Experimental evaluation of the prophylactic and therapeutic effects of hydrocortisone in haemorrhagic shock

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Summary

The prophylactic and therapeutic effects of hydrocortisone (50 mg/kg) in severe haemorrhagic shock were evaluated by metabolic, biochemical and haematological investigations in a rabbit model. It was found that administration of hydrocortisone prior to severe haemorrhage had no beneficial effect on any of the values measured. Owing to haemoconcentration and marked mobilization of leucocytes it would appear that in pretreated animals the magnitude of the hypoxia was increased and led to greater tissue damage and higher levels of lysosomal enzymes than in rabbits which had not received pretreatment with hydrocortisone.

On the other hand, hydrocortisone therapy combined with volume replacement 1 hour after the haemorrhagic insult had several beneficial effects. The metabolic capacity of liver and kidney tissues was improved, the lysosomal concentration remained within normal limits, and the mean blood pressure and pulse pressure were maintained better than in controls. However, it would appear that this beneficial effect is only exerted on tissue still in a reversible state of shock. There is therefore no beneficial effect on lung tissue metabolism, the lungs being more sensitive to hypoxic damage than either liver or kidney tissue.

Administration of hydrocortisone results in the immediate release of endotoxins into the circulation. This might be due to its vasodilatory action on the microcirculation of the intestinal viscera.

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A haemodynamic disturbance in the peripheral vascular bed invariably appears to be present in cases of shock, whether the latter is induced by haemorrhage, endotoxins, trauma or myocardial failure. Reversible shock is characterized at first by ischaemic hypoxia in which both the precapillary sphincters (resistance vessels) and post-capillary venular sphincters (capacitance vessels) are tightly constricted, thus allowing little blood to enter the splanchnic bed. Irreversible shock, on the other hand, is characterized by stagnant hypoxia in which the precapillary arterial sphincters have lost their tone while the post-capillary sphincters are still constricted, resulting in increased hydrostatic capillary pressure, leakage of plasma proteins and a decrease in blood volume.[1]

The acute loss of circulating blood volume initiates intense neurohormonal activity and the release of numerous vasoactive agents. Various metabolic, cellular and subcellular alterations in cell function and structure occur during shock and low-flow states.[2]

Apart from measuring haemodynamic disturbances and survival in shock conditions,[1] other investigations have been carried out to assess the degree of malfunction at the cellular and subcellular levels. Several studies have indicated that alterations occur in mitochondrial metabolism,[3] in the concentration of metabolites, in cellular nucleotide levels, in energy charge,[4] in cyclic nucleotides, in transmembrane potentials[5] and in cell membrane transport. Recently it was shown that the metabolic capacity of lung tissue to synthesize protein and lipid was lowered in haemorrhagic shock.[6] In spite of numerous studies, the precise cause of cell injury and death as a result of shock is still elusive. It appears that no single factor or group of factors indicates the reversibility or irreversibility of shock. Haemodynamic values can be maintained at a stable level even when the patient is irreversibly shocked.[7]

Treatment regimens for the correction of cellular dysfunction after shock and ischaemia are continually being evaluated. Usually blood or fluids are given to improve the microcirculation and to increase vascular volume.[1] Various adjunctive agents, i.e. buffers, steroids, energy-producing substrates, nicotinamide, tricarboxylic acid cycle intermediates, inosine, adenosine, creatinine phosphate, allopurinol, glucose-insulin-potasium, adenosine-triphosphate (ATP)-$MgCl_2$ and others have been used.[8] Other pharmacological agents, i.e. angiotensin-converting enzyme inhibitors, calcium channel blocking agents, naloxone, thromboxane inhibitors, prostacyclin and coenzyme Q_{10}, to mention a few, are being investigated.[8]

Of the many substances tested in the treatment of shock, only pharmacological doses of steroids are generally recommended for clinical use, in spite of the fact that steroid therapy as an adjunct in the treatment of shock is still controversial.[8] Corticosteroids are being advocated for numerous insults, i.e. sepsis, hypovolaemia, general trauma, cardiogenic shock and circulatory failure. They also decrease the immune response associated with anaphylaxis, stabilize lysosomal and endothelial cell membranes, and inhibit the release of mediators from endothelial and mast cells.[8]

