Creatine and Exercise – Strong Evidence for Stronger Heart Muscle?

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ABSTRACT

Webster I, Huisamen B, Du Toit EF. Creatine and Exercise – Strong Evidence for Stronger Muscles? JEPonline 2011;14(5):85-108. There has been a dramatic increase in the use of dietary creatine supplementation among sports men and women, and by clinicians as a therapeutic agent in muscular and neurological diseases. The effects on skeletal muscles have been documented and reviewed extensively. However, this review looks at another important muscle – the heart – and both the advantages and disadvantages to creatine supplementation, exercise, and the combination. The proposed mechanisms of each are examined and explained.

Key Words: Cardioprotection, Ischemia, Reperfusion Injury
INTRODUCTION

In 1992, the American Heart Association [39] declared that physical inactivity is an independent risk factor for the development of coronary artery disease (CAD), highlighting what a large role physical activity plays in procuring health and physiological harmony. For decades exercise has been described as both a preventative measure and a prophylactic for many diseases and ailments. This is especially relevant in cardiovascular disease prevention and treatment. The beneficial cardiovascular effects of regular exercise were documented as early as 1960 [114], which was followed by many studies that support the initial research findings [42,56,98,152].

Creatine supplementation has been used for years by sportsmen and women as a legal and natural aid to enhance endurance, power, and decrease recovery time. It is advertised on numerous websites as the safe and easy way to improve athletic performance and increase muscle mass. Creatine monohydrate, creatine phosphate, and creatine ethyl esters are all forms of creatine that are taken by athletes and body builders to enhance exercise performance [30,132]. Irrespective of which form of creatine athletes use, the results all seem to favor increased muscle power [63], decreased recovery time, and increased time to fatigue [116]. Although the focus has been on the impact of
creatine on skeletal muscle, this review investigates the effects of creation supplementation primarily on another vitally important muscle - the heart.

**EXERCISE**

**Beneficial Effects of Exercise**

Exercise from early on in life has been seen to be beneficial to the myocardium [121], and has been found to prolong life expectancy and quality of life [89]. Exercise also protects against death from CAD and other causes [123]. An increase in physical activity, albeit moderate, can decrease the chances of a myocardial infarction (MI) and may accelerate recovery after an MI [78]. Animal and human studies also indicate that regular exercise decreases myocardial ischemia and reperfusion injury [12,100]. In normal subjects, regular exercise or training results in enhanced body sensitivity to insulin [70]. This has implications for diabetic and insulin sensitive people, where increased physical activity is beneficial in counteracting a high-fat diet-induced insulin resistance [72] as well as delaying the onset of non insulin-dependent diabetes mellitus (type 2 diabetes) or even preventing the disease.

Other risk factors for coronary heart disease include body weight, body mass index (BMI), cholesterol, LDL cholesterol, and triacylglycerols; all are decreased with an exercise regime [109], as is the progression of atherosclerosis [75]. In addition, physical training improves cardiac function as evidenced by an increase in left ventricular end-diastolic volume, stroke volume, and ejection fraction. Eccentric hypertrophy is due to hypertrophic growth of the walls of a hollow organ, especially the heart, in which the overall size and volume are enlarged [25]. This hypertrophy is associated with an improved left ventricular systolic and diastolic function rather than fibrosis which would be expected to compromise mechanical function [95].

Regular exercise also results in weight loss, and thus helps to decrease blood pressure resulting in reduced hypertension in both men and women [7,118]. Hemodynamic changes in response to exercise can also decrease the chance of ischemic heart disease by reducing platelet aggregation and increased fibrinolytic activity [146].

**Detrimental Effects of Exercise**

Article titles such as “Runners who don’t train well can have a marathon of miseries” [40] and “Ironman athletes put hearts at risk of fatal damage, experts warn” [122], imply that exercise is not necessarily as infallible as it is made out to be. Thompson et al. [134] suggest that exercise is not always beneficial as forceful activity can also acutely and rapidly increase the risk of sudden cardiac death or myocardial infarction in susceptible persons. Exercise is a stressor, and although prolonged exposure to moderate episodes may precondition the heart and protect it, the question of “how much is too much” is a relevant concern [43,74]. Cardiac hypertrophy and associated alterations in the structural properties of the microvasculature have been seen with chronic strenuous exercise [86]. Similarly, alterations in the structure and function of the sarcoplasmic reticulum with acute strenuous exercise have been observed [20]. For example, acute strenuous exercise has been linked to depression in the rate of Ca\(^{2+}\) uptake, a diminished Ca\(^{2+}\) release, and an increase in the intracellular free Ca\(^{2+}\) concentration, which in turn could activate proteolytic pathways.

