e
(%)	2	23	34.96	5.62	1.17				a
	3	23	32.78	4.45	0.93				a,e,f
	4	23	33.48	3.75	0.78				a,f
	5	23	36.57	5.22	1.09				a,c
	6	23	38.39	5.59	1.17				c,d
Temp	1	23	36.00	0.69	0.14	36.0	35.70	36.48	b,c,d,e
(°C)	2	23	35.40	0.85	0.18	35.5	34.73	36.00	a,c
	3	23	35.06	0.89	0.19	35.3	34.43	35.70	a,b,f
	4	23	35.25	0.91	0.19	35.4	34.70	35.88	a,f
	5	23	35.23	0.88	0.18	35.4	34.73	35.93	a,f
	6	23	36.43	1.08	0.22	36.0	36.00	36.85	c,d,e
TNT	1	23	0						
(μg.kg^{-1}·min^{-1})	2	23	1.7	1.24	0.26				f
	3	23	1.83	1.74	0.36				f
	4	23	1.96	1.78	0.37				f
	5	23	1.52	0.85	0.18				f
	6	23	0.52	0.10	0.02				b,c,d,e

a = significantly different from step 1($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$); e = significantly different from step 5 ($p < 0.05$); f = significantly different from step 6 ($p < 0.05$).

ANOVA; Student-Newman-Keuls (Hct, TNT).
Friedman ANOVA on ranks; Student-Newman-Keuls (Temp).

Hct = hematocrit; Temp = blood temperature; TNT = maximum intravenous infusion rate of nitroclycerine.

Table 3.14   Differences in arterial isotope counts between two samples per measurement time in 23 patients who received mannitol and dopamine

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc	Interstep differences
% Cr^{51}	1	23	4.85	4.13	0.86				
	2	23	5.97	4.29	0.89				
	3	23	4.35	2.76	0.58				
	4	23	4.08	2.19	0.46				
	5	23	5.26	4.08	0.85				
	6	20	3.44	2.78	0.62				
% I^{125}	1	23	8.71	7.14	1.49	7.8	4.55	11.55	c
	2	23	6.57	5.25	1.10	6.4	1.80	9.92	
	3	23	4.13	3.70	0.77	2.9	1.95	5.52	a
	4	23	4.97	3.38	0.71	5.3	2.18	6.77	
	5	23	4.50	3.55	0.74	2.8	2.08	7.57	
	6	20	5.16	5.19	1.16	2.9	1.70	8.15	

a = significantly different from step 1 ($p < 0.05$); c = significantly different from step 3 ($p < .05$).

ANOVA; Student-Newman-Keuls (% Cr^{51}).
Friedman ANOVA on ranks; Student-Newman-Keuls (% I^{125}).

% Cr^{51} = % difference in arterial Cr^{51} concentrations between 1st and 2nd blood sample per measurement step;
% I^{125} = % difference in arterial I^{125} concentrations between 1st and 2nd blood sample per measurement step.

3.1.2 Inter-group differences between control and mannitol plus dopamine groups of patients

There were no differences in the preoperative demographic parameters of age, length, body mass, body surface area (BSA), male: female ratio, the presence of diabetes, hypertension or ischemic heart disease, or preoperative medication between the control patients and the mannitol plus dopamine group of patients (Table 3.15)

Aortic cross clamp times were similar in the two patient groups (Table 3.16). Patients in the mannitol plus dopamine group received significantly more intravenous crystalloids in the immediate perioperative period (1 hour preoperatively until the end of surgery) than control patients, but there were no differences between the two groups in volumes of colloid and blood infused (Table 3.16).

In both groups of patients the creatinine clearance done on a 24 hour urine sample one week postoperatively was significantly reduced relative to the C_{creat} done prior to surgery (after admission to the ward) (Table 3.16). There were, however, no differences between the control and mannitol plus dopamine groups in either the pre- or postoperative C_{creat} values. Total 24 hour urinary creatinine excretion was 12210.8 (± 1052 (SD)) μmol and 12683.5 (± 1281 (SD)) μmol in control and mannitol plus dopamine patient groups respectively.

Six patients (3 in the control group and 3 in the mannitol and dopamine group) had serum creatinine concentrations greater than the upper limit of normal ($120 \mu mol.l^{-1}$) 7 days postoperatively. These patients are grouped together and compared with all patients with postoperative serum creatinine levels of less than $120 \mu mol.l^{-1}$ in Table 3.16a. Although the preoperative serum creatinine concentrations were significantly higher in the former group, both group means were still well within normal limits. The preoperative as well as postoperative C_{creat} values in the patient group with abnormal postoperative creatinine concentrations were significantly lower than the patients with normal postoperative creatinine concentrations. While the postoperative C_{creat} values were significantly lower than their respective preoperative values in both groups, the preoperative-postoperative differences were substantially greater in the patients with abnormal postoperative creatinine concentrations ($18ml.min^{-1}$ vs $6.5 ml.min^{-1}$).

There were no differences in RBF (Figure 3.1 and Tables 3.1 and 3.8 respectively) or the $^{RBF}/_{CO}$ ratio (Figure 3.2 and Tables 3.1 and 3.8 respectively) between the control group and the mannitol plus dopamine group of patients at any of the measurement

times in the perioperative period. Similarly, calculated RVR did not differ between the two groups at any of the sampling times (Figure 3.3 and Tables 3.1 and 3.8 respectively). Although there was a numerical difference of 7.5% in awake control E_{HIP} values between the control and mannitol plus dopamine groups (Tables 3.1 and 3.8 respectively), this difference was not statistically significant and the other perioperative values were almost identical with significant overlap of SEM's (Figure 3.4).

Table 3.15 **Preoperative demographic data of control patients and patients who received mannitol and dopamine during infrarenal aortic aneurysm repair**

	Control patients (n = 22)			Patients who received mannitol and dopamine (n = 23)		
	Mean	SD	SE	Mean	SD	SE
Age (years)	66.5	7.49	1.6	63.13	10.16	2.12
Length (centimetre)	167.36	8.96	1.91	168	9.22	1.92
Mass (kilogram)	68.27	15.32	3.27	66.06	15.35	3.2
BSA (m^2)	1.76	0.2	0.04	1.74	0.22	0.05
Male : Female	16:6			16:7		
Diabetics	4			3		
Presence of ischemic heart disease	15			13		
Presence of (controlled) hypertension	12			10		
Preoperative medication	5	Diuretics *		7		
	5	α-methyldopa		4		
	3	ß-blockers		4		
	5	Glyceryltrinitrate		6		
	3	Digitalis		2		
	0	Prazosin		1		
	1	Nifedipine		1		

No significant differences between groups (t-test).

∗ Diuretics were stopped 2 days before surgery.

BSA = body surface area. Presence of ischemic heart disease based on previous myocardial infarct on resting ECG and/or history of previous infarct and/or taking medication for angina and/or a positive stress ECG with coronary artery disease demonstrated on coronary angiography. Serum electrolytes were within normal limits in all patients.

Table 3.16 **Perioperative demographic and other relevant data in control patients and patients who received mannitol and dopamine in the intra- and postoperative periods**

	Control patients (n = 22)			Patients who received mannitol and dopamine (n = 23)		
	Mean	SD	SE	Mean	SD	SE
C_{creat} (ml.min^{-1}):						
1 day preoperatively.	† 89.05	16.32	3.48	† 93.27	17.69	3.77
7 days post-operatively	80.47	19.48	4.47	83.57	18.25	3.98
Aortic cross clamp time (minutes)	73.0	14.13	3.01	75.91	15.45	3.22
Intravenous fluids (ml):						
Crystalloid	5350.0∗	991.7	211.4	6233.5∗	1218.4	254.0
Colloid	1090.9	382.2	81.5	1130.4	438.6	91.5
Packed Red Cells (ml):	1323.9	408.1	85.1	1336.4	478.6	102.0

† = intra-group difference ($p < 0.01$)

∗ = intergroup difference ($p < 0.05$)

t – test

C_{creat} = creatinine clearance (24 hour urine sample collection)

Table 3.16a **Creatinine clearance and serum creatinine values 1 day preoperatively and 7 days postoperatively in both patient groups**

	Cr pre-op			Cr post-op			C$_{cr}$ pre-op			C$_{cr}$ post-op		
	Mean	SD	95%	Mean	SD	95%	Mean	SD	95%	Mean	SD	95%
Postop Cr <120 μmol.l^{-1} (n = 34)	83.7	11.5	79.7-87.7	83.8	11.2	81.8-86.7	95.0	13.4	92.7-97.4	88.5 †	14.9	85.8-91.1
	*			**			**			**		
Postop Cr >120 μmol.l^{-1} (n = 6)	96.7	9.0	92.2-101.2	155.8 †	13.2	149.3-162.4	61.2	3.8	59.3-63.1	43.2 †	4.7	40.8-45.5

* $p < 0.05$ ⎫
** $p < 0.001$ ⎬ differences between groups

† $p < 0.01$ differences between postop and preop values within a group

differences between groups: unpaired t-test
differences within groups (between pre- and postop values): paired t-test

Cr = serum creatinine (μmol.l^{-1}); C$_{cr}$ = creatinine clearance (ml.min^{-1}); 95% = 95% confidence limits

Figure 3.1   **Perioperative changes in renal blood flow in control patients and patients who received mannitol and dopamine**
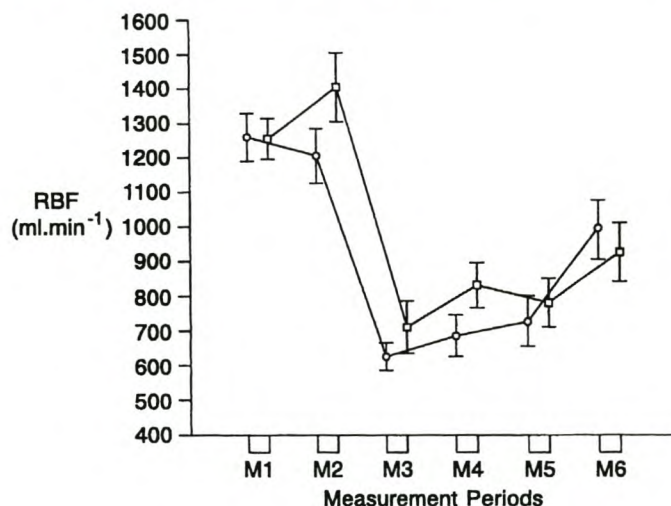
o = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant differences between
control and mannitol + dopamine groups
at the various measurement periods

M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp

Figure 3.2   **Perioperative changes in renal blood flow as a fraction of cardiac output ($^{RBF}/_{CO}$) in control patiens and patients who received mannitol and dopamine**

o = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant differences between
control and mannitol + dopamine groups
at the various measurement periods

M1 = awake control

M2 = Intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp

Figure 3.3   **Perioperative changes in renal vascular resistance (RVR) in control patients and patients who received mannitol and dopamine**

o = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant differences between
control and mannitol + dopamine groups
at the various measurement periods

M1 = awake control

M2 = Intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp

Figure 3.4 **Perioperative changes in hippuran extraction fraction (E_{HIP}) in control patients and patients who received mannitol and dopamine**

o = control patients
□ = mannitol + dopamine patients
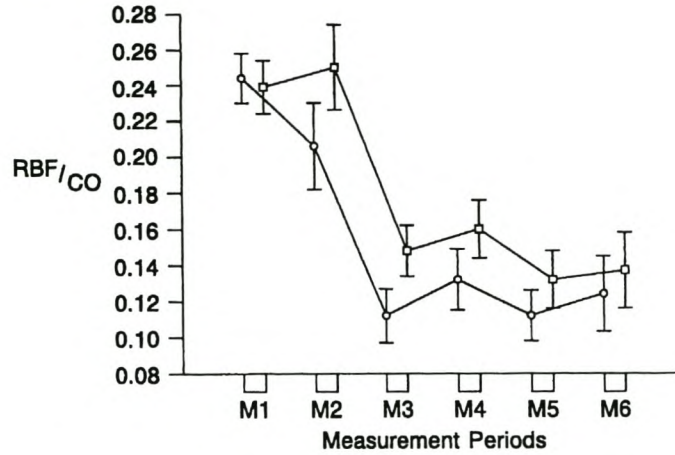
Values are given as means, ± 1 SEM

No significant differences between control and mannitol + dopamine groups at the various measurement periods

M1 = awake control

M2 = intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp
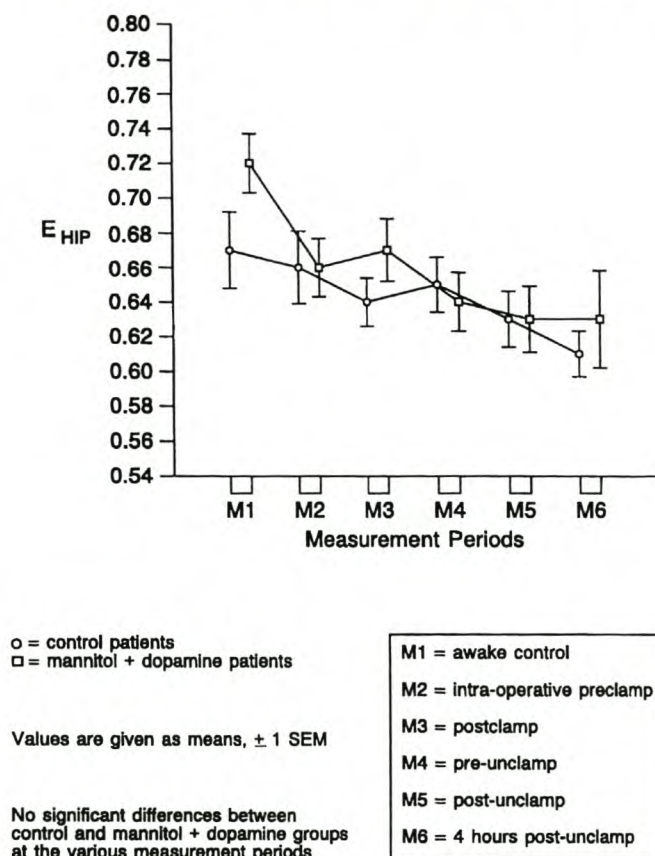
Despite the 16.6% decrease in GFR induced by anaesthesia and exploratory surgery in the mannitol plus dopamine group (versus maintenance of preoperative GFR in the initial surgical period in the control group), none of the GFR values differed significantly between the two patient groups (Figure 3.5 and Tables 3.2 and 3.9 respectively). Calculated C_{creat} did not differ between the control and drug manipulated groups at any of the measurement periods (Figure 3.6 and Tables 3.2 and 3.9 respectively). Filtration fractions were identical in the two groups preoperatively, but the mannitol plus dopamine group demonstrated significantly reduced values just before application of the aortic clamp and during the perclamp period relative to the control patients (Figure 3.7 and Tables 3.2 and 3.9).

Volumes of urine production were similar between the two patient groups before induction of anaesthesia (Figure 3.8 and Tables 3.4 and 3.11). Mannitol and dopamine infusion had not been commenced at this stage (in that group of patients). Mannitol plus dopamine infusion induced increased urine production relative to the control group during the preclamp measurement period (p < 0.05). This difference was maintained throughout the rest of the experimental period at an even more significant level (p < 0.01). Predictably, as urinary sodium concentration (not shown in tables or

figures) was consistently increased after commencement of the mannitol and dopamine infusions, the TU_{Na} was much greater throughout the rest of the experimental period in the latter group in comparison to control patients ($p < 0.001$; Figure 3.9, Tables 3.4 and 3.11). Similarly, FE_{Na} was also greater in the mannitol plus dopamine patients than in the control group for the duration of surgery and into the postoperative period ($p < 0.01$; Figure 3.10, Tables 3.4 and 3.11). There were no differences in C_{H2O} values between the two groups of patients at any of the measurement times (Figure 3.11, Tables 3.4 and 3.11 respectively). Urinary $ß_2$-microglobulin concentrations demonstrated identical rising trends from the post-unclamp period onwards in the two patient groups with no significant differences between them at any of the measurement periods (Figure 3.12, Tables 3.4 and 3.11).

Figure 3.5   **Perioperative changes in glomerular filtration rate in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

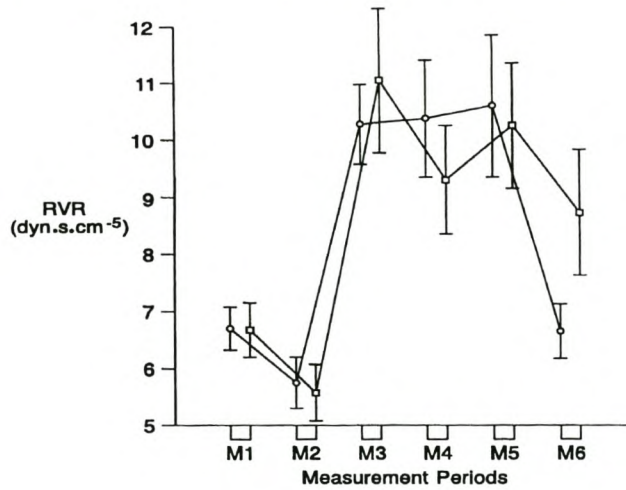No significant difference between control and mannitol + dopamine at the various measurement periods

M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp
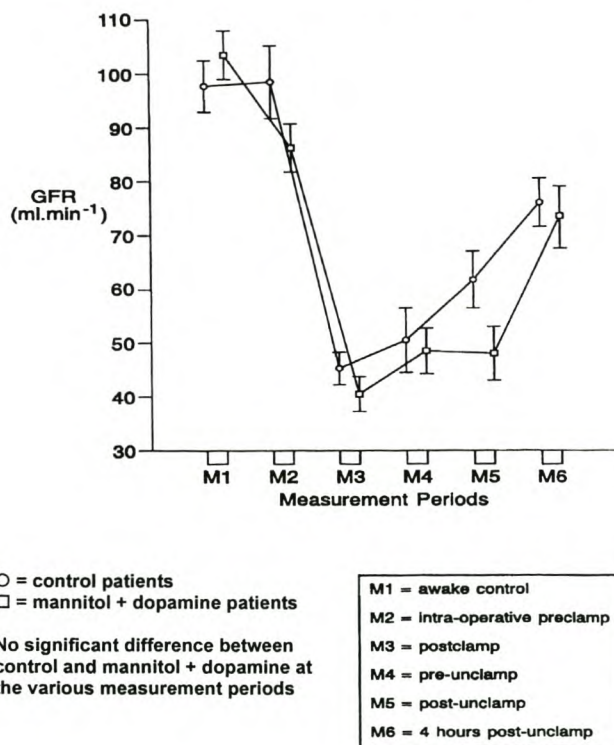
Figure 3.6   **Perioperative changes in creatinine clearance in control patients and patients who received mannitol and dopamine**
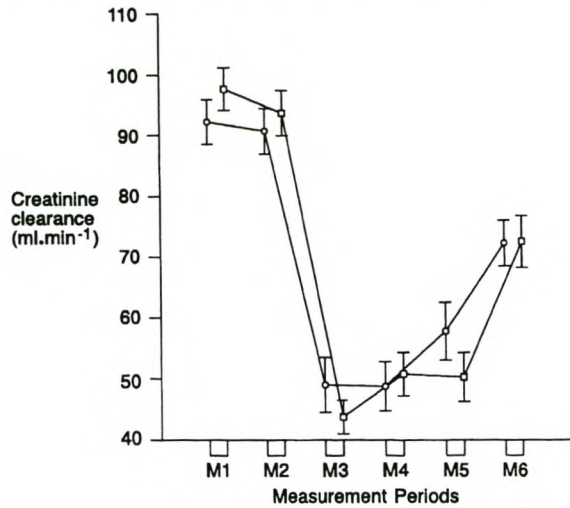
O = control patients
□ = mannitol + dopamine patients

No significant difference between control and mannitol + dopamine at the various measurement periods

M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp

Figure 3.7   **Perioperative changes in filtration fraction in control patients and patients who received mannitol and dopamine**
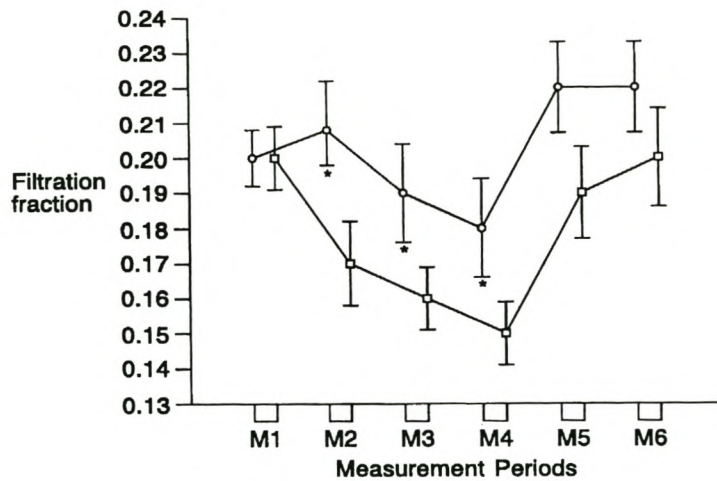
O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

* Significant difference between control and mannitol + dopamine groups (p < 0.05)

M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp

Figure 3.8   Perioperative changes in urine volume (Uvol) in control patients and patients who received mannitol and dopamine

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

Differences between control and
mannitol + dopamine groups:
* p < 0.05
** p < 0.01

M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp

Figure 3.9   Comparison of total urinary sodium excretion (TU_{Na}) at different perioperative measurement periods in control patients and patients who received mannitol and dopamine

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

*** Significant difference between control
    and mannitol + dopamine groups
    (p < 0.01)

M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp

Figure 3.10   **Perioperative changes in fractional excretion of sodium (FE_{NA}) in control patients and patients who received mannitol and dopamine**
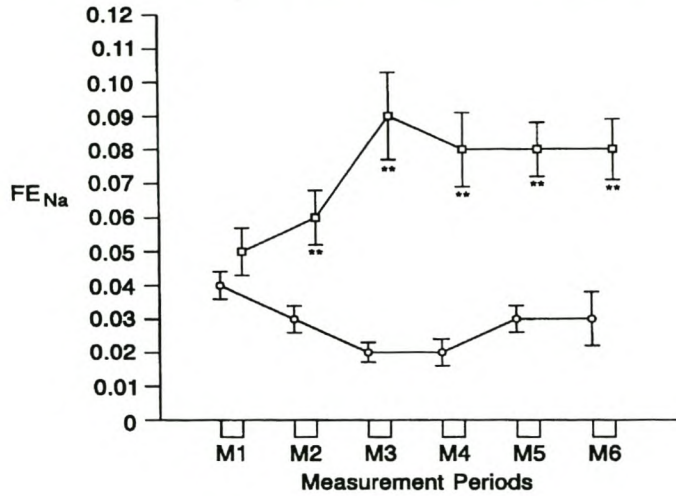
O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

**   Significant difference between control and mannitol + dopamine patients (p < 0.01)

M1 = awake control

M2 = Intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp

Figure 3.11   **Perioperative changes in free water clearance (C_{H2O}) in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant differences between control and mannitol + dopamine groups at the various measurement periods

M1 = awake control

M2 = Intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp

Figure 3.12   **Perioperative changes in urinary ß₂-microglobulin concentrations in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

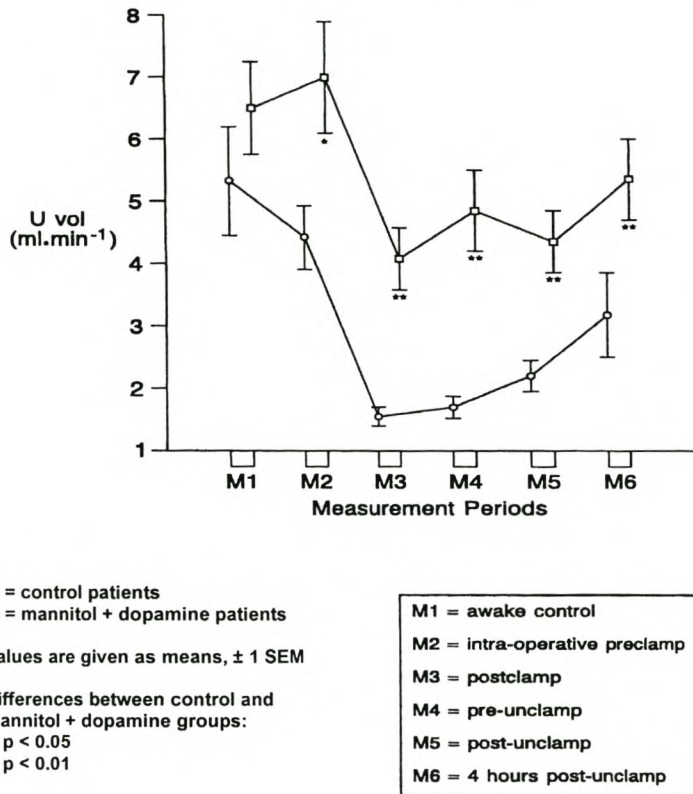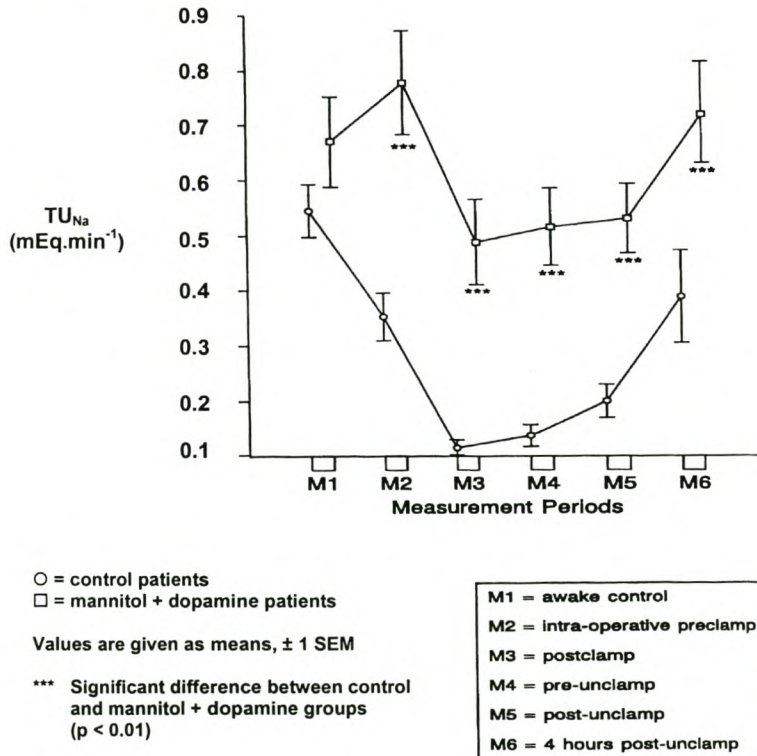Values are given as means, ± 1 SEM

No significant differences between control and mannitol + dopamine groups at the various measurement periods

M1 = awake control

M2 = intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp

M7 = 24 hours post-unclamp
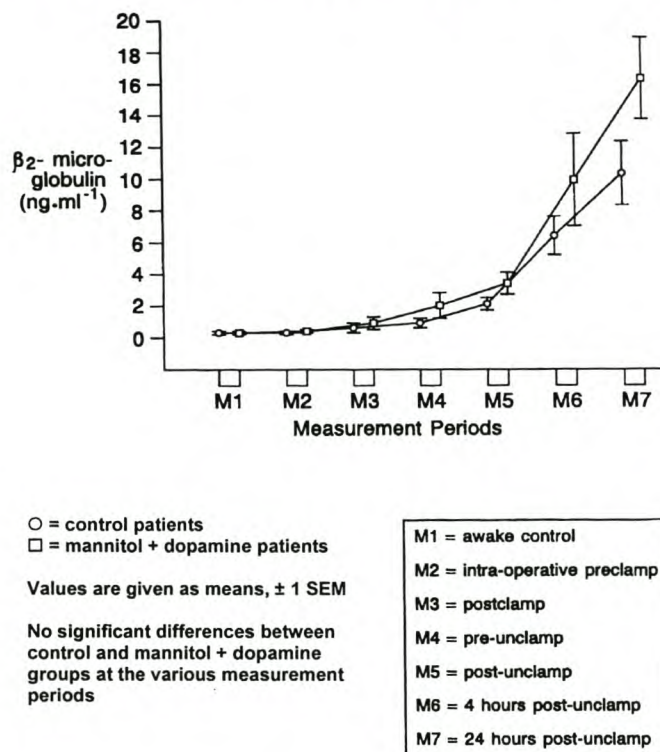
Figures were produced only for those hemodynamic variables, which may influence renal hemodynamics and kidney function. The mean value for MAP in mannitol plus dopamine patients was significantly greater than in control patients 4 hours after aortic unclamping (Figure 3.13, Tables 3.3 and 3.10), without any significant differences at the other measurement times. The PAWP immediately after aortic cross clamping was higher in the control group than in mannitol plus dopamine patients ($p < 0.05$), with no inter-group differences at any of the other measurement times (Figure 3.14, Tables 3.3 and 3.10). CVP measurements (Tables 3.3. and 3.10, no figure) were comparable between the two groups at all measurement periods. There were no significant differences in measured CO between the two groups of patients at any of the measurement periods (Figure 3.15, Tables 3.3 and 3.10).

Other measured and calculated hemodynamic parameters (heart rate and SVR) were not different between the two patient groups with the exception of the SVR 4 hours after aortic unclamping which was significantly higher ($p < 0.05$) in the mannitol plus dopamine group (Tables 3.3. and 3.10, no figures).

None of the measured hormonal concentrations (with the exception of the catecholamine concentrations) demonstrated any differences between groups at any of the measurement periods (P$_{ren}$: Figure 3.16, Tables 3.5 and 3.12; RV$_{ren}$: Figure 3.17,

Tables 3.5 and 3.12; ACTH: Figure 3.18, Tables 3.5 and 3.12; Aldosterone: Figure 3.19, Tables 3.5 and 3.12; ADH: Figure 3.20, Tables 3.5 and 3.12). The plasma noradrenaline and dopamine concentrations were both significantly greater in mannitol plus dopamine patients than in control patients after application of the aortic cross clamp while no differences were apparent prior to cross clamping (Table 3.17).

Table 3.17 Plasma catecholamine concentrations before and after aortic cross clamping in control patients and patients who received mannitol and dopamine

	Control (n = 11)					Mannitol + Dopamine (n = 14)			
	Mean	Median	25 Perc	75 Perc		Mean	Median	25 Perc	75 Perc
Preclamp Noradrenaline	0.265	0.25	0.15	0.35		0.307	0.27	0.16	0.35
Postclamp Noradrenaline	0.360	0.29	0.21	0.41	†	0.753	0.55	0.37	0.99
Preclamp Adrenaline	0.128	0	0	0.23		0.062	0	0	0.11
Postclamp Adrenaline	0.132	0	0	0		0.088	0	0	0.20
Preclamp Dopamine	0	0	0	0		0.029	0	0	0
Postclamp Dopamine	0	0	0	0	†	59.99	52.0	48.32	56.40

Wilcoxon signed rank test

*   significant difference between preclamp and postclamp concentration within the group ($p < 0.05$)

†   significant difference between patient groups at the same measurement time ($p < 0.05$)

Catecholamine concentrations in $ng.ml^{-1}$ plasma

Figure 3.13 Perioperative changes in mean arterial pressure (MAP) in control patients and patients who received mannitol and dopamine
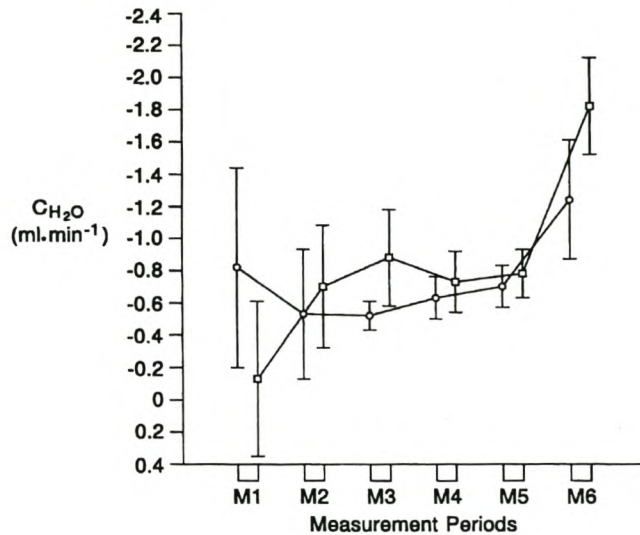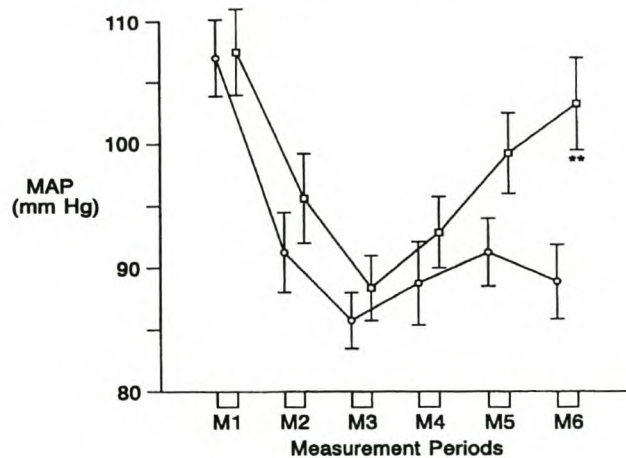

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

** Significant difference between control and mannitol + dopamine groups ($p < 0.01$)

M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp

Figure 3.14   **Perioperative changes in pulmonary artery wedge pressure (PAWP) in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

* Significant difference between control and mannitol + dopamine groups (p < 0.05)

| M1 = awake control |
| M2 = intra-operative preclamp |
| M3 = postclamp |
| M4 = pre-unclamp |
| M5 = post-unclamp |
| M6 = 4 hours post-unclamp |

Figure 3.15   **Perioperative changes in cardiac output (CO) in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant difference between control and mannitol + dopamine groups at the various measurement periods

| M1 = awake control |
| M2 = intra-operative preclamp |
| M3 = postclamp |
| M4 = pre-unclamp |
| M5 = post-unclamp |
| M6 = 4 hours post-unclamp |

Figure 3.16   **Perioperative changes in arterial plasma renin concentrations (P_{ren}) in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant difference between control and mannitol + dopamine groups at the various measurement periods

M1 = awake control

M2 = intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp

Figure 3.17   **Perioperative changes in renal venous renin (RV_{ren}) concentrations in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant difference between control and mannitol + dopamine groups at the various measurement periods

M1 = awake control

M2 = intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp

Figure 3.18 · **Perioperative changes in plasma adrenocorticotrophic hormone (ACTH) concentrations in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant difference between control and mannitol + dopamine groups at the various measurement periods

M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp

Figure 3.19 **Perioperative changes in plasma aldosterone concentrations in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

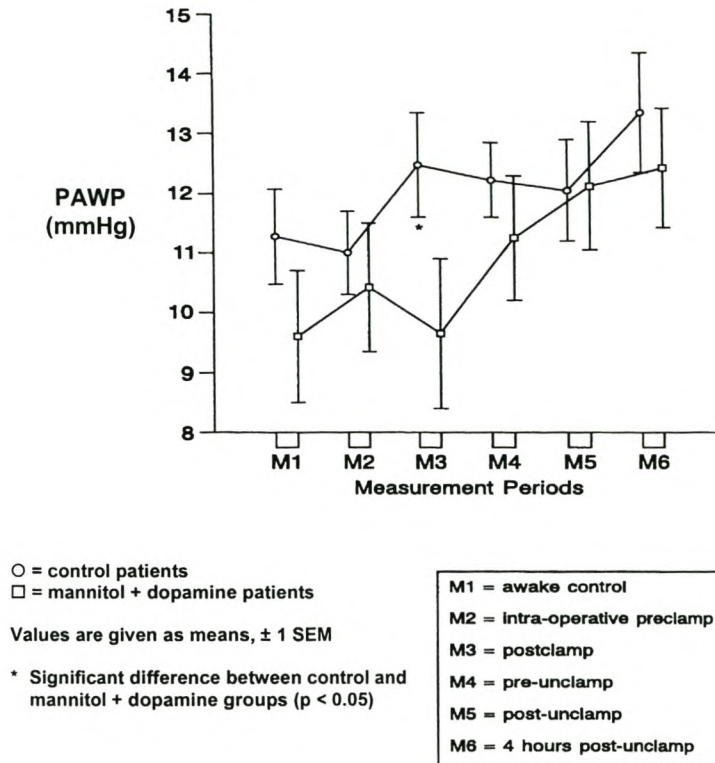Values are given as means, ± 1 SEM

No significant difference between control and mannitol + dopamine groups at the various measurement periods
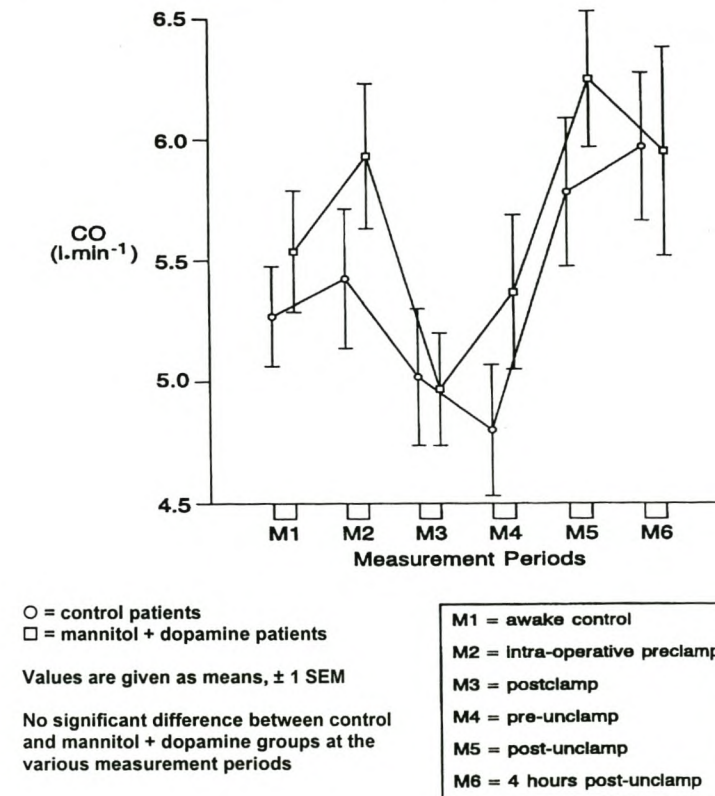
M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp

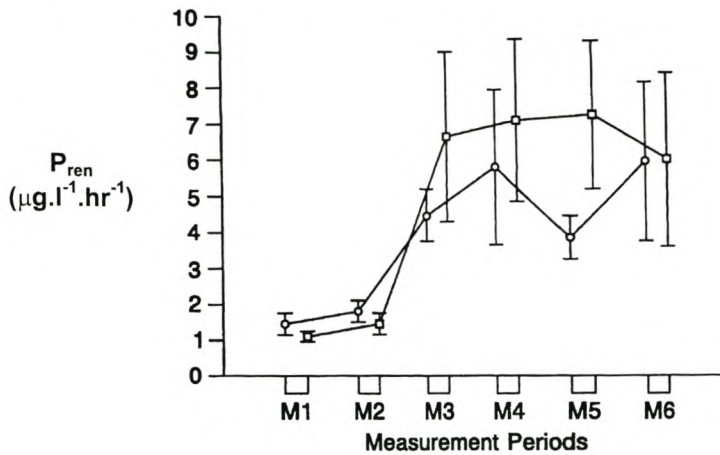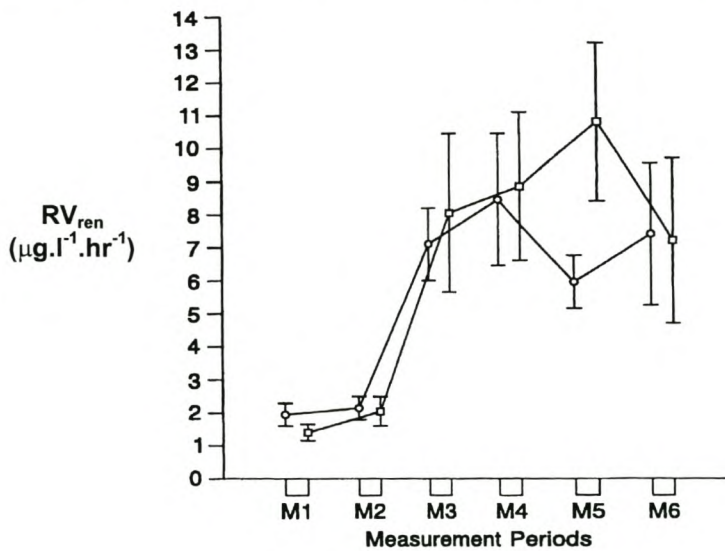**Figure 3.20**   **Perioperative changes in plasma ADH concentrations in control patients and patients who received mannitol and dopamine**

ADH (pg.ml^{-1})

Measurement Periods

○ = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant difference between control and mannitol + dopamine groups at the various measurement periods

M1 = awake control
M2 = intra-operative preclamp
M3 = postclamp
M4 = pre-unclamp
M5 = post-unclamp
M6 = 4 hours post-unclamp

Measurements of other parameters which may influence renal hemodynamics and kidney function were also similar at all measurement times (Hct: Figure 3.21, Tables 3.6 and 3.13; Temp: Figure 3.22, Tables 3.6 and 3.13; TNT: Figure 3.23, Tables 3.6 and 3.13).