Pharmacological doses of glucocorticoids exert a direct vasodilatory action on traumatized vascular smooth muscle, especially that of the microcirculation, by inhibiting the vasoconstrictor action of catecholamines, peptides, serotonin and prostanoids as well as the uptake of excessive calcium ions. The beneficial therapeutic value of steroids in low-flow states is only exhibited when they are administered early and in high doses.[8] Several clinicians feel that prophylactic treatment of shock with steroids may be far superior to post-shock treatment, although little evidence is available to support this view.

Recently the haemodynamic effects of massive doses of dexamethasone (12,8 mg/kg) in combination with the α-

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adrenergic blocking agent fenoxybenzamine were studied and no positive beneficial effects on peripheral blood flow were found.[9] Massive doses of methylprednisolone (60 mg/kg) given to dogs prior to severe lethal haemorrhagic shock had no significant effect on cardiac output, mean arterial blood pressure, superior mesenteric arterial flow or survival, although peripheral resistance tended to be lower in the treated animals.[10]

In view of the controversy regarding the beneficial effects of steroids in haemorrhagic shock on haemodynamic values and survival, the present study was designed to investigate the effects of hydrocortisone (Solu Cortef; Upjohn) 50 mg/kg administered intravenously before and after a period of severe, controlled haemorrhage. The following were investigated: (*i*) the metabolic capacities of lung, liver and kidney tissue to oxidize 1-^{14}C- and 6-^{14}C-glucose *in vitro* after periods of severe shock; (*ii*) the rates of oxygen consumption of tissues *in vitro* from the same organs after shock; (*iii*) the liberation of lysosomal enzymes during shock; and (*iv*) the appearance of endotoxins in the circulation.

Material and methods

The experimental protocol has previously been described in part.[6] New Zealand White rabbits weighing 1,6 ± 0,2 kg were used to study the effects of hydrocortisone sodium succinate in severe haemorrhagic shock.

Two series of experiments were performed. In the first series each rabbit was anaesthetized with intravenous 2,5% thiopentone sodium (Intraval Sodium; Maybaker) 30 mg/kg. Immediately thereafter a bolus of hydrocortisone 50 mg/kg was administered intravenously. The animal was then transferred to a constant-temperature operating table (38°C), tracheostomy was performed, and a cannula was inserted into the trachea to ensure free breathing. A catheter connected to a three-way stopcock was secured in the carotid artery. One opening of the stopcock was attached to a polyethylene tube filled with heparinized saline (Pularin; Evans Medical) 15 U/ml and attached to a mercury manometer or to a pressure transducer of the polygraph (Harvard) to monitor blood pressure. The ECG, pulse rate, and respiratory depth and frequency were also recorded by means of the polygraph. A 20 ml syringe was fitted to the other opening of the stopcock for the withdrawal of blood. The operation lasted 10 minutes, and after a further 10-minute stabilizing period, the control mean arterial pressure was recorded.

Hypovolaemia was then induced by the withdrawal of blood over a 10-minute period until the mean arterial pressure reached 30 mmHg (zero time). Small volumes of blood were withdrawn during the experiment to maintain an arterial pressure of 30 ± 5 mmHg for periods of 1 and 2 hours. Arterial blood samples were taken after stabilization of the blood pressure, i.e. at zero time, at 1 hour and at termination after 2 hours for the determination of haematocrit, total and differential counts, and determination of ß-glucuronidase activity in the blood.[11]

In the second series of experiments, hypovolaemia was induced as described above. One hour after zero time, an intravenous bolus of hydrocortisone 50 mg/kg was administered, immediately followed by infusion of a volume of fluid (50% plasma + 50% saline) equivalent to the blood volume withdrawn. (The plasma was prepared from the heparinized blood withdrawn from the same animal.) After the hydrocortisone treatment and infusion, the animal was allowed to survive for another 2 hours. The mean arterial pressure was recorded until the end of the experiment. On termination of the hypovolaemic period, the rabbits were exsanguinated and their lungs were perfused *in situ* with 50 ml cold phosphate-buffered saline (PBS) via the pulmonary artery. The lungs, liver and kidneys were excised and transferred to cold PBS until further processing.