There is also evidence for a simultaneous activation of the coagulation, fibrinolysis, and complement system as well as for a release of histamine after a short maximal intensity exercise regime [35]. Short-term, high-intensity exercise can lead to significant and prolonged dysfunction of the mitochondrial energy status of peripheral blood leucocytes, and an increased predisposition to apoptosis and raised pro-inflammatory mediators [137]. This could in turn lead to CAD [33]. These results suggest an immunosuppressive effect of excessive exhaustive exercise training [58].
Mechanisms of Exercise Induced Cardiac Protection
As expressed in the preceding sections of this review, exercise training has been shown to not only protect the heart against ischemia and reperfusion induced damage, but also has the known benefit of decreasing the risk of CAD and myocardial infarction. There are two mechanisms thought to induce protection. First, by decreasing many of the causes of ischemia, that is, by reducing risk factors for coronary artery disease (such as blood pressure, cholesterol, risk of atherosclerosis), coronary blood flow is adequate to maintain myocardial integrity. Second, although not fully understood, intrinsic cardioprotective mechanisms such as exercise induced increases in coronary circulation, increases in heat shock protein expression (HSPs) in the heart, increases in myocardial antioxidant levels, and improved function of the sarcolemma \( K_{\text{ATP}} \) channels are implicated in the protection from CAD. In the following section we will briefly discuss each of these exercise induced changes and the implications of these changes on the ischemic/reperfused heart.

Sheer Stress and Vascular Remodeling
Exercise increases oxygen demand of working skeletal muscles, which leads to an increase in cardiac output and blood flow through the vasculature [75]. Shear stress, the stress placed on the vascular wall by the circulating blood, increases during exercise and elevates free radical production in endothelial cells, up-regulates protective antioxidant enzymes and heat-shock proteins and down-regulates pro-apoptotic factors [90]. Exercise also activates endothelial- and inducible-nitric oxide synthase (eNOS and iNOS) that leads to greater nitric oxide (NO) availability [28]. Nitric oxide contributes to vessel homeostasis by inhibiting vascular smooth muscle contraction thus inducing blood vessel dilation, platelet aggregation, and leukocyte adhesion to the endothelium.

Long term chronic exercise training can result in angiogenesis and arteriogenesis in the heart [147] and skeletal muscle [48]. Both adaptations result in an increase in blood flow and an improved blood flow capacity to the vasculature and muscle [82]. See Figure 1.

Figure 1: Shear stress induced NO production by vascular endothelial cells.

Heat Shock Proteins
Heat shock proteins (HSP) are a class of functionally related proteins whose expression is increased when cells are exposed to stress (such as with increased temperature, ischemia, and exercise). They reduce apoptotic and necrotic cell death by antagonizing apoptosis inducing factors (e.g., caspases [115] or by enhancing the activity of mitochondrial complexes I-V) [124]. HSP70’s role in exercise
induced cardioprotection has been studied and shown to be effective in protecting the myocardium from ischemic injury [10,50].

**Antioxidants**

Increased reactive oxygen species (ROS) production by the mitochondria during reperfusion is at least in part responsible for injury. Antioxidants stop the reactions by removing free radicals, and inhibit oxidation reactions by being oxidized themselves [127]. An increase in antioxidants thus helps scavenge the ROS. Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Important nonenzymatic antioxidants include reduced glutathione and vitamins E and C [111].

Although there are reports suggesting that GPx and CAT activity increases with exercise [59], there are also reports that suggest the contrary [29]. MnSOD is however the antioxidant which has been shown to be increased with exercise [41]. But despite this association it has not been established whether this antioxidant is essential for cardioprotection [80]. See Figure 2.