The differences in arterial isotope counts per measurement period (both Cr^{51} and I^{125}) did not differ between the two patient groups at any of the measurement periods (Table 3.7 and 3.14, no figures).

Figure 3.21   **Perioperative changes in hematocrit in control patients and patients who received mannitol and dopamine**

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant difference between control and mannitol + dopamine groups at the various measurement periods

M1 = awake control

M2 = intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp

Figure 3.22   **Perioperative changes in body temperature in control patients and patients who received mannitol and dopamine**
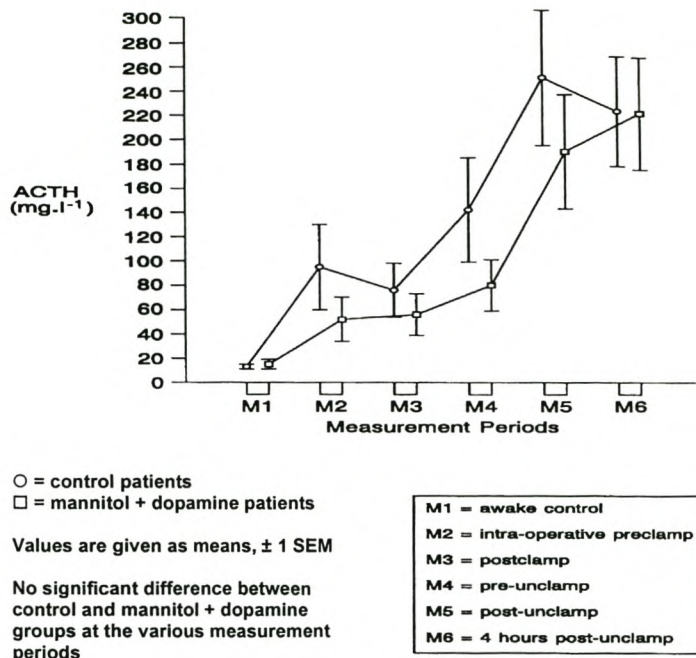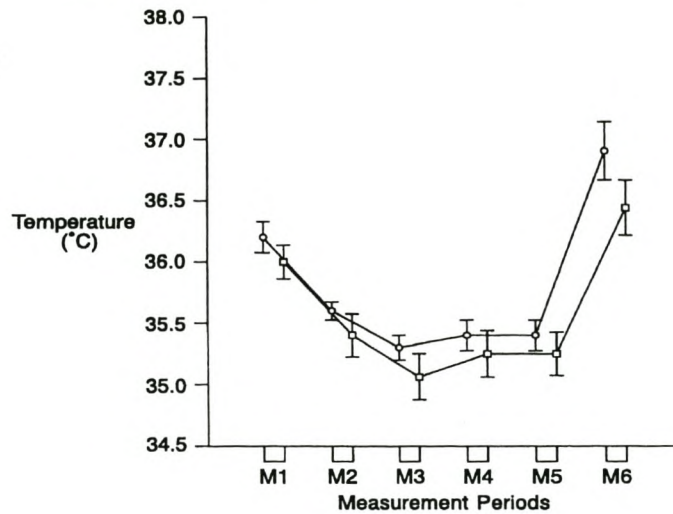

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant difference between control and mannitol + dopamine groups at the various measurement periods

M1 = awake control

M2 = intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp

Figure 3.23   **Perioperative changes in nitroglycerin (TNT) infusion rate in control patients and patients who received mannitol and dopamine**

TNT ($\mu g.kg^{-1}.min^{-1}$)

Measurement Periods

O = control patients
□ = mannitol + dopamine patients

Values are given as means, ± 1 SEM

No significant difference between
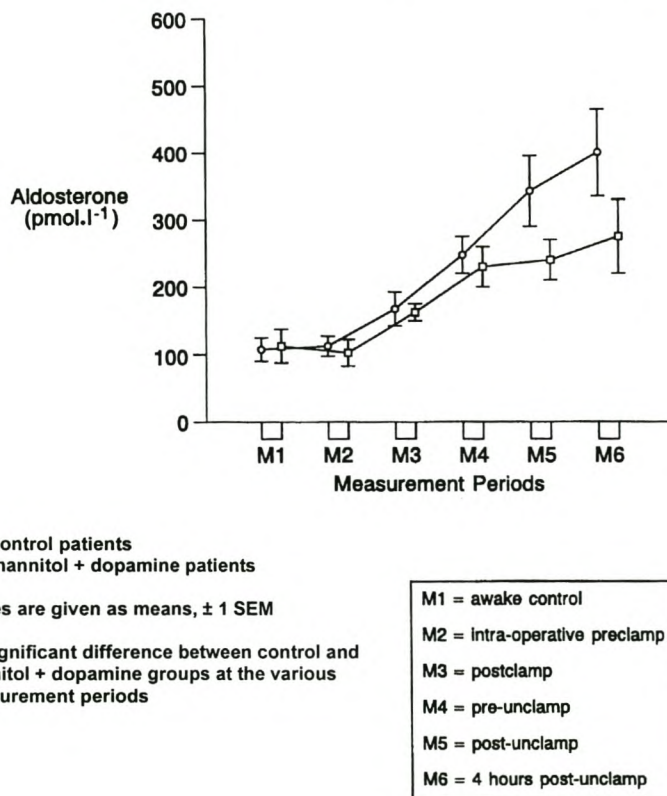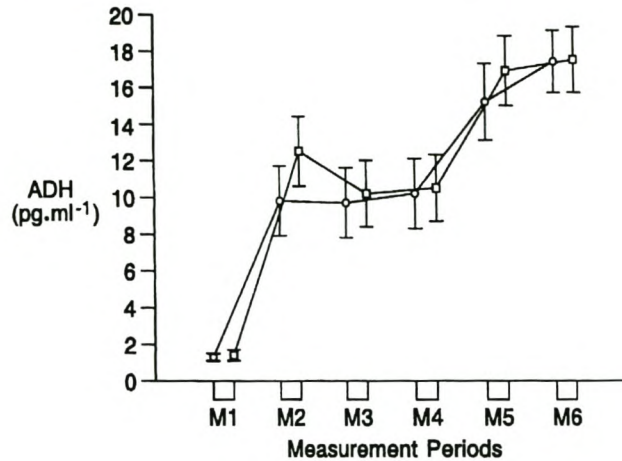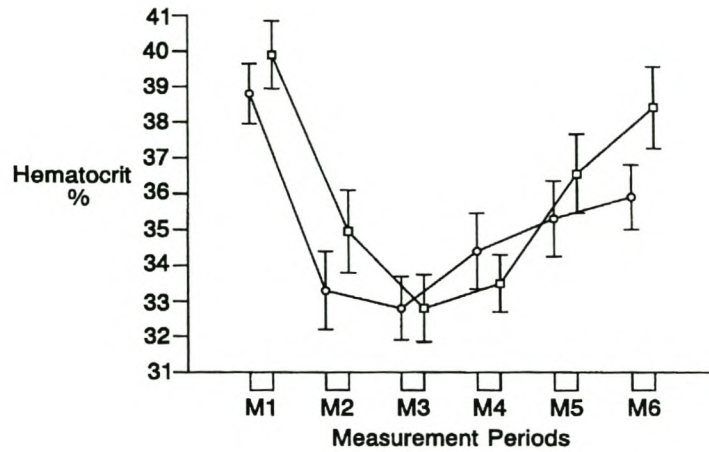control and mannitol + dopamine groups
at the various measurement periods

M2 = intra-operative preclamp

M3 = postclamp

M4 = pre-unclamp

M5 = post-unclamp

M6 = 4 hours post-unclamp
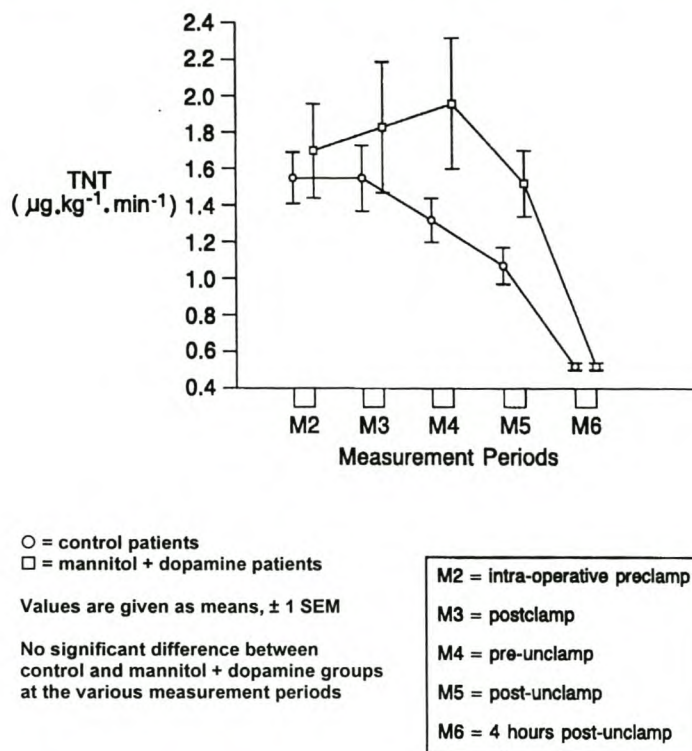
3.2   ANIMAL STUDIES

3.2.1   INTRA-GROUP CHANGES AT VARIOUS MEASUREMENT TIMES IN EXPERIMENTAL ANIMALS

3.2.1.1   Control group (no pharmacological manipulation)

Timing of measurement steps

Step 1: preclamp

Step 2: immediately post-clamp (postclamp)

Step 3: immediately before release of clamp (pre-unclamp) } perclamp

Step 4: starts 30 minutes after release of clamp (post-unclamp)

There were no differences in the hemodynamic variables of heart rate, mean arterial pressure, pulmonary artery occlusion pressure or cardiac output between the four measurement steps. The hematocrit was similar in the four experimental steps (Table 3.18).

Both RBF and GFR decreased after application of the aortic cross clamp and remained significantly reduced relative to preclamp control values immediately before unclamping, as well as 30 minutes after release of the clamp (Table 3.19). Similarly, RBF expressed as a fraction of CO, was decreased in the postclamp stages relative to

preclamp control values. Extraction of hippuran was marginally greater after release of the cross clamp than immediately prior to unclamping, but nevertheless statistically significant because of very little scatter of data.

Urine volume was significantly reduced in all three postclamp measurement periods relative to preclamp control values (Table 3.20). Free water clearance was more positive immediately after aortic clamping than both preclamp and post-unclamp measurements.

Both arterial and renal venous measurements of renin activity increased significantly after aortic cross clamping and remained raised relative to preclamp values for the rest of the experimental period (Table 3.21).

Table 3.18   **Systemic hemodynamic parameters and hematocrit in 8 control animals**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
HR	1	8	130.13	7.74	2.73		125.5	135
(beats.min^{-1})	2	8	126.25	10.9	3.85		123	134
	3	8	127.63	14.93	5.28		117.5	136.5
	4	8	129.38	13.97	4.94		122.5	138.5
MAP	1	8	82.06	6.33	2.24		77.5	86
(mmHg)	2	8	83.38	10.51	3.72		74	95.5
	3	8	86.00	11.53	4.08		76.5	93.5
	4	8	80.19	7.5	2.65		74.5	86.25
PAWP	1	8	11.81	3.34	1.18	13	9.25	14.5
(mmHg)	2	8	12.75	3.12	1.10	13.25	10.25	15
	3	8	13.19	3.05	1.08	14	11	15.5
	4	8	11.81	2.12	0.75	12	10	13.5
CO	1	8	4.05	0.70	0.25	3.87	3.53	4.65
(l.min^{-1})	2	8	3.91	0.96	0.34	3.78	3.0	4.78
	3	8	3.69	1.05	0.37	3.33	2.78	4.73
	4	8	3.73	0.90	0.32	3.6	2.95	4.6
Hct	1	8	32.50	2.78	0.98			
(%)	2	8	31.25	2.66	0.94			
	3	8	31.25	2.49	0.88			
	4	8	32.56	2.38	0.84			

No interstep differences

ANOVA; Student-Newman-Keuls (HR, MAP, Hct).
Friedman ANOVA on ranks; Student-Newman-Keuls (PAWP,CO).

HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery occlusion pressure; CO = cardiac output; Hct = hematocrit.

Table 3.19   Renal hemodynamic and glomerular function data in 8 control animals

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
RBF	1	7	551.29[b,c,d]	182.8	68.86	560	420	578.25
(ml.min^{-1})	2	7	260.14[a]	134.31	50.77	243	152	311.25
	3	7	348.57[a]	155.17	58.65	342	220.5	409.5
	4	7	276[a]	113.13	42.76	274	198.25	309.5
GFR	1	8	80.63[b,c,d]	20.16	7.13			
(ml.min^{-1})	2	8	38.63[a]	12.22	4.32			
	3	8	49.88[a]	11.97	4.23			
	4	8	53.88[a]	21.64	7.65			
FF	1	8	0.33	0.06	0.02			
	2	8	0.33	0.08	0.03			
	3	8	0.33	0.05	0.02			
	4	8	0.37	0.06	0.02			
E_{HIP}	1	7	0.72	0.05	0.02	0.73	0.68	0.76
	2	7	0.70	0.09	0.04	0.73	0.68	0.77
	3	7	0.70[d]	0.05	0.02	0.68	0.66	0.75
	4	7	0.72[c]	0.04	0.02	0.73	0.70	0.75
RBF/CO	1	7	0.138[b,c,d]	0.024	0.009			
	2	7	0.074[a]	0.041	0.015			
	3	7	0.097[a]	0.028	0.011			
	4	7	0.076[a]	0.023	0.009			

a = significantly different from step 1 (p < 0.05); b = significantly different from step 2 (p < 0.05) c = significantly different from step 3 (p< 0.05); d = significantly different from step 4 (p < 0.05).

ANOVA; Student-Newman-Keuls (GFR, FF, $^{RBF}/_{CO}$)
Friedman ANOVA on ranks; Student-Newman-Keuls (RBF,E_{Hip}).

RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; E_{HIP} = Hippuran extraction; RBF/CO = renal blood flow as a fraction of cardiac output.

Table 3.20   Urine volumes and indices of renal tubular function in control animals

Variable	Step	N	Mean	SD	SE
Uvol	1	8	138.38[b,c,d]	69.91	24.72
(ml)	2	8	85.25[a]	46.44	16.42
	3	8	79.88[a]	44.63	15.78
	4	8	63.0[a]	38.51	13.62
FE_{Na}	1	8	0.13	0.08	0.03
	2	8	0.13	0.06	0.02
	3	8	0.11	0.05	0.02
	4	8	0.06	0.03	0.02
C_{H2O}	1	8	-21.3[b]	18.77	6.64
(ml.min^{-1})	2	8	-9.99[a,d]	12.75	4.51
	3	8	-12.44	9.11	3.22
	4	8	-22.58[b]	10.5	3.71

a = significantly different from step 1 (p < 0.05); b = significantly different from step 2 (p < 0.05); c = significantly different from step 3 (p < 0.05); d = significantly different from step 4 (p < 0.05)

ANOVA; Student-Newman-Keuls

Uvol = urine volume / 20 minutes; FE_{Na} = fractional excretion of sodium; C_{H2O} = free water clearance.

Table 3.21   **Arterial and renal venous measurements of renin activity in control animals**

Variable	Step	N	Mean	SD	SE
P_{ren}	1	8	0.55[b,c,d]	0.26	0.09
$(\mu g.l^{-1}.hr^{-1})$	2	8	3.29[a]	2.17	0.77
	3	8	3.41[a]	2.0	0.71
	4	8	5.26[a]	3.11	1.1
RV_{ren}	1	8	0.79[b,c,d]	0.4	0.14
$(\mu g.l^{-1}.hr^{-1})$	2	8	4.5[a]	2.98	1.05
	3	8	5.07[a]	3.15	1.11
	4	8	7.47[a]	4.12	1.46

a = significantly different from step 1 (p < 0.05); b = significantly different from step 2 (p < 0.05); c = significantly different from step 3 (p < 0.05); d = significantly different from step 4 (p < 0.05)

ANOVA; Student-Newman-Keuls.

P_{ren} = arterial renin activity; RV_{ren} = renal venous renin activity.

Table 3.22   **Differences in arterial isotope counts between two samples per measurement time in 8 control pigs**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
% Cr^{51}	1	8	8.1	5.26	1.86	6.8	4.15	10.15
	2	8	12.24	16.34	5.78	7.2	3.05	11.6
	3	8	3.31	2.19	0.77	3.5	1.4	5.1
	4	8	6.06	4.7	1.66	5.55	2.05	9.85
% I^{123}	1	8	7.39	8.42	2.98	4.7	2.35	7.8
	2	8	10.46	16.39	5.79	5.65	1.6	9.45
	3	8	3.54	3.83	1.35	2.05	1.1	4.75
	4	8	3.21	3.6	1.27	1.4	0.3	6.8

No interstep differences

Friedman ANOVA on ranks; Student-Newman-Keuls

% Cr^{51} = % difference in arterial Cr^{51} concentrations between 1st and 2nd blood sample per measurement step;
% I^{123} = % difference in arterial I^{123} concentrations between 1st and 2nd blood sample per measurement step.

3.2.1.2   Intra-group changes in pigs which received esmolol prior to aortic cross clamping

> Timing of measurement steps
>
> Step 1: preclamp
>
> Step 2: immediately post-clamp (postclamp)
>
> Step 3: immediately before release of clamp (pre-unclamp) ⎫ perclamp
>
> Step 4: starts 30 minutes after release of clamp (post-unclamp)

Although RBF decreased significantly in the perclamp period (steps 2 and 3) in ß-blocked pigs, this decrease was quantitatively less significant than in control animals (13% and 19% reduction in postclamp and pre-unclamp values respectively in ß-blocked animals versus 52% and 36% reductions in control animals during the same

periods) (Table 3.23). After removal of the aortic cross clamp, RBF decreased further relative to control preclamp values and both perclamp measurements. RBF as a fraction of CO did not decrease upon application of the aortic cross clamp, but decreased significantly in comparison to preclamp and both perclamp measurements when the cross clamp was released (Table 3.23). GFR was maintained in the perclamp period in ß-blocked pigs, but decreased significantly relative to control and both perclamp measurement steps subsequent to release of the cross clamp Table 3.23). FF was increased relative to control and post-unclamp values immediately before removal of the cross clamp (Table 3.23). E_{HIP} remained constant throughout the experimental period (Table 3.23).

MAP was significantly greater before aortic unclamping in comparison to all other measurement periods (Table 3.24), although this difference was never more than 14%. All other hemodynamic measurements (HR, PAWP and CO) and the hematocrit remained constant throughout the experimental period (Table 3.24).

The volume of urine production was not influenced by aortic cross clamping in ß-blocked pigs, but urine production decreased significantly relative to control and perclamp values upon removal of the aortic clamp (Table 3.25). Indices of renal tubular function (FE_{Na}, C_{H2O}) remained unchanged by aortic manipulation in the ß-blocked animals (Table 3.25).

Both P_{ren} and RV_{ren} measurements were uninfluenced by clamping and unclamping of the aorta (Table 3.26).

Table 3.23   Renal hemodynamic and glomerular function data in 8 ß-blocked pigs

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
RBF	1	8	$524.0^{b,c,d}$	130.54	46.15			
(ml.min^{-1})	2	8	$453.88^{a,d}$	139.67	49.38			
	3	8	$423.0^{a,d}$	129.38	45.74			
	4	8	$327.5^{a,b,c}$	83.3	29.45			
GFR	1	8	101.63^{d}	30.38	10.74			
(ml.min^{-1})	2	8	81.88^{d}	10.6	3.75			
	3	8	88.38^{d}	27.08	9.57			
	4	8	$58.63^{a,b,c}$	9.57	3.31			
FF	1	8	0.37^{c}	0.06	0.02	0.36	0.31	0.43
	2	8	0.39	0.06	0.02	0.41	0.31	0.44
	3	8	$0.46^{a,d}$	0.06	0.02	0.47	0.39	0.51
	4	8	0.34^{c}	0.09	0.03	0.39	0.25	0.41
E_{HIP}	1	8	0.73	0.04	0.002			
	2	8	0.72	0.04	0.002			
	3	8	0.73	0.03	0.002			
	4	8	0.72	0.06	0.002			
$^{RBF}/_{CO}$	1	8	0.146^{d}	0.045	0.016			
	2	8	0.153^{d}	0.068	0.024			
	3	8	0.147^{d}	0.063	0.022			
	4	8	$0.106^{a,b.}$	0.030	0.011			

a = significantly different from step 1 (p < 0.05); b = significantly different from step 2 (p < 0.05) c = significantly different from step 3 (p< 0.05); d = significantly different from step 4 (p < 0.05).

ANOVA; Student-Newman-Keuls (RBF, GFR, E $_{HIP}$, $^{RBF}/_{CO}$)
Friedman ANOVA on ranks; Student-Newman-Keuls (FF)

RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; E_{HIP} = Hippuran extraction; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output.

Table 3.24   Systemic hemodynamic parameters and hematocrit in 8 ß-blocked pigs

Variable	Step	N	Mean	SD	SE
HR	1	8	102.19	3.05	1.08
(beats.min^{-1})	2	8	98.38	6.67	2.36
	3	8	97.63	9.09	3.21
	4	8	96.25	5.83	2.06
MAP	1	8	84.06^{c}	11.38	4.02
(mmHg)	2	8	87.63	15.81	5.59
	3	8	$93.81^{a,b,d}$	15.66	5.54
	4	8	81.38^{c}	9.66	3.42
PAWP	1	8	12.56	2.24	0.79
(mmHg)	2	8	12.63	1.9	0.67
	3	8	12.25	2.75	0.97
	4	8	11.69	2.72	0.96
CO	1	8	3.65	0.43	0.15
(l.min^{-1})	2	8	3.12	0.55	0.19
	3	8	3.02	0.64	0.23
	4	8	3.14	0.62	0.22
Hct	1	8	31.13	3.44	1.22
(%)	2	8	31.25	3.01	1.06
	3	8	31.38	3.25	1.15
	4	8	31.50	2.51	0.89

a = significantly different from step 1 (p < 0.05); b = significantly different from step 2 (p < 0.05); c = significantly different from step 3 (p < 0.05); d = significantly different from step 4 (p < 0.05).

ANOVA; Student-Newman-Keuls.

HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery occlusion pressure; CO = cardiac output; Hct = hematocrit.

Table 3.25   **Urine volumes and indices of renal tubular function in 8 ß-blocked pigs**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
Uvol	1	8	162.38[d]	88.63	31.33			
(ml)	2	8	185.38[d]	95.01	33.59			
	3	8	164.0[d]	81.99	28.99			
	4	8	96.38[a,b.]	58.98	20.85			
FE_{Na}	1	8	0.12	0.08	0.03			
	2	8	0.15	0.07	0.02			
	3	8	0.15	0.07	0.02			
	4	8	0.09	0.03	0.003			
C_{H2O}	1	8	-34.83	21.98	7.77	-26.9	-33.89	-22.74
$(ml.min^{-1})$	2	8	-20.2	17.99	6.36	-14.51	-30.77	-8.26
	3	8	-15.67	12.70	4.49	-19.53	-23.69	-8.42
	4	8	-39.89	25.06	8.86	-32.82	-57.41	-20.99

a = significantly different from step 1 ($p < 0.05$);   b = significantly different from step 2 ($p < 0.05$);   c = significantly different from step 3 ($p < 0.05$);   d = significantly different from step 4 ($p < 0.05$)

ANOVA; Student-Newman-Keuls

Uvol = urine volume / 20 minutes; FE_{Na} = fractional excretion of sodium; C_{H2O} = free water clearance

Table 3.26   **Arterial and renal venous measurements of renin activity in 8 ß-blocked pigs**

Variable	Step	N	Mean	SD	SE
P_{ren}	1	8	0.64	0.62	0.22
$(\mu g.l^{-1}.hr^{-1})$	2	8	0.48	0.2	0.07
	3	8	0.33	0.2	0.07
	4	8	0.42	0.27	0.10
RV_{ren}	1	8	0.86	0.8	0.28
$(\mu g.l^{-1}.hr^{-1})$	2	8	0.75	0.33	0.12
	3	8	0.60	0.32	0.11
	4	8	0.69	0.54	0.19

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$)

ANOVA; Student-Newman-Keuls.

P_{ren} = arterial renin activity; RV_{ren} = renal venous renin activity

Table 3.27   **Differences in arterial isotope counts between two samples per measurement time in 8 ß-blocked pigs**

Variable	Step	N	Mean	SD	SE
% Cr^{51}	1	8	5.88	3.35	1.18
	2	8	3.18	1.90	0.67
	3	8	3.52	2.25	0.80
	4	8	5.21	3.84	1.36
% I^{123}	1	8	5.51	4.95	1.75
	2	8	2.48	1.55	0.55
	3	8	3.29	2.97	1.05
	4	8	4.03	3.38	1.20

No interstep differences

Friedman ANOVA on ranks; Student-Newman-Keuls

% Cr^{51} = % difference in arterial Cr^{51} concentrations between 1st and 2nd blood sample per measurement step;
% I^{123} = % difference in arterial I^{123} concentrations between 1st and 2nd blood sample per measurement step.

3.2.1.3 **Intra-group changes in 2 groups of pigs which received enalaprilat prior to aortic cross clamping**

Timing of measurement steps
Step 1: preclamp
Step 2: immediately post-clamp (postclamp) ⎫
Step 3: immediately before release of clamp (pre-unclamp) ⎬ perclamp
Step 4: starts 30 minutes after release of clamp (post-unclamp)

The intragroup changes of the two enalaprilat groups of pigs described in sections 2.2.1 and 2.2.2 of the methods chapter, are described together in this section of the results chapter, for reasons elaborated upon in section 2.2.2. The group of 7 pigs refers to the animals described in section 2.2.1 and the group of 6 pigs refers to the animals of section 2.2.2 (see methodology section for reasons why both these groups were reduced from their original numbers of 8 each).

In the first group of 7 pigs which received enalaprilat, RBF only decreased relative to the control value when the aortic cross clamp was released (Table 3.28). This also occurred in the second group of 6 animals that received enalaprilat, but in this case the post-unclamp value was also significantly less than the two perclamp measurements (Table 3.33). In both enalaprilat groups RBF as a fraction of CO decreased subsequent to aortic unclamping relative to control and both perclamp measurements (Tables 3.28 and 3.33). In both groups of pigs where enalaprilat was administered, GFR decreased after aortic unclamping in comparison to preclamp control and the two perclamp measurements (Tables 3.28 and 3.33). FF and E_{HIP} remained unchanged throughout the experimental period in the first and second groups of enalaprilat animals (Tables 3.28 and 3.33).

MAP was increased relative to preclamp and post-unclamp measurements during the perclamp period, although this difference did not exceed 15% in either of the two groups of pigs which received enalaprilat (Tables 3.29 and 3.34). In the first group of pigs that received enalaprilat, the mean PAWP in the post-unclamp period was 2 mmHg greater than the preclamp control measurement (Table 3.29), while the PAWP was unchanged throughout in the second group of enalaprilat animals (Table 3.34). CO was significantly reduced in the perclamp measurement periods relative to preclamp and post-unclamp measurements, albeit that the maximum difference was no more than 11.6% in the first group of enalaprilat pigs (Table 3.29). The same trend did not reach statistical significance in the second group of animals which received the ACE-inhibitor (Table 3.34). HR and hematocrit were unchanged throughout the

experimental periods in both groups of pigs which received enalaprilat (Tables 3.29 and 3.34).

Urine volume decreased after removal of the aortic cross clamp relative to the perclamp measurement periods in the second group of pigs, which received enalaprilat (Table 3.35). The same trend did not reach statistical significance in the first enalaprilat group of animals (Table 3.30). In the first enalaprilat group, C_{H2O} was positive in the period immediately after application of the aortic cross clamp relative to post-unclamp calculated values (Table 3.30). Again, a similar trend did not reach statistical significance in the second group of animals, which received enalaprilat (Table 3.35). FE_{Na} remained unchanged throughout experimentation in both groups of pigs subjected to intravenous enalaprilat administration (Tables 3.30 and 3.35).

P_{ren} and RV_{ren} measurements remained high, but unchanged throughout the experimental period, in all four measurement periods in both enalaprilat groups of pigs (Tables 3.31 and 3.36).

Percentage differences in arterial Cr^{51} and I^{123} concentrations between the first and second blood samples per measurement step remained unaltered throughout the experimental period in both groups of enalaprilat animals (Tables 3.32 and 3.37).

Comparisons of all parameters at all measurement steps between the two enalaprilat groups of animals, demonstrated no statistically significant differences.

Table 3.28 **Renal hemodynamic and glomerular function data in 7 pigs which received intravenous enalaprilat**

Variable	Step	N	Mean	SD	SE
RBF	1	7	402.29^d	56.45	21.34
(ml.min^{-1})	2	7	345.57	84.93	32.1
	3	7	361.71	37.81	14.29
	4	7	311.43^a	32.64	12.34
GFR	1	7	75.43^d	12.91	4.88
(ml.min^{-1})	2	7	69.57^d	15.88	6.0
	3	7	78.29^d	10.26	3.88
	4	7	$52.29^{a,b,c}$	10.97	4.14
FF	1	7	0.37	0.03	0.002
	2	7	0.4	0.08	0.03
	3	7	0.4	0.07	0.03
	4	7	0.36	0.07	0.03
E_{HIP}	1	7	0.74	0.05	0.002
	2	7	0.71	0.03	0.002
	3	7	0.72	0.03	0.002
	4	7	0.72	0.05	0.002
$^{RBF}/_{CO}$	1	7	0.101^d	0.022	0.008
	2	7	0.096^d	0.026	0.01
	3	7	0.103^d	0.017	0.006
	4	7	$0.078^{a,b,c}$	0.01	0.004

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$)
c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls

RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; E_{HIP} = Hippuran extraction; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output.

Table 3.29 **Systemic hemodynamic parameters and hematocrit in 7 pigs which received intravenous enalaprilat**

Variable	Step	N	Mean	SD	SE
HR	1	7	117.93	8.58	3.24
(beats.min^{-1})	2	7	116.79	10.68	4.04
	3	7	123.00	17.66	6.67
	4	7	128.64	16.62	6.28
MAP	1	7	75.5^{b,c}	8.43	3.18
(mmHg)	2	7	83.57^{a,d}	4.67	1.76
	3	7	88.43^{a,d}	9.2	3.48
	4	7	76.86^{b,c}	5.67	2.14
PAWP	1	7	13.07^{d}	2.88	1.09
(mmHg)	2	7	13.79	2.53	0.96
	3	7	14.29	1.93	0.73
	4	7	15.29^{a}	2.21	0.84
CO	1	7	4.06^{b,c}	0.7	0.26
(l.min^{-1})	2	7	3.65^{a,d}	0.68	0.26
	3	7	3.59^{a,d}	0.66	0.25
	4	7	4.06^{b,c}	0.67	0.26
Hct	1	7	31.43	3.1	1.17
(%)	2	7	31.0	2.16	0.82
	3	7	31.57	2.23	0.84
	4	7	32.0	2.45	0.93

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$);
c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls.

HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery occlusion pressure; CO = cardiac output;
Hct = hematocrit.

Table 3.30 **Urine volumes and indices of renal tubular function in pigs which received intravenous enalaprilat**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
Uvol	1	7	191.14	60.6	22.9	185.0	146.75	223.5
(ml)	2	7	233.29	53.66	20.28	228.0	206.5	245.0
	3	7	197.0	53.09	20.07	212.0	145.0	238.75
	4	7	168.29	93.84	35.47	131.0	97.25	216.0
FE$_{Na}$	1	7	0.15	0.08	0.03	0.14	0.08	0.21
	2	7	0.20	0.09	0.03	0.16	0.13	0.28
	3	7	0.42	0.72	0.27	0.18	0.09	0.20
	4	7	0.13	0.10	0.04	0.08	0.06	0.17
C$_{H2O}$	1	7	-5.69	19.32	7.3			
(ml.min^{-1})	2	7	2.63^{d}	16.3	6.16			
	3	7	-24.09	19.68	7.44			
	4	7	-32.26^{b}	28.61	10.84			

b = significantly different from step 2 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$)

ANOVA; Student-Newman-Keuls (C$_{H2O}$)
Friedman ANOVA on ranks; Student-Newman-Keuls (Uvol, FE$_{Na}$)

Uvol = urine volume / 20 minutes; FE$_{Na}$ = fractional excretion of sodium; C$_{H2O}$ = free water clearance.

Table 3.31   **Arterial and renal venous measurements of plasma renin activity in pigs which received intravenous enalaprilat**

Variable	Step	N	Mean	SD	SE
P_{ren}	1	7	5.02	1.12	0.42
$(\mu g.l^{-1}.hr^{-1})$	2	7	4.16	1.7	0.64
	3	7	4.04	0.94	0.35
	4	7	4.63	1.17	0.44
RV_{ren}	1	7	6.96	1.86	0.7
$(\mu g.l^{-1}.hr^{-1})$	2	7	5.58	2.66	1.01
	3	7	5.83	1.75	0.66
	4	7	6.68	1.46	0.55

No interstep differences.

ANOVA; Student-Newman-Keuls.

P_{ren} = arterial renin activity; RV_{ren} = renal venous renin activity.

Table 3.32   **Differences in arterial isotope counts between two samples per measurement time in 7 pigs which received intravenous enalaprilat**

Variable	Step	N	Mean	SD	SE
% Cr^{51}	1	7	4.8	4.46	1.68
	2	7	7.5	7.94	3.0
	3	7	5.54	4.42	1.67
	4	7	4.96	6.26	2.37
% I^{123}	1	7	5.43	3.3	1.25
	2	7	7.64	3.38	1.28
	3	7	6.09	4.13	1.56
	4	7	4.04	3.64	1.38

No interstep differences

ANOVA; Student-Newman-Keuls

% Cr^{51} = % difference in arterial Cr^{51} concentrations between 1st and 2nd blood sample per measurement step;
% I^{123} = % difference in arterial I^{123} concentrations between 1st and 2nd blood sample per measurement step.

Table 3.33   **Renal hemodynamic and glomerular function data in 6 pigs which received enalaprilat**

Variable	Step	N	Mean	SD	SE
RBF	1	6	413.67^d	156.14	63.75
$(ml.min^{-1})$	2	6	380.83^d	129.67	52.94
	3	6	393.5^d	159.83	65.25
	4	6	$291.17^{a,b,c}$	102.73	41.94
GFR	1	6	65.5^d	16.88	6.89
$(ml.min^{-1})$	2	6	67.33^d	20.6	8.41
	3	6	68.33^d	17.52	7.15
	4	6	$44.5^{a,b,c}$	10.29	4.2
FF	1	6	0.36	0.06	0.020
	2	6	0.39	0.04	0.002
	3	6	0.38	0.04	0.002
	4	6	0.36	0.03	0.002
E_{HIP}	1	6	0.72	0.08	0.03
	2	6	0.71	0.04	0.002
	3	6	0.69	0.05	0.02
	4	6	0.70	0.06	0.02
$^{RBF}/_{CO}$	1	6	0.11^d	0.029	0.012
	2	6	0.105^d	0.02	0.008
	3	6	0.113^d	0.035	0.014
	4	6	$0.079^{a,b,c}$	0.024	0.01

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$);
c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls.

RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; E_{HIP} = Hippuran extraction; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output.

Table 3.34   Systemic hemodynamic parameters and hematocrit in 6 pigs which received enalaprilat

Variable	Step	N	Mean	SD	SE
HR	1	6	117.0	5.78	2.36
(beats.min^{-1})	2	6	115.83	9.15	3.73
	3	6	118.67	8.62	3.52
	4	6	123.92	15.64	6.39
MAP	1	6	70.67[b,c]	2.16	0.88
(mmHg)	2	6	79.83[a,d]	5.79	2.36
	3	6	84.58[a,d]	3.6	1.47
	4	6	71.83[b,c]	2.82	1.15
PAWP	1	6	11.0	2.0	0.82
(mmHg)	2	6	11.67	2.77	1.13
	3	6	10.92	3.22	1.31
	4	6	11.25	3.06	1.25
CO	1	6	3.69	0.45	0.18
(l.min^{-1})	2	6	3.54	0.57	0.23
	3	6	3.4	0.49	0.2
	4	6	3.67	0.56	0.23
Hct	1	6	27.0	2.0	0.82
(%)	2	6	27.33	2.16	0.88
	3	6	26.83	3.25	1.33
	4	6	26.5	3.08	1.26

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls.

HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery occlusion pressure; CO = cardiac output; Hct = hematocrit.

Table 3.35   Urine volumes and indices of renal tubular function in 6 pigs which received enalaprilat

Variable	Step	N	Mean	SD	SE
Uvol	1	6	163.17	68.44	27.94
(ml)	2	6	232.33[d]	89.37	36.49
	3	6	237.33[d]	49.56	20.23
	4	6	115.17[b,c]	65.18	26.61
FE$_{Na}$	1	6	0.32	0.19	0.08
	2	6	0.36	0.3	0.12
	3	6	0.22	0.08	0.03
	4	6	0.19	0.11	0.04
C$_{H2O}$	1	6	-0.98	25.8	10.53
(ml.min^{-1})	2	6	2.8	27.23	11.11
	3	6	-38.91	62.28	25.43
	4	6	-21.07	23.84	9.73

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$) d = significantly different from step 4 ($p < 0.05$)

ANOVA; Student-Newman-Keuls

Uvol = urine volume / 20 minutes; FE$_{Na}$ = fractional excretion of sodium; C$_{H2O}$ = free water clearance.

Table 3.36   **Arterial and renal venous measurements of renin activity in 6 pigs which received enalaprilat**

Variable	Step	N	Mean	SD	SE
P_{ren}	1	6	5.8	1.26	0.51
$(\mu g.l^{-1}.hr^{-1})$	2	6	5.71	1.3	0.53
	3	6	5.66	1.48	0.6
	4	6	5.17	1.36	0.55
RV_{ren}	1	6	6.76	1.22	0.5
$(\mu g.l^{-1}.hr^{-1})$	2	6	6.76	1.22	0.5
	3	6	7.45	1.59	0.65
	4	6	8.98	4.67	1.91

No interstep differences

ANOVA; Student-Newman-Keuls (P_{ren})
Friedman ANOVA on ranks; Student-Newman-Keuls (RV_{ren})

P_{ren} = arterial renin activity; RV_{ren} = renal venous renin activity.