Control rabbits of approximately the same weight and age as the experimental animals were treated similarly to the experimental animals in the first and second series, except that no blood was withdrawn and no infusion was given. The animals were bled to death and their lungs were perfused *in situ* and removed together with the liver and kidneys and stored in cold PBS.

In the second series, arterial blood samples from the experimental animals were collected at the beginning of the experiment, 10 minutes after hydrocortisone administration and at the end, i.e. 2 hours after the infusion was completed.

Tissue blocks from the excised organs of control and experimental animals were selected and sliced into 0,7 mm slices with a McIlwain chopper (only renal cortical tissue was used).

Determination of metabolic capacity of tissue[12]

Triplicate samples of lung (200 mg), liver (300 mg) and kidney (100 mg) from control and experimental slices were weighed accurately. The samples were incubated separately in metabolic flasks containing 4 ml Krebs-Ringer bicarbonate, pH 7,4, and saturated with 95% O_2 and 5% carbon dioxide. As substrate 5,5 mM cold glucose and approximately 0,20 μCi 1-^{14}C-glucose (56,8 mCi/mmol) or 6-^{14}C-glucose (56,1 mCi/mmol) (New England Nuclear) were used. Incubation was performed in a shaking water-bath (120 cycles/min) at 37,5°C for 60 minutes. The $^{14}CO_2$ was trapped in 0,2 ml Carbo-sorb II (Packard Instrument Co.), added after termination of the incubation period into the centre well of the flask. The $^{14}CO_2$ trapped in the medium was liberated by adding 2,0 ml 6% perchloric acid to the medium in the flasks, which were then incubated for another hour. The Carbo-sorb was then transferred quantitatively to glass scintillation vials each containing 10 ml Instagel (Packard Instrument Co.), and the radioactivity was measured in a Beckman liquid scintillation counter until a counting error of 1% was obtained. Results were expressed as disintegrations per minute (dpm) per milligram of DNA.[12] DNA determinations were done according to the method of Burton.[13]

Determination of the endotoxin concentration in blood[14]

Blood endotoxin concentrations were determined using the Limulus amebocyte lysate chromogenic reagent set (M.A. Bioproducts). Values of less than 0,05 ng/ml were regarded as insignificant.

O_2 consumption[15]

Triplicate tissue samples from control and experimental organs were weighed for the determination of O_2 consumption by the direct Warburgh method[15] over 1 hour in a Krebs-Ringer phosphate medium with air as the gas phase. Results were expressed as microlitres of O_2 per milligram of wet tissue per hour. All experiments were repeated at least six times. Standard methods were used to compute the mean and the standard error of the mean, using Student's *t*-test.

Results

In the first series of experiments the prophylactic effect of intravenous hydrocortisone 50 mg/kg was investigated. The results are recorded in Table I.

TABLE I. EFFECT OF HYDROCORTISONE PRETREATMENT ON THE RATE OF $^{14}CO_2$ PRODUCTION FROM 1-^{14}C- AND 6-^{14}C-GLUCOSE (dpm/mg DNA/h) BY LUNG, LIVER AND KIDNEY TISSUE, 2 HOURS AFTER SEVERE HAEMORRHAGIC SHOCK*

	Lung		Liver		Kidney	
	1-^{14}C-glucose	6-^{14}C-glucose	1-^{14}C-glucose	6-^{14}C-glucose	1-^{14}C-glucose	6-^{14}C-glucose
Control	**6 476 ± 425**	**1 319 ± 233**	**3 964 ± 504**	**1 451 ± 233**	**13 092 ± 1 014**	**10 808 ± 558**
Control + hydrocortisone	**6 500 ± 1 123 (NS)**	**1 572 ± 284 (NS)**	**3 930 ± 367 (NS)**	**1 125 ± 336 (NS)**	**13 999 ± 1 776 (NS)**	**10 839 ± 2 534 (NS)**
Shock for 2 h	**3 690 ± 797 ($P<0,001$)‡**	**846 ± 159 ($P<0,05$)‡**	**2 142 ± 448 ($P<0,001$)‡**	**775 ± 153 ($P<0,001$)‡**	**8 304 ± 1 371 ($P<0,001$)‡**	**7 120 ± 661 ($P<0,001$)‡**
Shock + hydrocortisone for 2 h†	**3 245 ± 709 (NS)§**	**804 ± 147 (NS)§**	**2 435 ± 390 (NS)§**	**656 ± 130 (NS)§**	**10 062 ± 2 291 (NS)§**	**7 726 ± 2 060 (NS)§**