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**K\(_{\text{ATP}}\) Channels**

The ATP-sensitive potassium channel (K\(_{\text{ATP}}\)) is normally inhibited by intracellular ATP and opens during periods of energy depletion [101]. K\(_{\text{ATP}}\) channels are known to exist in the sarcolemmal membrane as well as the mitochondrial membrane of cardiomyocytes. There is evidence both for [27] and against [16] a role for the mitochondrial channels’ in cardioprotection. It has been shown to be a mediator of cardioprotection induced by preconditioning either by ischemia [18], pharmacological manipulation [34] or exercise [16].
Although sarcolemmal K<sub>ATP</sub> channel activation in the ischemic myocardium is critically important for cell survival and protection of function, its electrophysiological effects include shortening of the action potential duration and the refractory period. These effects are potentially proarrhythmic and can promote the development of lethal arrhythmias [64]. Consequently, the inhibition of sarcolemmal K<sub>ATP</sub> channels in ischemic myocardial cells can prevent lethal ventricular arrhythmias and sudden cardiac death [37,138], implicating increased K<sub>ATP</sub> opening in sudden cardiac death associated with exercise. The opening of the mitochondrial K<sub>ATP</sub> channels has also been implicated in improved calcium handling by the cell, reduced mitochondrial matrix swelling, increased oxidative metabolism, and decreased release of ROS by the mitochondria during preconditioning [47,102]. However, Brown et al. [16] have shown that the mitochondrial K<sub>ATP</sub> channels are not an essential mediator in exercised induced cardioprotection but rather the sarcolemmal K<sub>ATP</sub> channels that were infarct sparing after regional ischemia.

**Mitochondria**

The mitochondria are the powerhouses of the cell. During exercise, when the energy demand of the myocardium increases substantially, the mitochondria’s ATP output is increased to meet the demand. Besides ATP synthesis, mitochondria also play a significant role in osmotic regulation, pH control, signal transduction, and calcium homeostasis [14,21].

Exercise training has been shown to improve mitochondrial efficiency of oxidative phosphorylation by increasing the removal of ROS and decreasing free radical production in skeletal muscle [126]. Bo et al. [8] showed that exercise training also increases mitochondrial ATP synthetase activity, ADP to oxygen consumption (P/O) ratio, respiratory control ratio (RCI), and MnSOD activity in cardiac muscle. Ascensao and colleagues [4] showed that endurance training decreased heart mitochondrial susceptibility to MPTP opening. However, not all studies have shown that exercise benefits the mitochondrial. Leucocyte mitochondria show a lowered energy status and a higher incidence of apoptosis during high intensity training [58].

**Pro-Survival Pathways**

Exercise training activates components of the RISK pathway. Exercise training has been shown both to increase PKB/Akt phosphorylation in the hearts of spontaneously hypertensive rats [76] and normalize the PKB/Akt phosphorylation in the myocardium of Zucker diabetic rats [77]. Increased PKB/Akt signaling would also be expected to increase Glut4 translocation for increased glucose uptake and usage [145]. Cardioprotection via the pro-survival pathways is emphasized by the findings of Siu et al. [2004] and Quindry et al. [113] who found that exercise training decreased the extent of apoptosis in cardiac and skeletal muscle.

Iemitsu et al. [60] concluded that exercise training activated multiple mitogen activated protein kinase (MAPKs: ERK, JNK, and p38) pathways in the heart. P38-MAPK is important in many biological processes including cell growth, differentiation, myocyte hypertrophy, and apoptosis [6,144], but it has been implicated as a mediator of ischemic injury [26]. P38-MAPK activation has been seen to gradually decline with the development of exercise-induced cardiac hypertrophy after approximately 12 weeks [60].

**AMPK**

AMP-activated protein kinase (AMPK) plays a key role in the regulation of fuel supply and energy-balance. AMPK is generally inactive under normal conditions, but it is activated in response to hormonal signals and stressors such as strenuous exercise, anoxia, and ischemia that increase the AMP/ATP ratio. Once active, muscle AMPK enhances both the uptake and oxidative metabolism of fatty acids, glucose transport, and glycolysis [3]. AMPK enhances glucose uptake via activation of
GLUT4 translocation, fatty acid oxidation via acetyl-CoA carboxylase [51], and glycolysis by inhibiting glycogen synthase [49]. AMPK is activated during exercise [23,24]. However it has also recently been shown that although AMPK is activated by exercise, the alpha2 isoform of AMPK seems to not be essential for glucose uptake in exercising, AMPK deficient mice [87].