Table 3.37   **Differences in arterial isotope counts between two samples per measurement time in 6 pigs which received enalaprilat**

Variable	Step	N	Mean	SD	SE
% Cr^{51}	1	6	4.57	2.49	1.02
	2	6	4.8	4.02	1.64
	3	6	3.63	3.08	1.26
	4	6	4.15	2.5	1.02
% I^{123}	1	6	7.27	3.78	1.54
	2	6	4.35	4.84	1.98
	3	6	4.6	3.07	1.25
	4	6	5.27	4.26	1.74

No interstep differences

ANOVA; Student-Newman-Keuls

% Cr^{51} = % difference in arterial Cr^{51} concentrations between 1st and 2nd blood sample per measurement step;
% I^{123} = % difference in arterial I^{123} concentrations between 1st and 2nd blood sample per measurement step.

3.2.1.4   Intra-group changes in 7 pigs which received intravenous verapamil

Timing of measurement steps
Step 1: preclamp
Step 2: immediately post-clamp (postclamp) ⎫
Step 3: immediately before release of clamp (pre-unclamp) ⎬ perclamp
Step 4: starts 30 minutes after release of clamp (post-unclamp)

Left ventricular filling pressures and cardiac output remained uninfluenced by aortic cross clamping and unclamping (Table 3.38). Heart rate increased significantly relative to all previous measurements subsequent to release of the aortic clamp. MAP was greater in the perclamp period than measurements prior to application of the cross

clamp. Although MAP decreased upon clamp release (7.5% reduction), it remained significantly higher than the preclamp control measurement, albeit a difference of only 6%. Hematocrit was unchanged by the experimental procedure (Table 3.38).

In contrast to changes in all other experimental groups, RBF, the RBF : CO ratio, as well as GFR were uninfluenced by aortic clamping and unclamping (Table 3.39). Filtration fraction and hippuran extraction also remained unchanged throughout the experimental period.

The volumes of urine production during the two perclamp measurement periods were significantly more than preclamp measurements (Table 3.40). Unclamping of the aorta reduced urine production relative to perclamp volumes, to values which were similar to preclamp control measurements. Free water clearance and fractional excretion of sodium were uninfluenced by aortic clamping and unclamping (Table 3.40).

Arterial and renal venous renin concentrations remained similar to control measurements throughout the aortic clamping periods (Table 3.41). However, in both instances, renin concentrations after unclamping were significantly higher than preclamp and perclamp measurements.

Similar to the other experimental groups, percentage differences in arterial Cr^{51} and I^{123} concentrations between the first and second blood samples per measurement period remained unchanged throughout the experimental period (Table 3.42).

Table 3.38 Systemic hemodynamic parameters and hematocrit in 7 pigs which received verapamil

Variable	Step	N	Mean	SD	SE
HR	1	7	104.43^d	6.12	2.31
(beats.min^{-1})	2	7	104.79^d	8.84	3.34
	3	7	109.21^d	6.36	2.4
	4	7	121.36^{a,b,c}	7.10	2.69
MAP	1	7	73.64^{b,c,d}	5.24	1.98
(mmHg)	2	7	83.86^{a,d}	5.73	2.16
	3	7	84.79^{a,d}	10.86	4.1
	4	7	78.43^{a,b,c}	6.69	2.53
PAWP	1	7	12.14	2.39	0.9
(mmHg)	2	7	12.79	3.07	1.16
	3	7	11.64	2.06	0.78
	4	7	11.14	2.38	0.9
CO	1	7	3.8	0.38	0.14
(l.min^{-1})	2	7	3.56	0.46	0.17
	3	7	3.5	0.56	0.21
	4	7	3.87	0.60	0.23
Hct	1	7	28.86	2.97	1.12
(%)	2	7	27.43	2.76	1.04
	3	7	29.71	2.93	1.11
	4	7	30.0	3.56	1.35

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls.

HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery occlusion pressure; CO = cardiac output; Hct = hematocrit.

Table 3.39   **Renal hemodynamic and glomerular function data in 7 pigs which received verapamil**

Variable	Step	N	Mean	SD	SE
RBF	1	7	417.86	89.15	33.69
$(ml.min^{-1})$	2	7	466.33	154.23	62.96
	3	7	396.83	83.32	34.02
	4	7	424.86	129.33	48.88
GFR	1	7	79.43	19.16	7.24
$(ml.min^{-1})$	2	7	82.43	21.73	8.21
	3	7	81.00	21.47	8.12
	4	7	88.57	25.11	9.49
FF	1	7	0.39	0.05	0.002
	2	7	0.38	0.03	0.002
	3	7	0.37	0.04	0.002
	4	7	0.39	0.08	0.030
E_{HIP}	1	7	0.68	0.08	0.030
	2	7	0.69	0.05	0.002
	3	7	0.70	0.05	0.002
	4	7	0.67	0.04	0.002
$^{RBF}/_{CO}$	1	7	0.110	0.023	0.009
	2	7	0.135	0.043	0.017
	3	7	0.119	0.031	0.013
	4	7	0.112	0.037	0.014

No interstep differences

ANOVA; Student-Newman-Keuls

RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; E_{HIP} = Hippuran extraction; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output.

Table 3.40   **Urine volumes and indices of renal tubular function in 7 pigs which received verapamil**

Variable	Step	N	Mean	SD	SE
Uvol	1	7	99.0[b,c]	49.03	18.53
(ml)	2	7	172.0[a,d]	91.25	34.49
	3	7	167.43[a,d]	72.53	27.41
	4	7	106.14[b,c]	62.14	23.75
FE_{Na}	1	7	0.12	0.08	0.03
	2	7	0.14	0.06	0.02
	3	7	0.13	0.04	0.002
	4	7	0.08	0.04	0.002
C_{H2O}	1	7	-27.3	11.12	4.2
$(ml.min^{-1})$	2	7	-23.68	16.64	6.29
	3	7	-22.32	15.21	5.75
	4	7	-34.21	18.98	7.17

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$);
c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$)

ANOVA; Student-Newman-Keuls

Uvol = urine volume / 20 minutes; FE_{Na} = fractional excretion of sodium; C_{H2O} = free water clearance.

Table 3.41   **Arterial and renal venous measurements of renin activity in 7 pigs which received verapamil**

Variable	Step	N	Mean	SD	SE
P_{ren}	1	7	1.63^d	1.09	0.41
$(\mu g.l^{-1}.hr^{-1})$	2	7	1.19^d	0.57	0.21
	3	7	1.16^d	0.72	0.27
	4	7	$3.07^{a,b,c}$	1.52	0.58
RV_{ren}	1	7	2.32^d	1.53	0.58
$(\mu g.l^{-1}.hr^{-1})$	2	7	1.72^d	0.91	0.34
	3	7	1.70^d	1.07	0.40
	4	7	$6.45^{a,b,c}$	6.43	2.43

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < .05$).

ANOVA; Student-Newman-Keuls.

P_{ren} = arterial renin activity; RV_{ren} = renal venous renin activity.

TABLE 3.42   **Differences in arterial isotope counts between two samples per measurement time in 7 pigs which received verapamil**

Variable	Step	N	Mean	SD	SE
$\% Cr^{51}$	1	7	8.49	5.50	2.08
	2	7	6.57	5.13	1.94
	3	7	7.89	7.26	2.75
	4	7	3.0	1.99	0.75
$\% I^{123}$	1	7	4.91	4.83	1.83
	2	7	9.8	19.18	7.25
	3	7	4.5	4.59	1.73
	4	7	3.79	3.32	1.25

No interstep differences

ANOVA; Student-Newman-Keuls

$\% Cr^{51}$ = % difference in arterial Cr^{51} concentrations between 1st and 2nd blood sample per measurement step; $\% I^{123}$ = % difference in arterial I^{123} concentrations between 1st and 2nd blood sample per measurement step.

3.2.1.5   Intra-group changes in 5 pigs which received intravenous diclofenac

> Timing of measurement steps
>
> Step 1: preclamp
>
> Step 2: immediately post-clamp (postclamp)
>
> Step 3: immediately before release of clamp (pre-unclamp)   } perclamp
>
> Step 4: starts 30 minutes after release of clamp (post-unclamp)

Although the mean heart rate of this group of pigs was significantly increased after unclamping of the aorta when compared with the preclamp and first postclamp measurements, these differences were only 7.5% in both cases (Table 3.43). Both perclamp MAP measurements were greater than preclamp measurements, as well as the post-unclamp measurements. PAWP was unchanged throughout the experimental

period. Cardiac output was decreased during both perclamp measurement periods relative to the preclamp control value with recovery to control measurement after aortic unclamping. The hematocrit remained unchanged in the four experimental periods (Table 3.43).

RBF decreased by 50% from the control measurement upon application of the infrarenal cross clamp and was only 33% of control value prior to aortic unclamping (Table 3.44). Although RBF improved after unclamping (relative to the pre-unclamp measurements), it remained significantly lower than the control measurements. RBF expressed as a fraction of CO was less than 50% of control values during both perclamp measurements and after release of the aortic clamp. GFR was reduced to 40% of control measurements upon aortic cross clamping and remained at similar decreased levels throughout the experimental period without recovery during the unclamping phase. Both filtration fraction and hippuran extraction remained unchanged at all measurement times (Table 3.44).

Urine production was significantly reduced in both perclamp as well as the post-unclamp measurement periods relative to control values (Table 3.45). Although mean values of fractional excretion of sodium and free water clearance changed substantially after aortic cross clamping, it never reached statistical significance because of large scatter of the data (Table 3.45). Two animals developed anuria after aortic cross clamping which persisted for the rest of the study period. Because this prevented the radio-isotope clearance measurements and thus the calculation of RBF, GFR and other derived parameters, these animals were excluded from the study.

Scatter of data also prevented raised mean arterial renin concentrations from reaching statistical significance after aortic cross clamping (Table 3.46). All postclamp renal venous renin levels, however, were significantly greater than the preclamp control concentration.

Percentage differences in arterial Cr^{51} and I^{123} concentrations between the first and second blood samples per measurement period remained unaltered for the duration of the experiments (Table 3.41).

Table 3.43 Systemic hemodynamic parameters and hematocrit in 5 pigs which received diclofenac intravenously

Variable	Step	N	Mean	SD	SE
HR	1	5	119.7[d]	3.87	1.73
(beats.min⁻¹)	2	5	119.7[d]	2.22	0.99
	3	5	125.0	4.17	1.86
	4	5	128.7[a,b]	7.22	3.23
MAP	1	5	82.0[b,c]	3.26	1.46
(mmHg)	2	5	92.7[a,d]	3.4	1.52
	3	5	95.2[a,d]	4.91	2.19
	4	5	80.1[b,c]	2.16	0.97
PAWP	1	5	10.6	2.07	0.93
(mmHg)	2	5	12.3	1.57	0.7
	3	5	12.4	2.1	0.94
	4	5	11.9	1.78	0.8
CO	1	5	3.59[b,c]	0.37	0.17
(l.min⁻¹)	2	5	3.13[a,d]	0.2	0.09
	3	5	2.96[a,d]	0.2	0.09
	4	5	3.6[b,c]	0.56	0.25
Hct	1	5	28.2	3.56	1.59
(%)	2	5	28.4	2.88	1.29
	3	5	29.2	2.95	1.32
	4	5	30.2	2.49	1.11

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls.

HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery occlusion pressure; CO = cardiac output; Hct = hematocrit.

Table 3.44   **Renal hemodynamic and glomerular function data in 5 pigs which received diclofenac intravenously**

Variable	Step	N	Mean	SD	SE	95 % CI
RBF	1	5	$363.0^{b,c,d}$	61.83	27.65	71.08
$(ml.min^{-1})$	2	5	152.4^{a}	39.79	17.79	45.74
	3	5	$120.0^{a,d}$	33.77	15.10	37.82
	4	5	$170.4^{a,c}$	34.05	15.23	39.14
GFR	1	5	$79.6^{b,c,d}$	7.33	3.28	8.43
$(ml.min^{-1})$	2	5	32.0^{a}	7.28	3.26	8.37
	3	5	28.6^{a}	7.09	3.17	8.15
	4	5	33.0^{a}	5.24	2.35	6.03
FF	1	5	0.41	0.07	0.03	0.09
	2	5	0.42	0.09	0.04	0.11
	3	5	0.47	0.10	0.04	0.11
	4	5	0.42	0.09	0.04	0.10
E_{HIP}	1	5	0.75	0.03	0.002	0.04
	2	5	0.72	0.06	0.03	0.07
	3	5	0.72	0.07	0.03	0.08
	4	5	0.70	0.06	0.03	0.07
$^{RBF}/_{CO}$	1	5	$0.101^{b,c,d}$	0.012	0.005	0.014
	2	5	0.048^{a}	0.011	0.005	0.013
	3	5	0.040^{a}	0.011	0.005	0.012
	4	5	0.047^{a}	0.003	0.001	0.004

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls

RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; E_{HIP} = Hippuran extraction; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output.

Table 3.45   **Urine volumes and indices of renal tubular function in 5 pigs which received diclofenac intravenously**

Variable	Step	N	Mean	SD	SE
Uvol	1	5	$260.8^{b,c,d}$	78.81	35.25
(ml)	2	5	$124.4^{a,d}$	28.01	12.52
	3	5	79.2^{a}	38.61	17.27
	4	5	$67.0^{a,b}$	28.52	12.76
FE_{Na}	1	5	0.46	0.6	0.27
	2	5	1.41	0.99	0.49
	3	5	1.52	1.12	0.5
	4	5	1.36	0.91	0.41
C_{H2O}	1	5	-16.69	23.1	10.33
$(ml.min^{-1})$	2	5	-0.37	11.15	4.99
	3	5	-3.58	11.15	4.99
	4	5	-4.32	12.75	5.7

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$)

ANOVA; Student-Newman-Keuls

Uvol = urine volume / 20 minutes; FE_{Na} = fractional excretion of sodium; C_{H2O} = free water clearance.

Table 3.46   **Arterial and renal venous measurements of renin activity in 5 pigs which received diclofenac intravenously**

Variable	Step	N	Mean	SD	SE
P_{ren}	1	5	1.79	2.67	1.2
$(\mu g.l^{-1}.hr^{-1})$	2	5	3.77	1.60	0.71
	3	5	3.91	0.39	0.17
	4	5	4.69	1.42	0.67
RV_{ren}	1	5	$1.1^{b,c,d}$	0.44	0.2
$(\mu g.l^{-1}.hr^{-1})$	2	5	5.05^{a}	1.71	0.77
	3	5	7.97^{a}	2.96	1.33
	4	5	6.59^{a}	1.55	0.69

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls.

P_{ren} = arterial renin activity; RV_{ren} = renal venous renin activity.

Table 3.47   **Differences in arterial isotope counts between two samples per measurement time in 5 pigs which received diclofenac**

Variable	Step	N	Mean	SD	SE
% Cr^{51}	1	5	7.16	5.92	2.65
	2	5	6.2	6.54	2.93
	3	5	4.82	3.55	1.59
	4	5	3.22	2.76	1.24
% I^{123}	1	5	3.34	3.25	1.45
	2	5	4.28	4.48	2.01
	3	5	2.46	2.59	1.16
	4	5	2.96	3.31	1.48

No interstep differences

ANOVA; Student-Newman-Keuls

% Cr^{51} = % difference in arterial Cr^{51} concentrations between 1st and 2nd blood sample per measurement step;
% I^{123} = % difference in arterial I^{123} concentrations between 1st and 2nd blood sample per measurement step.

3.2.1.6   Intra-group changes in 7 pigs which received both enalaprilat and diclofenac intravenously

> Timing of measurement steps
>
> Step 1: preclamp
>
> Step 2: immediately post-clamp (postclamp)
>
> Step 3: immediately before release of clamp (pre-unclamp) ⎫ perclamp
>
> Step 4: starts 30 minutes after release of clamp (post-unclamp)

Similar to other experimental groups, PAWP was maintained at constant levels throughout the experimental procedure (Table 3.48). MAP was also uninfluenced by aortic clamping and unclamping. Heart rate accelerated after aortic unclamping when compared with all three previous measurement periods. Cardiac output decreased upon aortic cross clamping (8% reduction). During the second perclamp measurement period, CO returned to levels similar to control measurements, a recovery, which

persisted after aortic unclamping. Hematocrit remained similar in all four experimental periods (Table 3.48).

RBF was decreased by aortic cross clamping, a reduction which persisted after removal of the clamp (Table 3.49). The RBF : CO ratio demonstrated similar changes. The GFR decreased significantly upon application of the aortic clamp and remained at virtually unchanged (reduced) levels throughout the rest of the experimental period. Filtration fraction and hippuran extraction remained unchanged by aortic clamping and unclamping (Table 3.49).

Urine volumes decreased significantly after aortic clamping and remained at similar reduced levels for the duration of the experiment (Table 3.50). Large scatter prevented mean changes in free water clearance in excess of 60% (becoming less negative) during clamping, from reaching statistical significance. Fractional excretion of sodium was unchanged by aortic manipulation (Table 3.50).

Both arterial and renal venous concentrations of renin were greater than accepted normal values during the control period and remained at similar concentrations during the other three measurement periods (Table 3.51).

Again, percentage differences in arterial Cr^{51} and I^{123} concentrations between the first and second blood samples per measurement step, remained unaltered for the duration of the experiments (Table 3.52).

Table 3.48   **Systemic hemodynamic parameters and hematocrit in 7 pigs which received enalaprilat and diclofenac**

Variable	Step	N	Mean	SD	SE
HR	1	7	115.29^d	12.72	4.81
(beats.min^{-1})	2	7	110.64^d	11.85	4.48
	3	7	116.0^d	11.99	4.53
	4	7	136.36^{a,b,c}	14.21	5.37
MAP	1	7	77.07	5.85	2.21
(mmHg)	2	7	85.43	5.02	1.9
	3	7	86.79	6.29	2.38
	4	7	77.0	4.28	1.62
PAWP	1	7	11.64	1.91	0.72
(mmHg)	2	7	12.79	2.34	0.89
	3	7	13.07	1.88	0.71
	4	7	12.64	2.35	0.9
CO	1	7	3.86^b	0.32	0.12
(l.min^{-1})	2	7	3.54^{a,d}	0.37	0.14
	3	7	3.71	0.48	0.18
	4	7	4.0^b	0.5	0.19
Hct	1	7	28.71	4.23	1.60
(%)	2	7	28.57	4.28	1.62
	3	7	27.43	4.83	1.82
	4	7	28.14	5.15	1.94

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls.

HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery occlusion pressure; CO = cardiac output; Hct = hematocrit.

Table 3.49 **Renal hemodynamic and glomerular function data in 7 pigs which received enalaprilat and diclofenac**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
RBF	1	7	$542.14^{b,c,d}$	154.55	58.42			
$(ml.min^{-1})$	2	7	335.57^{a}	217.24	82.11			
	3	7	316.0^{a}	164.31	62.1			
	4	7	282.0^{a}	140.1	52.95			
GFR	1	7	$97.0^{b,c,d}$	27.87	10.54	103.0	74.75	120.50
$(ml.min^{-1})$	2	7	58.0^{a}	28.76	10.87	48.0	34.75	76.50
	3	7	57.86^{a}	29.61	11.19	49.0	38.5	60.25
	4	7	58.86^{a}	48.39	18.29	49.0	25.75	63.25
FF	1	7	0.42	0.04	0.002			
	2	7	0.41	0.05	0.002			
	3	7	0.42	0.06	0.02			
	4	7	0.41	0.03	0.002			
E_{HIP}	1	7	0.66	0.10	0.04			
	2	7	0.66	0.08	0.03			
	3	7	0.66	0.09	0.03			
	4	7	0.62	0.08	0.03			
$^{RBF}/_{CO}$	1	7	$0.141^{b,c,d}$	0.046	0.017			
	2	7	0.093^{a}	0.056	0.021			
	3	7	0.083^{a}	0.034	0.013			
	4	7	0.07^{a}	0.034	0.013			

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3($p < 0.05$); d = significantly different from step 4 ($p < 0.05$).

ANOVA; Student-Newman-Keuls (RBF, FF, E_{HIP}, $^{RBF}/_{CO}$)
Friedman ANOVA on ranks; Student-Newman-Keuls (GFR)

RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; E_{HIP} = Hippuran extraction; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output.

Table 3.50 **Urine volumes and indices of renal tubular function in 7 pigs which received enalaprilat and diclofenac**

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
Uvol	1	7	$141.86^{b,c,d}$	90.82	34.33			
(ml)	2	7	67.71^{a}	35.33	13.35			
	3	7	62.0^{a}	37.56	14.2			
	4	7	49.29^{a}	29.03	10.97			
FE_{Na}	1	7	0.12	0.07	0.03			
	2	7	0.15	0.08	0.03			
	3	7	0.12	0.08	0.03			
	4	7	0.11	0.1	0.04			
C_{H2O}	1	7	-35.64	70.35	26.59	-9.07	-2.74	-32.05
$(ml.min^{-1})$	2	7	-13.87	9.61	3.63	-11.65	-5.78	-21.66
	3	7	-8.60	17.70	6.69	-7.96	0.96	-13.74
	4	7	-22.84	19.76	7.47	-16.95	-13.98	-28.69

a = significantly different from step 1 ($p < 0.05$); b = significantly different from step 2 ($p < 0.05$); c = significantly different from step 3 ($p < 0.05$); d = significantly different from step 4 ($p < 0.05$)

ANOVA; Student-Newman-Keuls (Uvol, FE_{Na})
Friedman ANOVA on ranks; Student-Newman-Keuls (C_{H2O})

Uvol = urine volume / 20 minutes; FE_{Na} = fractional excretion of sodium; C_{H2O} = free water clearance.

Table 3.51   Arterial and renal venous measurements of renin activity in 7 pigs which received enalaprilat and diclofenac

Variable	Step	N	Mean	SD	SE	Median	25 Perc	75 Perc
P_{ren}	1	7	5.10	0.92	0.35	5.04	4.57	5.55
$(\mu g.l^{-1}.hr^{-1})$	2	7	5.06	1.44	0.54	4.46	4.16	6.52
	3	7	4.53	1.91	0.72	4.86	2.74	5.82
	4	7	6.39	4.62	1.75	4.64	3.90	6.91
RV_{ren}	1	7	6.63	1.27	0.48	6.42	5.98	7.04
$(\mu g.l^{-1}.hr^{-1})$	2	7	6.80	2.02	0.76	6.50	5.54	7.92
	3	7	6.79	1.98	0.75	6.48	4.98	8.70
	4	7	10.4	7.38	2.79	7.47	6.63	10.14

No interstep differences

Friedman ANOVA on ranks; Student-Newman-Keuls.

P_{ren} = arterial renin activity; RV_{ren} = renal venous renin activity.

Table 3.52   Differences in arterial isotope counts between two samples per measurement time in 7 pigs which received enalaprilat and diclofenac

Variable	Step	N	Mean	SD	SE
% Cr^{51}	1	7	4.46	2.47	0.94
	2	7	6.84	7.29	2.76
	3	7	4.44	3.09	1.17
	4	7	5.8	5.49	2.08
% I^{123}	1	7	9.17	8.31	3.14
	2	7	5.3	2.17	0.82
	3	7	5.8	3.55	1.34
	4	7	5.17	7.51	2.84

No interstep differences

ANOVA; Student-Newman-Keuls

% Cr^{51} = % difference in arterial Cr^{51} concentrations between 1st and 2nd blood sample per measurement step;
% I^{123} = % difference in arterial I^{123} concentrations between 1st and 2nd blood sample per measurement step.

3.2.2   INTER-GROUP COMPARISONS OF *CHANGES* BETWEEN MEASURE-MENT TIMES IN VARIOUS GROUPS OF EXPERIMENTAL ANIMALS

3.2.2.1   Comparison of inter-measurement *changes* in control animals, animals pretreated with esmolol and animals pretreated with enalaprilat respectively, as well as comparison of renal electron-microscopic changes in the same groups

Timing of measurement steps

Step 1: preclamp

Step 2: immediately post-clamp (postclamp)

Step 3: immediately before release of clamp (pre-unclamp) ⎫ perclamp

Step 4: starts 30 minutes after release of clamp (post-unclamp) ⎭

There were no significant differences in changes of systemic hemodynamic parameters (MAP, PAWP and CO) with a potential influence on renal hemodynamics or function in

successive measurement periods (or between the first and last measurement periods) between any of the three groups (Table 3.53).

The decrease in RBF upon aortic cross clamping (x1-2) was greater in the control group of animals than in both the esmolol and enalaprilat groups with no difference between the latter two groups (Figure 3.24, Table 3.54). The total decrease in RBF over the duration of the experiment (from M1 to M4) was significantly greater in the control animals than the enalaprilat group, but the esmolol group did not differ from any of the other two groups. RBF as a fraction of CO demonstrated significant changes that were similar to the changes in RBF (Table 3.54).

The reduction in GFR due to aortic clamping was significantly greater in the control group than in the enalaprilat group, but the changes in these two groups did not differ significantly from the esmolol group (Figure 3.25, Table 3.54). In both the esmolol and the enalaprilat groups, the GFR decreased significantly more than the control group (which demonstrated a small, non-significant increase) upon release of the cross clamp. This reversal of the direction of change was responsible for the fact that there were no differences in the total change (from M1 to M4) in GFR between the preclamp and the post-unclamp measurements when the three groups of pigs were compared (x1-4; Figure 3.25, Table 3.54).

The changes in FF between the control and esmolol groups were significantly different between the postclamp and pre-unclamp measurements due to a decrease in the former group and a small increase in the latter group (Table 3.54). These changes were significantly reversed between the pre-unclamp and post-unclamp (x3-4) measurements.

There were no significant differences in changes of E_{HIP} values in successive measurement periods or over the duration of the experiments between any of the groups (Table 3.54).

Clamping the aorta in the control group led to a mean decrease (x1-2) in urine volume production (Tables 3.20, 3.55) that was significantly different from the non-significant step-change in the enalaprilat group (Tables 3.30, 3.55). Due to a progressive, non-significant decline in urine output in the enalaprilat group (Tables 3.30, 3.55), there were no differences in the total urine output decrease over the duration of the experiment (x1-4) between any of the groups (Table 3.55).

Between the postclamp and pre-unclamp measurements (x2-3), the C_{H20} in the

enalaprilat group decreased significantly relative to the control and esmolol groups (Table 3.55). However, the initial (preclamp and postclamp) absolute C_{H2O} values in the enalaprilat group were positive relative to the other two groups, so that the **absolute** C_{H2O} values at the pre-unclamp measurement period are similar (means of -12.44, -15.67 and -24.08 for the control, esmolol and enalaprilat groups respectively).

There were no significant differences in changes of FE_{Na} values in successive measurement periods or in first-to-last measurement period (x1-4) changes between any of the experimental groups (Table 3.55).

Plasma renin measurements increased significantly between preclamp and postclamp measurements (x1-2) in control animals relative to the other two groups (Figure 3.26, Table 3.56). Due to this cross clamp induced increase in renin measurements in control animals, the change from preclamp to post-unclamp (x1-4) values were also significantly different in control animals (increase) in comparison to the esmolol and enalaprilat groups (Table 3.56). Although plasma renin did not change significantly during the entire experimental period in either the esmolol or the enalaprilat groups, all measurement period values were low in the esmolol group (0.63, 0.47, 0.33 and 0.42 at the respective measurement periods) and much higher (5.02, 4.16, 4.04 and 4.62) in the enalaprilat group (due to the inhibited negative feedback on renin release caused by the ACE-inhibitory effect of enalaprilat).

The renal electronmicroscopic changes in proximal tubular cells are shown for each individual animal in Table 3.57. Because there were no significant differences in any of the renal hemodynamic or renal function parameters between the two ACEI groups, these two groups were combined for the comparisons of ultrastructural changes with other animal groups. The severity grading for changes in each subcellular structure (microvilli of the brush border, granular endoplasmic reticulum (gER), mitochondria and nuclear chromatin) demonstrates great variation within and also between animal groups.

Changes ascribable to immersion fixation in glutaraldehyde were present in all specimens, including the five animals used as controls for all experimental groups where renal biopsies were taken under anaesthesia though a laparotomy **without** aortic clamping or other potential insult. These changes entailed varying degrees of cellular swelling with protrusion of apical cytoplasm and associated collapse of tubular lumina (Photographs 3.1, 3.2 and 3.3). Varying degrees of cytoplasmic vacuolization were also seen in non-experimental control biopsies and in all experimental groups.

Since these changes may (at least in part) constitute fixation related artefact, it would be unreliable to consider them as indicators of cellular injury and were therefore not taken into account. Despite the above shortcomings, other significant subcellular structural changes indicating degrees of cellular injury could be clearly observed.

Comparisons of structural abnormality severity scores and numbers of changed parameters between the control (no drug), enalaprilat and esmolol animal groups are shown in Table 3.58. A spectrum of ultrastructural changes suggestive of ischemic injury was observed in control (photograph 3.4), enalaprilat (photograph 3.5) and esmolol (photograph 3.6) animals.

Table 3.59 shows the numbers of animals in each group classified as demonstrating clearly abnormal histology and those with normal histology or only minimal change. Although the enalaprilat and esmolol animals invariably demonstrated better mean and median severity scores, a lesser number of abnormal parameters, as well as a smaller percentage of biopsies classified as clearly abnormal when compared with control animals, these differences never reached statistical significance.

Table 3.53   Comparisons of absolute *changes* in relevant systemic hemodynamic parameters between measurement times in control, esmolol and enalaprilat groups of pigs

MAP	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	-1.3	7.4	-2.6	9.6	5.8	7.7	1.8	9.7
Esmolol	-3.5	5.4	-6.1	6.6	12.4	8.4	2.6	6.4
Enalaprilat	-8.0	5.0	-4.8	5.6	11.5	8.5	-1.3	10.6
PAWP								
Control	-0.93	2.16	-0.43	1.65	1.37	3.19	0	3.09
Esmolol	-0.06	1.61	0.37	1.66	0.56	1.26	0.87	1.86
Enalaprilat	-0.7	1.82	-0.5	2.04	-1.0	1.52	-2.21	1.31
CO								
Control	0.13	0.45	0.22	0.30	-0.03	0.57	0.32	0.66
Esmolol	0.53	0.32	0.10	0.23	-0.11	0.17	0.51	0.44
Enalaprilat	0.4	0.29	0.06	0.08	-0.47	0.08	-0.01	0.23

No differences in changes between groups.
ANOVA
MAP = mean arterial pressure (mmHg); PAWP = pulmonary artery wedge pressure (mmHg); CO = cardiac output ($l.min^{-1}$); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.54 Comparisons of absolute *changes* in renal hemodynamic and glomerular function parameters between measurement times in control, esmolol and enalaprilat groups of pigs

RBF	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	291.14[bc]	239.7	-88.43	193.3	72.57	158.9	275.29[c]	117.5
Esmolol	70.1[a]	111.7	30.88	68.9	95.50	99.3	196.5	72.5
Enalaprilat	56.7[a]	41.6	-16.14	68.8	50.29	40.9	90.86[a]	69.1
GFR								
Control	42.0[c]	27.9	-11.25	16.1	-4.0[bc]	24.2	26.75	26.9
Esmolol	19.75	26.0	-6.5	25.17	29.75[a]	26.16	43.0	27.15
Enalaprilat	5.86[a]	14.6	-8.71	16.93	26.0[a]	15.37	23.14	17.45
FF								
Control	0.0009	0.059	0.006[b]	0.066	-0.047[b]	0.055	-0.0404	0.075
Esmolol	-0.016	0.024	-0.0698[a]	0.041	0.119[a]	0.074	0.034	0.061
Enalaprilat	-0.028	0.057	-0.0024	0.07	0.041	0.136	0.0101	0.094
E_{HIP}								
Control	0.019	0.086	0.0005	0.077	-0.02	0.035	-0.0007	0.056
Esmolol	0.012	0.022	-0.017	0.031	0.015	0.044	0.01	0.043
Enalaprilat	0.021	0.043	-0.004	0.013	0.001	0.048	0.019	0.062
$^{RBF}/_{CO}$								
Control	0.063[b.]	0.052	-0.022	0.04	0.02	0.041	0.061[c]	0.021
Esmolol	-0.006[a]	0.051	0.005	0.018	0.04	0.049	0.039	0.025
Enalaprilat	0.005[a]	0.01	-0.006	0.021	0.025	0.012	0.023[a]	0.021

a = significantly different from control animals (p < 0.05); b = significantly different from esmolol animals (p < 0.05); c = significantly different from enalaprilat animals (p < 0.05).

ANOVA

RBF = renal blood flow (ml.min^{-1}); GFR = glomerular filtration rate (ml.min^{-1}); FF = filtration fraction; E_{HIP} = hippuran extraction fraction; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output; x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.55 Comparisons of absolute *changes* in urine volumes and indices of renal tubular function between measurement times in control, esmolol and enalaprilat groups of pigs

Uvol	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	53.12[c]	27.17	5.37	9.75	16.88	23.14	75.38	46.33
Esmolol	-23.00	83.67	21.37	36.0	67.62	79.20	66.0	46.28
Enalaprilat	-42.14[a]	51.50	36.28	44.7	28.71	62.72	22.0	64.75
FE_{Na}								
Control	0.001	0.045	0.014	0.029	0.055	0.042	0.071	0.075
Esmolol	-0.024	0.094	-0.005	0.072	0.064	0.062	0.033	0.079
Enalaprilat	-0.043	0.052	-0.219	0.656	0.29	0.637	0.027	0.059
C_{H2O}								
Control	-11.31	8.92	2.45[c]	8.4	10.14	11.27	1.28	14.79
Esmolol	-14.62	32.21	-4.53[c]	21.86	24.21	30.66	5.06	10.75
Enalaprilat	-8.33	14.63	26.72[a,b]	27.93	8.17	18.32	26.57	43.81

a = significantly different from control animals (p < 0.05); b = significantly different from esmolol animals (p < 0.05); c = significantly different from enalaprilat animals (p < 0.05).

ANOVA

Uvol = urine volume (ml in 20 min); FE_{Na} = fractional excretion of sodium; C_{H2O} = free water clearance (ml.min^{-1}); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.56 Comparisons of absolute *changes* in plasma renin levels between measurement times in control, esmolol and enalaprilat groups of pigs
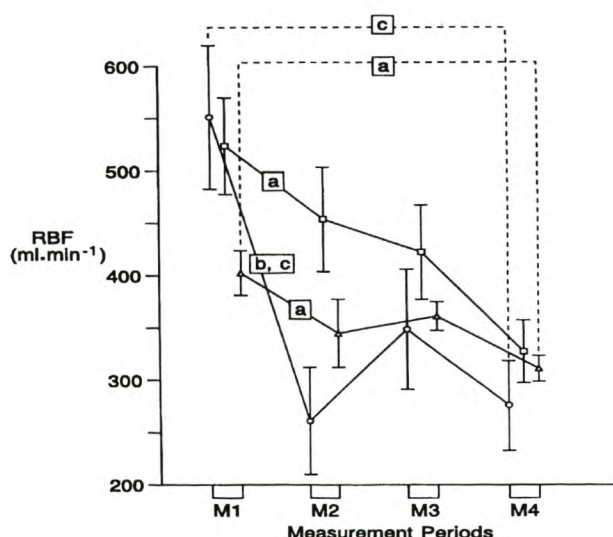
P_{ren}	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	$-2.74^{b,c}$	2.25	-0.12	1.81	-1.86	2.43	$-4.71^{b,c}$	3.05
Esmolol	0.16^{a}	0.47	0.14	0.11	-0.09	0.18	0.21^{a}	0.42
Enalaprilat	0.86^{a}	1.79	0.12	1.52	-0.59	1.26	0.39^{a}	0.85

a = significantly different from control animals ($p < 0.05$); b = significantly different from esmolol animals ($p < 0.05$); c = significantly different from enalaprilat animals ($p < 0.05$).