*Results expressed as mean ± SE of 6 experiments.
†Hydrocortisone 50 mg/kg was administered intravenously as a bolus prior to haemorrhage.
‡Compared with control value.
§Compared with shock for 2 h.

Control animals injected with hydrocortisone showed insignificant changes with regard to the capacities of lung, liver and kidney tissues to metabolize 1-^{14}C- and 6-^{14}C-glucose after an exposure period of 2 hours.

In animals suffering from severe haemorrhagic shock (blood pressure 30 ± 5 mmHg) for 2 hours, the oxidation rate of glucose by lung, liver and kidney tissues was significantly lowered when compared with control values.

Treatment of animals with hydrocortisone prior to the haemorrhagic insult did not significantly affect the metabolic capacities of lung, liver and kidney tissues. However, the 1-^{14}C-glucose oxidation rate in liver tissue was higher in hydrocortisone-treated animals, and both 1-^{14}C- and 6-^{14}C-glucose oxidation rates of kidney tissue were markedly increased although not restored to normal levels.

In Table II the effects of haemorrhage and administration of hydrocortisone prior to haemorrhage on some blood values are summarized. Haemorrhage and the accompanying haemodilution resulted in a drop in the haematocrit from a mean of 39,7% to 23,0% over a period of 120 minutes. Hydrocortisone treatment prior to haemorrhage retarded haemodilution, resulting in a mean haematocrit of 29,3%, compared with 23,0% in animals which had not received pretreatment.

The mean total white cell count 2 hours after haemorrhage (blood pressure 30 ± 5 mmHg) dropped to 40% of the normal level, whereas in the animals which received hydrocortisone pretreatment a highly significant increase above the normal level was found. The percentage distribution of granulocytes and lymphocytes remained stable after haemorrhage, but after hydrocortisone pretreatment a relative granulocytosis was evident.

The release of lysosomal enzymes as represented by ß-glucuronidase activity was signficantly elevated by the haemorrhagic insult; this elevation was particularly marked in animals which received pretreatment with hydrocortisone before the 2 hours of hypovolaemia.

In general, it would appear that pretreatment with hydrocortisone before haemorrhagic insult shortened survival time. About 40% of the animals which received pretreatment with hydrocortisone but were not included in this series died after 60 - 90 minutes of hypovolaemia (30 ± 5 mmHg).

In the second series of experiments the effect of intravenous injection of a bolus of hydrocortisone followed by an infusion of fluid was compared with the effect of an infusion alone (Table III). The animals were subjected to severe haemorrhagic shock for 60 minutes prior to treatment. Most values measured after 60 minutes of shock were significantly lower than control values, except in the case of liver tissue. Fluid therapy (50% plasma + 50% saline, equal to the volume of blood withdrawn) had a beneficial but insignificant effect on the rates of glucose oxidation by lung, liver and kidney tissue. Rates of O_2 consumption by lung and liver tissues were significantly improved when compared with values after 60 minutes of shock.

Treatment of haemorrhagic, shocked animals with hydrocortisone followed by a fluid infusion resulted in a significant elevation in $^{14}CO_2$ production from 1-^{14}C-glucose by liver and kidney tissue. O_2 uptake by lung and liver tissue was increased to significantly higher levels than values after 60 minutes of shock. Comparing hydrocortisone and fluid therapy with fluid therapy alone, $^{14}CO_2$ production from 1-^{14}C-glucose as well as O_2 uptake by liver tissue were raised significantly to levels exceeding control values. In lung tissue these values were adversely affected.

TABLE II. EFFECT OF HYDROCORTISONE PRETREATMENT ON ß-GLUCURONIDASE ACTIVITY, HAEMATOCRIT AND TOTAL AND DIFFERENTIAL COUNTS, 2 HOURS AFTER SEVERE HAEMORRHAGIC SHOCK*

	Haematocrit (%)	White cell count (x 10^9/l)†	Differential count		Serum ß-glucuronidase (µmol/min/l)
			Granulocytes (%)	Lymphocytes (%)	
Control (0 min)	**39,7 ± 0,6**	**7,845 ± 0,435**	**50,3 ± 1,7**	**49,7 ± 1,7**	**108,2 ± 5,2**
2 h after shock	**23,0 ± 0,32**	**3,138 ± 0,578**	**49,0 ± 5,8**	**51,0 ± 5,8**	**546,8 ± 115,8**
2h after hydrocortisone + shock‡	**29,3 ± 2,35**	**16,518 ± 4,606**	**56,3 ± 6,24**	**43,7 ± 6,24**	**2 100,4 ± 361,7**

*Results expressed as mean ± SE of 6 experiments.
†Values are corrected for haemodilution.
‡Hydrocortisone 50 mg/kg was administered intravenously 10 min prior to haemorrhage.

TABLE III. EFFECT OF HYDROCORTISONE AND FLUID THERAPY ON THE RATE OF $^{14}CO_2$ PRODUCTION FROM 1-^{14}C- AND 6-^{14}C-GLUCOSE AND ON THE RATE OF O_2 CONSUMPTION (μl O_2/mg TISSUE /h) BY LUNG, LIVER AND KIDNEY TISSUE OF RABBITS EXPOSED TO SEVERE HAEMORRHAGIC SHOCK FOR 1 HOUR*

	Lung			Liver			Kidney		
	1-^{14}C-glucose	6-^{14}C-glucose	O_2	1-^{14}C-glucose	6-^{14}C-glucose	O_2	1-^{14}C-glucose	6-^{14}C-glucose	O_2
Control (0 min)	6 476 ± 425	1 319 ± 233	1,016 ± 0,124	3 964 ± 504	1 451 ± 233	0,512 ± 0,053	13 092 ± 1 014	10 808 ± 558	1,130 ± 0,119
1 h after shock	4 153 ± 1 256 ($P<0,01$)†	979 ± 127 ($P<0,05$)†	0,668 ± 0,150 ($P<0,05$)†	3 077 ± 547 ($P<0,05$)†	1 087 ± 399 (NS)†	0,446 ± 0,112 (NS)†	10 597 ± 173 ($P<0,01$)†	8 049 ± 580 ($P<0,01$)†	0,935 ± 0,289 (NS)†
1 h shock + fluid + 2 h recovery	5 271 ± 611 (NS)‡	1 144 ± 151 (NS)‡	0,843 ± 0,089 ($P<0,05$)‡	3 179 ± 453 (NS)‡	1 131 ± 200 (NS)‡	0,571 ± 0,054 ($P<0,05$)‡	10 952 ± 2 268 (NS)‡	7 160 ± 1 704 (NS)‡	0,926 ± 0,141 (NS)‡
1 h shock + hydrocortisone and fluid + 2 h recovery	4 216 ± 962 (NS)§ (NS)¶	1 043 ± 108 (NS)§ (NS)¶	0,870 ± 0,129 ($P<0,05$)§ (NS)¶	4 175 ± 295 ($P<0,01$)§ ($P<0,01$)¶	1 621 ± 530 (NS)§ (NS)¶	0,698 ± 0,080 ($P<0,01$)§ ($P<0,01$)¶	9 592 ± 698 ($P<0,05$)§ (NS)¶	7 586 ± 507 (NS)§ (NS)¶	1,027 ± 0,084 (NS)§ (NS)¶

*Results expressed as mean ± SE of 6 experiments.
†Compared with control value.
‡Compared with 1 h shock value.
§Compared with 1 h shock value.
¶Compared with 1 h shock and infusion value.