ANOVA

P_{ren} = plasma renin levels ($\mu g.l^{-1}.hr^{-1}$); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Figure 3.24 Comparisons of changes in renal blood flow between measurement times in control, esmolol and enalaprilat animals

O = control animals
□ = esmolol animals
△ = enalaprilat animals

Values are given as absolute means, ± 1 SEM at the individual measurement periods

a = change between measurement times significantly different from control group
b = change between measurement times significantly different from esmolol group
c = change between measurement times significantly different from enalaprilat group

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

$p < 0.05$

**Figure 3.25   Comparisons of changes in glomerular filtration rate between measure-
ment times in control, esmolol and enaparilat animals**

O = control animals
□ = esmolol animals
△ = enalaprilat animals

Values are given as absolute means, ± 1 SEM at
the individual measurement periods

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

a = change between measurement times
    significantly different from control group
b = change between measurement times
    significantly different from esmolol group
c = change between measurement times
    significantly different from enalaprilat group

p < 0.05
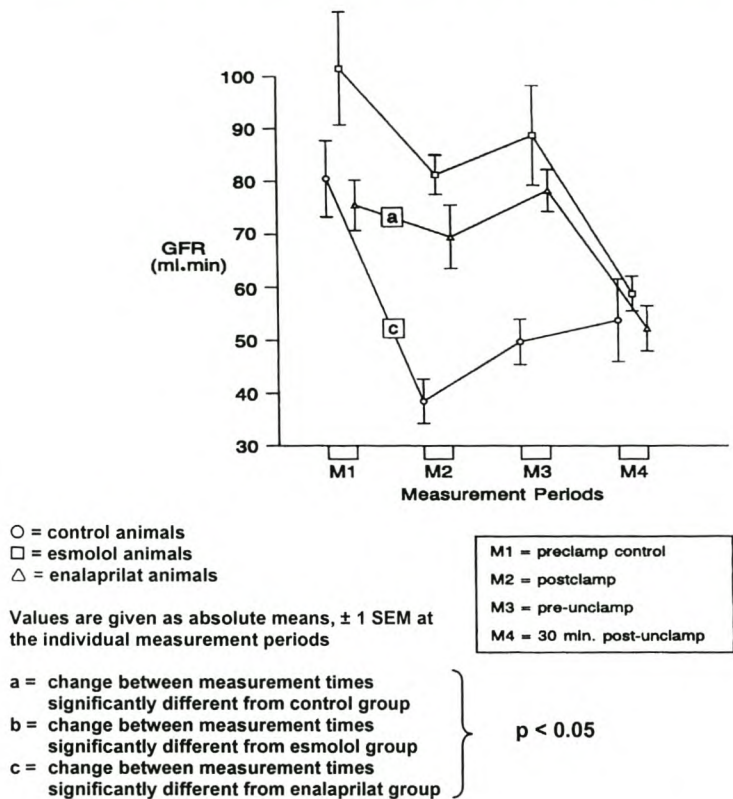
**Figure 3.26   Comparisons of changes in plasma renin concentrations between
measurement times in control, esmolol and enaparilat animals**

O = control animals
□ = esmolol animals
△ = enalaprilat animals

Values are given as absolute means, ± 1 SEM at
the individual measurement periods

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

a = change between measurement times
    significantly different from control group
b = change between measurement times
    significantly different from esmolol group
c = change between measurement times
    significantly different from enalaprilat group

p < 0.05
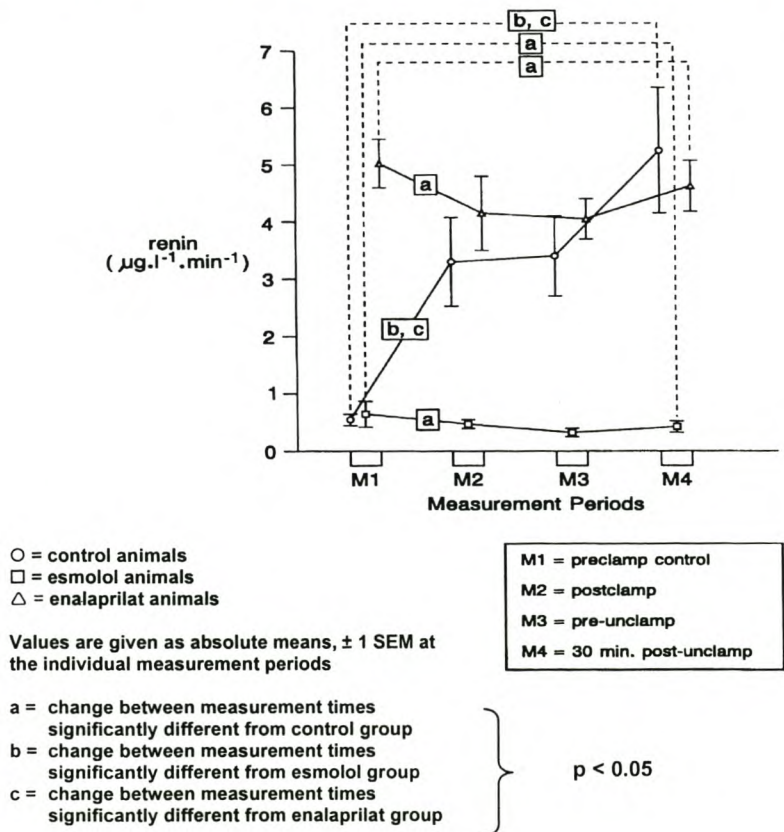
Table 3.57 **Electronmicroscopic ultrastructural change: severity grading in control animals, animals which received enalaprilat (ACEI) and animals which received esmolol (ß-blocker)**

Group & animal No.	Villi	gER	Mitochondria	Chromatin	Total Severity Score	No. abnormal parameters
Control						
1	2	1	2	0	5	3
2	2	0	0	0	2	1
3	0	0	2	0	2	1
4	1	0	0	0	1	1
5	1	1	1	0	3	3
6	2	2	0	0	4	2
7	0	1	2	0	3	2
8	1	0	1	0	2	2
ACEI						
1	0	0	0	0	0	0
2	2	0	0	0	2	1
3	0	0	2	0	2	1
4	2	1	2	0	5	3
5	0	0	0	0	0	0
6	0	0	0	0	0	0
7	3	0	0	0	3	1
8	0	0	0	0	0	0
9	2	0	0	0	2	1
10	2	1	1	0	4	3
11	3	0	0	0	3	1
12	0	2	1	0	3	2
ß-blocker						
1	1	1	1	0	3	3
2	2	1	1	0	4	3
3	0	0	0	0	0	0
4	0	2	1	0	3	2
5	0	0	0	0	0	0
6	0	0	0	0	0	0
7	1	1	0	0	2	2

Severity grading per parameter: 0 – 3
Total severity score: Sum of parameter severity gradings (maximum = 12)
No. abnormal parameters: Number of parameters with grading > 0 (maximum = 4)

Table 3.58 **Comparison of electronmicroscopic structural abnormalities between control animals, animals which received enalaprilat (ACEI) and animals which received esmolol (ß-block)**

	Severity Score				No. Abnormal parameters			
	Mean	Median	25 Perc	75 Perc	Mean	Median	25 Perc	75 Perc
Control (n = 8)	2.75	2.5	2.0	3.5	1.8	2.0	1.0	2.5
ACEI (n = 12)	2.0	2.0	0.25	3.0	1.0	1.0	0.25	1.5
ß-block (n= 7)	1.7	2.0	0.25	3.0	1.4	2.0	0.25	2.75

No significant differences between groups
Kruskal-Wallace

Table 3.59   **Comparison of numbers of animals which had clearly abnormal ultrastructure vs those with minimal change or normal ultrastructure between control, ACEI and ß-blocked animals**

	Minimal change – normal animals	Clearly abnormal animals
Control (n = 8)	3	5
ACEI (n = 12)	8	4
ß-block (n = 7)	3	4

No significant differences between any groups: Chi Square

Clearly abnormal: Severity score = 3 for at least one parameter and/or $\geq$ 2 parameters with any degree of abnormality
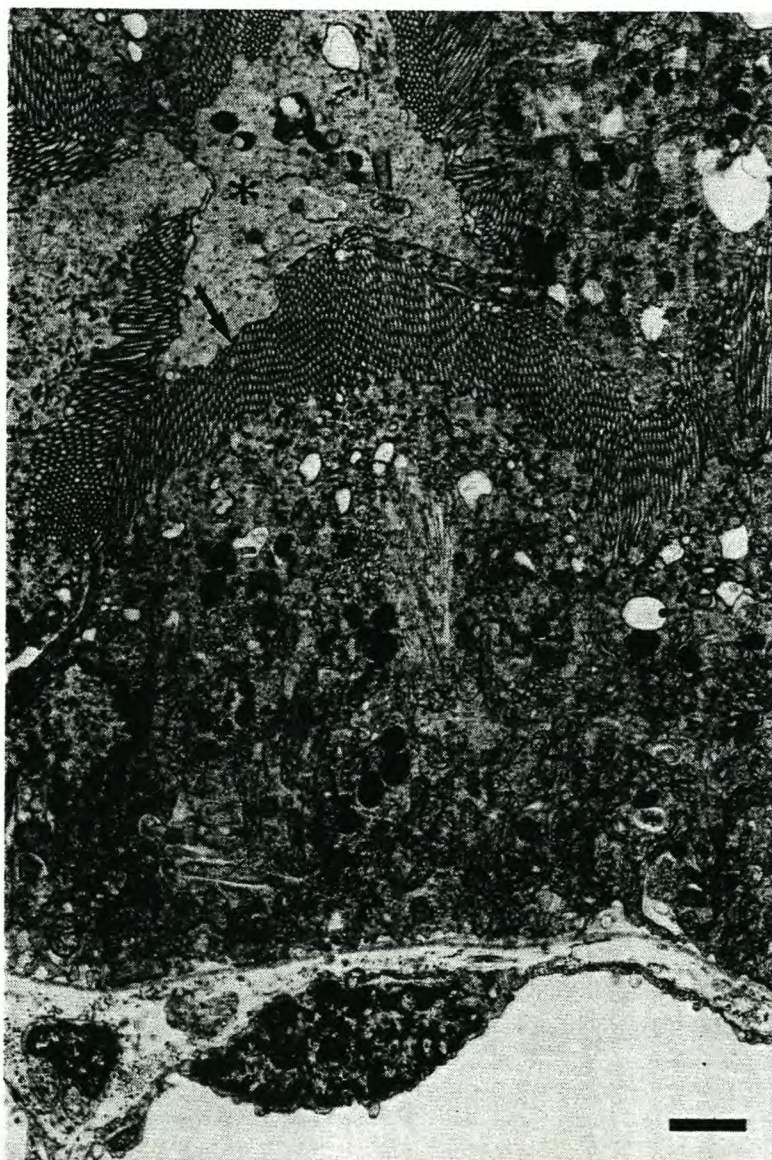
Photograph 3.1   Proximal convoluted tubule (non-experimental animal without aortic clamping) showing a normal appearance with an intact brush border (arrow). Protrusion of apical cytoplasm is present with luminal occlusion (asterisk). Scale bar, 1cm = 2µm.
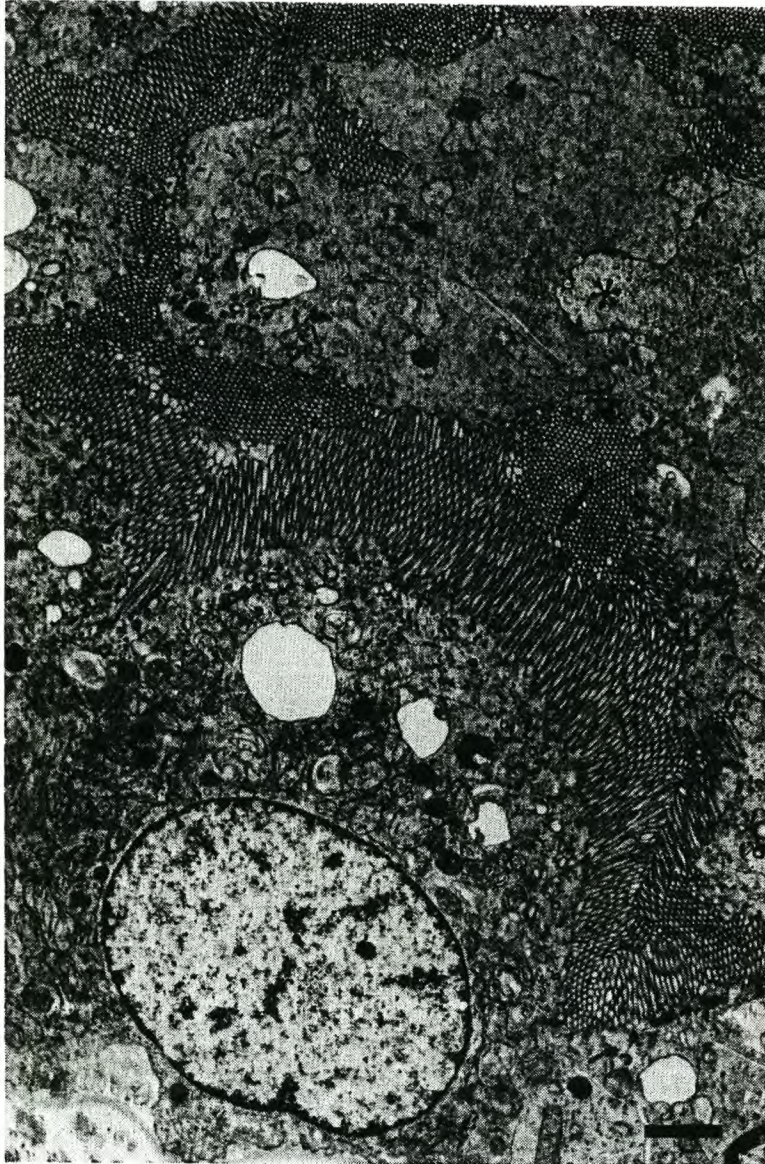
Photograph 3.2   Proximal straight tubule (non-experimental animal without aortic clamping) showing apical cytoplasmic swelling and protrusion with luminal obliteration (asterisk) and mild vacuolization. Normal brush border (arrow). Scale bar, 1cm = 1,8μm.
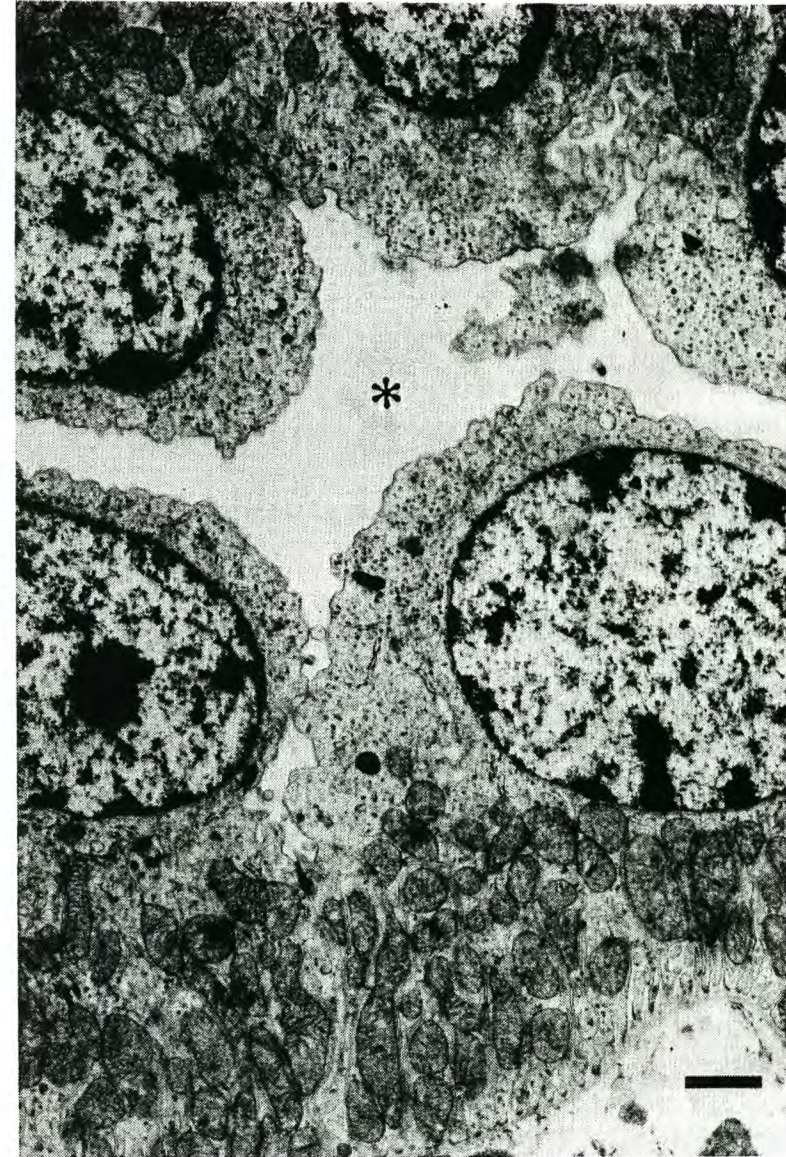
Photograph 3.3   Thick ascending limb (non-experimental animal without aortic clamping) showing mild apical protrusion with luminal narrowing (asterisk). The chromatin shows a normal distribution. No organellar swelling apparent.
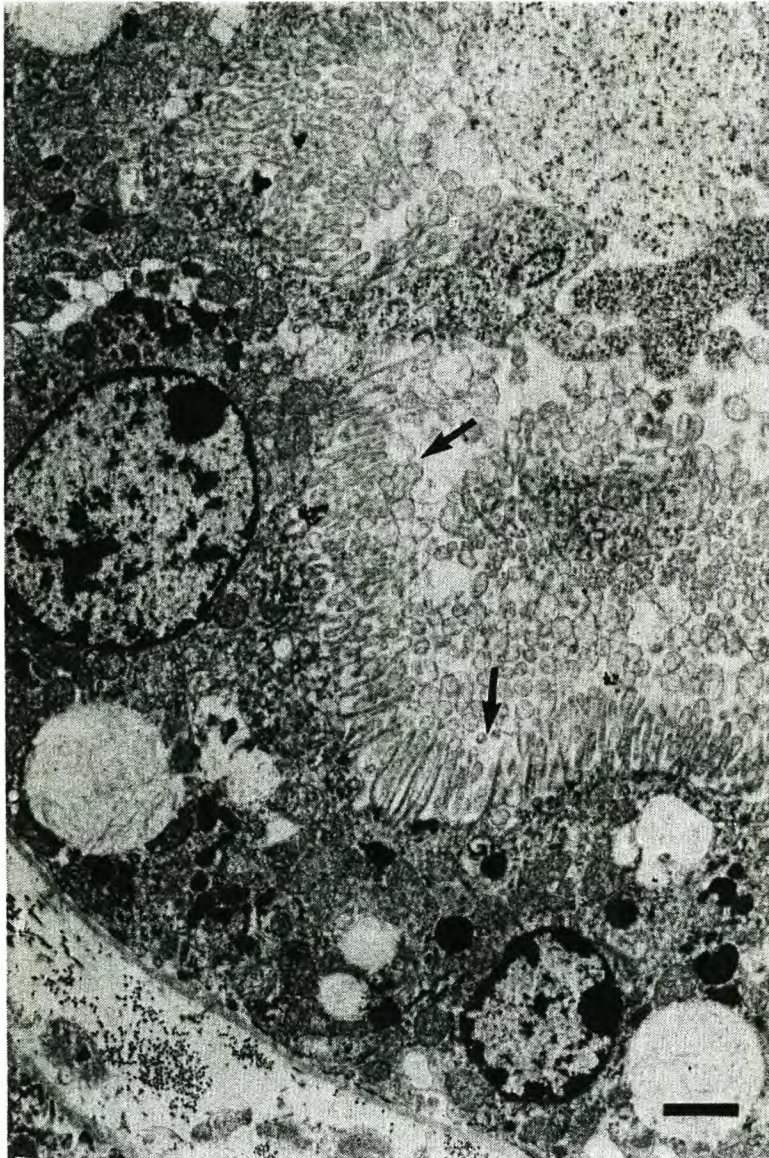
Photograph 3.4   Proximal convoluted tubule (control group, no drugs administered) showing irregularity of the brush border with clubbing and loss of microvilli (arrows). Cytoplasmic vacuolization is also apparent. Scale bar, 1cm = 1,8μm.
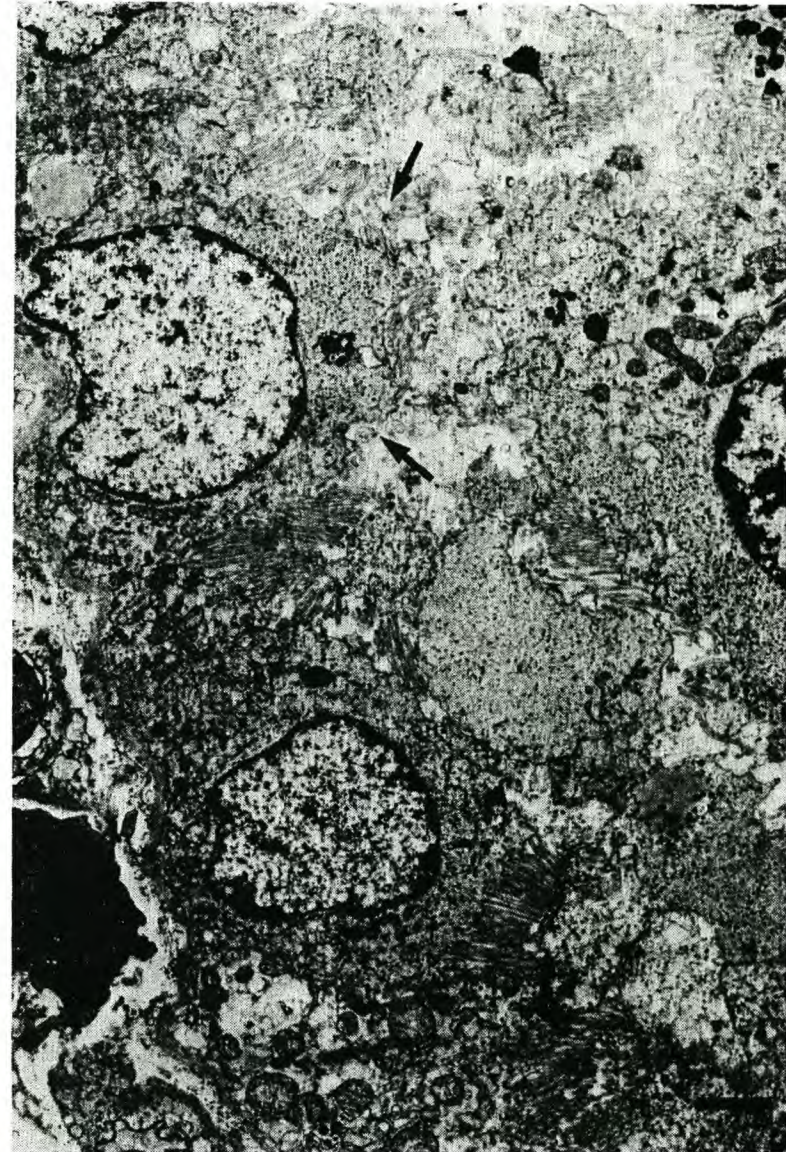
Photograph 3.5   Proximal straight tubule (ACEI group) showing brush border irregularity with loss of microvilli (arrows). Scale bar, 1cm = 1,8μm.

Photograph 3.6   Thick ascending limb (ß-blocker group) showing mitochondrial swelling (arrowheads) and dilatation of the granular endoplasmic reticulum (arrows). Scale bar, 1cm = 1,4µm.

3.2.2.2 **Comparison of inter-measurement *changes* in control animals, animals pretreated with verapamil and animals pretreated with enalaprilat, as well as comparison of renal electronmicroscopic changes in the same groups**

Timing of measurement steps

Step 1: preclamp

Step 2: immediately post-clamp (postclamp)

Step 3: immediately before release of clamp (pre-unclamp)

$\left.\begin{array}{c} \\ \\ \end{array}\right\}$ perclamp

Step 4: starts 30 minutes after release of clamp (post-unclamp)

Systemic hemodynamic parameters relevant to renal hemodynamics and function (MAP, PAWP, CO) demonstrated comparable changes between measurement periods with the exception of the x1-2 change in MAP where, surprisingly, a greater increase was recorded in the verapamil group than in the control group due to aortic cross clamping (Table 3.60). The actual mean MAP measurements after aortic clamping were, however, almost identical (verapamil group MAP = 83.85 mmHg; Control group MAP = 83.37 mmHg).

The clamp-induced (x1-2) decrease in RBF was significantly greater in the control animals than in the two drug manipulated groups, with the verapamil group even demonstrating a small increase, although this change was not significantly different from the enalaprilat animals (Figure 3.27, Table 3.61). Due to the decrease in RBF subsequent to release of the aortic clamp (x3-4) in the enalaprilat group and a further decrease in the control group in the same period (the former being significantly different from the verapamil group), the x1-4 changes (decrease) in these two groups were significantly different relative to the verapamil animals (Figure 3.27, Table 3.61). The extent of the x3-4 decrease in RBF in the enaparilat group was responsible for the significant x1-4 change (decrease) relative to verapamil animals, although the x1-4 change in enalaprilat pigs was still significantly less than the control group (Figure 3.27, Table 3.61). The RBF as a fraction of CO showed the same significant changes as RBF as independent parameter between the three groups of animals (Table 3.61).

The x1-2 change in GFR in control animals (decrease) was significantly different from the verapamil and enalaprilat groups with no difference between the latter two groups of animals (Figure 3.28, Table 3.61). A GFR decrease in the enalaprilat group between the pre-unclamp and post-unclamp periods (x3-4) induced a change which was significantly different from the verapamil group. The extent of this x3-4 decrease in the

enalaprilat group deemed the difference in the x1-4 change between the latter group and control animals insignificant despite the significant x1-2 difference between the groups. It was also responsible for a significantly different x1-4 change (decrease) relative to verapamil animals, the latter also being significantly different from the control group (Figure 3.28, Table 3.61).

There were no significant changes in either the FF or E_{HIP} in successive measurement periods or over the duration of the experimental period (x1-4) between any of the animal groups (Table 3.61).

There was a significantly different change (decrease) in urine volume produced between the preclamp and postclamp measurements (x1-2) in the control animals relative to the other two groups (Table 3.62). The x3-4 decrease in urine volume in the enalaprilat group was significantly different from control animals. This reversal of the x1-2 change between these two groups made the x1-4 change similar, while the x1-4 change between control and verapamil animals was significantly different (Table 3.62). The urine volume change (decrease) from the first to the last measurement period in control animals was thus significantly different from verapamil animals.

Neither C_{H2O} nor FE_{Na} changes demonstrated any significant differences between any of the three groups (Table 3.62).

Plasma renin measurements changed (increased) significantly between preclamp and postclamp values in control animals relative to both other experimental groups (Figure 3.29, Table 3.63). Changes (increases) in P_{ren} in both control and verapamil animals were significantly different from the enalaprilat group between the pre-unclamp and post-unclamp periods. Due to the progressive increase in P_{ren} in control animals, the change from x1-4 values in the latter group was significantly different from both the verapamil and the enalaprilat groups. Again, changes during the whole experimental period was minimal in the enalaprilat group with high absolute values at all measurement periods (5.8, 5.7, 5.66 and 5.16 respectively) due to inhibition of the negative feedback on renin release.

The renal electronmicroscopic changes in proximal tubular cells for each individual animal in the three relevant groups are shown in Table 3.64. The two ACE inhibitor animal groups are again combined for comparison with the control and verapamil groups. The severity grading for changes in each subcellular structure demonstrates substantial variation both within and between animal groups. It is conspicuous that mitochondrial swelling was the only abnormality which occurred in (some) verapamil

animals (photograph 3.7, 3.8, 3.9, 3.10), while gER and microvillous changes were also noted in animals in the control (photograph 3.4) and enalaprilat (photograph 3.5) groups.

Structural abnormality severity scores and numbers of changed parameters in the control, enalaprilat and verapamil groups are compared in Table 3.65. Although both these cumulative indices demonstrate a severity trend of control > enalaprilat > verapamil, these differences do not reach statistical significance (control vs verapamil : $p = 0.059$).

Table 3.66 shows the number of animals in each group classified as demonstrating clearly abnormal histology, versus those with normal histology or minimal change in accordance with previously defined criteria. None of the animals in the verapamil group was classified as "clearly abnormal" which was significantly different from both the other two groups.

Table 3.60 **Comparisons of absolute *changes* in relevant hemodynamic parameters between measurement times in control, verapamil and enalaprilat groups of pigs**

MAP	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	-1.3[b]	7.4	-2.6	9.6	5.8	7.7	1.8	9.7
Verapamil	-10.2[a]	2.2	-0.9	6.1	6.3	5.7	-4.7	4.3
Enalaprilat	-9.1	5.0	-4.7	4.5	12.7	3.5	-1.1	2.7
PAWP								
Control	-0.93	2.16	-0.43	1.65	1.37	3.19	0	3.09
Verapamil	-0.06	1.61	0.37	1.66	0.56	1.26	0.87	1.86
Enalaprilat	-0.66	2.01	0.75	0.82	-0.33	1.60	-0.25	2.36
CO								
Control	0.13	0.45	0.22	0.3	-0.03	0.57	0.32	0.66
Verapamil	0.23	0.42	0.06	0.34	-0.37	0.30	-0.07	0.44
Enalaprilat	0.15	0.15	0.14	0.22	-0.26	0.26	0.02	0.30

a = significantly different from control animals ($p < 0.05$); b = significantly different from verapamil animals ($p < 0.05$)

ANOVA

MAP = mean arterial pressure (mmHg); PAWP = pulmonary artery wedge pressure (mmHg) CO = cardiac output ($l.min^{-1}$); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.61 **Comparisons of absolute *changes* in renal hemodynamics and glomerular function parameters between measurement times in control, verapamil and enalaprilat groups of pigs**

RBF	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	$291.14^{b,c}$	239.7	-88.43	193.3	72.57	158.9	$275.29^{b,c}$	117.5
Verapamil	-38.17^a	93.6	69.5	83.9	-64.83^c	77.3	$-7.0^{a,c}$	106.4
Enalaprilat	32.83^a	50.4	-12.67	84.9	102.33^b	96.6	$122.5^{a,b}$	94.6
GFR								
Control	$42.0^{b,c}$	27.9	-11.25	16.10	-4.0	24.20	26.75^b	26.90
Verapamil	-3.0^a	18.57	1.43	12.22	-7.57^c	21.59	$-9.14^{a,c}$	31.73
Enalaprilat	-1.83^a	6.15	-1.0	10.79	23.83^b	17.72	21.0^b	16.80
FF								
Control	0.0009	0.059	0.006	0.066	-0.0473	0.055	-0.0404	0.075
Verapamil	0.0008	0.034	0.0071	0.033	0.0086	0.045	0.0032	0.061
Enalaprilat	-0.0241	0.028	0.0035	0.043	0.0246	0.052	0.004	0.044
E_{HIP}								
Control	0.019	0.086	0.0005	0.077	-0.02	0.035	-0.0007	0.056
Verapamil	0.021	0.046	-0.0135	0.013	0.0358	0.035	0.0105	0.092
Enalaprilat	0.002	0.073	-0.0116	0.042	-0.0031	0.015	-0.0124	0.046
$^{RBF}/_{CO}$								
Control	$0.063^{b,c}$	0.052	-0.022	0.04	0.02	0.041	$0.061^{b,c}$	0.021
Verapamil	-0.021^a	0.027	0.016	0.022	-0.004^c	0.021	$-0.008^{a,c}$	0.027
Enalaprilat	0.005^a	0.015	-0.008	0.026	0.034^b	0.025	$0.031^{a,b}$	0.025

a = significantly different from control animals ($p < 0.05$); b = significantly different from verapamil animals ($p < 0.05$); c = significantly different from enalaprilat animals ($p < 0.05$).

ANOVA

RBF = renal blood flow (ml.min^{-1}); GFR = glomerular filtration rate (ml.min^{-1}); FF = filtration fraction; E_{HIP} = hippuran extraction fraction; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output; x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.62 **Comparisons of absolute *changes* in urine volumes and indices of renal tubular function between measurement times in control, verapamil and enalaprilat groups of pigs**

Uvol	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	$53.12^{b,c}$	27.17	5.37	9.75	16.88^c	23.14	75.38^b	46.33
Verapamil	-73.0^a	66.06	4.57	90.49	61.29	73.16	-7.14^a	41.58
Enalaprilat	-69.17^a	42.48	-5.0	64.98	122.17^a	69.04	48.0	75.03
FE_{Na}								
Control	0.001	0.045	0.014	0.029	0.055	0.042	0.071	0.076
Verapamil	-0.027	0.066	0.013	0.059	0.047	0.05	0.033	0.084
Enalaprilat	-0.043	0.139	0.136	0.338	0.032	0.053	0.125	0.246
C_{H2O}								
Control	-11.31	8.92	2.45	8.4	10.14	11.27	1.28	14.79
Verapamil	-3.62	12.18	-1.36	25.97	11.89	15.98	6.91	20.27
Enalaprilat	-3.78	12.76	41.71	39.11	-17.84	42.94	20.09	28.01

a = significantly different from control animals ($p < 0.05$); b = significantly different from verapamil animals ($p < 0.05$); c = significantly different from enalaprilat animals ($p < 0.05$).

ANOVA

Uvol = urine volume (ml in 20 min); FE_{Na} = fractional excretion of sodium; C_{H2O} = free water clearance (ml.min^{-1}); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.63   **Comparisons of absolute *changes* in plasma renin levels between measurement times in control, verapamil and enalaprilat groups of pigs.**
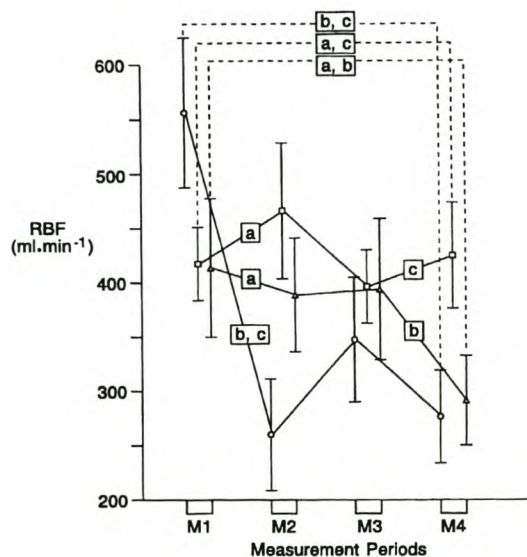
P_{ren}	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	-2.74[b,c]	2.25	-0.12	1.81	-1.86[c]	2.43	-4.71[b,c]	3.05
Verapamil	0.44[a]	0.66	0.03	0.42	-1.91[c]	1.33	-1.43[a]	1.04
Enalaprilat	0.09[a]	1.48	0.05	1.94	-0.49[a,b]	1.17	0.63[a]	1.61

a = significantly different from control animals ($p < 0.05$); b = significantly different from verapamil animals ($p < 0.05$); c = significantly different from enalaprilat animals ($p < 0.05$).

ANOVA

P_{ren} = plasma renin levels ($\mu g.l^{-1}.hr^{-1}$); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Figure 3.27   **Comparisons of changes in renal blood flow between measurement times in control, verapamil and enalaprilat animals**

O = control animals
□ = verapamil animals
△ = enalaprilat animals

Values are given as absolute means, ± 1 SEM at the individual measurement periods

a = change between measurement times significantly different from control group
b = change between measurement times significantly different from verapamil group
c = change between measurement times significantly different from enalaprilat group

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

$p < 0.05$

Figure 3.28   Comparisons of changes in glomerular filtration rate between measurement times in control, verapamil and enalaprilat animals

O = control animals
□ = verapamil animals
△ = enalaprilat animals

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

Values are given as absolute means, ± 1 SEM at the individual measurement periods

a = change between measurement times significantly different from control group
b = change between measurement times significantly different from verapamil group
c = change between measurement times significantly different from enalaprilat group

$p < 0.05$
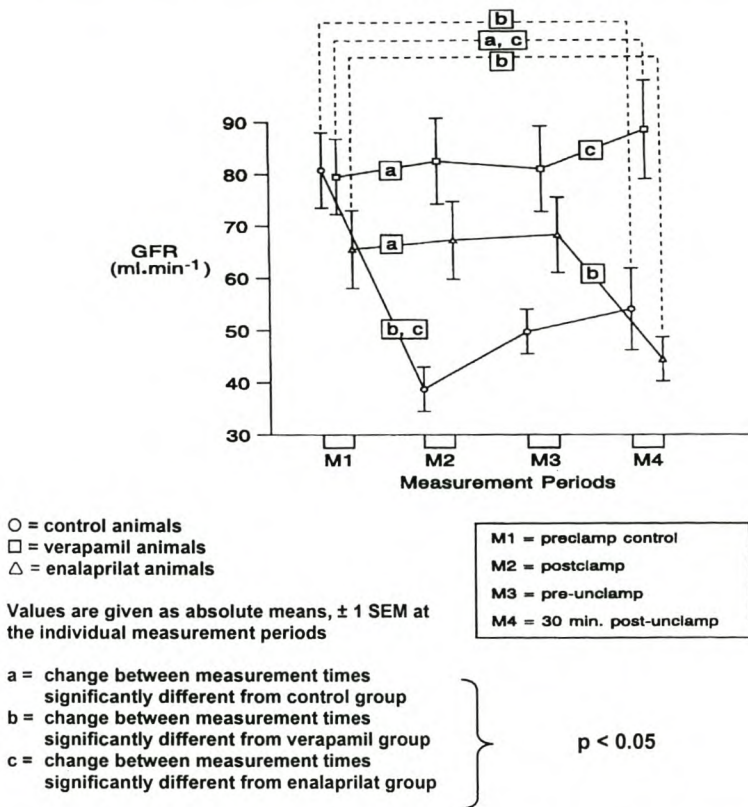
Figure 3.29   Comparisons of changes in plasma renin concentrations between measurement times in control, verapamil and enalaprilat animals

O = control animals
□ = verapamil animals
△ = enalaprilat animals

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

Values are given as absolute means, ± 1 SEM at the individual measurement periods

a = change between measurement times significantly different from control group
b = change between measurement times significantly different from verapamil group
c = change between measurement times significantly different from enalaprilat group

$p < 0.05$
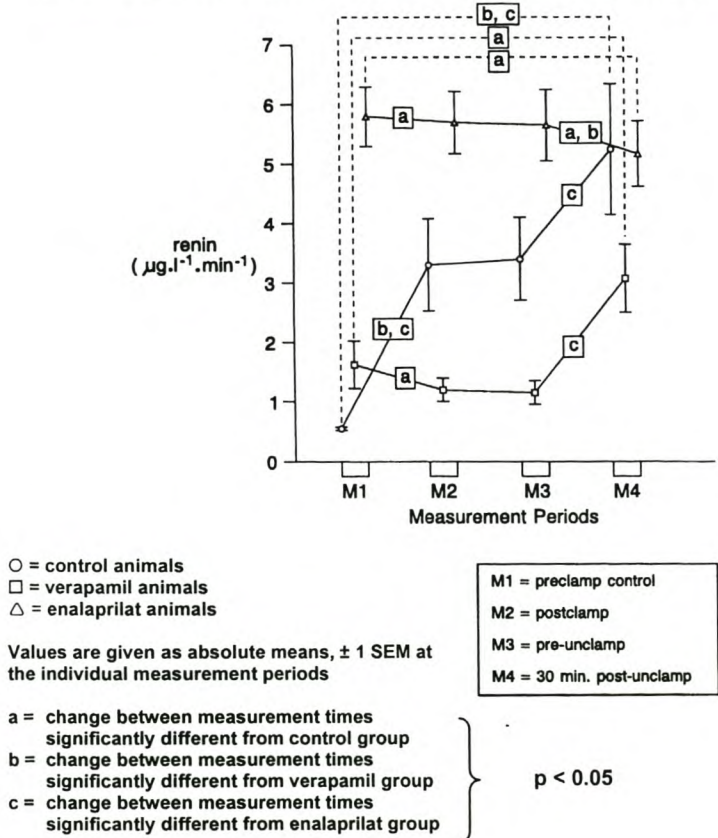
Table 3.64   Electronmicroscopic ultrastructural change: severity grading in control animals, animals which received enalaprilat (ACEI) and animals which received verapamil (Ca^{2+}-blocker)

Group & animal No.	Villi	gER	Mitochondria	Chromatin	Total Severity Score	No. abnormal parameters
Control						
1	2	1	2	0	5	3
2	2	0	0	0	2	1
3	0	0	2	0	2	1
4	1	0	0	0	1	1
5	1	1	1	0	3	3
6	2	2	0	0	4	2
7	0	1	2	0	3	2
8	1	0	1	0	2	2
ACEI						
1	0	0	0	0	0	0
2	2	0	0	0	2	1
3	0	0	2	0	2	1
4	2	1	2	0	5	3
5	0	0	0	0	0	0
6	0	0	0	0	0	0
7	3	0	0	0	3	1
8	0	0	0	0	0	0
9	2	0	0	0	2	1
10	2	1	1	0	4	3
11	3	0	0	0	3	1
12	0	2	1	0	3	2
Ca^{2+}-blocker						
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	2	0	2	1
4	0	0	2	0	2	1
5	0	0	1	0	1	1
6	0	0	1	0	1	1
7	0	0	1	0	1	1

Severity grading per parameter: 0 – 3
Total severity score: Sum of parameter severity gradings (maximum = 12)
No. abnormal parameters: Number of parameters with grading > 0 (maximum = 4)

Table 3.65   Comparison of electronmicroscopic structural abnormalities between control animals, animals which received enalaprilat (ACEI) and animals which received verapamil (Ca^{2+}-block)

	Severity Score				No. Abnormal parameters			
	Mean	Median	25 Perc	75 Perc	Mean	Median	25 Perc	75 Perc
Control (n = 8)	2.75	2.5	2.0	3.5	1.8	2.0	1.0	2.5
ACEI (n = 12)	2.0	2.0	0.25	3.0	1.0	1.0	0.25	1.5
Ca^{2+}-block (n= 7)	1.0	1.0	0.25	1.75	0.7	1.0	0.25	1.0

No significant differences between groups
(Severity Score: Control vs Ca^{2+}-block: p = 0.06)
Kruskal-Wallace

Table 3.66   **Comparison of numbers of animals which had clearly abnormal ultrastructure vs those with minimal change or normal ultrastructure between control, ACEI and Ca^{2+}-block animals**

	Minimal change – normal animals	Clearly abnormal animals
Control (n = 8)	3	5
ACEI (n = 12)	8	4
Ca^{2+}-block (n = 7)	7	0

Control vs ACEI: NS
Control vs Ca^{2+}-block: $p < 0.05$ }   Chi Square
ACEI vs Ca^{2+}-block: $p < 0.05$

Clearly abnormal: Severity score = 3 for at least one parameter and/or ≥ 2 parameters with any degree of abnormality