It would appear that hydrocortisone had a beneficial effect on liver tissue only if the tissue was in a reversibly shocked state at the time of treatment.

In Table IV the effects of fluid infusion plus hydrocortisone and fluid infusion alone on ß-glucuronidase activity and endotoxin concentrations and also on the mean arterial pressure of experimental animals are summarized.

Serum ß-glucuronidase activity in shocked animals treated with fluid infusion or hydrocortisone plus fluid infusion was not significantly different 120 minutes after the therapy began.

The plasma endotoxin concentration was negative in the blood of controls and also after the animals had been in a state of shock for 60 minutes. Following fluid infusion and a recovery period of 120 minutes, the test remained negative. In contrast, injection of a bolus of hydrocortisone (50 mg/kg) followed by fluid infusion, resulted in a positive test for endotoxin after 10 minutes; this result remained positive (for 120 minutes) until the experiments were terminated.

The mean arterial pressures of animals treated with hydrocortisone and fluid infusion were significantly higher after a 2-hour recovery period than those of animals which received a fluid infusion alone (Table IV). In Fig. 1 typical blood pressure tracings of 2 experimental animals are recorded — one (A) received fluid alone and the other (B) hydrocortisone plus fluid. Both infusions resulted in increased systolic and pulse pressures. When fluid was given alone (A), a progressive decline in both pressures was seen over the 2-hour recovery period. Simultaneous administration of hydrocortisone and fluid (B) resulted in a sustained systolic pressure and an increase in diastolic pressure.

Discussion

The importance of glucocorticoids in homeostasis is well documented. However, the use of corticosteroids as a therapeutic or prophylactic adjunct in conditions of shock is still controversial.[1,8,10] It is claimed that administration of pharmacological doses of corticosteroids stabilizes lysosomal membranes,[1,8] exerts a positive inotropic action on the heart,[1] counteracts the effect of the myocardial-depressant factor (MDF)[16] and lengthens the survival time of shocked animals.[1,17]

The effects of shock at the cellular level were reviewed recently.[2] Loss of membrane and mitochondrial function with disturbances in ion fluxes and lowering of metabolic co-factors with disruption of energy production appeared to be prominent factors determining the magnitude of tissue damage. Previously we showed that the *in vitro* rate of $^{14}CO_2$ production from 1-^{14}C- and 6-^{14}C-glucose as well as the rate of O_2 utilization by lung, liver and kidney tissues from animals subjected to severe haemorrhagic shock were significantly retarded.[12]

In the study described in this paper we used these metabolic measurements together with others to quantitate the magnitude of tissue damage due to shock and also to evaluate the effects of corticosteroids in shock therapy in terms of these measurements.

In the first series of experiments, the prophylactic effect of hydrocortisone (50 mg/kg) was examined without volume replacement. When given to control animals in pharmacological doses it had no significant effect on any of the values measured, and the same observation was made regarding the metabolic capabilities of lung, liver and kidney tissue of animals subjected to severe haemorrhage soon after administration (Table I). This finding emphasizes the importance of restoration of the macrocirculation before adjunct therapy is attempted.[1] However, if the magnitude of shock was such that it was irreversible, no beneficial effect could be expected. Most of these animals died soon after 2 hours of shock.

TABLE IV. EFFECT OF HYDROCORTISONE THERAPY AND FLUID ON SERUM ß-GLUCURONIDASE ACTIVITY, PLASMA ENDOTOXIN CONCENTRATION AND ARTERIAL PRESSURE IN CONTROL AND SEVERELY SHOCKED RABBITS*

	Serum ß-glucuronidase activity (µmol/min/l)	Plasma endotoxin concentration (ng/ml)	Mean arterial pressure (mmHg) after infusion‡	Mean arterial pressure (mmHg) after hydrocortisone + infusion†
Control (0 min)	**125,10 ± 35,20**	**< 0,05**	**97,5 ± 9,1**	**93,4 ± 10,8**
1 h shock	**—**	**< 0,05**	**30,1 ± 4,5**	**30,5 ± 4,9**
1 h shock + 10 min after infusion	**—**	**< 0,05**	**58,1 ± 15,8**	
1 h shock + hydrocortisone + 10 min after infusion†	**—**	**0,14**	**—**	**52,4 ± 9,3**
1 h shock + 2 h after infusion‡	**516,40 ± 186,00**	**< 0,05**	**43,9 ± 10,9**	
1 h shock + hydrocortisone + 2 h after infusion	**561,20 ± 160,00 (NS)**	**0,13**	**—**	**53,7 ± 7,5 ($P < 0,01$)§**

*Results expressed as mean ± SE of 6 experiments.
†The volume of the infusate (50/50 v/v, plasma/saline) was equal to the volume of blood withdrawn from each animal.
‡Hydrocortisone 50 mg/kg was administered intravenously as a bolus.
§Compared with 2 h value after infusion.

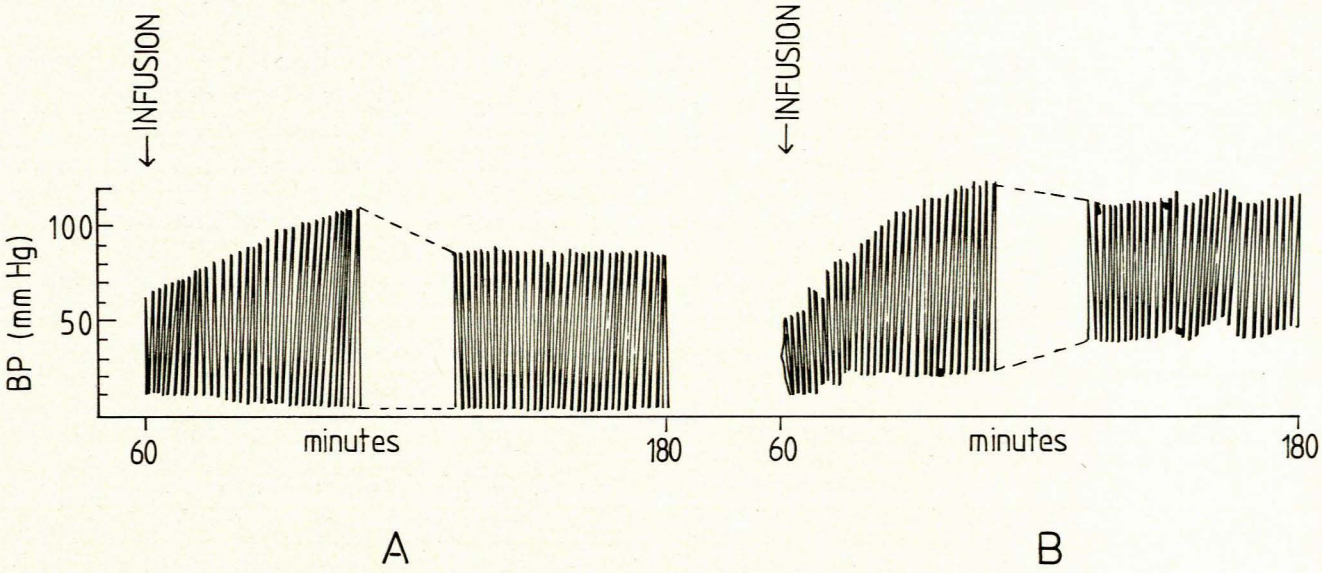

Fig. 1. Blood pressure tracings from 2 rabbits bled to a mean arterial pressure of 30 ± 5 mmHg for 1 hour and then given fluid alone (A) and fluid plus hydrocortisone (B). Carotid arteries were cannulated and coupled to a Harvard blood pressure transducer and the pressures were recorded on a Harvard recorder. Parts of the tracings at the time of infusion (60 min) and at the termination of the experiment (180 min) are shown.

The high mortality rate of animals treated with hydrocortisone prior to severe shock and not receiving fluid replacement points to the importance of the compensatory mechanisms operating in haemorrhagic shock. The massive dose of hydrocortisone prevented haemodilution and aggravated the already compromised circulation, resulting in significantly raised serum ß-glucuronidase levels (Table II).