Photograph 3.7   Proximal convoluted tubule (Ca^{2+}-blocker group) showing an appearance similar to that of normal, non-experimental animals. Scale bar, 1cm = 1,1µm.
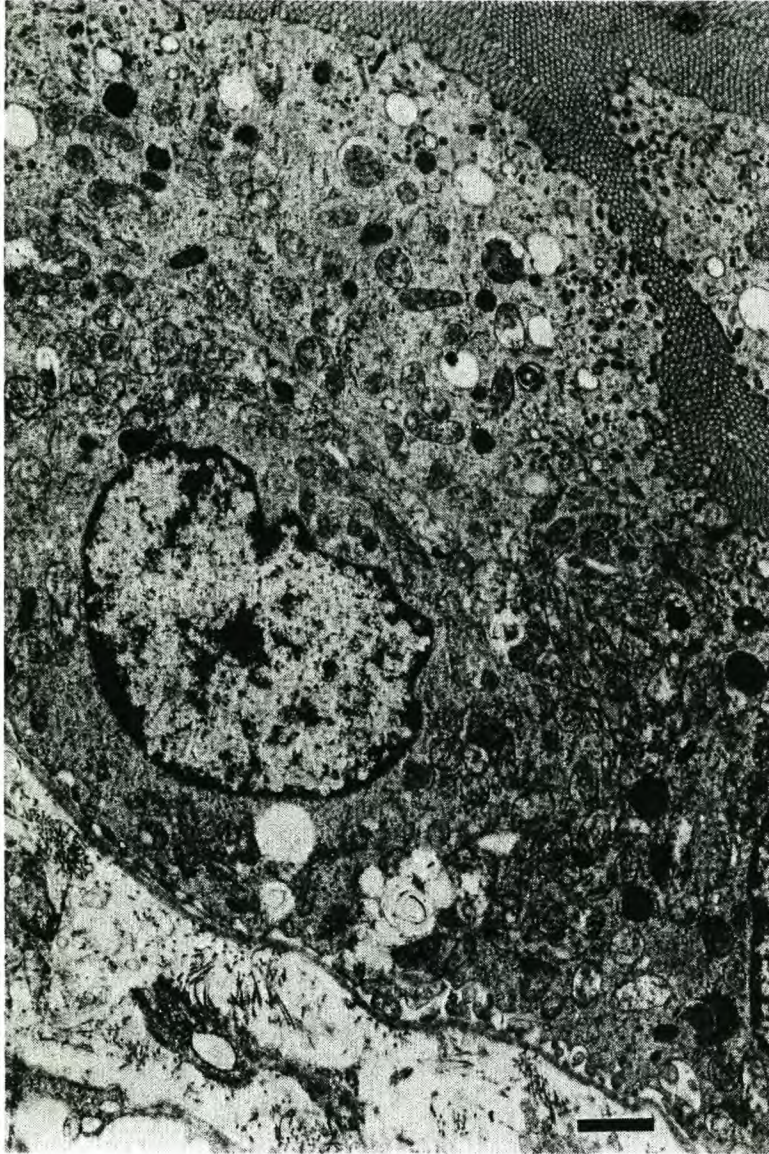
Photograph 3.8   Proximal straight tubule (Ca^{2+}-blocker group) showing an appearance similar to that of normal, non-experimental animals. Scale bar, 1cm = 1,3µm.
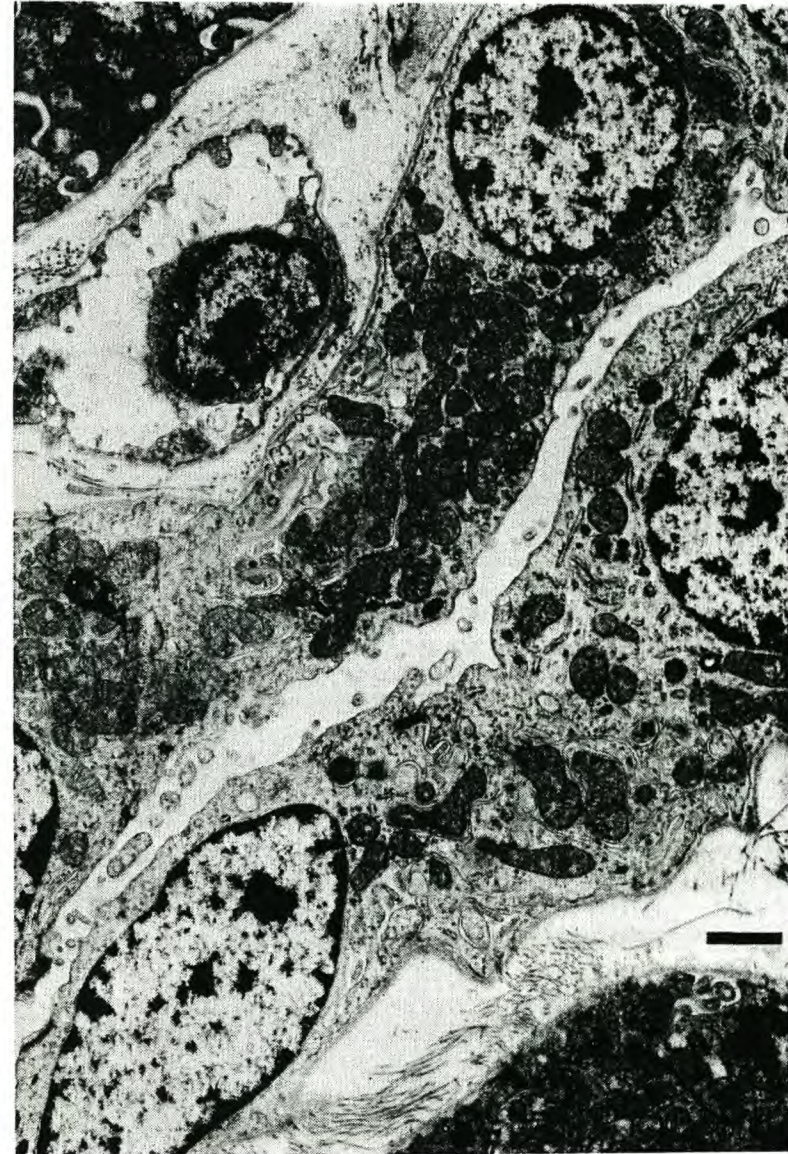
Photograph 3.9   Thick ascending limb (Ca-blocker group) showing an appearance similar to that of normal, non-experimental animals. Scale bar, 1cm = 1,3µm.
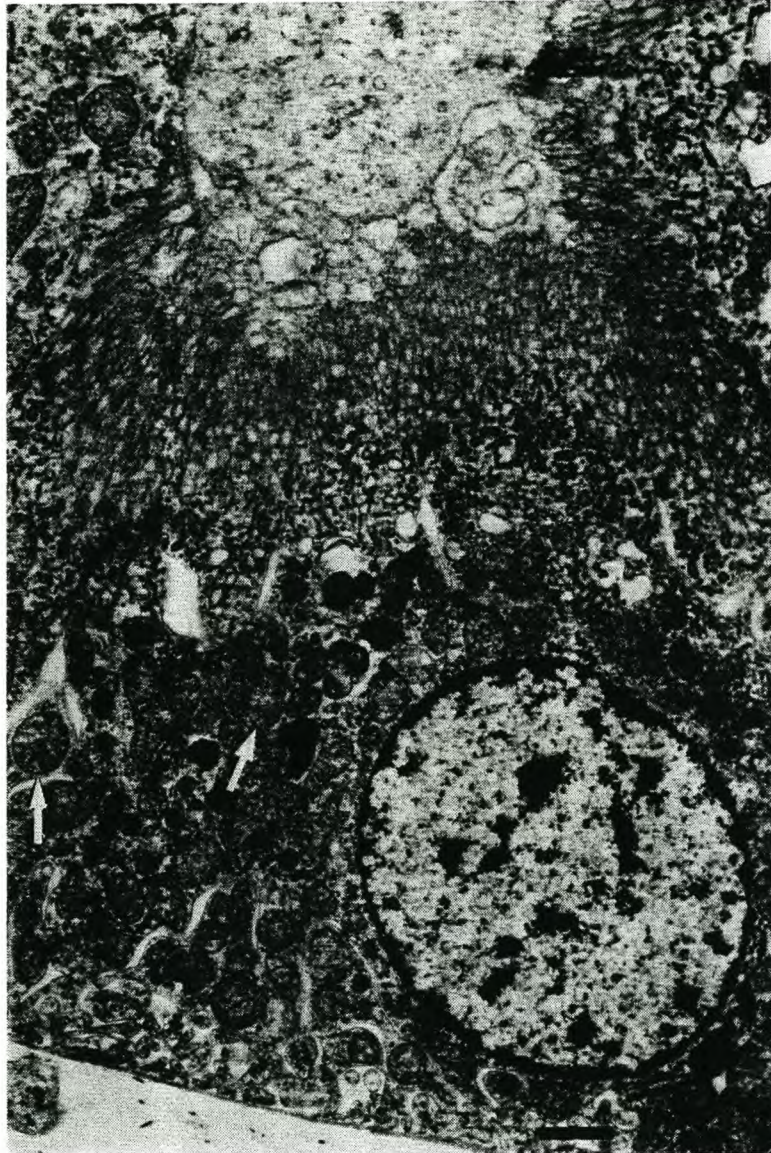
Photograph 3.10   Proximal convoluted tubule (Ca-blocker group) showing an intact brush border with slight mitochondrial swelling (arrows). Scale bar, 1cm = 1,3μm.

3.2.2.3 **Comparison of inter-measurement *changes* in control animals and animals pretreated with diclofenac, as well as comparison of renal electronmicroscopic changes in the same groups**

Timing of measurement steps

Step 1: preclamp

Step 2: immediately post-clamp (postclamp)

Step 3: immediately before release of clamp (pre-unclamp) } perclamp

Step 4: starts 30 minutes after release of clamp (post-unclamp)

There were no significant differences in changes of hemodynamic parameters (HR, MAP, PAWP and CO) in successive measurement periods (or between the first and fourth measurement periods) between the two groups of pigs. The most relevant of these parameters in the context of renal hemodynamics and glomerular function are given in Table 3.67.

Although the **changes** in RBF between measurement times were not different between the two groups of animals (Table 3.68, Figure 3.30), the absolute RBF measurements in diclofenac animals were invariably in excess of 40% lower than control animals at the same measurement periods (Figure 3.30). RBF as a fraction of CO demonstrated similar trends (Table 3.68).

Due to some degree of recovery of GFR just before release of the aortic clamp in control animals, there was a significant difference in the change between the two groups of animals in this period (x2-3), as the GFR in the diclofenac pigs continued to decrease (Table 3.68, Figure 3.31). Similar to RBF, the absolute GFR values immediately before and again 30 minutes after release of the aortic clamp, were > 40% lower in the diclofenac than control animals (Figure 3.31).

There were no differences in changes of either E_{HIP} or FF in sequential measurement periods or from preclamp to post-unclamp (x1-4) between the two groups of pigs (Table 3.31).

Differences in changes in the volume of urine production were in sharp contrast to the relative lack of significant differences in changes in RBF and GFR between the two groups. There were much more significant reductions in urine production in diclofenac pigs (relative to controls) in both the pre- to postclamp periods (x1-2) and the postclamp to pre-unclamp periods (x2-3) (Table 3.69). These changes were responsible for the fact that the x1-4 change was also significantly different between the two groups of animals (Table 3.69).

The diclofenac animals were the only group in which FE_{Na} consistently exceeded a value of 1.0 subsequent to aortic cross clamping (Table 3.45). The changes (increase) from postclamp to pre-unclamp (x2-3) and over the duration of the experiment (x1-4) were significantly different between the two groups of animals (Table 3.69). Although the absolute C_{H2O} value at the end of the experimental period were more positive in the diclofenac pigs than any of the other experimental groups (Table 3.45), there were no statistically significant differences in changes between measurement periods between control and diclofenac animals (Table 3.69).

Changes in plasma renin concentrations between measurement periods were similar in control and diclofenac animals (Table 3.70, Figure 3.32).

Because the difference in RBF between the two animal groups at the control (preclamp) measurement was statistically significant (unlike comparisons of RBF control measurements between **any** of the other animal groups reported in this thesis), comparisons of values **at the specific measurement periods** are also shown for RBF, GFR, FF and renin concentrations (Figures 3.30, 3.31, 3.31a and 3.32 respectively).

The renal ultrastructural changes for individual animals in the control and diclofenac animals are listed in Table 3.71. While the control animals demonstrate a range of abnormalities (Table 3.71, photograph 3.4), substantial structural abnormalities involving at least 3 of the 4 cellular structures were evident in all animals in the diclo-fenac animals (Table 3.71; photographs 3.11, 3.12, 3.13). While nuclear chromatin abnormalities manifested in 4 of the 5 NSAID animals (photograph 3.13), such changes were absent in control animals (and all other experimental groups).

Comparison of both structural abnormality severity score and mean number of abnormal parameters, demonstrate significant differences between the groups, with the diclofenac animals more severely affected (Table 3.72). Comparison of numbers of animals classified as either clearly abnormal or normal to minimal abnormality, shows no difference between the groups (p = 0.057). It is likely that, had the 2 animals which were excluded because of anuria (and which presumably had not only substantial functional, but also ultrastructural abnormalities) also been biopsied, a statistically significant difference would also have been achieved with this comparison.

The diclofenac group was the only experimental group where structural abnormalities could be detected with light microscopy. The toluidine blue stained semithin sections demonstrated shortening of the proximal tubular brush borders in this group.

Table 3.67   Comparisons of absolute *changes* in relevant hemodynamic parameters between measurement times in control and diclofenac groups of pigs
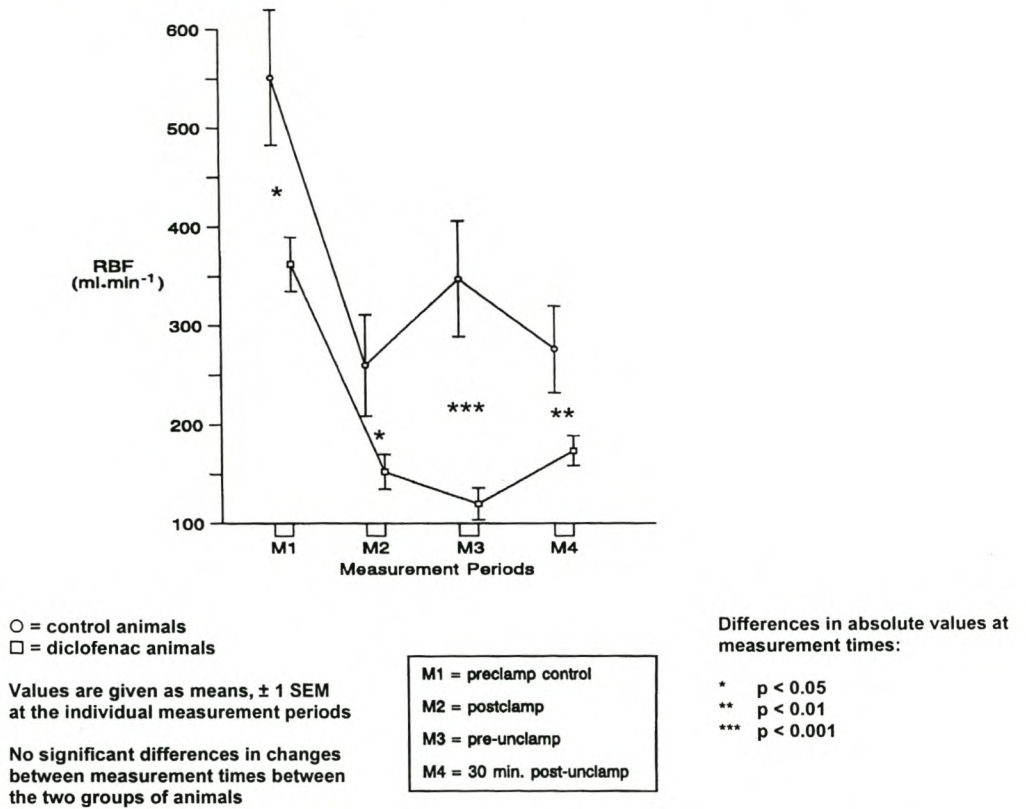
MAP	x1-2	SD	x2-3	SD	X3-4	SD	x1-4	SD
Control	-1.3	7.4	-2.6	9.6	5.8	7.7	1.8	9.7
Diclofenac	-10.7	2.9	-2.5	3.0	15.1	5.4	1.9	4.6
PAWP								
Control	-0.93	2.16	-0.43	1.65	1.37	3.19	0	3.09
Diclofenac	-1.7	1.09	-0.10	1.91	0.5	3.10	-1.3	1.98
CO								
Control	0.13	0.45	0.22	0.30	-0.03	0.57	0.32	0.66
Diclofenac	0.46	0.21	0.17	0.07	-0.63	0.41	0	0.20

No differences in changes between groups.

ANOVA

MAP = mean arterial pressure (mmHg); PAWP = pulmonary artery wedge pressure (mmHg); CO = cardiac output ($l.min^{-1}$); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.68   Comparisons of absolute *changes* in renal hemodynamic and glomerular function parameters between measurement times in control and diclofenac groups of pigs

RBF	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	291.14	239.7	-88.43	193.3	72.57	158.9	275.29	117.5
Diclofenac	210.6	33.8	32.4	25.8	-50.4	41.8	192.6	39.37
GFR								
Control	42.0	27.9	-11.25^b	16.1	-4.0	24.20	26.75	26.90
Diclofenac	47.6	9.07	3.4^a	7.8	-4.4	11.84	46.6	11.55
FF								
Control	0.0009	0.059	0.006	0.066	-0.0473	0.055	-0.0404	0.075
Diclofenac	-0.0094	0.062	-0.055	0.071	0.049	0.035	-0.015	0.063
E_{HIP}								
Control	0.019	0.086	0.0005	0.077	-0.02	0.035	-0.0007	0.056
Diclofenac	0.033	0.07	-0.0004	0.049	0.022	0.041	0.055	0.071
$^{RBF}/_{CO}$								
Control	0.063	0.052	-0.022	0.040	0.02	0.041	0.061	0.021
Diclofenac	0.052	0.009	0.007	0.007	-0.006	0.009	0.053	0.009

a = significantly different from control animals ($p < 0.05$); b = significantly different from diclofenac animals ($p < 0.05$).

ANOVA

RBF = renal blood flow ($ml.min^{-1}$); GFR = glomerular filtration rate ($ml.min^{-1}$); FF = filtration fraction; E_{HIP} = hippuran extraction fraction; $^{RBF}/_{CO}$ = renal blood flow as a fraction of cardiac output; x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.69   **Comparisons of *changes* in urine volumes and indices of renal tubular function between measurement times in control and diclofenac groups of pigs**

Uvol	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	53.12[b]	27.17	5.37[b]	9.75	16.88	23.14	75.38[b]	46.33
Diclofenac	136.4[a]	63.75	45.2[a]	24.32	12.2	13.2	193.8[a]	66.17
FE_{Na}								
Control	0.001	0.045	0.014	0.029	0.055	0.042	0.071[b]	0.076
Diclofenac	-0.874	1.226	-0.219	0.303	0.163	0.575	-0.9[a]	0.94
C_{H2O}								
Control	-11.31	8.92	2.45	8.40	10.14	11.26	1.28	14.79
Diclofenac	-16.32	14.34	3.21	7.14	0.74	6.26	-12.37	21.84

a = significantly different from control animals ($p < 0.05$); b = significantly different from diclofenac animals ($p < 0.05$).

ANOVA

Uvol = urine volume (ml in 20 min); FE_{Na} = fractional excretion of sodium; C_{H2O} = free water clearance ($ml.min^{-1}$); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.70   **Comparisons of absolute *changes* in plasma renin levels between measurement times in control and diclofenac groups of pigs**

P_{ren}	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Control	-2.74	2.25	-0.12	1.81	-1.86	2.43	-4.71	3.05
Diclofenac	-1.98	3.30	-0.14	1.51	-0.77	1.76	-2.9	2.82

No significant differences between groups.

ANOVA

P_{ren} = plasma renin levels ($\mu g.l^{-1}.hr^{-1}$); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Figure 3.30 **Comparisons of changes in renal blood flow between measurement times and differences in absolute values at measurement times in control and diclofenac animals**

O = control animals
□ = diclofenac animals

Values are given as means, ± 1 SEM
at the individual measurement periods

No significant differences in changes
between measurement times between
the two groups of animals

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

Differences in absolute values at
measurement times:

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Figure 3.31 Comparisons of changes in glomerular filtration rate between measurement times and differences in absolute values at measurement times in control and diclofenac animals

O = control animals
□ = diclofenac animals

Values are given as means, ± 1 SEM
at the individual measurement periods

a = change between measurement
    times significantly different from
    control group
b = change between measurement
    times significantly different from
    diclofenac group

$p < 0.05$

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

Differences in absolute values at
measurement times:

* $p < 0.05$
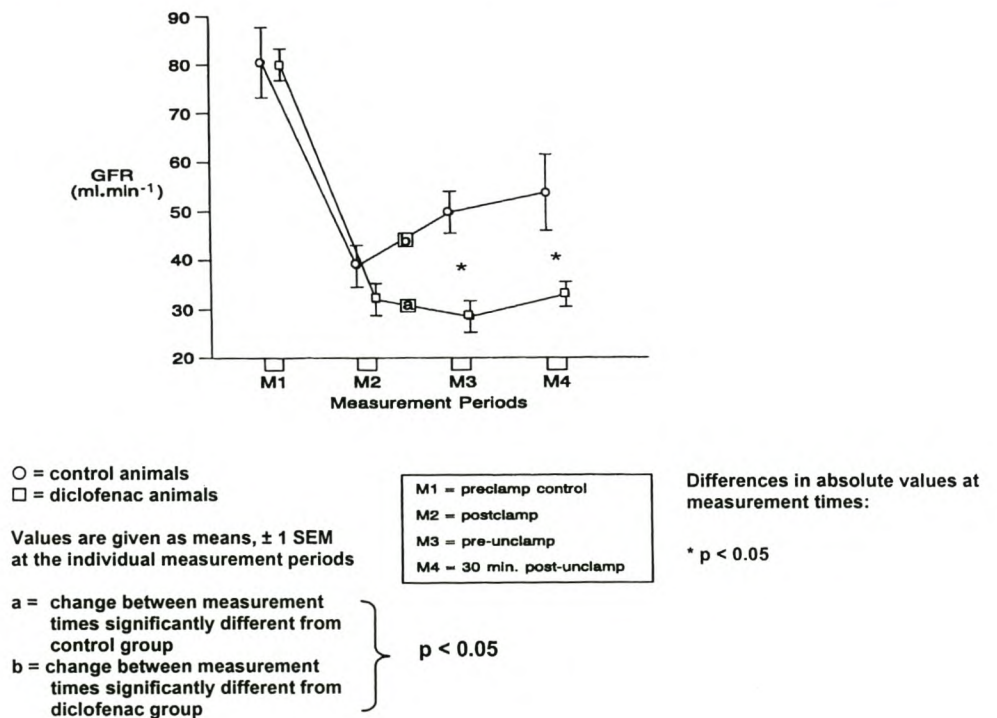
Figure 3.31a **Comparisons of changes in filtration fraction (FF) between measurement times and differences in absolute values at measurement times in control and diclofenac animals**
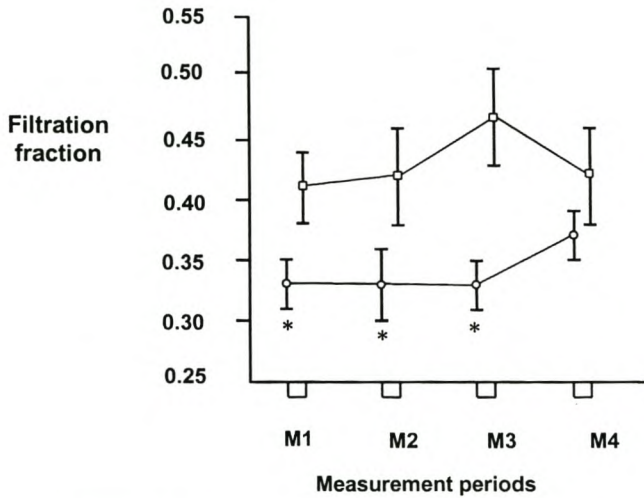
○ = control animals
□ = diclofenac animals

Values are given as means, ± 1 SEM
at the individual measurement periods

No significant differences in changes
between measurement times between
the two groups of animals

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min.post-unclamp

Differences in absolute values at
measurement times:

* $p < 0.05$

Figure 3.32 **Comparisons of changes in plasma renin concentrations between measurement times and differences in absolute values at measurement times in control and diclofenac animals**
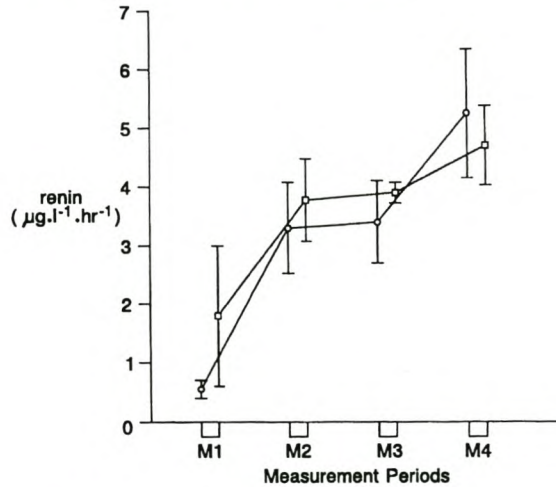
○ = control animals
□ = diclofenac animals

Values are given as means, ± 1 SEM
at the individual measurement periods

No significant differences in changes
between the two groups of animals

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

No differences in absolute values at any
measurement time

Table 3.71   **Electronmicroscopic ultrastructural change: severity grading in control animals and animals which received diclofenac (NSAID)**

Group & animal No.	Villi	gER	Mitochondria	Chromatin	Total Severity Score	No. abnormal parameters
NSAID						
1	2	2	2	3	9	4
2	2	3	3	3	11	4
3	2	2	2	3	9	4
4	1	2	3	3	9	4
5	1	2	2	0	5	3
Control						
1	2	1	2	0	5	3
2	2	0	0	0	2	1
3	0	0	2	0	2	1
4	1	0	0	0	1	1
5	1	1	1	0	3	3
6	2	2	0	0	4	2
7	0	1	2	0	3	2
8	1	0	1	0	2	2

Severity grading per parameter: 0 – 3
Total severity score: Sum of parameter severity gradings (maximum = 12)
No. abnormal parameters: Number of parameters with grading > 0 (maximum = 4)

Table 3.72   **Comparison of electronmicroscopic structural abnormalities between control animals and animals which received diclofenac (NSAID)**

	Severity Score				Number of abnormal parameters				Minimal change – normal animals		Clearly abnormal animals
	Mean	Median	25 Perc	75 Perc	Mean	Median	25 Perc	75 Perc			
Control (n = 8)	2.75 *	2.5	2.0	3.5	1.8 *	2.0	1.0	2.5	3	NS	5
NSAID (n = 5)	8.6	9.0	8.0	9.5	3.8	4.0	3.75	4.0	0		5

*   Significant difference between control and NSAID groups (p < 0.005)

Mann-Whitney: Severity Score and number of abnormal parameters
Fisher exact: Minimal change - normal/clearly abnormal comparisons

Clearly abnormal: Severity score = 3 for at least one parameter and/or ≥ 2 parameters with any degree of abnormality
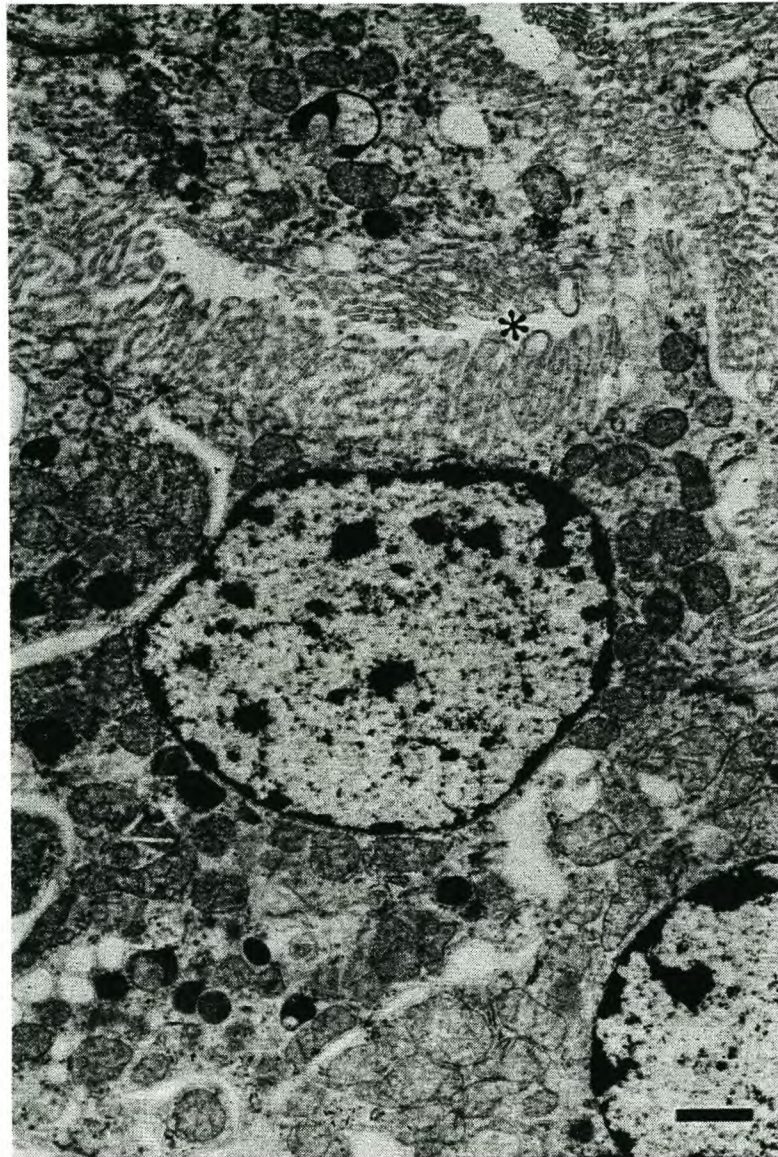
Photograph 3.11   Proximal convoluted tubule (NSAID group) showing irregularity of the brush border with shortened, abnormal microvilli (asterisk). Scale bar, 1cm = 1,3µm.
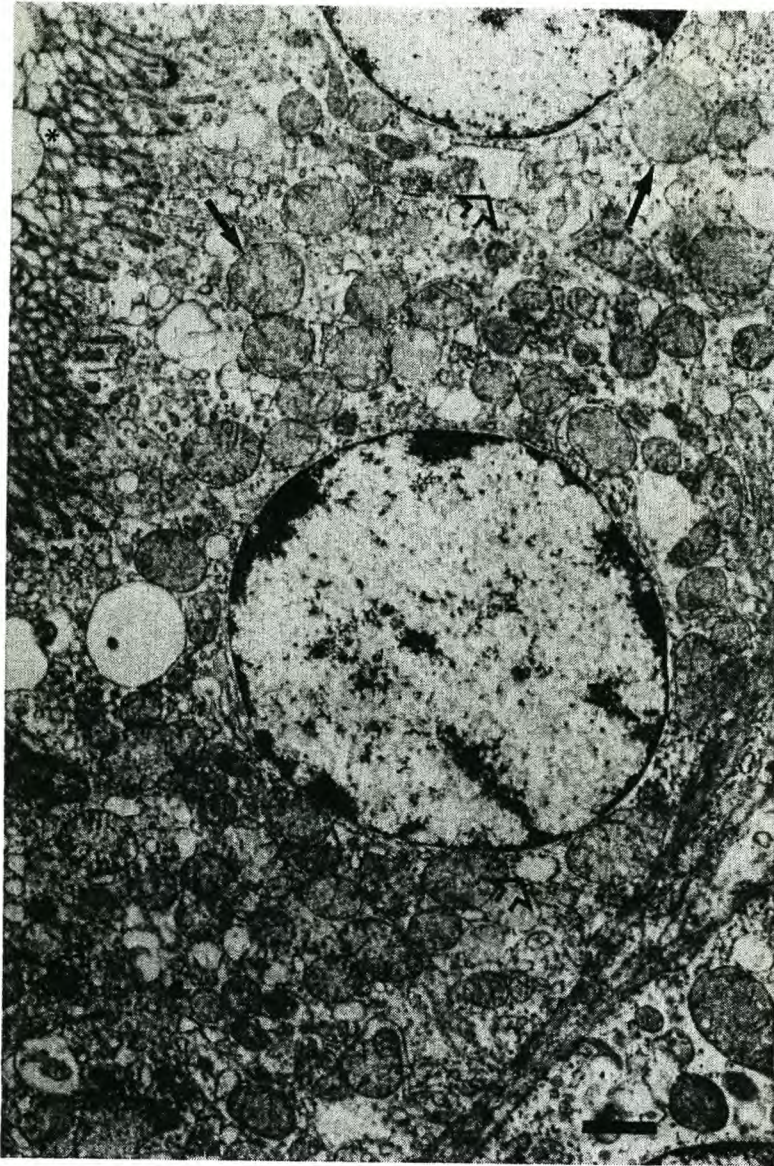
Photograph 3.12   Proximal straight tubule (NSAID group) showing brush border disarray with villous clubbing (asterisk), mitochondrial swelling (arrows) and dilatation of the granular endoplasmic reticulum (arrowheads). Scale bar, 1cm = 1,3μm.
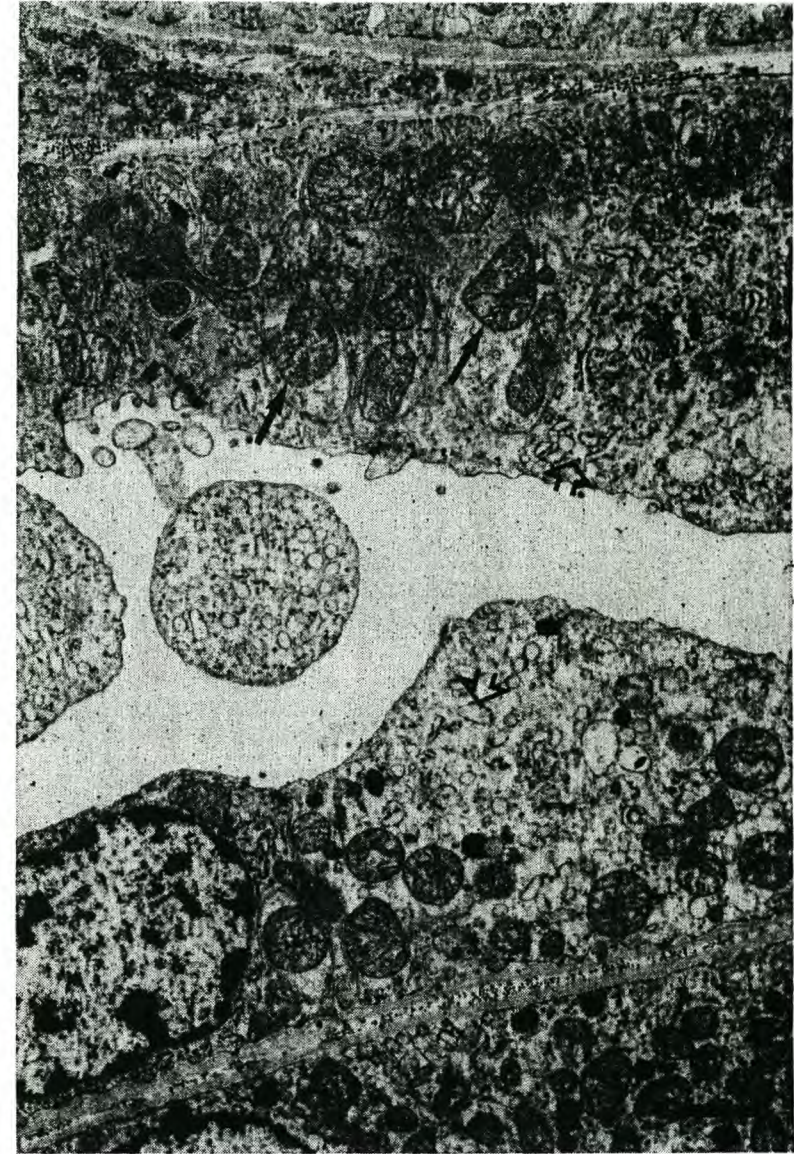
Photograph 3.13   Thick ascending limb (NSAID group) showing mitochondrial swelling (arrows), dilatation of the granular endoplasmic reticulum (arrowheads) and slight peripheral nuclear chromatin condensation. Scale bar, 1cm = 1,4μm.

3.2.2.4 **Comparison of inter-measurement *changes* in animals pretreated with enalaprilat or enalaprilat plus diclofenac, as well as comparison of renal electronmicroscopic changes in the same groups**

Timing of measurement steps

Step 1: preclamp

Step 2: immediately post-clamp (postclamp)

Step 3: immediately before release of clamp (pre-unclamp) ⎱ perclamp

Step 4: starts 30 minutes after release of clamp (post-unclamp)

The systemic hemodynamic parameters, which could potentially influence renal hemodynamics and function (MAP, PAWP and CO) demonstrated no significant differences between the two animal groups in changes between successive or in first-to-last (x1-4) measurement periods (Table 3.73).

The RBF change induced by aortic cross clamping (x1-2) was significantly more pronounced in the enalaprilat plus diclofenac group, although the same change in $^{RBF}/_{CO}$ did not reach statistical significance (Figure 3.33, Table 3.74). By comparison, both RBF and $^{RBF}/_{CO}$ decreased significantly subsequent to aortic cross clamping in the enalaprilat plus diclofenac group with intragroup comparisons (Table 3.74), without significant changes in the same parameters in the enalaprilat group (Table 3.74).

The x1-2 GFR change in the enalaprilat plus diclofenac group (decrease) was significantly different from the enalaprilat animals (Figure 3.34, Table 3.74). Although the x3-4 change in GFR was not significantly different between the two groups of animals (p = 0.054), the extent of the GFR decrease from the pre-unclamp to post-unclamp measurements in the enalaprilat group, rendered the x1-4 change not significantly different between the two groups.

There were no significant differences in changes between consecutive measurement periods or first-to-last (x1-4) changes of either FF or E_{HIP} between the two experimental groups (Table 3.74).

The change in urine volume between the preclamp and postclamp measurement periods were significantly different between the two animal groups (x1-2, Table 3.75) due to a doubling of urine production in the enalaprilat group (Table 3.35) and a reduction in excess of 50% in the enalaprilat plus diclofenac group (Table 3.50). Another change (x3-4) was significantly different between the two experimental groups, predominantly as a result of a 50% decrease in the volume of urine produced in the

enalaprilat group subsequent to release of the aortic cross clamp (Table 3.35). Again, this reversal in change relative to the x1-2 change, rendered the x1-4 change not significantly different between the two groups of animals.

There was a significantly different x2-3 change between the two experimental groups in C_{H2O} (Table 3.75), primarily due to the fact that C_{H2O} became significantly more negative between the postclamp and pre-unclamp measurement periods in the enalaprilat animals (Table 3.35). Just focussing on the change, obscures the fact that the initial (preclamp control) value of C_{H2O} in the enalaprilat group was much less negative than any of the other experimental groups (Table 3.35).

There were no significant differences in changes of plasma renin concentrations between the two animal groups with P_{ren} sustained at high levels throughout the experimental periods in both groups (Figure 3.35, Table 3.76).

Table 3.77 lists the extent of renal electronmicroscopic changes in individual animals in the enalaprilat and enalaprilat plus diclofenac animals. A spectrum of subcellular structural changes was apparent in both enalaprilat (photograph 3.5) and enalaprilat plus diclofenac animals, with the latter group seemingly more prone to microvillous changes and dilatation of the granular endoplasmic reticulum (Table 3.77, photographs 3.14, 3.15).

Comparisons of structural abnormality scores and numbers of abnormal structures between the two animal groups are shown in Table 3.78. Although a tendency towards more severe ischemic changes is apparent in the diclofenac plus enalaprilat group, statistical significance is not achieved in either comparison. Numbers of animals classified as demonstrating clearly abnormal histology versus those with normal histology or minimal change were not significantly different between the two groups (Table 3.78).

Table 3.73   **Comparisons of absolute *changes* in relevant systemic hemodynamic parameters between measurement times in pigs which received either enalaprilat or enalaprilat plus diclofenac**

MAP	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Enalaprilat	-9.1	5.0	-4.7	4.5	12.7	3.5	-1.1	2.7
Enalaprilat & Diclofenac	-8.3	2.2	-1.3	2.3	9.7	4.6	0.1	5.2
PAWP								
Enalaprilat	-0.66	2.01	0.75	0.82	-0.33	1.60	-0.25	2.36
Enalaprilat & Diclofenac	-1.14	2.40	-0.28	1.31	0.42	1.59	-1.0	1.47
CO								
Enalaprilat	0.15	0.15	0.14	0.22	-0.26	0.26	0.02	0.30
Enalaprilat & Diclofenac	0.32	0.30	-0.16	0.30	-0.29	0.18	-0.13	0.32

No differences in changes between groups.