The increase in the white cell count in the terminal stages of the experiments is difficult to explain. During the early stages of shock a decrease in the white cell count is a general phenomenon, mainly due to margination of the polymorphs during low-flow states.[16] The leucocytosis seen in hydrocortisone-pretreated shocked animals which did not receive fluid replacement could be due to an inhibition of the adhesive properties of these cells, thus preventing their margination in the microcirculation.

Fluid therapy for animals which had been in severe shock for 1 hour partially restored the capabilities of lung and liver tissue to metabolize glucose (Table III). A combination of plasma from the same animal and 0,9% saline for infusion was used so as to provide volume replacement with a lower viscosity than whole blood and also to compensate the dehydrated tissues and thus avoid further dehydration. It has been shown that mitochondrial function is more significantly improved after shock by a combination of whole blood and Ringer's lactate than by whole blood alone.[3] It would therefore appear that increased perfusion of the tissues is as important as an ample O_2 supply in recovery from shock, since it was also

stated that underperfused liver was unable to utilize O_2 efficiently from blood with a normal partial arterial oxygen concentration.[3]

Adjunct therapy with hydrocortisone significantly improves the metabolic capability of liver tissue (Table III). Undoubtedly this is partially due to the pronounced improvement of the splanchnic circulation after hydrocortisone administration.[2,17] While the beneficial effect of hydrocortisone therapy is attributable to haemodynamic effects such as a decreased peripheral resistance and an increase in central venous pressure and cardiac output,[1,9] some benefit is certainly derived from its salutary effect on the circulation of the digestive tract and the decrease in MDF production.[18]

Restoration of the circulatory volume *per se* does not necessarily imply increased tissue perfusion.[2] However, hydrocortisone has its maximum benefit in the microcirculation.[1] Administration of hydrocortisone together with fluid resulted in detectable levels of endotoxin in the systemic circulation (Table IV). This endotoxaemia, however, is not associated with a bacteraemia.

The presence of endotoxins in the circulation only after administration of both hydrocortisone and fluid indicates improved gut perfusion accompanied by an increased absorption of endotoxins from the intestinal lumen. It is suggested that endotoxins cause shock in man and animals by their sympathomimetic effect, resulting in intense vasospasm of the small arterioles and veins in the lungs, bowel and kidneys.[1] The effect of these endotoxins on the course of haemorrhagic shock is open to speculation, since the dual effect of haemorrhagic shock and endotoxins has so far not been investigated. However, it has been shown that perfusion of the intestinal circulation of a dog in severe haemorrhagic shock with arterial blood obtained from a normal donor dog prevents the death of the shocked dog following retransfusion.[1]

Our results also confirm those of Raflo *et al.*[10] in that administration of hydrocortisone plus fluid to rabbits does not diminish the concentration of circulating ß-glucuronidase, a lysosomal enzyme (Table IV). This finding contradicts the concept that corticosteroids stabilize lysosomal membranes.[8] What we have seen could be a wash-out effect due to the improved circulation of the ischaemic tissues after hydrocortisone administration.

The apparent lack of effect of hydrocortisone on the metabolic capabilities of lung and kidney cortex tissues may be due to membrane damage.[2] However, this is contrary to other findings, which indicate that Na^+-K^+ transport and energy levels remain intact in haemorrhagic shock. The significant increase in O_2 consumption by both lung and liver slices *in vitro*, which we found after severe shock, might therefore be due to uncoupling of oxidative phosphorylation (Table III) or to the loss of intermediary metabolites, nucleotides or co-factors by leakage from the cells during shock.[4] Whatever the cause, any of these factors will inevitably lead to an inability of the tissues to respond metabolically to an improved circulation, especially after irreversible damage has been incurred.

The slightly lower but better-sustained mean arterial pressure observed after a combined hydrocortisone plus fluid infusion was also found in monkeys,[16] dogs[17] and cats,[18] confirming the validity of our rabbit model. The beneficial effects of hydrocortisone on haemodynamic values is further emphasized by an increase in diastolic pressure, as reflected in Fig. 1.

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