ANOVA

MAP = mean arterial pressure (mmHg); PAWP = pulmonary artery wedge pressure (mmHg); CO = cardiac output $(l.min^{-1})$; x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.
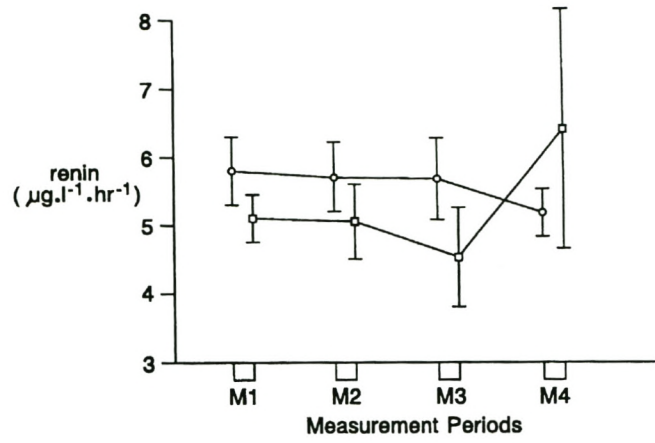
Table 3.74   **Comparisons of absolute *changes* in renal hemodynamic and glomerular function parameters between measurement times in enalaprilat and enalaprilat plus diclofenac groups of pigs**

RBF	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Enalaprilat	32.8[a]	50.4	-12.67	84.86	102.3	116.6	122.5	94.6
Enalaprilat & Diclofenac	206.6[b]	186.7	19.57	105.54	34.0	157.6	260.1	199.7
GFR								
Enalaprilat	-1.83[a]	6.15	-1.0	10.79	23.83	17.72	21.0	16.8
Enalaprilat & Diclofenac	39.29[b]	19.61	0.14	12.81	-1.0	22.88	38.43	47.78
FF								
Enalaprilat	-0.024	0.028	0.0035	0.043	0.0246	0.052	0.004	0.044
Enalaprilat & Diclofenac	0.011	0.052	-0.0095	0.073	0.0124	0.065	0.0145	0.054
E_{HIP}								
Enalaprilat	0.0023	0.073	-0.0116	0.041	-0.0031	0.015	-0.012	0.046
Enalaprilat & Diclofenac	-0.0045	0.038	0.0064	0.09	0.037	0.069	0.0388	0.071
$RBF/_{CO}$								
Enalaprilat	0.004	0.015	-0.007	0.026	0.034	0.035	0.03	0.025
Enalaprilat & Diclofenac	0.048	0.056	0.01	0.032	0.012	0.037	0.071	0.057

a = significantly different from enalaprilat animals ($p < 0.05$); b = significantly different from enalaprilat plus diclofenac animals ($p < 0.05$).

ANOVA

RBF = renal blood flow $(ml.min^{-1})$; GFR = glomerular filtration rate $(ml.min^{-1})$; FF = filtration fraction; E_{HIP} = hippuran extraction fraction; $RBF/_{CO}$ = renal blood flow as a fraction of cardiac output; x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.75   **Comparisons of absolute *changes* in urine volumes and indices of renal tubular function between measurement times in pigs which received either enalaprilat or enalaprilat plus diclofenac**

Uvol	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Enalaprilat	-69.17[b]	42.48	-5.0	64.98	122.17[b]	69.04	48.0	75.03
Enalaprilat & Diclofenac	74.14[a]	88.21	5.71	20.63	12.71[a]	24.84	92.57	69.01
FE_{Na}								
Enalaprilat	-0.043	0.139	0.136	0.338	0.032	0.053	0.125	0.246
Enalaprilat & Diclofenac	-0.025	0.094	0.031	0.028	0.011	0.052	0.018	0.067
C_{H2O}								
Enalaprilat	-3.78	12.76	41.71[b]	39.11	-17.84	42.94	20.09	28.01
Enalaprilat & Diclofenac	-21.77	69.15	-5.26[a]	13.74	14.24	31.69	-12.79	81.62

a = significantly different from enalaprilat animals ($p < 0.05$); b = significantly different from enalaprilat plus diclofenac animals ($p < 0.05$).

ANOVA

Uvol = urine volume (ml in 20 min); FE_{Na} = fractional excretion of sodium; C_{H2O} = free water clearance ($ml.min^{-1}$); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Table 3.76   **Comparisons of absolute *changes* in plasma renin levels between measurement times in pigs which received either enalaprilat or enalaprilat plus diclofenac**

P_{ren}	x1-2	SD	x2-3	SD	x3-4	SD	x1-4	SD
Enalaprilat	0.09	1.48	0.05	1.94	0.49	1.17	0.63	1.61
Enalaprilat & Diclofenac	0.05	0.87	0.53	2.39	-1.86	5.39	-1.28	4.65

No significant differences between groups.

ANOVA

P_{ren} = plasma renin levels ($\mu g.l^{-1}.hr^{-1}$); x1-2 = mean difference between 1st and 2nd measurement periods; x2-3 = mean difference between 2nd and 3rd measurement periods; x3-4 = mean difference between 3rd and 4th measurement periods; x1-4 = mean difference between 1st and 4th measurement periods.

Figure 3.33   Comparisons of changes in renal blood flow between measurement times in animals receiving either enalaprilat or enalaprilat plus diclofenac

O = enalaprilat animals
□ = enalaprilat + diclofenac animals

Values are given as absolute means, means, ± 1 SEM at the individual measurement periods

a = change between measurement times significantly different from enalaprilat group
b = change between measurement times significantly different from enalaprilat + diclofenac group

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

p < 0.05
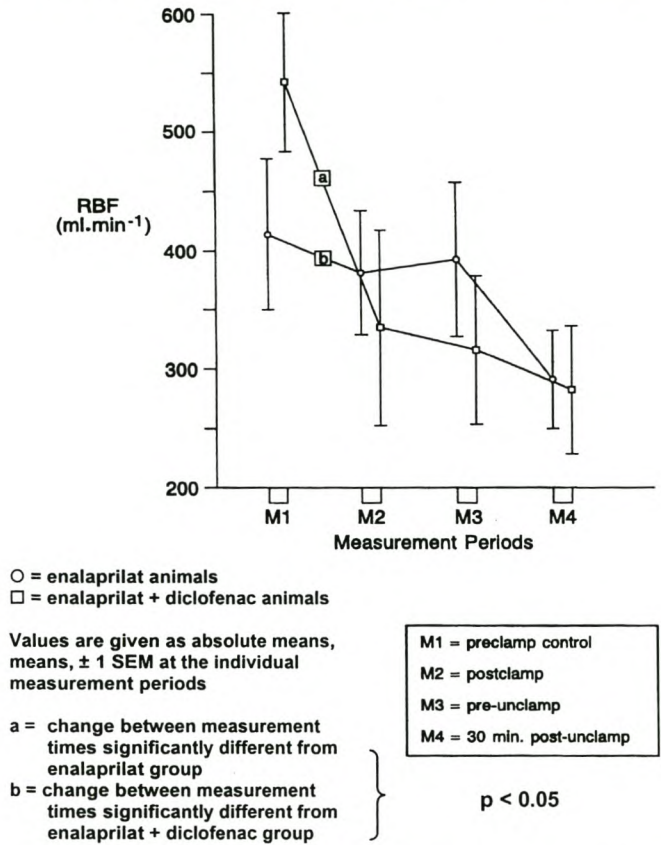
Figure 3.34   Comparisons of changes in glomerular filtration rate between measurement times in animals receiving either enalaprilat or enalaprilat plus diclofenac

O = enalaprilat animals
□ = enalaprilat & diclofenac animals

Values are given as means, ± 1 SEM at the individual measurement periods

a = change between measurement times significantly different from control group
b = change between measurement times significantly different from

M1 = preclamp control
M2 = postclamp
M3 = pre-unclamp
M4 = 30 min. post-unclamp

p < 0.05
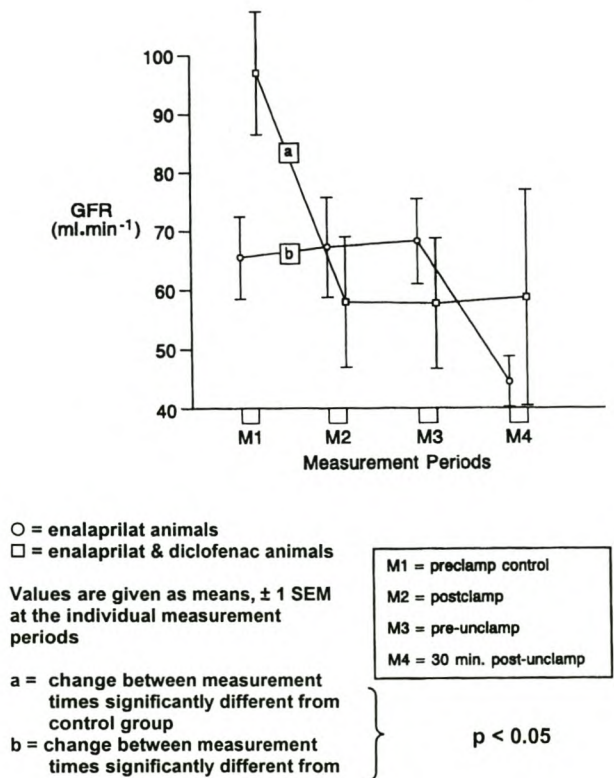
Figure 3.35   **Comparisons of changes in plasma renin concentrations between measurement times in animals receiving either enalaprilat or enalaprilat plus diclofenac**

O = enalaprilat animals
□ = enalaprilat + diclofenac animals

Values are given as absolute means, ± 1 SEM
at the individual measurement periods

No significant differences in changes
between measurement times between the two
groups of animals

M1 = preclamp control

M2 = postclamp

M3 = pre-unclamp

M4 = 30 min. post-unclamp

Table 3.77 **Electronmicroscopic ultrastructural change: severity grading in animals which received enalaprilat (ACEI) and animals which received enalaprilat and diclofenac (ACEI +NSAID)**

Group & animal No.	Villi	gER	Mitochondria	Chromatin	Total Severity Score	No. abnormal parameters
ACEI						
1	0	0	0	0	0	0
2	2	0	0	0	2	1
3	0	0	2	0	2	1
4	2	1	2	0	5	3
5	0	0	0	0	0	0
6	0	0	0	0	0	0
7	3	0	0	0	3	1
8	0	0	0	0	0	0
9	2	0	0	0	2	1
10	2	1	1	0	4	3
11	3	0	0	0	3	1
12	0	2	1	0	3	2
ACEI + NSAID						
1	1	2	1	0	4	3
2	1	2	3	0	6	3
3	3	0	0	0	3	1
4	1	2	2	0	5	3
5	2	0	0	0	2	1
6	2	1	1	0	4	3
7	0	0	1	0	1	1

Severity grading per parameter: 0 – 3
Total severity score: Sum of parameter severity gradings (maximum = 12)
No. abnormal parameters: Number of parameters with grading > 0 (maximum = 4)

Table 3.78 **Comparison of electronmicroscopic structural abnormalities between animals which received enalaprilat (ACEI) and those which received enalaprilat and diclofenac (ACEI + NSAID)**

	Severity Score				Number of abnormal parameters				Minimal change – normal animals		Clearly abnormal animals
	Mean	Median	25 Perc	75 Perc	Mean	Median	25 Perc	75 Perc			
ACEI (n = 12)	2.0	2.0	0.25	3.0	1.0	1.0	0.25	1.5	8	NS	4
ACEI + NSAID (n = 7)	3.6	4.0	2.25	4.75	2.1	3.0	1.0	3.0	2		5

No significant differences between groups

Mann-Whitney: Severity Score and number of abnormal parameters
Fisher exact: Minimal change - normal/clearly abnormal comparisons

Clearly abnormal: Severity score = 3 for at least one parameter and/or $\geq$ 2 parameters with any degree of abnormality
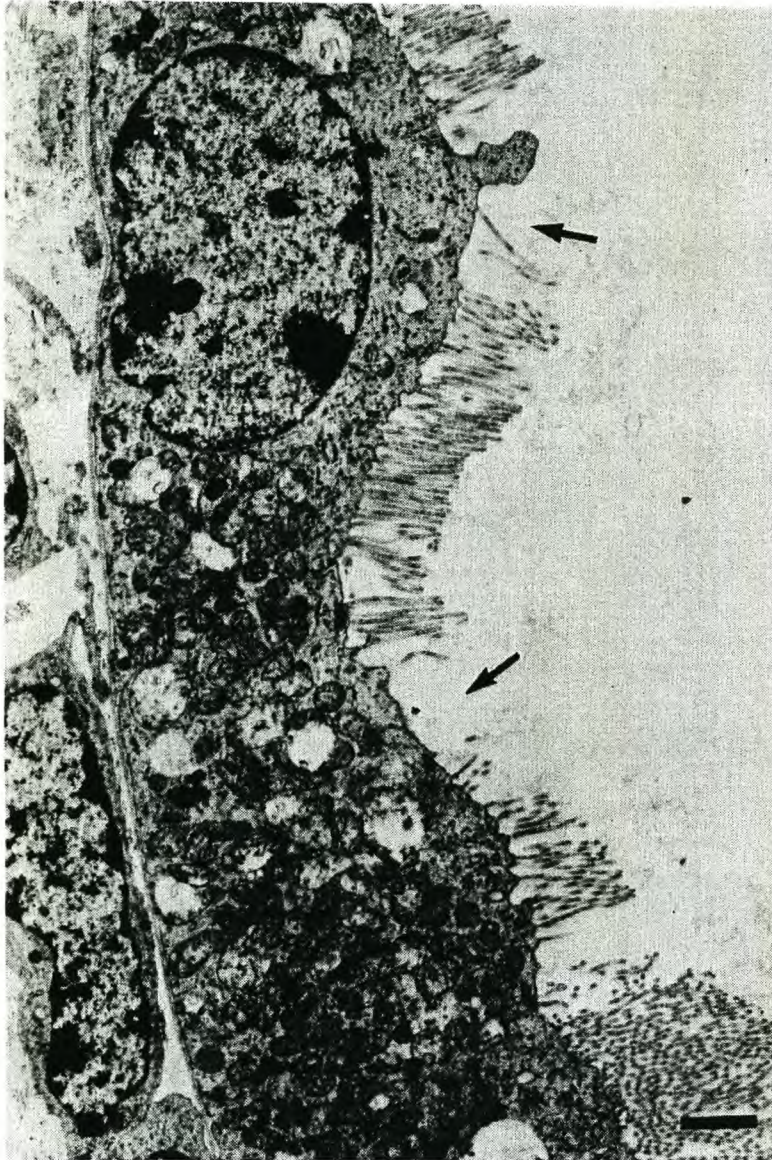
Photograph 3.14   Proximal straight tubule (ACEI plus NSAID group) showing brush border irregularity with loss of microvilli (arrows). Scale bar, 1cm = 1,8μm.
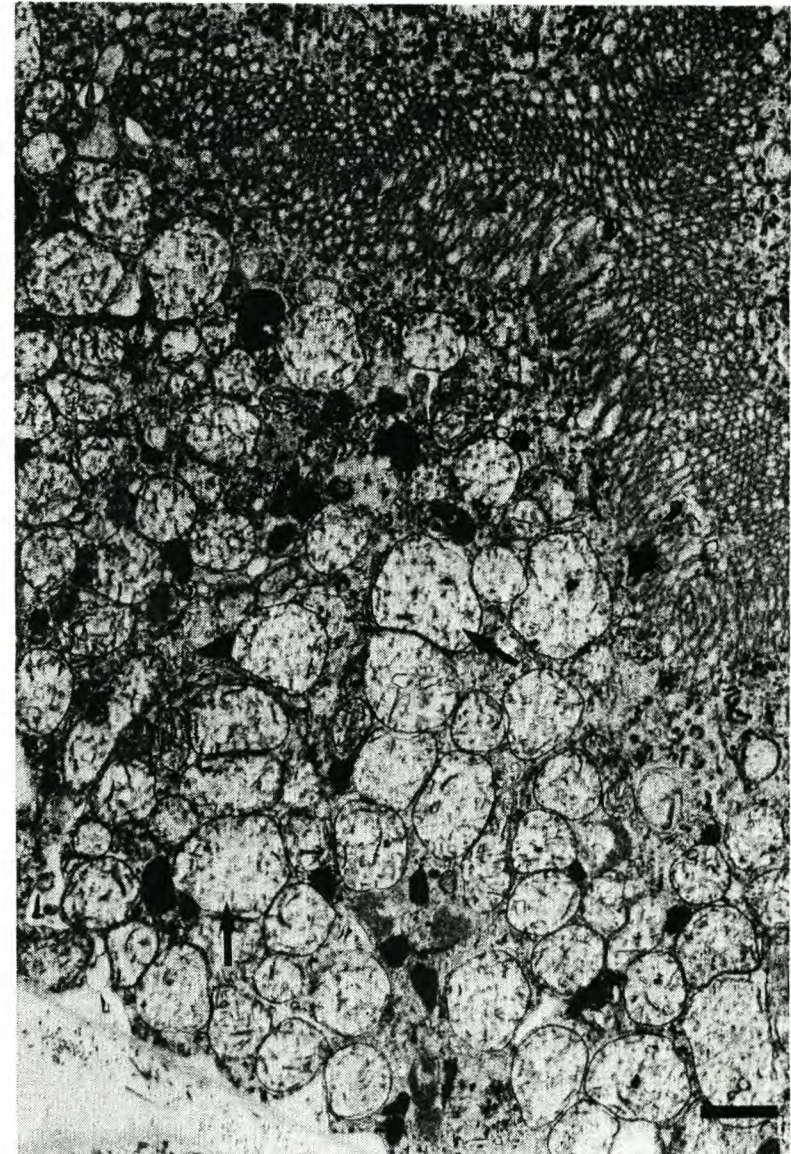
Photograph 3.15   Proximal straight tubule (ACEI plus NSAID group) showing brush border irregularity with loss of microvilli (arrows). Scale bar, 1cm = 1,3μm.

4. DISCUSSION

4.1 The patient model

The preoperative demographic profile of the patients included in the study (Table 3.15) is similar to other recent reports where renal hemodynamics and function were studied during infrarenal aortic surgery (Gamulin et al. 1984 and 1986; Colson et al. 1992a; Licker et al. 1996). The preoperative creatinine clearance (Table 3.16) was within the normal range in both groups of patients studied.

Preoperative insertion of a renal venous catheter made it possible to use isotopes to determine control RBF measurements while patients were still awake and also to continue measurements into the postoperative period. In previous studies where isotope-labelled hippuran was used for the determination of RBF (Gamulin et al. 1984 and 1986; Colson et al. 1992a and 1992b), renal blood samples were taken by the surgeon directly from the renal vein with the abdomen open in the intraoperative period. This method not only precluded assessment of the influence of anaesthesia on the renal hemodynamics, but also of the process of recovery of RBF, which was still compromised after aortic unclamping (Gamulin et al. 1984 and 1986). **This study is therefore the first to report on renal hemodynamics from the preoperative into the postoperative phase, with the concomitant changes in glomerular and renal tubular function in patients subjected to infrarenal aortic aneurysm repair.** Unfortunately the renal venous catheter had to be removed 4 hours after surgery because of concerns about the possibility of catheter-induced renal venous thrombosis (in the absence of evidence to the contrary in the literature) if the catheter remained in situ overnight. We were thus unable to follow progress of recovery of the renal hemodynamics after the 4 hours post-unclamp measurements.

It is clear from the results that RBF and GFR were not influenced by anaesthesia and surgical manipulation prior to aortic cross clamping. The fact that halothane at or below I MAC apparently did not compromise RBF or GFR is supported by some studies in different populations (RBF: Gelmann et al. 1984b; Bastron et al. 1979) (GFR: Mazze et al. 1984). It is in contrast with indirect evidence to the contrary in a study by Colson et al. (1992b) that demonstrated higher intra-operative RBF and GFR values in patients anaesthetized with isoflurane than those who received halothane, both before and after cross clamping of the aorta. However, after unclamping of the

aorta, no differences in renal hemodynamics or function could be demonstrated between Colson's rather small experimental groups (no group bigger than 10 patients). The same group reported similar findings in another study where the differences could, at least in part, be explained by the fact that firstly the two agents were not administered in equipotent concentrations (halothane in higher concentrations than isoflurane relative to their respective MAC values) and that secondly the isoflurane patients received approximately 30% more intravenous fluid than the halothane group (Colson et al. 1992c). In higher concentrations (> 0.9%) halothane does appear to consistently decrease RBF and GFR (Deutsch et al. 1966; Hill et al. 1977; Tranquilli et al. 1982).

Autoregulation of renal blood is maintained with halothane concentrations from 0.9% to 1.5% in experimental animals (Bastron et al. 1977; Priano 1983). This is confirmed in both control and mannitol plus dopamine patients in our study where a 10 - 15% decrease in MAP (between awake control and intraoperative preclamp measurements) was accompanied by a similar reduction in RVR with maintenance of RBF.

A nitroglycerin infusion was used after induction, primarily to reduce afterload during the perclamp period (Peterson et al. 1978) and to allow intravenous volume loading before releasing the aortic cross clamp. At the latter period, a reduction in nitroglycerin infusion rate was synchronised with release of the aorta cross clamp. It is also considered to be the vasodilator of choice in this population group because of the prevalence of ischemic heart disease and the frequency of myocardial ischemic events in the perioperative period of aortic reconstruction surgery (Attia et al. 1976; McPail et al. 1988). In addition, it has been proven to be beneficial on mycardial oxygen balance during cross clamping of the aorta (Hummel et al. 1982).

No reference could be found which elucidates the effects of nitroglycerin on the renal vasculature, renal hemodynamics or renal function. It is, however, possible that the administration of intravenous nitroglycerin, which was initiated just after induction of anaesthesia, could have played a role in the maintenance of RBF at pre-induction levels prior to aortic cross clamping. If this had been the case, it would imply that nitroglycerin exerted an equivalent vasodilatory effect on the afferent and efferent arterioles to prevent significant change in intraglomerular capillary hydrostatic pressure, given the maintenance of GFR at awake control values (Table 3.2). Alternatively, if the vasodilatory effect of nitroglycerin had been more extensive on the

efferent arterioles, the drop in intracapillary hydrostatic pressure would have had to be compensated for by nitroglycerin-induced mesangial cell relaxation with resultant increased glomerular permeability, to prevent a decrease in GFR. However, if nitroglycerin played a role in the maintenance of RBF and GFR after induction of anaesthesia, it was unable to prevent the increase in RVR and decrease in RBF during the perclamp and initial unclamp periods despite similar dosages during those measurement periods (Table 3.6).

The method used for the measurement of RBF (and GFR) is considered to be acceptably accurate to the extent that it has been used in the majority of recent human studies where RBF was measured during surgery of the abdominal aorta (Gamulin et al. 1984 and 1986; Colson et al. 1992a and 1992b; Myers et al. 1984; Licker et al. 1996 - in the latter two studies clearance of PAH were used). Our period of equilibration of plasma isotope concentrations before the first measurements were done, was similar to the above studies. The fact that there were no differences in the concentration variation between the two samples during the six measurement periods (Tables 3.7 and 3.14) indicate that adequate equilibration took place before the first measurement period. Some degree of variation in isotope count, even over the 20 or 30 minutes of one measurement period, is unavoidable due to variations in isotope loss from the body through the urine and surgical blood loss, and dilution from the administration of intravenous fluid. We consider our method of determination of mean plasma isotope concentration per measurement period (calculating the mean isotope count from two samples taken at the middle and at the end of the measurement period, each taken over a five minute period) a more accurate reflection of the true mean value for the full duration of the measurement as opposed to the method employed by Gamulin et al. (1984 and 1986) where only one blood sample was taken per measurement period.

The aims of intravenous fluid administration, namely to maintain PAWP at 10 mmHg or above and Hct at 30% or above, was achieved throughout the perioperative period in both groups of patients. It is therefore probably safe to suggest that changes in vascular filling pressures (Tables 3.3 and 3.10) and hematocrit (Tables 3.6 and 3.13) did not compromise renal hemodynamics. If anything, RBF might have benefited most from the reduced viscosity conferred by the lowest hematocrit (Crystal et al. 1988; Von Restorf et al. 1975) just after cross clamping of the aorta, which was at the time when the lowest RBF's were in fact recorded. Paul et al. (1986) argued that their approach

of intravenous volume expansion was probably responsible for the fact that GFR was maintained during aortic cross clamping and only decreased significantly after unclamping (they did not measure RBF), in contrast to Gamulin et al. (1984) where GFR decreased immediately after infrarenal clamping of the aorta. The volumes infused intraoperatively in our patients (Table 3.16) corresponds closely with the experimental groups in the study by Paul et al. (crystalloids between 5813 ml and 6833 ml mean; blood between 1.8 and 2.2 units mean). The left ventricular filling pressures in both patient groups in our study (Tables 3.3 and 3.10) resembled the PAWP measurements recorded by Paul et al. with mean values which varied from 11.6 mmHg to 17.1 mmHg. Despite these similarities between our patients and the study by Paul et al. in terms of intravascular (and, presumably, extracellular) fluid volumes, our patients responded to aorta cross clamping with a significant decrease in GFR (Tables 3.2 and 3.9). These changes in GFR emulated those reported by Gamulin et al. (1984 and 1986) and raises doubts about the explanation suggested by Paul et al. (1986) for the difference between their results and those of Gamulin et al. (1984).

4.2   Control patients

The awake control measurements of RBF and $^{RBF}/_{co}$ are consistent with values which have been described as normal for humans (Thurau, 1964). Maintenance of RBF after induction of anaesthesia and in the preclamp surgical phase is in conflict with some evidence that comparable concentrations of halothane decreased RBF at the same stage of surgery in a similar population (Colson et al. 1992b). The MAP of the patients in the Colson study were perilously close to the lowest acceptable level for outoregulation of RBF even for young, healthy adults (76.9 mmHg ± 2.5 (SEM)). The fact that these patients were elderly and at least some of them were probably hypertensive (5/9 received ACE inhibitors preoperatively and 6/9 calcium antagonists), suggests that the blood pressure was probably below the autoregulatory range in at least some of their patients. The increase in RBF after release of the aortic cross clamp (relative to the preclamp measurement) may, at least in part, be due to a higher MAP (83.9 mmHg) ± 2.6 (SEM)). The effective renal plasma flow (ERPF) in the preclamp period was also much lower in all anaesthetic subgroups of the Colson (1992b) study than those reported in a comparable study (Licker et al. 1996) where higher MAP's were maintained. Unfortunately, ERPF (rather than RBF) was reported in the studies by Licker et al. (1996) and Colson (1992a and 1992b) without providing hematocrit values (which would make it possible to calculate RBF) so that comparisons

of absolute values of RBF between the above studies and those of Gamulin et al. (1984 and 1986) and our own, are not possible. Myers et al. (1984) reported preclamp RBF measurements (using a PAH clearance technique in a patient subgroup subsequently subjected to infrarenal aorta clamping) of 676 ml.min^{-1} (391 ± 80 (SEM) ml.min^{-1} per 1.73m^2 BSA) which suggests that RBF in those patients was significantly impaired by anaesthesia and initial surgical exploration. Although awake control RBF measurements could not be done in the studies by Gamulin et al. (1984 and 1986), the RBF: CO ratios of 0.215 (Gamulin et al. 1984) and 0.283 (Gamulin et al. 1986) before aorta cross clamping suggest that anaesthesia and exploratory surgery did probably not compromise RBF significantly since these ratios resemble the value of 0.25 considered to be normal in awake humans (Dworkin and Brenner 1996).

The 48% decrease in RBF after infrarenal cross clamping in our patients relative to both awake control and preclamp values (Table 3.1) is similar to changes reported by Gamulin et al. (1984 and 1986). The persistence of the decreased RBF into the early post-unclamp period also corresponds with the Gamulin (1984 and 1986) studies. The fact that anaesthesia and early surgical exploration probably induced a decrease in RBF in the studies by Myers (1984) and Colson (1992a and 1992b), may obscure the influence of aortic clamping in those studies, since awake measurements were not available as controls. Nevertheless, Colson et al. (1992a) reported a decreased perclamp RBF relative to (a probably already compromised) preclamp RBF measurement. Our study is the first to measure and report RBF 4 hours after unclamping of the aorta which, although significantly improved on perclamp and the first unclamp measurements, was still significantly less than awake control and preclamp flows (Table 3.1). This occurred despite the fact that calculated RVR had returned to awake values. It should, however, be pointed out that RVR is a calculated parameter dependent on MAP to CVP gradient and the RBF. With a mean pressure gradient that was 21.8% lower than the awake control value, RVR at the 4 hours post-unclamp measurement should have been even lower than the calculated value in our study to allow RBF to return to normal values. Potential causes for this apparent lack of adequate vasodilatory ability could be the presence of renal vasoconstrictive substances (Bengston et al. 1987; Frank et al. 1988) and/or compromised auto-regulation after the preceding period of ischemia (Kelleher et al. 1984; Conger and Robinette 1979).

The progressive decrease in E_{HIP} which eventually became statistically significant 4 hours after unclamping of the aorta (relative to awake control and preclamp measurements; Table 3.1) is suggestive of redistribution of renal blood flow away from the cortex since hippuran clearance corresponds to the cortical or effective renal plasma flow (Ram et al. 1967; Maher and Elveback 1970). This redistribution is consistent with redistribution of flow found in acute renal failure in man (Hollenberg et al. 1968) and was also demonstrated in studies in experimental animals after infrarenal aortic cross clamping (Gelman et al. 1984a, Abbott et al. 1973 and 1974). The changes in our study are, however, in conflict with the studies by Gamulin et al. (1984 and 1986). They suggested, on the grounds of a statistically significant increase in E_{HIP} from 0.67 to 0.74, that RBF was redistributed towards the cortex. Gelman and Navar (1985) expressed reservations about this conclusion and suggested that increased extraction could have been the result of prolonged exposure of hippuran to the secretory mechanisms due to the reduction in total blood flow. Even if there had been a redistribution of blood flow to the renal cortex in the studies by Gamulin, it might have been caused by mannitol (Abbott et al. 1974) which they used as a constant infusion (20 g.hour^{-1}) "in order to maintain an adequate urine output" (Gamulin et al. 1984).

Absolute values and changes in GFR as measured by clearance of Cr^{51} EDTA were very similar to calculated C_{creat}. The decreased GFR in the perclamp (steps 3 and 4, Table 3.2) and immediately post-unclamp (step 5) periods corresponds with the findings of most human studies in which both GFR and RBF were measured (Gamulin et al. 1986; Colson et al. 1992a; Licker et al. 1996), although infrarenal aortic clamping did not decrease GFR significantly in other studies (Colson et al. 1992b). Persistence of the decreased GFR in the early postoperative period (step 6) was also demonstrated by Licker et al. (1996) 12 hours postoperatively while Myers et al. (1984) reported no significant change between GFR measured preoperatively and again 24 hours postoperatively.

There are a number of potential reasons for the reduction in glomerular ultrafiltration induced by aorta cross clamping in our patients. A decrease in glomerular capillary hydrostatic pressure (Pgc) could have been responsible through either a decrease in MAP or an imbalance in vascular tone between the afferent and efferent glomerular arterioles with greater prominence of vascular tone in the afferent (relative to efferent) arterioles. It is unlikely that the significant decrease in MAP demonstrated in our patients was responsible because this decrease had already occurred in the preclamp

intraoperative phase without any influence on GFR. Vital organ perfusion is not compromised in elderly patients during mild hypotension provided that MAP's are maintained within 20-30% normal resting pressure, which was relevant in our patient population (Standgaard 1976). The release of vasoconstrictive substances after aortic cross clamping could have mediated a decrease in P_{cg} provided that such (an) agent(s) induced a more significant increase in vascular tone in the afferent than the efferent arterioles. Individually, however, potential endogenous vasoactive substances usually induce greater increases in resistance in the efferent than in the afferent arterioles (Maddox and Brenner 1996). A decrease in the glomerular ultrafiltration coefficient (K_f) could have played a role in the decreased GFR. Endogenous mediators such as angiotensin II (Blantz et al. 1976), ADH (Schor et al. 1981), noradrenaline (Kon et al. 1983), endothelin (Badr et al. 1989), leukotrienes (Badr et al. 1987) and adenosine (Olivera et al. 1989) have all been demonstrated to induce mesangial cell contraction and decrease K_f through mechanisms which involve the influx of Ca^{2+} (Maddox and Brenner 1996). Finally, the decrease in RBF might also have contributed, because a reduction in renal plasma flow has been demonstrated to decrease GFR in the absence of significant changes in the other determinants of GFR (Deen et al. 1972). During conditions of reduced RBF, the rate of increase in plasma protein concentration (and therefore the oncotic pressure) rises more rapidly along the glomerular capillary so that filtration pressure equilibrium (balance between hydrostatic and oncotic pressures) is reached closer to the afferent side of the capillaries. It is possible that, in our patients, the predominance of the decrease in RBF together with a speculative mediator-induced reduction in K_f, over a mediator-induced increase in P_{gc}, was responsible for the decrease in GFR. However, even P_{gc} might have been decreased through the combined effect of more than one vasoactive substance (Maddox and Brenner 1996). Predominance of efferent arteriolar vasoconstriction with increased P_{gc} should have been responsible for an increase in FF, while our patients responded with a small decrease in FF (Table 3.2), albeit not statistically significant.

The baseline FE_{Na} in excess of 0.01 in our patients (0.04 ± 0.019 SD; Table 3.4) is higher than one would expect in a normal, resting adult (Oken 1981). A number of factors could have been instrumental in mean preoperative FE_{Na} values being greater than those reported for normal, resting adults. One contributing factor could have been the fact that the patients had already been volume-loaded with intravenous fluid (Ringers lactate) at the time of measurement, constituting a high sodium load (Steiner 1984). The renal changes associated with ageing are also documented to produce

similar findings (Epstein et al. 1976; Sporn et al. 1962). With the decrease in GFR and particularly with the increase in aldosterone concentrations in the measurement steps subsequent to aortic cross clamping (Table 3.5), one would expect a decrease in FE_{Na}, which did not occur. FE_{Na} in excess of 0.01 under such circumstances would be suggestive of renal tubular injury (Steiner 1984; Miller TR et al. 1978) although only when FE_{Na} exceeds 0.06 is it considered to be diagnostic (Oken 1981). Such an unequivocal conclusion is compromised by the high initial FE_{Na} values. Both Licker et al. (1996) and Colson et al. (1992a) reported increased FE_{Na} during the perclamp and post-unclamp periods (relative to preclamp control), but failed to comment on these changes in the discussion of their results. In the latter study, the increase in FE_{Na} predictably occurred earlier in a patient subgroup who received enalapril (which would decrease aldosterone secretion) than in a control group.

C_{H2O} is a sensitive indicator of renal tubular concentrating function (Smith 1956) and a valuable early predictor of the development of acute renal insufficiency (Landes et al. 1976, Baek et al. 1973 and 1975). It becomes increasingly positive in states of renal tubular dysfunction. A progression towards positive values occurred in our patients in the perclamp period failed to reach statistical significance (Table 3.4), which is similar to results reported by Gamulin et al. (1984) while Licker et al. (1996) demonstrated significant changes in C_{H2O} suggesting tubular dysfunction.

An increase in urinary ß$_2$-microglobulin concentration indicative of proximal tubular damage only became apparent in our patients after release of the aortic cross clamp with progressively increasing mean concentrations until 24 hours after surgery. ß$_2$-microglobulin is a nonpolymorphic protein component of the two-chain structure of the HLA class I molecule (Schwartz 1996) which is filtered by the glomerulus and almost completely (99.9%) reabsorbed and metabolized by the cells of the proximal tubules, even in conditions with increased production and plasma concentrations (Hall et al. 1981). Increased urinary concentrations of ß$_2$-microglobulin have been demonstrated in a wide range of renal diseases and renal failure where proximal tubular damage with associated dysfunction of tubular cells is a feature (Schardijn and Van Eps 1987). In ischemic injury of the kidney, the proximal tubule has been demonstrated to be particularly susceptible to such damage (Shanley et al. 1986a; Donohoe et al. 1978; Venkatachalam et al. 1978). Lysozymuria, another indicator of proximal tubular injury, had been demonstrated in more than 70% of patients after both elective and emergency repair of abdominal aorta aneurysms by Powis (1975), in contrast to the

studies by Gamulin et al. (1984 and 1986) where lysozymuria was absent during and immediately after clamping of the aorta. It is possible that the last urine sample tested for lysozymuria in the Gamulin studies (just after release of the aortic cross clamp) preceded the biochemically overt manifestation of proximal tubular injury. In our study, a relatively small (statistically significant) quantitative increase in $ß_2$-microblobulin was evident 30 minutes after unclamping of the aorta, with much more substantial increases in mean values recorded 4 hours and 24 hours after unclamping.

In summary, the changes in $ß_2$-microglubulin strongly suggest proximal tubular injury, while the other parameters of tubular function, although suggestive, do not conclusively prove proximal and/or distal tubular damage.

The decrease in urine volumes at all measurement steps after cross clamping of the aorta, corresponded closely with the reductions in GFR during the same steps in our control patients. Previous studies have demonstrated urine volume to be a poor predictor of postoperative renal function in patients undergoing abdominal aortic revascularization (Alpert et al. 1984).

The initial increase in serum ADH concentration, before application of the aorta cross clamp (Table 3.5), was probably due to surgical stimulation (Knight et al. 1986; Ishihara et al. 1978) rather than the effect of anaesthetic drugs, hemodynamic impairment or changes in serum osmolality. Intravascular filling pressures did not change in our patients (Table 3.3) and although MAP decreased significantly after induction of anaesthesia, the extent of this reduction was not sufficient to expect a significant increase in ADH concentration in response (Schrier et al. 1979; Woods et al. 1983). Serum osmolality (not shown in result tables) did not change at any stage in the course of our study. The anaesthetic drugs used in our patients do not increase ADH secretion in the absence of hemodynamic changes (Woods et al. 1983; Ishihara et al. 1978). Increases in angiotensin II concentration might have contributed in maintaining high levels of ADH (Stella and Zanchetti 1987; Schrier and Berl 1975) after aorta clamping, but did not play a role in the initial rise as plasma renin concentration was not influenced by anaesthesia and surgical stimulation prior to cross clamping of the aorta (Table 3.5). The increases in ADH concentrations at the various measurement steps correspond with the only other published study where ADH was also measured perioperatively in patients subjected to infrarenal aorta aneurysm repair (Kataja et al. 1989). They reported an increase in ADH levels prior to cross clamping

of the aorta, reaching a peak in the early postoperative period with increased levels still present on the first postoperative day. Changes in RBF and renal function were not reported in their study.

ADH was clearly not the primary pathogenic or pathophysiological factor which induced the changes in renal hemodynamics and glomerular function, as these parameters were not influenced by the preclamp increase in ADH. In addition, ADH concentration did not escalate further in the perclamp periods when the renal parameters did change. It is possible that the increased ADH might have contributed to the raised RVR at the times of decreased RBF and GFR by enhancing the vasoactive effects of other (primary) vasoconstrictor agent(s). ADH has been demonstrated to potentiate the vasoconstrictor response of angiotensin (Hostetter and Brenner 1988) and catecholamines (Medina et al. 1997; Ishikawa et al. 1984). These potentiating effects occur at ADH concentrations substantially lower than those required to produce a direct contractile response by ADH on its own. This indirect (potentiating) effect of ADH is suggested to involve increased Ca^{2+} entry into the vascular smooth muscle cells through voltage-dependent Ca^{2+} channels (Medina et al. 1997).

The increase in ADH concentrations would, at least partially, have been responsible for the maintenance of high FE_{Na} values, which persisted even when aldosterone was also increased during the later stages. This fact, due to the predominant effect of ADH on the distal tubule and collecting duct, which leads to a greater degree of water than sodium reabsorption, indirectly influences FE_{Na} and renders this parameter a less accurate predictor of acute renal failure (Zaloga et al. 1990). The perpetuation of sodium loss might also have been contributed to by high levels of atrial natriuretic hormone (ANH) (not measured in our study) due to stimulation of its secretion by ADH (Manoogian et al. 1988) and to the increased right atrial filling pressures in the latter part of our study (Table 3.3). The fact that the C_{H2O} was significantly more positive during the two perclamp measurement steps despite the high ADH concentrations which classically produce a negative C_{H2O} (Berry 1990; Fieldman et al. 1985), adds significance to the changes in this predictor of renal tubular injury and dysfunction.

The increase in arterial (P_{ren}) and renal venous (RV_{ren}) plasma concentrations of renin and therefore presumably also angiotensin II, coincided with cross clamping of the aorta and remained elevated into the postoperative period. Some of the mechanisms controlling renin release were observed in our study. A lack of change in MAP

between preclamp and postclamp measurements as well as maintenance of MAP above levels of 70 to 75 mmHg (Robertson and Michelakis 1972) makes renin release induced by pressure (reduction) unlikely. Catecholamine-induced renin release (Michelakis et al. 1969) is also unlikely since catecholamine concentrations did not change significantly subsequent to aortic cross clamping (Table 3.17). In addition, there was no correlation between the changes in renin and noradrenaline concentrations induced by aortic clamping (R=0.029; p=0.923). Although it is possible that placement of the aorta cross clamp could have produced stimulation of the renal nerve which would have induced renin release (Vander 1965), this is again an unlikely scenario. Infrarenal para-aortic dissection in preparation for aortic clamping had already been performed during the preclamp period without apparent renin release. In addition, subsequent perpetuation of increased renin levels occurred in the absence of surgical stimulation in the proximity of the renal neurovascular structures, particularly during the two measurement periods after release of the aortic clamp. Increased levels of ADH, a known stimulus for renin release (Stella and Zanchetti 1987) had no influence on P_{ren} of Rv_{ren} before aortic clamping. The increased concentrations of both ADH and renin after application of the cross clamp were therefore probably largely coincidental. Salt depletion and a decreased extracellular fluid volume (Davis and Freeman 1976) was clearly not responsible for the increase in renin concentrations, considering the volumes of isotonic intravenous fluid with high sodium concentration adminstered and the maintenance of intravascular pressures in the capacitance vessels (Table 3.3). None of the known physiological and pathophysiological stimulants for renin release can therefore be considered as clearly responsible for the aortic clamp-induced increase and the sustained elevation in P_{ren} and RV_{ren} relative to the control and preclamp concentrations.

In concurrence with our study, the majority of publications which report on perioperative changes in P_{ren} in humans subjected to infrarenal aorta surgery, demonstrated increased renin and/or angiotensin concentrations induced by aorta clamping (Kataja et al. 1989; Salem et al. 1988; Grant and Jenkins 1983; Grind-linger et al. 1981). The increased renin levels progressed into the postoperative period, with the exception of the study by Salem et al. where renin was not measured postoperatively. In only one published study (Gal et al. 1974) did an increase in P_{ren} (relative to awake control measurements) precede application of the aorta cross clamp. None of the above studies reports on concomitant measurement of RBF or nephron function although the potential role of angiotensin in the etiology of renal

hemodynamic changes during infrarenal aorta surgery was alluded to (Kataja et al. 1989; Salem et al. 1988; Grant and Jenkins 1983).

Experimental studies (in dogs) where P_{ren} was measured with infrarenal aortic clamping, also measured RBF (Cronenwett and Lindenauer 1977; Berkowitz and Shetty 1974). They produced conflicting results with Berkowitz reporting clamp-induced raised P_{ren} and redistribution of RBF away from the renal cortex and Cronenwett no change in either P_{ren} or RBF.

In our study the decreases in RBF and GFR clearly coincided with the increased P_{ren} and RV_{ren}. It is therefore possible that the increased renin release, through activation of angiotensin, could have been responsible for the changes in renal hemodynamics and nephron function. If angiotensin had been exclusively or predominantly responsible for the changes, one would perhaps have expected a less extensive effect on GFR than on RBF due to the greater effect of angiotensin II on the efferent arteriole with maintenance (and even increase) of P_{gc}. This would also have increased FF (Tucker et al. 1986). None of these changes predicted by an exclusive influence of angiotensin occurred in our patients (RBF vs GFR, Table 3.1 and 3.2; FF, Table 3.2). The changes demonstrated in our patients does not, however, exclude a primary role for angiotensin as similar angiotensin-mediated changes in RBF, GFR and FF have been demonstrated in a number of clinical and experimental circumstances (Ichikawa and Brenner 1984; Kon et al. 1985; Navar et al. 1982). In addition, the renal effects of angiotensin could have been modified by the nitroglycerin administered to our patients after induction of anaesthesia for the duration of the study. The elevated levels of ADH demonstrated in our patients would have potentiated the (renal) vasoconstrictive effects of angiotensin (Hostetter and Brenner 1988). Angiotensin enhancement of prejunctional noradrenaline release (Zimmerman 1978) from the renal nerves might also have contributed to the renovascular and functional changes, despite the fact that circulating levels of the catecholamines did not change significantly in our patients (Table 3.17). The increased levels of angiotensin probably also exerted some of its renovascular effects through stimulation of endothelin synthesis and release (Kohno et al. 1991) and by increasing vascular responsiveness to endothelin (Dohi et al. 1992). The increase in endothelin plasma levels after infrarenal cross clamping of the aorta described by Antonucci et al. (1990) might in fact have been in response to increased levels of renin and angiotensin, a possibility not suggested by the authors.

Our human study does not prove conclusively that renin-mediated increases in angiotensin concentration played a primary pathogenic role in the renal changes induced by infrarenal aortic cross clamping. It is possible that the renin-angiotensin mechanism, although certainly contributing to the measured changes and therefore to the global pathophysiological process, were only activated after (and because of) initial functional and vascular changes similar to the role suggested in ischemic and other forms of acute renal failure (Myers and Moran 1986). Complete abolition of the renal response to infrarenal aorta clamping by either inhibition of renin release or prevention of angiotensin effects (through ACE-inhibition or angiotensin receptor blockade), would provide evidence for a significant, if not exclusive, pathogenic and pathophysiologic role for angiotensin. Unfortunately, evidence in this regard is inconclusive. Colson et al. (1992a) were unable to prevent clamp-induced reduction in RBF by preoperative administration of an ACE-inhibitor. This lack of success can possibly be attributed to inadequate ACE-inhibitor dosage which, even if it had been sufficient to prevent systemic activation of angiotensin, might not have been enough to block intrarenal angiotensin activation which requires higher dosages (Gunning et al. 1996). Successful prevention of renal hemodynamic changes in another human study by Licker et al. (1996) might be confounded by the fact that 5 of their 11 patients also received calcium channel blockers preoperatively, despite their suggestion that more appropriate ACE-inhibitor dosage was responsible for the difference between their study and that of Colson et al. (1992a). The ambiguity of the two relevant animal studies (Cronenwett and Lindenauer 1977; Berkowitz and Shetty 1974) has already been alluded to.

The increase in serum aldosterone concentrations was predictable due to the renin-induced increase in angiotensin II production. The raised aldosterone levels lagged behind the initial increase in P_{ren} to become statistically significantly increased only later in the perclamp period. The changes in aldosterone concentrations in our study are in accordance with results of other similar studies (Cochrane 1978). Changes in aldosterone concentrations do not correlate with altered ACTH concentrations (Table 3.5), which concur with the normal physiological control of aldosterone secretion as well as the mechanisms which pertain perioperatively (Le Quesne et al. 1985). The extent of urinary sodium loss (FE_{Na} and total urinary sodium) is again surprising if one considers the increased aldosterone concentration and may reflect some degree of functional impairment of the proximal and/or distal tubules. The patients in our study demonstrated an almost 4-fold increase in aldosterone levels while the increase is

usually limited to double the preoperative concentration if sodium intake and intravascular volume status are adequate (Cochrane 1978). This was probably due to the extent of P_{ren} increase after aortic cross clamping.

4.3 Mannitol plus dopamine patients and comparison with control patients

The significantly greater volumes of crystalloids infused in mannitol plus dopamine patients relative to the control group (Table 3.16), can at least partially be ascribed to the larger volumes of urine produced in the former group. The larger volumes of intravenous crystalloids in mannitol plus dopamine patients should also be interpreted in the context of the consistently lower PAWP in this group (relative to controls), reaching statistical significance after aortic cross clamping (Figure 3.14). Infusion of intravenous fluids to equivalent left ventricular filling pressures would have resulted in an even greater difference in fluid volumes administered. The difference in intravenous fluid volumes in our study contrasts with two studies where perioperative fluid volumes were similar between control and mannitol plus dopamine patients subjected to infrarenal aortic surgery (Paul et al. 1986; Mazer et al. 1984).

Mannitol and dopamine failed to protect the kidney against a reduction in C_{creat} when comparing preoperative values with (24 hour urine sample) measurements one week postoperatively. This result in our study is contrary to the findings of both Paul et al. (1986) and Mazer et al. (1984) where initial intraoperative decreases in C_{creat} returned to preoperative control values within 24 hours postoperatively in patients who received mannitol and dopamine. Other studies where mannitol and dopamine were not administered perioperatively in aortic surgery, showed variable results with regard to changes in C_{creat}. Myers et al. (1984) and Cohn et al. (1970) demonstrated complete recovery of C_{creat} to preoperative values within 24 hours and 7 days after surgery respectively. Licker et al. (1996) reported lack of C_{creat} recovery 12 hours postoperatively, while Pollock and Johnson (1973), when retrospectively dividing patients in high and low intravenous fluid volume groups, demonstrated recovery of C_{creat} in the former and reduced C_{creat} in the latter group postoperatively. Powis (1975) did not publish statistical analysis on postoperative C_{creat} measurements, but reported postoperative recovery of C_{creat} in 3 patients, improved values in 9 patients and reduced measurements in 21 patients relative to their individual preoperative controls. It is possible that the majority of studies demonstrating no significant difference between preoperative and postoperative C_{creat}, were unable to do so because of a

small sample size. When reported, they almost invariably indicated either a mean postoperative C_{creat} less than the preoperative mean (statistically not significant), or some individual patients with considerably reduced values postoperatively.

The aortic cross clamp-induced decrease in RBF was clearly not prevented by the administration of mannitol and dopamine (Figure 3.1). Ours is the first study to report on the influence of the combination of these two agents on RBF during infrarenal aortic surgery. In a study of patients subjected to suprarenal aortic cross clamping of the aorta, Pass et al. (1988) were unable to establish any benefit from the use of mannitol and dopamine (both individually and as a combination) in the continued reduction of RBF (for the first 150 minutes) subsequent to release of the suprarenal cross clamp.

Mannitol had been demonstrated to correct the reversal of RBF away from the renal cortex induced by infrarenal aortic cross clamping (Abbott and Austen 1974) in experimental animals. The clinical relevance of this study is compromised by the fact that the mannitol was administered directly into the renal artery. Barry et al. (1961) reported an increase in urine flow effected by a high dose of mannitol (a minimum of 237 gram per patient) during infrarenal aortic surgery with a small population (5 mannitol and 5 control patients). They interpreted the increased urine volume as an indication of increased RBF and GFR based on a previous study, which demonstrated a correlation between urine volume and RBF (Barry et al. 1960). This relationship has subsequently been shown not to exist universally (Alpert et al. 1984). In addition, another experimental study in dogs could not demonstrate that mannitol prevented a decrease in RBF with infrarenal aortic cross clamping, despite a significant improvement in urine volume (Stein et al. 1972).

The lack of clear evidence of maintenance or improvement of RBF by mannitol in aortic surgery contrasts with other experimental models where benefit has been demonstrated. Such improvement in RBF has been shown in both cortical and medullary blood flow in normal dogs (Velasques et al. 1973; Wendling et al. 1969), in the post-ischemic kidney (Zager et al. 1985) and during partial occlusion of the renal artery (Behnia et al. 1996). Mechanisms proposed for the beneficial effect of mannitol on the renal circulation had been the release of intrarenal vasodilatory prostaglandins (Johnston et al. 1981), the release of atrial natriuretic hormone (ANH) (Kurnik et al. 1990), and a decrease in renin release (Lang 1987). Although ANH concentrations were not measured in our study, there is no reason to suspect a higher concentration

of ANH in the mannitol plus dopamine patients relative to the control group, particularly with atrial filling pressures being comparable or even lower in the former group of patients. Mannitol clearly did not suppress renin secretion in our patients (Figures 3.16, 3.17), an effect which should not have been influenced by the concurrent administration of a low dose of dopamine (Levinson et al. 1985). Urinary concentrations of prostaglandins were not measured in our study.

Low dose dopamine (2 μg.kg^{-1}.min^{-1}), in a very small sample (n = 5) of patients **after** abdominal aorta surgery was shown to increase RBF (Schwartz et al. 1988). However, this study suffers from the same methodological problem as many other studies where PAH clearance had been used to calculate RBF. Dopamine alters PAH extraction, so that PAH clearance becomes invalid as method of RBF calculation unless PAH extraction is measured through arterial and renal venous blood sampling (Duke and Bersten 1992).

Although there are numerous animal (Kapusta and Robie 1988; Hollenberg et al. 1973) and human (Stevens et al. 1989; McDonald et al. 1964) studies which report increased RBF with low dose continuous infusion of dopamine, the majority of these studies suffer from the failure to adequately control for the other direct and indirect effects of dopamine such as an increase in CO, raised renal perfusion pressure and its effect on tubular function, which may also influence RBF. The methodological caveat alluded to above and the fact that plasma dopamine levels correlate poorly with the infused dose, particularly in critically ill patients (Zaritsky et al. 1988), are also frequently ignored. Some studies failed to show an increase in RBF (Wassermann et al. 1980; Hilberman et al. 1984), or suggested the increase in RBF to be a secondary phenomenon to an increase in CO, even with low dose dopamine infusion (Gordon et al. 1995; Shoemaker et al. 1989). Cardiac output was not influenced by dopamine in our patients, as significant differences did not exist at any measurement period between control and mannitol plus dopamine patients (Figure 3.15). It is possible that the renovascular effects of increasing age (nephrosclerosis) in our patients could have limited the renovascular effects of dopamine (Hollenberg et al. 1973). On the other hand, the fact that some of our patients had been hypertensive should have enhanced the renal vasodilatory effect of dopamine (Breckenridge et al. 1971) due to upregulation of dopamine receptors in these patients (Andrejak and Hary 1986).

The pattern of changes in RVR (given the changes in RBF without prominent fluctuations in MAP and venous pressures) is predictable in the mannitol plus dopamine patients. Where both dopamine (Hollenberg et al. 1973) and mannitol (Velasques et al. 1973) have been demonstrated to decrease RVR in conditions not involving aortic manipulation, these drugs were clearly unable to induce such a beneficial effect in our vascular surgery population.

Similar to control patients, mannitol plus dopamine patients responded to aortic cross clamping with a substantial decrease in GFR. GFR improved progressively after release of the cross clamp, but was still almost 30% below awake control values 4 hours after unclamping. This lack of positive influence of mannitol plus dopamine on GFR in aortic surgery has been demonstrated previously (Paul et al. 1986; Mazer et al. 1984). Where mannitol or dopamine has been reported to enhance GFR, it has almost invariably been associated with a coincidental improvement in RBF when both parameters were measured (Andrejak and Harry 1986; Blantz 1974). Mannitol and dopamine clearly did not enhance RBF in the patients in our study.

Only Cohn et al. (1970) measured C_{creat} in the later postoperative phase and were unable to show significant differences with preoperative control values. Our study is therefore the first to demonstrate persistence of decreased GFR (as measured with C_{creat}) as late as 1 week postoperatively (Table 3.16). Adequacy of urine collection is suggested by the total urine creatinine values reported in chapter 2 (section 2.1) of this thesis (Gonin and Molitoris 1997). A reduction of 8.58 or 9.7 ml.min.$^{-1}$ (the mean decreases found in our control and mannitol plus dopamine groups respectively) will be of no immediate significance in patients with normal preoperative renal function. However, such a decrease in GFR may induce an increase in plasma creatinine and other sequelae of renal failure in patients who preoperatively have significant compromise of renal glomerular reserve with loss of functional glomeruli in excess of 50% of normal, while still maintaining a normal serum creatinine concentration (McLachlan 1978). Such a scenario would not be uncommon in our surgical population of elderly patients with diseases such as hypertension and diabetes, which compromise renal ultrastructure and function (McLachlan 1978). A specific subgroup of patients at risk of progressing towards renal failure with postoperative serum creatinine concentrations in excess of 120μmol.l^{-1} 7 days after surgery, were identified in our study. Statistical analysis of our data suggest that 95% of such a population at risk would present with a preoperative C_{creat} of less than 68ml.min^{-1}. Preoperative serum

creatinine concentrations are not helpful to identify this subgroup of patients. Despite the possibility that C_{creat} may still improve in the period subsequent to 7 days post-surgery, our data suggests that the determination of creatinine clearance should be a component of the preoperative work-up of patients scheduled for abdominal aorta aneurysm repair, rather than serum creatinine measurement which is a poor indicator of renal function until its serum concentration starts to increase appreciably, which only occurs when approximately 50% of renal function is lost (Rowe 1977). In the presence of a preoperative C_{creat} below 68ml.min^{-1} a conservative (rather than surgical) approach with regular follow up to monitor change in aneurysm size could be considered, particularly in patients with other risk factors for the development of perioperative ARF.

More than one factor could have been responsible for the mannitol plus dopamine intragroup decrease in FF during the perclamp period (Table 3.9), and relative to the control patients in both the perclamp period and prior to aortic clamping (Figure 3.7). Vascular dopamine-1 receptor stimulation results in a predominantly postglomerular response by direct vasodilation of the efferent arterioles (Girbes et al. 1990, Wee et al. 1986). Such an effect would decrease intraglomerular capillary hydrostatic pressure in the mannitol plus dopamine patients and therefore reduce FF. The difference between the mannitol plus dopamine group and control patients can also be accounted for by a tubuloglomerular feedback-induced lower FF (Maddox and Brenner 1996) in the former group. The intragroup decrease in FF is difficult to ascribe to a tubuloglomerular feedback mechanism in the presence of a decrease in urine volume and TU_{Na} at the measurement times, which coincided with the reduced FF. It is possible that the TNT infusion could, through a predominant effect on the efferent arteriole, have contributed to the decrease in FF. The highest TNT infusion rates coincided with the lowest FF values.

Mannitol and dopamine prevented the aortic cross clamp-induced decrease in volume of urine produced and was responsible for significantly higher volumes at all measurement times subsequent to aortic clamping relative to control patients. In the study by Paul et al. (1986) mannitol and dopamine induced the production of urine during and after aortic clamping which was significantly more than the mean post-induction volume. It is a consistent feature of published trials that dopamine increases urine output during (Salem et al. 1988, Schwartz et al. 1988) and after (Girbes et al. 1996; Schwartz et al. 1988) infrarenal aortic surgery. Mannitol has also been demonstrated to induce increased volumes of urine production perioperatively in

patients subjected to aortic reconstructive surgery (Abbott and Austen 1974, Luck and Irvine 1965; Barry et al. 1961). The maintenance of urine output induced by the combination of mannitol and dopamine may, when more specific parameters of renal function are not available, lead to a false sense of security. Three of the patients in the mannitol plus dopamine group became anuric during the night after surgery with adequate urine volumes produced until sudden cessation of urine flow. In all three cases, assessment revealed that intravascular volume status became progressively compromised with PAWP decreasing to zero over a period of 2-4 hours without the attending staff taking cognisance of this fact. Intravenous fluid resuscitation led to prompt stabilization of hemodynamic status and resumption of urine production in all three patients.

The fact that there were no differences in urinary sodium concentrations between control and mannitol plus dopamine patients (results not shown) and the higher urine volumes in the latter group, predicts the higher TU_{Na} in the mannitol plus dopamine patients at all measurement times subsequent to starting administration of the drugs (relative to control patients; Figure 3.9). Dopamine had previously been shown to increase total urinary sodium excretion both during (Salem et al. 1988) and after (Schwartz et al. 1988) infrarenal aortic cross clamping. The natriuretic effect of dopamine becomes more evident under states of extracellular fluid expansion (Agnoli et al. 1987). This might have contributed to the sodium excretion in the mannitol plus dopamine patients in our study with the maintenance of PAWP at mean values in excess of 10 mmHg. The natriuretic effect of dopamine had also been demonstrated to prevail in the absence of increases in RBF and GFR (Jose et al. 1987), a situation which was pertinent in our study. The maintenance of urinary sodium concentrations, despite an initial decrease in urine volume in the mannitol plus dopamine patients (Table 3.11), might have been due to inhibition of tubular reabsorption of sodium (Krishna et al. 1985) or impairment of the tubuloglomerular feedback mechanism by dopamine (Schnermann et al. 1990). Mannitol also increases **total** urinary sodium in aortic surgery despite a decrease in urinary sodium **concentration** (Abbott and Austen 1974). The mechanism of mannitol-induced natriuresis is the result of osmotic inhibition of water (more than sodium) transport in the proximal tubule (Warren and Blantz 1981) which diminishes the gradient for passive sodium absorption in the thin ascending limb of Henle (Seely and Dirks 1969).

While FE_{Na} decreased in control patients after the awake control measurement, mannitol and dopamine maintained this parameter at mean values which were higher than the pre-induction values, although this did not reach statistical significance. The FE_{Na} in the mannitol plus dopamine group was, however, significantly higher than in control patients at al measurement times after commencement of the drugs in the former group (Figure 3.10). This was predictable as both mannitol (Warren and Blantz 1981) and low-dose dopamine (Andrejak and Hary 1986) have been demonstrated to increase FE_{Na}. The dopamine-induced enhancement of FE_{Na} was probably augmented by the fact that some of our patients were hypertensive, a condition which enhances the natriuretic effect of dopamine (Andrejak and Hary 1986). The use of mannitol and dopamine renders the FE_{Na} an unreliable predictor of renal tubular injury, despite the fact that FE_{Na} values were consistently higher than 0.06, which is considered to be diagnostic of tubular damage (Oken 1981).

Despite the fact that mannitol induces an even bigger water than sodium loss (Gennari and Kassirer 1974), thus obligating a more positive C_{H2O} (Gann et al. 1964), there was no difference in C_{H2O} values between control and mannitol plus dopamine patients at any measurement time. C_{H2O} values in mannitol plus dopamine patients gave no indication of the development of acute renal insufficiency (Landes et al. 1976).

The progression and extent of $ß_2$-microglobulinuria was similar in control and mannitol plus dopamine patients. Mannitol and dopamine were therefore unable to protect the kidney from proximal tubular injury (Schardijn and Van Eps 1987).

P_{ren} and RV_{ren} in mannitol plus dopamine patients increased at the same measurement times as in control patients. Neither P_{ren} or RV_{ren} was different in the mannitol plus dopamine group from the measurements in control patients at any measurement time, despite higher plasma noradrenaline concentrations in the former group. Higher doses of dopamine have been demonstrated to increase renin levels through ß-receptor stimulation (Lopez et al. 1979) and by stimulating dopaminergic receptors (Williams et al. 1983). However, at a dose of $3\mu g.kg^{-1}.min^{-1}$ no increase in plasma renin concentration has been recorded despite an increase in plasma noradrenaline concentration (Levinson et al. 1985).

Although mean serum aldosterone concentrations were consistently lower in mannitol plus dopamine patients than in the control group (after starting the drugs in the former group), these differences never reached statistical significance. Dopamine had been

shown to inhibit zona glomerulosa function which decreased aldosterone release (Carey et al. 1979) and also specifically to inhibit both angiotensin-stimulated biosynthesis and release of aldosterone (McKenna et al. 1979). This effect may contribute to the natriuretic and diuretic effect of dopamine.

Although dopamine, via dopamine-2 receptor stimulation, can inhibit the release of ADH from the posterior pituitary gland (Pittman et al. 1983), this was not evident in the mannitol plus dopamine patients in our study. ADH release, induced by surgical stress, was similar in control and in mannitol plus dopamine patients.

In summary, mannitol and dopamine was unsuccessful in preventing the aortic cross clamp-induced decrease in RBF and nephron dysfunction. Although both mannitol (Cronin et al. 1978) and low dose dopamine (Davis et al. 1982) have been suggested to modify the course of ischemic acute renal failure (ARF), there are no properly controlled studies showing a decrease in the incidence of ARF with the use of these potentially protective agents in populations at risk. Indeed, there is growing concern that the increased sodium load presented to the thick ascending limb of the loop of Henle and to the distal tubules with the use of these agents, may increase the tubular oxygen demand and therefore compromise tubular survival (Duke and Bersten 1992, Cottee 1995). In our study, the combination of mannitol and dopamine also had no significant influence on the hormonal changes potentially involved with the pathogenesis or pathophysiology of altered renal hemodynamics and nephron function with infrarenal aortic cross clamping.

4.4   Potential benefit of ACE inhibition and ß-adrenergic blockade

Appropriate methods to investigate the pathophysiological role of angiotensin II in the renal hemodynamic and functional changes associated with infrarenal aortic cross clamping, would be to block angiotensin receptors or to prevent activation of angiotensin with ACE inhibitors, or to prevent release of renin with a ß-blocker. We chose the latter two methods as these drugs are more readily available and are more likely to be used in the relevant clinical situation if demonstrated to be beneficial.

To assess the influence of drugs on the renal parameters, the ideal would be to take control measurements intraoperatively, then administer the drugs and allow adequate time for the agents to take full effect before another set of preclamp control measurements are taken. Such an approach would add substantially to the experi-

mental time, as adding another measurement period would extend the experiment by more than 30 minutes (20 minutes sampling period plus taking measurements and samples at the end). In addition, at least 60 minutes would have to be allowed for maximum (renal) biophase effect to be achieved after drug administration before the (post-drug) preclamp measurements could be taken. This would have been necessary, even with the short half life, rapid acting drugs esmolol and enalaprilat as the former drug has been demonstrated to require 32.1 (± 15 (SD)) minutes to achieve 90% of maximum effect on plasma renin activity (Ornstein et al. 1995). The onset time for enalaprilat is in excess of 60 minutes (Waeber et al. 1989; Mirenda et al. 1991). The total time added would have compelled the radioisotope counts to be done on the following day and the relatively short half-lives of the isotopes would have rendered these measurements inaccurate. The "control" (preclamp) measurements are therefore not truly comparable between the three animal groups (esmolol, enalaprilat and control groups), as parameters in the experimental drug groups might already have been influenced by those agents. Although there were no statistically significant differences between the groups in any of the important parameters at the "control" (preclamp) measurement time, mean values between groups did demonstrate some variation in some parameters such as RBF (Tables 3.19, 3.23 and 3.28). To accommodate the above, statistics were performed to measure the differences in *changes* between groups induced by interventions (clamping = *change* from measurement time 1 to 2; duration of clamping = *change* from measurement time 2 to 3; unclamping = *change* from measurement time 3 to 4; whole procedure = *change* from measurement time 1 to 4). For comparison of sequential measurements **within** a specific animal group (intragroup differences), however, conventional parametric/ non-parametric statistical methods remain valid.

It is conspicuous that RBF decreased significantly in control animals upon application of the aortic cross clamp (Table 3.19) while cross clamping did not induce such a change in the enalaprilat (Table 3.28) group. Although RBF did decrease in the esmolol group upon application of the aortic clamp, this reduction was much less than in control animals in absolute (71 vs 291ml.min^{-1}) and relative (13.5% vs 52.8% lower than preclamp values) terms. **The protective effects of esmolol and enalaprilat** are confirmed by the fact that the comparison of intergroup changes from measurement 1 to 2 also demonstrates differences between control and the esmolol as well as the control and enalaprilat groups (Figure 3.24). The beneficial effect of ACE inhibition in our study concurs with the findings in the clinical study of Licker et al. (1996), but is in

conflict with the results of Colson et al. (1992a) who failed to demonstrate significant advantage with ACE inhibition. However, the adequacy of the preoperative oral dosages of enalapril in the latter study may be questioned. The higher doses of ACE inhibitors used in our study and the Licker et al. (1996) report, are likely to have been more successful in maintaining renal hemodynamics through more effective blockade of intrarenal angiotensin activation (Dzau 1987). Prevention of renin release with ß-blockade (and therefore, presumably, activation of angiotensin) with infrarenal aortic clamping were demonstrated to prevent redistribution of RBF to the deeper cortex and medulla in a study on dogs (Berkowitz and Shetty 1974). Unfortunately, RBF was not measured in any of the human studies which reported on the influence of ß-blockade on renin release during abdominal aortic surgery (Grindlinger et al. 1981; Grant and Jenkins 1983).

It therefore appears that angiotensin plays an important role in the decrease in RBF induced by infrarenal aortic cross clamping. Although angiotensin might have played a primary role in this context, it is also possible that renal vasoconstriction was mediated through the permissive effect of angiotensin on the influence of other vasoactive substances. Such a role for angiotensin has been described with endothelin (Miller et al. 1989) and adenosine (Dietrich et al. 1990). The presence of angiotensin is essential for the renal vasoconstrictive effects of both these substances. Endothelin release could also have been the instigating event, since it could theoretically induce a decrease in RBF through enhancing the activity of ACE (Kawaguchi et al. 1990) which could explain the beneficial effect of ACE inhibition. A significant role for the latter mechanism is unlikely, however, since that would have resulted in a much more beneficial effect of ACE-inhibition on RBF than that achieved with ß-blockade which reduces angiotensin through inhibition of renin release without any direct influence on the ACE. A somewhat better protective effect on RBF by ACE inhibition is suggested by the fact that RBF did decrease significantly in the esmolol group upon application of the aortic clamp without any significant change in enalaprilat animals (intragroup differences), although the *changes* between measurements 1 and 2 were no different between the groups. This could be explained by some degree of primary release of endothelin and its effect on ACE activity described above (Kawaguchi et al. 1990), or possibly by the renal vasodilatory effects of bradykinin. The ACE is responsible for the degradation of the latter substance; ACE inhibition would consequently increase bradykinin concentration (Williams 1988). Bradykinin induces renal vasodilation on its own, as well as possibly through stimulating the synthesis of various prostaglandins

(Rotmensch et al. 1988; Williams 1988). Increased bradykinin concentration through the influence of ACE inhibition also produces renal vasodilatation indirectly (particularly under pathophysiological circumstances) by inhibiting endothelin (a potent renal vasoconstrictor) synthesis (Momose et al. 1993).

Considering the clamp induced increase in noradrenaline concentration in one patient group in our human study which has also been reported previously (Kataja et al. 1989), both ß-blockade and ACE inhibition is likely to have been of benefit through modulating the interaction between the sympathetic and renin-angiotensin systems. By decreasing angiotensin II concentrations, both enalaprilat and esmolol would have decreased presynaptic noradrenaline release (Zimmerman 1978). ß-receptor blockade by esmolol would also have decreased vascular production of angiotensin II and the consequent effect of the latter substance on the renal vascular tone (Kawasaki et al. 1984). ß-blocker inhibition of vascular angiotensin production would also be of indirect benefit since the latter substance enhances presynaptic noradrenaline release which promotes additional vasoconstriction (Kawasaki et al. 1984, Nakamaru et al. 1986).

In both the enalaprilat and esmolol animals, RBF decreased significantly upon release of the aortic clamp (relative to its mean preclamp value in enalaprilat animals and relative to all three previous measurements in esmolol pigs), while no further significant decrease in control animals occurred. This clearly suggests the release of (a) vasoactive substance(s) or (a) hemodynamic event(s) in which the two experimental drugs proved ineffective protective agents. Changes in hemodynamic variables as causative events are unlikely. Decreases in cardiac filling pressures (which might have induced decreases in atrial natriuretic peptide, with indirect reduction of RBF (Weidmann et al. 1986)) did not occur after aortic unclamping in any of the groups. Both CO and MAP were also maintained relative to preclamp measurements in all groups, the latter parameter being consistently within autoregulatory range.

Since the plasma renin levels did not increase in the ß-blocked animals, it is probably safe to assume that circulating angiotensin II levels did not increase in that group. Consistently high renin concentrations in the enalaprilat group suggest adequate blockade of systemic ACE, with low angiotensin II concentrations abolishing the negative feedback on renin secretion. Although it is possible that intrarenal (rather than systemic) activation of angiotensin II could have been primarily responsible for the decrease in RBF after aortic unclamping in the two experimental drug groups, it is

unlikely. The dose of enalaprilat used, and its duration of action, should have been adequate even to inhibit intrarenal angiotensin activation (Dzau 1987). Unlike other similar studies, renin (and presumably also angiotensin) concentration did not increase further after release of the aortic clamp relative to postclamp values in our control group (Gal et al. 1974; Grindlinger et al. 1981; Grant and Jenkins 1983), providing further evidence for the involvement of other vasoactive substances in the curtailment of RBF after clamp release in the two drug groups.

It is quite possible that vasoactive substances can be released into the systemic circulation from (at least partially) ischemic tissues distal to the aortic cross clamp when the aorta is unclamped. Plasma purine degradation products, and adenosine in particular, could play such a role. Plasma adenosine concentrations have been reported in only one experimental study where an infrarenal aortic cross clamp was applied in a dog model (Frank et al. 1988). Although mean plasma adenosine levels after release of the clamp peaked at 92% above pre-unclamp controls, the difference was not significantly different due to data scatter. In addition, the mean difference dropped off to 34% after 10 minutes while RBF decreased significantly after clamp removal (relative to pre-unclamp measurements) and was still significantly reduced beyond the 10 minutes post-unclamp measurements. Clearly, although adenosine release could contribute to the initial decrease in RBF after aortic unclamping, it could not be responsible for the prolonged post-unclamp compromise evident in both our human and animal studies and reported in numerous other studies (Gamulin 1984, 1986; Colson 1992a, 1992b). While our own human study was restricted to patients scheduled for abdominal aortic aneurysm repair, the other four studies quoted above also included patients with aorto-iliac occlusive disease. Due to the development of collateral circulation in such individuals, clamp-induced distal ischemia with significant adenosine release upon unclamping is unlikely. Unfortunately a statistical analysis comparing the changes in aortic aneurysm patients with those with aorto-iliac disease was not performed in any of these studies, neither was there any reference to a possible difference between such patients.

Postischemic systemic release of endothelin (Battistini et al. 1993) might also have played a role in the post-unclamp decrease in RBF in the esmolol and enalaprilat animal groups. Plasma endothelin concentration has been reported to be raised even before aortic unclamping (Antonucci et al. 1990) and could quite possibly increase even more after aortic unclamping due to synthesis and release from ischemic tissue

distal to the clamp although this was not measured/reported in the Antonucci study. The duration of endothelin-induced renal vasoconstriction is also more likely to correspond with our reported post-unclamp renal ischemia as the contractile response of endothelin is sustained and more difficult to wash out than that effected by other vasoconstrictors (De Nucci et al. 1988). However, the inability of enalaprilat to prevent the aortic unclamp-induced decrease in RBF in that animal group, suggests a complementary role at most for endothelin in this phase as ACE-inhibition significantly reduces the renal vasoconstrictive effects of endothelin (Chan et al. 1994). If endothelin had played a significant role in post-unclamp renal ischemia, the administration of dihidropiridine Ca^{2+} channel blockers would have attenuated this response (Madeddu et al. 1990; Loutzenhiser et al. 1990). By contrast, verapamil should have been ineffective in blunting the renal vasoconstriction (Cao and Banks 1990) (see again in next section).

The role of other vasoactive substances in this unclamp-induced renal ischemia can only be speculated about. Inhibition of synthesis of both prostaglandins and nitric oxide (NO) have been demonstrated to greatly aggravate the unclamp-induced decrease in RBF in rats (Myers et al. 1996). The authors do not claim inhibition of these substances to be responsible for the renal ischemia induced by aortic unclamping, but rather suggest their presence to be important in the (partial) maintenance of autoregulation of RBF. However, it is conceivable that reactive oxygen intermediates released from ischemic tissues distal to the aortic clamp at the time of unclamping and reperfusion, can inactivate NO and also influence the synthesis of protective prostaglandins as have been previously demonstrated in other models (Marsden et al. 1996, Ardaillou and Baud 1992).

It is unlikely that reperfusion-induced changes in the vasculature of the kidney itself could be responsible for the decrease in RBF after unclamping in the two experimental groups. Firstly there was no decrease in total RBF during the aortic clamping period in these groups which could have induced the production of reactive oxygen intermediates. Secondly, regional ischemia in the kidney due to substantial redistribution of RBF (even with an unchanged total RBF), could theoretically render some areas sufficiently ischemic to effect the generation of reactive oxygen intermediates in such areas. Based on the fact that E_{HIP} were not influenced by aortic clamping in any of the groups, it can be assumed that redistribution of RBF between

the cortical and medullary/deeper cortical areas of the kidneys did not occur (Gamulin 1984).

The extent and time periods of changes in GFR in the three animal groups closely resembled the changes in RBF. GFR was preserved during aortic clamping in the two experimental groups while it decreased substantially (by 52.8%) upon aortic clamping in control animals (Figure 3.25). Nevertheless, the extent of the change was only significantly different between the control and enalaprilat groups, again suggesting a somewhat better protective effect of ACE inhibition (relative to ß-blockade). Aortic unclamping induced significant decreases in GFR in both enalaprilat (33.2% decrease) and esmolol (37% decrease) animals while it remained essentially unchanged relative to pre-unclamp measurements in control pigs. The extent of *change* in GFR induced by aortic unclamping was also significantly different between the two drug groups and control animals. The fact that the FF did not increase in association with the decrease in GFR upon aortic clamping in control animals suggests that factors other than angiotensin II also had an influence on glomerular dynamics. In the presence of angiotensin alone, predominant vasoconstriction of the efferent arterioles would occur, increasing hydrostatic pressure in glomerular capillaries and increasing nett filtration (prevailing over the angiotensin-induced mesangial cell contraction which would decrease the filtration coefficient and tend to have the opposite effect) (Edwards 1983; Ichikawa et al. 1991). The unchanged FF associated with the decreased GFR after aortic unclamping in the enalaprilat and esmolol groups also suggests the influence of vasoconstrictor agent(s) with a balanced effect on the afferent and efferent arterioles.

Although urine output is suggested to be a poor indicator of the status of RBF under surgical conditions (Alpert et al. 1984), changes in RBF were very similar to percentage changes in urine volumes at the various measurement times in the control and esmolol groups. The post-unclamp decrease in RBF in the enalaprilat group, however, was not associated with a significant reduction in urine output. The administration of an ACE inhibitor has previously been demonstrated to be accompanied by the maintenance or even increase of urine volumes in abdominal aortic surgery although RBF was not measured in this study (Kataja et al. 1989). This could possibly be mediated by increased intrarenal concentrations of bradykinin due to inhibition of its metabolism by ACE inhibitors (Williams 1988). The localization of the kallikrein-kininogen system in the collecting duct suggests that kinins may play a role in transport processes in that part of the nephron (Gunning et al. 1996). Inhibition of

endogenous bradykinin has been demonstrated to result in decreased sodium and water excretion (Marin-Grez 1974). Kinins have also been shown to inhibit ADH-stimulated water (Schuster et al. 1984) and sodium (Tomita et al. 1984) permeability in the collecting duct and thus restricting the antidiuretic effect of the hormone.

C_{H2O} and FE_{Na} calculations did not provide evidence of ischemic (distal) tubular dysfunction in any animal group except for the C_{H2O} becoming significantly more positive just after aortic clamping in the control group, but recovering subsequently. While increased FE_{Na} is regarded as an indicator of renal tubular dysfunction in the development of acute renal failure (Oken 1981), decreased angiotensin concentration (due to the influence of ACE inhibition or ß-blockade) could also increase FE_{Na} (Steiner 1984), particularly in the presence of raised levels of ADH such as during intense surgical stress (Fieldman et al. 1985; our own human study). The fact that FE_{Na} did not increase in the esmolol and enalaprilat animal groups could therefore be regarded as an indicator of the absence of significant tubular injury.

Although the severity scores and number of abnormal subcellular structures were better in esmolol and enalaprilat animals than in the control group, these differences did not reach statistical significance (Table 3.58). The same applies to the comparison of numbers of animals per group which were classified as clearly abnormal versus normal or only minimal change to the renal ultrastructure (Table 3.59). Since the renal biopsies were taken approximately 60 minutes after aortic unclamping, this constitutes periods of decreased RBF (relative to preclamp RBF values in the respective groups) of 60 minutes in the enalaprilat and esmolol groups and 120 minutes in control animals. Histological changes similar to those found in our animal groups, have previously been described after periods of 60 to 110 minutes of partial renal ischemia (Kreisberg et al. 1976, Dobyan et al. 1977). None of the ultrastructural changes found in our animal groups can be considered to be irreversible (Reimer et al. 1972, Glaumann et al. 1977). However, RBF was still decreased relative to preclamp values at the time of biopsy in all three animal groups. It is therefore likely that the extent of ischemic injury would have been worse if the biopsies had been taken at a later stage, depending on the duration of eventual ischemia (Glaumann et al. 1975a, 1975b).

While some studies claim a selective susceptibility of the medullary thick ascending limb (mTAL) for renal ischemic injury (Brezis et al. 1984a, 1984b, 1984c), the changes in all three animal groups in our study were restricted to the proximal tubule,

particularly the S3 segment in the inner cortex and outer medulla. This corresponds with the sensitivity for ischemic injury described for this part of the nephron (Venkatachalam et al. 1978, Endre et al. 1989).

In summary, ACE inhibition and ß-blockade prevented the aortic cross clamp induced decrease in RBF and GFR. However, aortic unclamping induced a significant decrease in both these parameters in animals "protected" by either enalaprilat or esmolol. A vasoconstrictive mechanism(s) other than angiotensin is therefore responsible for the pathophysiological changes induced by aortic unclamping. The fact that prevention of angiotensin II production inhibited the changes in renal hemodynamics and glomerular function induced by aortic clamping, does not establish a primary pathogenic role for the hormone in that time period. Both ACE inhibitors and ß-blockers have other renal protective effects unrelated to (preventing) the direct effects of angiotensin II.

4.5   The potential benefit of calcium channel blockers

As the renal changes in control and ACE-inhibited animals and differences between those groups have been discussed previously, this section will concentrate on the influence of calcium channel blockade and its comparison with the two other groups.

The dose of verapamil and the decision to use a continuous infusion is consistent with its relatively short duration of effect on renal hemodynamics and based on dosages previously demonstrated to be protective in models of experimental acute ischemic renal failure (Alvarez et al. 1994, Fisher and Grotta 1993, Wait et al. 1983).

Similar to the ACE-inhibitor group, RBF did not decrease in the verapamil group upon aortic cross clamping (Table 3.28, 3.39 Figure 3.27). This is consistent with the postclamp maintenance of RBF demonstrated during infrarenal aortic aneurysm repair by Colson et al. (1992a) in patients who received nicardepine preoperatively. In addition, the post-unclamp decrease in RBF which occurred in ACE-inhibited animals, was not evident in the verapamil group. The superior protective effect of Ca^{2+}-channel blockade after cross clamp release is confirmed by the difference in changes of RBF from measurement times 3 to 4 between the verapamil and enalaprilat groups. Post-unclamp maintenance of RBF despite a significant increase in renin concentration at that measurement time, is in keeping with calcium blocker inhibition of renal vasoconstriction induced by angiotensin (Ichikawa et al. 1979, Goldberg and Schrier

1984). However, calcium influx has also been demonstrated to be instrumental in the renal vasoconstrive effects of other potential causative agents such as noradrenaline (Steele and Challoner-Hue 1984), endothelin (Migas et al. 1993), thromboxane (Loutzenhiser et al. 1986) and ADH (Goldberg and Schrier 1984). Calcium channel blockers have been reported to successfully reverse the renal hemodynamic effects of these vasoconstrictors (Loutzenhiser and Epstein 1985, Loutzenhiser et al. 1986, Kiowsky et al. 1991).

If the beneficial renal hemodynamic effect of verapamil had been due to prevention/reversal of angiotensin induced renal vasoconstriction, one would have expected the FF to increase at the time (which did not occur) as the efferent arteriole is less responsive to calcium channel blockers under the influence of angiotensin than the afferent arteriole (Ichikawa 1979). This is possibly due to the fact that efferent arteriole vasoconstriction is mediated largely through mobilization of intracellular calcium in response to angiotensin II, rather than influx of extracellular calcium through voltage regulated channels (Smith et al. 1984). This is substantiated by the fact that the renal vasodilatation obtained with ACE-inhibition during coincident verapamil infusion could be partly reversed by angiotensin II administration, indicating partial transmembrane calcium flux independence of the renovascular effects of angiotensin (Navar et al. 1986). However, while dihidropyridine calcium channel blockers appear to preferentially decrease afferent arteriolar constriction (Loutzenhiser and Epstein 1985), verapamil has both afferent and efferent effects (Fisher and Grotta 1993) which would prevent major changes in intraglomerular capillary hydrostatic pressure and thus maintain FF relatively unchanged. It is also possible that FF did not increase because verapamil did not completely block the effect of angiotensin II on the glomerular filtration coefficient (angiotensin induced mesangial cell contraction which decreases the coefficient) (Ichikawa et al. 1974). However, it is perhaps most likely that the beneficial effect of calcium channel blockade after aortic unclamping had been due to inhibition of transmembrane calcium flux induced by other vasoconstrictors, since ACE-inhibition had been unsuccessful in preventing a post-unclamp decrease in RBF in that experimental group.

The maintenance of RBF in both perclamp and the post-unclamp periods with the administration of verapamil is not necessarily (only) due to the role of calcium in the final common pathway of vascular smooth muscle contraction induced by vasoconstrictors. Calcium channel blockers also interfere with the activation of some

cell types, which result in decreased synthesis and secretion of vasoactive substances. Calcium channel blockade has been demonstrated to decrease the synthesis and release of the potent vasoconstrictive prostanoid, thromboxane (Rostagno et al. 1991) and modulates the release of endothelin during infrarenal aortic surgery (Antonucci et al. 1996). It also suppresses the activation of macrophages (Wright et al. 1985), neutrophils (Jouvin-Marché et al. 1983) and platelets (DeCree et al. 1979), all of which are important sources of vasoactive substances.

One concern about the universal use of calcium channel blockers in infrarenal aortic surgery, is the fact that these agents have been demonstrated to block renal autoregulatory capability in vitro (Cohen and Fray 1982) and in vivo (Nava et al. 1986). The flow : pressure relationship below autoregulatory pressure range is however no worse with Ca^{2+}-blockade than without it (Navar et al. 1986). Other vasodilators including acetylcholine, dopamine and prostaglandin E_2 induce additional (beneficial) vasodilatation at arterial pressures below the autoregulatory range (Baer and Navar 1973; Gross et al. 1976). This leftward shift of the flow: pressure relationship at perfusion pressures below normal autoregulatory range, would effect improved renal perfusion under such detrimental clinical conditions which Ca^{2+}-blockade would not emulate. Conversely, verapamil prevents ischemia induced loss of autoregulation of RBF (Robinette et al. 1987), which would be beneficial in the event of an ischemic insult to the kidneys. Despite the beneficial effect of calcium channel blockade on RBF demonstrated in one human study (Colson et al. 1992a) and our own animal study, this matter needs further investigation in an appropriate model since unstable systemic hemodynamics with episodes of hypotension is the norm rather than the exception under these surgical circumstances.

Factors other than vasoconstrictive mediators, such as turbulence of blood flow proximal to the aortic cross clamp (close to the origin of the renal arteries) have been suggested as etiology for the decrease in RBF. Since pressure and flow lose their linear relationship with tubulence, renal blood flow would decrease for a given perfusion pressure at the origin of the renal arteries (Parbrook et al. 1990). These detrimental circumstances would be aggravated in patients with atheromatous lesions in their renal arteries. This scenario is unlikely for two reasons. It would firstly not explain the decreased RBF after aortic unclamping. Secondly, if calcium channel blockers compromise autoregulation of RBF (Cohen and Fray 1982, Navar et al. 1986),

these drugs should not protect RBF to the extent demonstrated in our own study and others (Colson et al. 1992a).

Maintenance of GFR during the preclamp and post-unclamp periods is a feature in the verapamil animals in contrast to the control group where GFR was decreased for the full duration of the experiment after clamping, as well as the enalaprilat animals where unclamping induced a significant decrease in this parameter. These **intragroup** changes are confirmed by the comparisons of changes **between** the experimental groups (Figure 3.28). Calcium channel blockers improved GFR in 14 of 19 studies where these agents were administered to anaesthetized animals (Loutzenhiser and Epstein 1985). All 5 studies in which an improvement in GFR did not occur, were performed in the absence of exogenous vasoconstrictors. Such a beneficial effect for calcium blockers during abdominal aortic surgery was also evident in two clinical studies (Colson et al. 1992a, Antonucci et al. 1996). The validity of the suggestion that endothelin (alone) is responsible for the decrease in GFR (Antonucci et al. 1990, 1996) is questionable since verapamil which was beneficial in our study, was reported to be unsuccessful in blunting the glomerular effects of endothelin-1 (Cao and Banks 1990) although other studies have shown a beneficial effect for calcium channel blockade (Luscher et al. 1992). This caveat, together with the fact that ACE inhibition (which had been demonstrated to significantly reduce the renal effects of endothelin (Chan et al. 1994)) was unsuccessful in influencing the decrease in GFR after unclamping (ACE inhibition animal group), suggest a supplementary rather than a comprehensive role for endothelin.

A more significant enhancement of calcium channel blockers on GFR than on RBF is suggested under the influence of renal vasoconstrictive agents (Loutzenhiser et al. 1984, 1985). This is considered to be due to a predominantly preglomerular vasodilatory effect of these drugs, which would increase glomerular capillary hydrostatic pressure. Verapamil has also been demonstrated to inhibit the tubuloglomerular feedback mechanism, thus preventing both afferent arteriolar vasoconstriction and the resultant decrease in GFR when an increased solute load is delivered to the renal tubules (Muller-Suur et al. 1976). Such preferential augmentation of GFR could not be assessed in our study as verapamil was given prophylactically rather than to reverse the established renal effects of vasoactive substance(s). A predominant preglomerular effect is unlikely, however, since there was no difference in FF between the verapamil animals and the other two groups.

Calcium channel blockers usually exert a stimulatory, rather than an inhibitory effect on renin release (Dietz et al. 1983, Amano et al. 1995). The fact that renin concentration did not increase in verapamil animals after aortic cross clamping suggests that the increase in renin levels in the control group (and the difference in change from pre- to postclamp values between the two groups: Figure 3.29) had been due to stimulation of its release secondary to the reduction in RBF and GFR rather than it being a primary cause of the changes in those parameters. If increased renin and angiotensin had been a primary cause, renin values would also have increased in the verapamil group, with verapamil then responsible for attenuation of the angiotensin induced renal changes. The fact that enalaprilat was successful in maintaining RBF and GFR at the two perclamp measurement periods, may nevertheless indicate an important supplementary role for angiotensin. This influence could manifest through direct renal effects of angiotensin or indirectly due to its stimulatory role in the release of other mediators such as endothelin (Chan et al. 1994) and noradrenaline (Zimmerman 1978). Conversely, at least part of the benefit of ACE inhibition could have been gained through increased bradykinin levels (Williams 1988).

The increase in renin concentration in verapamil animals after release of the aortic clamp could have been in response to the systemic release of other vasoactive substances from ischemic tissues distal to the clamp as described in the previous section. The renal effects of verapamil were clearly sufficient to counteract the deleterious influences of those agent(s) without causing detrimental effects of its own.

The verapamil animals were the only group where urine output increased after aortic clamping. Calcium channel blockers have previously been demonstrated to be natriuretic (Leonetti et al. 1982, MacLaughlin et al. 1985) and diuretic (Leonetti et al. 1982, Wait et al. 1983). The fact that renin concentration, and presumably therefore also angiotensin and aldosterone, did not increase in the two perclamp measurement periods in verapamil animals, would have assisted in the prevention of antinatriuresis and oliguria. Although FE_{Na} did not increase during aortic clamping in the verapamil group, the total sodium load excreted was significantly raised. The natriuretic effect of calcium channel blockers is suggested to be due to direct action of these agents on the proximal (McCarty and O'Neil 1991, Rose et al. 1994), as well as distal tubules and collecting ducts (Dibona and Sawin 1984). Inhibition of tubular sodium reabsorption would decrease renal oxygen consumption and thus be protective in the ischemically compromised kidney (Van Zwieten 1993, Lopez-Neblina et al. 1996). Inhibition of

ADH-mediated water reabsorption might also have played a role in the increased urine output, since ADH-stimulated water transport across the toad bladder has been demonstrated to be inhibited by verapamil (Humes et al. 1980.)

Mitochondrial swelling was the only ultrastructural change which was apparent in (some) verapamil animals, while changes in the gER and the brush border microvilli also occurred in the other two animal groups (Table 3.64). Although both the (mean/median) severity scores and numbers of abnormal parameters suggest a protective influence of verapamil, statistical significance is not achieved ($p = 0.06$, Table 3.65). The inability to achieve statistical significance can be attributed to the presence of mitochondrial changes in verapamil animals since, when only the other ultrastructural changes are considered in all three animal groups, verapamil animals demonstrate better total severity scores ($p < 0.05$ vs control and enalaprilat) and less numbers of abnormal parameters ($p < 0.01$ vs control, $p < 0.05$ vs enalaprilat). The possibility that mitochondrial swelling constitutes the earliest ultrastructural change, is contradicted by the fact that gER and/or microvillous changes occurred in a number of animals in the control and enalaprilat groups **without** mitochondrial swelling (Table 3.64). No potential explanation for this phenomenon could be found in the literature.

Comparing the numbers of animals per group classified as demonstrating clearly abnormal versus normal or minimally changed histology, do suggest a protective effect for verapamil relative to control and enalaprilat animals (Table 3.66).

At a cellular level, calcium influx into ischemically injured renal tubular cells is considered to be a fundamental component of damage and eventual necrosis (Young and Humes 1991, Rose et al. 1994). L-type Ca^{2+} channel blockers have been shown to reduce Ca^{2+} uptake of proximal tubular cells exposed to hypoxia (Almeida et al. 1992). Verapamil has also been demonstrated to preserve the ultrastructural integrity of renal tubules in animals exposed to ischemia (Alvarez et al. 1994). The protective effect of verapamil on the brush border microvilli was particularly impressive in the Alvarez study. At least part of the protective effect of Ca^{2+} channel blockade in vivo is due to a direct tubular effect of these drugs which, through inhibition of sodium reabsorption, decreases cellular oxygen consumption (Van Zwieten 1993).

The protective effect of calcium blockers on cellular integrity in our experimental study could therefore be established firstly through its demonstrated beneficial effect on

RBF, and secondly (even if ischemia does occur) by direct influence on the pathophysiological process induced by ischemia at cellular level.

In summary, the administration of verapamil was instrumental in the maintenance of RBF throughout the perclamp and post-unclamp periods, while ACE inhibition prevented a decrease in RBF only during aortic clamping, with a significant decrease occurring after release of the clamp. These results confirm a calcium-mediated vasoconstrictive response associated with the decreased RBF both during aortic clamping and after unclamping. It also suggests that different vasoactive mediators are responsible for the perclamp and post-unclamp reduction in RBF respectively. Preservation of perclamp RBF under the influence of ACE inhibition does not confirm a **primary** pathogenic role for angiotensin II in the renal hemodynamic changes during aortic clamping. ACE inhibitors have other effects such as the inhibition of bradykinin metabolism, which may also influence RBF. In addition, angiotensin also plays a permissive role in the vasoconstrictive effects of other vasoactive substances such as noradrenaline and endothelin, which may possibly be more important. Verapamil appears to inhibit the (ischemic) renal ultrastructural changes induced by infrarenal aortic cross clamping.

4.6   The role of prostaglandins

The dose of diclofenac used in our experimental animals had previously been demonstrated to block renal and systemic prostaglandin synthesis (Wanecek et al. 1997; Bayliss et al. 1978). A maximal reduction in urinary prostaglandin excretion of between 60 and 80% had been described with nonsteroidal anti-inflammatory drugs (Patrono and Dunn 1987).

As in the other experimental groups where drugs had been administered, the diclofenac was injected immediately after securing intravenous access. This implies that potential changes in prostaglandin homeostasis would have been influenced at all measurement times. The inhibition of prostaglandin synthesis most probably accounts for the fact that RBF prior to aortic cross clamping was already 27% lower in diclofenac animals than in the control group (Table 3.19, 3.44; Figure 3.30). Although renal prostaglandins do not appear to be important in the maintenance of renal homeostasis in normal man (Patrono and Dunn 1987) or experimental animals (Swan et al. 1975), prostanoids do influence renal hemodynamics and function during laparotomy under general anaesthesia similar to our experimental conditions (Terragno et al. 1977). In

the latter study, indomethasin induced a 40% reduction in RBF intraoperatively, with urinary prostaglandin E (PgE) concentrations significantly lower than in control animals. A similar pattern was demonstrated in the only published study which examined the influence of non-steroidal anti-inflammatory drugs (NSAID) in the course of infrarenal cross clamping of the aorta in rats (Myers et al. 1996). It appears that PgE_2 and PGI_2 are the most important prostaglandins in the regulation of RBF under pathophysiological circumstances with both prostanoids inducing renal vasodilatation (Harris 1992, Schlondorff et al. 1985, Stahl et al. 1984).

While our study demonstrated a further decrease in RBF immediately after infrarenal aortic clamping which deteriorated further during the 60 minute clamping period, Myers et al. (1996) could only show a significant clamp-induced reduction in RBF towards the end of a 60 minute clamping period in rats where prostaglandin synthesis was inhibited with a NSAID. Assessment of the validity and comparability of the results of the Myers study is compromised by the fact that they reported data as a percentage change in RBF, as a percentage of total aortic blood flow, without providing the absolute values of these parameters. The most significant decrease in RBF in the Myers (1996) study occurred in the 60 minutes subsequent to the release of the aortic cross clamp in the NSAID group, suggesting the release of vasoconstrictive agent(s) by unclamping, without the protective counterbalance of the vasodilatory prostaglandins. Our experimental animals did not demonstrate a further drop in RBF after aortic unclamping, but RBF values remained depressed relative to preclamp measurements and were also significantly lower than post-unclamp RBF in the control animals (Figure 3.30), again indicating the importance of the protective vasodilatory influence of the prostaglandins into the post-unclamp/postoperative period. Although an aortic clamp-induced increase in systemic (plasma) PgE concentration was shown to increase even further after release of the clamp (Rittenhouse et al. 1976), this is not necessarily a reflection of intrarenal prostaglandin status (Breyer and Bads 1996). The lung appears to be the predominant source of systemic prostaglandin release during surgery, at least partially induced by increased plasma levels of other vasoactive substances such as angiotensin II (Krausz et al. 1983, Mullane and Monaca 1980).

It is possible that the lower preclamp RBF in the diclofenac animals in comparison with control pigs could, at least partially, have been due to the threefold higher mean renin (and concomitant angiotensin II) levels in the former group, although this difference did not reach statistical significance due to scatter of data (Figure 3.32). The effect of

prostaglandin inhibition on the renal circulation has previously been shown to be related to the degree of activation of the renin-angiotensin system in anaesthetised dogs (Satoh and Simmerman 1975). Increased concentrations of other vasoactive substances not measured in our study which had previously been shown to be counterbalanced by the effect of prostaglandin release in the renal vasculature such as catecholamines (Dunn and Zambraski 1980), ADH (Edwards et al. 1989) and endothelin (Bugge 1995), could also have contributed to the low preclamp RBF in the diclofenac animals.

If a decrease in E_{HIP} is accepted as a valid indication of redistribution of RBF away from the outer cortex towards the inner cortex and medulla (Gamulin et al. 1984), our control animals did not demonstrate such redistribution statistically relative to diclofenac animals, although mean E_{HIP} was consistently lower in the former group. Changes in E_{HIP} are, however, not universally accepted as a valid parameter of altered distribution of RBF, particularly when total RBF is decreased (Gelman et al. 1985). Redistribution of RBF to the inner cortex and medulla is a universal finding under conditions of renal ischemia (Abbott et al. 1973, 1974, Hollenberg et al. 1968). Prostaglandins have been demonstrated to be responsible for this shift in distribution of RBF under a number of experimental conditions (Mark et al. 1977, Kirschenbaum et al. 1974, Itskovitz et al. 1973). Blockade of this prostaglandin-mediated response would therefore have predicted a higher E_{HIP} in the diclofenac group than in the control animals.

The maintenance of GFR in diclofenac animals to values similar to control animals at the preclamp measurement (Figure 3.31), despite the lower RBF in the former group (Figure 3.30), is clearly attributable to the increased FF in that group. It is possible that the higher mean renin concentration (accompanied by raised angiotensin II levels) in the diclofenac animals could have been responsible for this increase in FF (despite the fact that the mean renin concentration which was more than 100% higher in diclofenac than in control animals, did not reach statistical significance due to scatter of data in the former group). The predominant effect of angiotension II on the efferent arteriole would increase glomerular intracapillary hydrostatic pressure and increase FF in the absence of significant changes in glomerular ultrafiltration coefficient (Kastner et al. 1984, Edwards 1983). The persistence of the increased FF throughout the experimental period is rather difficult to explain. PgI_2, the predominant prostaglandin in both human (Stahl et al. 1984) and pig (Livio et al. 1988) glomeruli, dilates both

afferent and efferent arterioles (Edwards 1985). Blocking PgI_2 synthesis with diclofenac might have accentuated the predominant effect of angiotensin II on the efferent arteriole which in turn would have assisted in the maintenance of glomerular capillary hydrostatic pressure relative to glomerular plasma flow and thus increased FF. Although the GFR in both control and diclofenac animals decreased significantly with aortic clamping relative to their respective preclamp values, this reduction was much more significant in the diclofenac group in the later clamping and post-unclamp periods (Figure 3.31). The consequences of the abolition of the (partial) protective effect of the prostaglandins on GFR under these experimental conditions is similar to other states of increased endogenous levels of angiotensin II and other vasoconstrictors, such as a reduction in cardiac output (Oliver et al. 1981) and haemorrhage-induced hypotension (Henrich et al. 1978b).

The fact that urine volume should not be considered as an indication of RBF or nephron function (Alpert et al. 1984), is demonstrated by the significantly higher urine volume in the diclofenac group at the preclamp measurement time when compared with the control animals (Tables 3.20 and 3.45; $p < 0.05$). The lower urine volumes in control animals (relative to the diclofenac group) at the other measurement times were not statistically significant. The higher urine volumes in diclofenac animals relative to the control group, are in sharp contrast with RBF measurements which were consistently higher, as well as the GFR which were higher in control than diclofenac animals in the later measurement periods. The higher FF in the diclofenac group (Figure 3.31a) should have been responsible for an increase in the oncotic pressure and a decrease in the hydrostatic pressure in the peritubular capillaries. This change in the Starling forces across the walls of the peritubular capillaries should increase proximal tubular fluid reabsorption substantially (Ichikawa and Brenner 1979) and should also have contributed to lower urine volumes in the diclofenac animals (Ichikawa and Brenner 1980). Although the urine volumes decreased at all postclamp measurement periods relative to the preclamp value in diclofenac animals, the antidiuretic effect of prostaglandin inhibition (Walker 1983) was not apparent in comparison to control pigs.

Although FE_{Na} did not increase significantly during the experimental period in the diclofenac group due to scatter of data, this parameter was significantly increased ($p < 0.05$) relative to the values in control animals in all three postclamp measurement periods. Higher sodium excretion in diclofenac animals may be partly explained by the

fact that PgE_2 antagonises the effect of ADH (Lum et al. 1977), or conversely, NSAIDs potentiate ADH influence on the distal tubules and collecting ducts which mediates a greater reabsorption of water than sodium (Carmichael and Shankel 1984). However, the higher calculated FE_{Na} was largely due to a lower urinary creatinine in the diclofenac animals which, in the presence of reduced urine volume, is suggestive of intrinsic renal injury (Steiner 1984).

Due to the NSAID potentiation of the effect of ADH (Schlondorff 1986), a more negative C_{H2O} would be predicted in diclofenac animals (Power et al. 1992). This was not evident in our data. In fact, C_{H2O} mean values were consistently more negative in control animals than in the diclofenac group although data variability prevented these differences from reaching statistical significance. Significantly more positive (less negative) C_{H2O} would have provided further evidence of ischemic tubular injury (Landes et al. 1976, Baek et al. 1973) in the diclofenac group.

Other than the statistically nonsignificant threefold higher preclamp plasma renin concentration in the diclofenac group relative to control animals, plasma and renal venous renin concentrations were almost identical between the two animal groups at the various measurement times. Increased renal prostaglandin synthesis and release has been demonstrated to induce renin release and increase angiotensin II concentration subsequent to a decrease in renal perfusion pressure (Bugge and Stokke 1994) or due to a change in sodium chloride delivery to the macula densa (Bugge et al. 1988). Inhibition of prostaglandin synthesis decreases renin release related to these stimuli (Frölich et al. 1979, Frölich et al. 1976). The fact that renin release in response to renal nerve stimulation (Kopp et al. 1981) and ß-adrenergic stimulation due to circulating catecholamines (Franco-Saenz et al. 1980) is independent of prostaglandin influence, may explain the fact that renin concentration was not higher in control than in diclofenac animals, as both these mechanisms were probably involved in the increased renin levels in both diclofenac and control animals.

The ultrastructural damage observed in the NSAID group clearly demonstrated a greater degree of ischemic injury than the changes which occurred in the control animals. These changes were consistent with ultrastructural injury previously described in animals subjected to total (Shanley et al. 1986b, Glaumann et al. 1977, Reimer et al. 1972) or partial renal ischemia (Dobyan et al. 1977, Kreisberg et al. 1976). In all these studies, biopsies were taken after variable periods of recovery/

reperfusion. The segments of the nephron previously demonstrated to be most vulnerable to ischemic injury (medullary proximal (S3) tubule) were most affected in both our animal groups (Endre et al. 1989, Venkatachalam et al. 1978). The NSAID animals were the only group to exhibit significant ultrastructural changes in the medullary thick ascending limb (mTAL), which has been described to be selectively susceptible to ischemic cell damage (Brezis et al. 1984 a, 1984 b, 1984 c). The diclofenac animals were also the only group where nuclear chromatin clumping, which is considered to be an early demonstration of irreversible cell damage (Reimer et al. 1972), was evident electronmicroscopically. The extent of cellular injury in diclofenac animals clearly demonstrates the importance of the protective homeostatic role of intrarenal prostaglandins under these pathophysiological conditions.

In summary, blocking prostaglandin synthesis was clearly detrimental to the renal hemodynamics and glomerular function under these experimental conditions. This demonstrates the essential protective role of renal prostaglandins in the presence of vasoconstrictive influence(s) during and after infrarenal aortic cross clamping. The importance of the protective influence of prostaglandins under these pathophysiological circumstances is confirmed by the (ischemic) renal tubular dysfunction and the severity of the ultrastructural injury induced by the administration of a NSAID.

4.7   The relationship between angiotensin and prostaglandins

An important interactive relationship exists between angiotensin II and renal prostaglandins in both the control of renal hemodynamics under some pathophysiological circumstances (Satoh and Zimmerman 1975) and mutual influence on the release or activation of each other (Frölich et al. 1976, 1979, Bugge and Stokke 1994). This part of the study was designed to explore the importance of this relationship under these specific experimental/clinical conditions, and to shed additional light on the importance of angiotensin II in the pathogenesis and pathophysiology of the changed renal hemodynamics induced by infrarenal aortic clamping.

If the lower RBF **discussed in section 4.6** in diclofenac animals (relative to control animals) at the preclamp measurement time had been due to the (statistically non-significant) raised renin (Figure 3.32) (and angiotensin) concentrations, it should have been possible to prevent that decrease in RBF with the administration of an ACE

inhibitor (Satoh and Zimmerman 1975, Levenson et al. 1982). Such a scenario seems possible considering the fact that RBF measurements in enalaprilat and enalaprilat plus diclofenac animals were not statistically different at the preclamp measurement period (Figure 3.33).

By the same token, if angiotensin had been primarily responsible for the decrease in RBF after clamping of the aorta, prostaglandin synthesis inhibition by diclofenac should not produce a decrease of RBF in the presence of ACE inhibition (Satoh and Zimmerman 1975). The fact that RBF decreased significantly in diclofenac plus enalaprilat animals relative to enalaprilat pigs after aortic clamping (Table 3.74, Figure 3.33), therefore provides further, and perhaps conclusive, **evidence that angiotensin does not play a primary pathogenic role in the changed renal hemodynamics induced by infrarenal aortic clamping.** The beneficial effect of ACE inhibition at the time of aortic cross clamping should therefore be considered to be due to the prevention of the permissive effect of angiotensin on the influence of other vasoconstrictors such as noradrenaline (Zimmerman 1978), endothelin (Miller et al. 1989) and adenosine (Dietrich et al. 1991); and/or other beneficial effects of ACE inhibitors such as the prevention of the breakdown of bradykinin which would also evoke renal vasodilatation (Williams 1988). Despite initial evidence to the contrary, current data suggest that the vasodilatory action of bradykinin in the kidney is minimally dependent on prostaglandins (Blasingham and Nasjletti 1979). It therefore appears that renal prostaglandins are essential renal vasodilators to maintain RBF after aortic clamping in the presence of **renal vasoconstrictive agent(s) other than angiotensin,** a role which has been described for the eicosanoids under other pathophysiological circumstances (Patrono and Dunn 1987). The vasoconstrictive substances other than angiotensin which have been demonstrated to induce renal synthesis and release of PgE and/or PgI include ADH (Zipser et al. 1981, Ardaillou et al. 1985), endothelin (Rae et al. 1989), noradrenaline (Walshe and Venuto 1979) and adenosine (Gunning et al. 1996).

The changes in RBF between further consecutive measurement times did not demonstrate any differences between the two animal groups (Figure 3.33). The (intragroup) decrease in RBF in the enalaprilat group after aortic unclamping (Table 3.33) was probably responsible for the fact that the changes from preclamp to post-unclamp (x1-4; Table 3.74) were not statistically significant between the two groups. The post-unclamp RBF measurement in the enalaprilat group, which was very

similar to the diclofenac plus enalaprilat value, suggest a very potent vasoconstrictive influence at that time; to the extent that an **intact** prostaglandin protective influence (in the enalaprilat animals) could not effect more favourable renal hemodynamics than conditions where this beneficial mediator was **absent** (in enalaprilat plus diclofenac animals).

Considering the redistribution of RBF towards the inner cortex and medulla induced by renal prostaglandins under a number of experimental circumstances (Itskovitz et al. 1973, Kirschenbaum et al. 1974), a decrease in E_{HIP} suggesting such redistribution (Gamulin et al. 1984) in enalaprilat animals relative to the diclofenac plus enalaprilat could be predicted. Maximal redistribution of RBF should occur at the time of maximum vasoconstrictor influence (Levenson et al. 1982), which in our experimental model was presumably after release of the aorta cross clamp. E_{HIP} values were, however, almost identical between the two animal groups and no decrease was recorded after unclamping in enalaprilat animals (Tables 3.33 and 3.49). Other than the contested value of E_{HIP} as acceptable indicator of distribution of RBF (Gelman and Navar 1985), no pathophysiological explanation can be offered for these results.

The decrease in GFR in enalaprilat plus diclofenac pigs relative to the enalaprilat animals after aortic clamping (Table 3.74, Figure 3.34), coincided with the change in RBF of a similar magnitude. This decrease in GFR is consistent with reported changes under the influence of renal vasoconstrictors during blockade of prostaglandin synthesis (Bugge and Stokke 1994). The presence of the potential protective effect of prostaglandins were ineffective in preventing a decrease of GFR at aortic unclamping (again similar to RBF change) in the enalaprilat animals. Under (probably lesser) vasoconstrictive influences, PgE_2 synthesis has been shown to be effective in offsetting decrements in GFR (Scharschmidt et al. 1983).

The inability of prostaglandin protection to preserve GFR after aortic unclamping in enalaprilat animals was responsible for the fact that the decrease in GFR over the course of the experimental period was similar between the two animal groups (Figure 3.34).

Renal prostaglandins are involved in the stimulation of renin release in the majority of stimulatory mechanisms, to the extent that renin release is described to be "prostaglandin-dependent" (Bugge 1995). Renin release due to ß-adrenergic stimulation, however, is independent of renal prostaglandins (Vikse et al. 1985). Under

conditions of stress (such as was present in our experimental model), the administration of NSAID should reduce renin release (and hence the production of angiotensin II) (Bugge 1995). Quantitatively this effect is small, since ß-adrenergic activity plays a substantial role under such circumstances (Holdaas et al. 1985). The angiotensin-renin feedback loop also requires an intact prostaglandin system (Campbell et al. 1979). This loop controls renin in inverse proportion to angiotensin II concentration under the influence of renal prostaglandins, so that prostaglandin synthesis inhibition blocks the increase in renin secretion associated with ACE inhibition (Abe et al. 1980). Although mean plasma renin concentrations in diclofenac plus enalaprilat pigs were slightly lower at the first three measurement periods than in animals which received only the ACE inhibitor (Figure 3.35), these differences were minimal considering the response one would predict in the context of the interaction described by Abe et al. (1980). The most likely explanation for this similarity in plasma renin concentrations, is the presence of significant ß-receptor stimulated renin release which is independent of the presence of renal prostaglandins (Vikse et al. 1985).

Changes in urine volumes and FE_{Na} between measurement times were not different between the two animal groups (Table 3.75). Although statistics were not done on the differences between the two groups **at** the 4 measurement periods (for reasons discussed in section 4.4), the mean values for both urine volume and FE_{Na} were at least 130% and 70% higher respectively than in the diclofenac plus enalaprilat group at the two postclamp and the post-unclamp measurement periods (Tables 3.35 and 3.50). Considering the results of our animal studies discussed in sections 4.4 to 4.6, it can be suggested that renal prostaglandin synthesis was stimulated at all measurement periods after aortic clamping, due to the presence of renal vasoconstrictor influences. Prostaglandin E_2 inhibits sodium chloride reabsorption in the thick ascending limb of the loop of Henle and in the collecting tubule (Schlondorff 1986). Prostaglandin E_2 also antagonizes the antidiuretic effect of ADH in the collecting tubules (Berl et al. 1977), an influence which may be important in our experimental model considering the increased ADH levels recorded in our human study. Inhibition of the above renal tubular effects of prostaglandins are probably responsible for the relatively low urine volume and FE_{Na} values in the diclofenac plus enalaprilat animals (particularly in view of the similarity in GFR values between the two animal groups). Prevention of the inhibitory effect of prostaglandins on tubular reabsorption (by the NSAID in the enalaprilat plus diclofenac group) would also compromise the oxygen balance in ischemic kidneys due to the oxygen consumptive

nature of the reabsorption process (Jabs et al. 1989) and may therefore aggravate ischemic injury.

Although the mean total severity score, mean number of abnormal parameters, as well as percentage of biopsies considered to be clearly abnormal in the enalaprilat plus diclofenac animals were all approximately double that of the enalaprilat group, these differences were not statistically significant (Table 3.78). More severe ischemic injury in the diclofenac plus enalaprilat animals would not have been surprizing since blocking synthesis of the protective prostaglandins should prevent redistribution of RBF to the most vulnerable deeper cortical layer and the medulla (Itskovitz et al. 1973). Even if this protective redistribution of RBF had not been compromised, the more extensive tubular sodium chloride reabsorption (due to prostaglandin inhibition) with the associated oxygen consumption in an ischemically threatened kidney, would aggravate ischemic injury (Jabs et al. 1989).

In summary, the inability of ACE inhibition to prevent a decrease in RBF in the presence of prostaglandin synthesis inhibition at the time of aortic cross clamping, confirms a supplementary role at most for angiotensin II in renal hemodynamic and glomerular changes induced by that surgical intervention. The more substantial energy and oxygen dependent tubular reabsorption of sodium chloride and possibly also the absence of redistribution of RBF to the potentially compromised corticomedullary region effected by prostaglandin inhibition, are responsible for the tendency towards greater ultrastructural injury in diclofenac plus enalaprilat animals, although this comparative difference with the enalaprilat group was not statistically significant.

4.8   Conclusions and recommendations

Our patient study demonstrated no significant influence of the anaesthetic technique employed, on renal hemodynamics and nephron function. The decrease in both RBF and GFR induced by infrarenal aortic cross clamping correspond with results previously published (Gamulin et al. 1984, 1986, Colson et al. 1992a, Licker et al. 1996). We have demonstrated persistence of the compromise in these parameters as long as 4 hours into the postoperative phase, which has previously only been reported for the period immediately after aortic unclamping with the abdomen still open. Unfortunately we have been unable to follow the course of full restoration of RBF and its relationship with the GFR recovery. The persistence of a depressed GFR until just before discharge of the patients, is cause for concern, particularly in patients with

compromised glomerular function prior to surgery. This information establishes the need for the determination of creatinine clearance as part of the preoperative assessment of patients presenting for infrarenal aortic surgery.

Of the measured hormones with a potential influence on RBF and nephron function, renin was the only mediator where changes in plasma concentrations coincided with the decreases in RBF and GFR at the time of aortic cross clamping. The design of our study did not allow us to conclude whether the concomitant increase in angiotensin II was primarily responsible for the change in renal hemodynamics, or whether the raised renin (and angiotensin) levels were stimulated by the decrease in RBF induced by another mechanism(s).

The combination of mannitol plus dopamine was clearly of no benefit in preventing the deleterious renal effects of aortic clamping. In fact, the high volumes of urine produced under the influence of these two agents, which did not correlate with RBF at the corresponding time periods, is likely to prompt a false sense of security (and lack of the necessary vigilant attention to other parameters which are important for optimal renal perfusion and function and/or provide evidence of the renal status). Mannitol and dopamine also render some parameters of renal functional status, such as FE_{Na}, unreliable. The use of these agents in these clinical circumstances should therefore be discouraged. The lack of a favourable influence on the kidney by mannitol and dopamine may be partly due to an increase in circulating noradrenaline induced by the latter drug, which may cause renal vasoconstriction directly via α-adrenergic stimulation, or indirectly through stimulating the activation of other vasoactive substances such as angiotensin (subsequent to ß-adrenergically mediated renin release).

The animal studies were aimed at elucidation of the exact role of angiotensin in the pathogenesis and pathophysiology of the renal changes associated with infrarenal aortic clamping, as well as the interaction of angiotensin with other modulators for which an interactive relationship had been described previously under other experimental and/or clinical circumstances.

The first study showed that, although renin (and thus angiotensin) concentrations were high **after aortic unclamping,** the hormone had no pathogenic or pathophysiological role of substance in the observed renal changes **during this period** (since blocking angiotensin II activation by the prevention of renin release, or by inhibiting the

conversion enzyme, did not prevent a substantial decrease in RBF or GFR during that period). Preventing angiotensin II activation did, however, **prevent renal changes during aortic clamping.** This beneficial effect did **not** establish a **primary** role for angiotensin during that period, since the favourable influence could also (at least partially) be explained by prevention of the permissive influence of angiotensin on other vasoconstrictors and/or other vasodilatory influences of ACE inhibition and ß-blockade which are unrelated to angiotensin. This study did indicate that (at least partially) different mechanisms are responsible for the renal changes seen **during aortic clamping**, and **after aortic unclamping.**

The second study explored the role of calcium in the renal pathophysiological changes **during aortic clamping** and **after unclamping.** The protective influence effected by the administration of a Ca^{2+}-blocker suggest the dependence of the renal vasoconstrictive and glomerular pathophysiological process(es) on the cellular influx of Ca^{2+} through voltage-gated channels. It unfortunately provides no definitive insight into the primary instigators of these processes. However, it does offer a clinically useful method of preventing these changes and protecting the kidney against ischemic injury during abdominal aortic surgery.

The third component of the animal studies demonstrates the importance of the protective effect of renal prostaglandins during the specific experimental (and probably also the clinical) circumstances. Again, it does not provide definitive information on the mediators responsible for the renal changes, since the deleterious effects of numerous endogenous substances have previously been shown to be counterbalanced by intrarenal synthesis of prostaglandins under various experimental and clinical circumstances. The extent of the pathophysiological and ultrastructural changes which occurred under the influence of a NSAID does, however, suggest that these drugs should not be used under these clinical circumstances.

The last component of the study provides evidence that angiotensin only plays a **secondary/supplementary role** in the renal pathophysiological process **even during aortic clamping.** This may explain the contradictory evidence regarding the potential beneficial effect of ACE inhibition (on renal hemodynamics and glomerular function) during abdominal aortic surgery (Licker et al. 1996, Colson et al. 1992a). Based on our studies, ACE inhibition can not be supported for this purpose.

Unanswered questions which should be explored with future studies, are the following:

1. The question of which vaso-active substances are responsible for the renal changes during aortic cross clamping and after unclamping remains unresolved. This should be investigated experimentally (and clinically), preferably by the direct measurement of concentrations of potential mediators and/or indirectly by the administration of specific antagonists or antibodies to these substances.

2. The renal hemodynamic and functional course after aortic surgery in humans should be investigated to determine the full extent and duration of RBF and GFR recovery. Improved doppler technology should enable accurate non-invasive blood flow measurement.

3. The difference in changes in RBF and renal function in aortic surgery between patients with aortic aneurysms and those with aorto-iliac occlusive disease should be explored. It is possible that collateral blood flow to tissues distal to the aortic clamp in the latter group, may be responsible for a lesser degree of compromise after unclamping.

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