**CREATINE**

The heart is an aerobic or oxygen consuming organ and, therefore, relies almost exclusively on the oxidation of substrates for creation of energy. It can only withstand oxygen deprivation for a short while and still have enough energy to function normally. Thus, in a steady state, determination of the rate of myocardial oxygen consumption provides an accurate measure of its total metabolism. When the supply cannot meet the demand, an energy imbalance ensues. The principle behind creatine supplementation is to provide limitless energy.

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\text{PCr} + \text{ADP} \leftrightarrow \text{Cr} + \text{ATP}
\]

The bidirectional phosphocreatine shuttle highlighted above [8], catalyzed by creatine kinase (CK), prompted the use of creatine supplementation that has been predominant in the last decade. Phosphocreatine is particularly important in muscle [67], sperm [79], and nerve tissues that are subjected to fluctuations in energy demand. With the high delivery of phosphocreatine to the muscle after supplementation, driving the constant restoration of ATP supply, energy supply is expected to be indefatigable [148].

**Sources of Creatine**

Creatine is a non-essential amino acid which is derived from both the diet and synthesized de novo from arginine and glycine by glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT) [142]. This synthesis takes place mostly in the liver and pancreas and to a lesser extent in the brain and testes [13,97]. Creatine is non-enzymatically broken down into creatinine and excreted by the kidneys in urine [11]. The rate at which creatine is degraded is 1.6% which equates to 2 gm per day. This amount needs to be replenished either by endogenous synthesis or by dietary intake [55]. About half of this (±1 gm per day) is provided by the diet, from sources such as meat and fish and the remainder is synthesized endogenously [57]. However, an increase in serum levels of creatine as a result of supplementation results in a decrease in AGAT enzyme activity, enzyme level, and mRNA expression in rat kidney [94], thus producing less creatine [36].

**Creatine Absorption**

The ingestion of a carbohydrate containing solution (e.g., fruit juice) aids in the absorption of creatine from the gut, and may increase total creatine in the muscle by up to 60% [46]. However, while insulin and insulin secretion stimulating food appears to enhance muscle uptake of creatine, high carbohydrate meals may slow the absorption of creatine from the intestine [91].

**Cellular Creatine Uptake and Storage**

Skeletal muscle is the tissue in which most (approximately 95%) of the body’s creatine is stored. The remaining 5% is stored in the heart, brain, and testes [129]. Generally, creatine is transported in the blood from areas of production (liver, kidney, and pancreas) to tissues requiring it (skeletal and heart muscle, brain, and testes). Also, the brain and testes produce their own creatine. Creatine is then taken up into cells by a special creatine transporter called the CreaT, which is located on the cell membrane [143].
Over 90% of cellular creatine uptake occurs via the Na\(^+\)/Cl\(^-\) CreaT, against a large concentration gradient [84]. The extracellular creatine content regulates the transport of creatine into cells [85]. CreaT content is reduced in heart failure [99]. This may contribute to the depletion of intracellular creatine compounds and thus to the reduced energy reserve in the failing myocardium. This discovery has clinical implications, suggesting that the CreaT is a target for therapeutic studies.

**Beneficial Effects of Creatine Supplementation**

Building body bulk [151], increased muscle power and strength [30,132], increased endurance [83], increased muscle glycogen accumulation [103,139] for increased energy storage and utilization capacity, decreased lactate production [22] and decreased inflammation and muscle soreness [125] are all associated with creatine supplementation.

**Clinical Use of Creatine**

Not only does creatine have ergogenic effects, but it has also been used as a prophylactic in many muscular and neurological diseases. Since the decrease in cellular creatine is a possible reason for muscle weakness and atrophy and disturbances in cellular homeostasis in diseased states, the normalization of creatine in the cells with supplementation may be a reason for its effectiveness in relieving the effects in these circumstances [150]. Studies investigating the effects of creatine supplementation on muscular dystrophies have shown the efficacy of creatine to alleviate the clinical symptoms of the disease [38,69]. Creatine supplementation in heart failure patients also increases skeletal muscle’s performance. This is possibly due to an increase in muscle creatine [45].

In mitochondrial encephalopathy, lactic acidosis disease (MELAS) creatine supplementation completely abolished the symptoms after 4 weeks [5], and in Parkinson’s disease creatine supplementation enhances the benefits of weight training [52]. Also, creatine supplementation has positive effects on bone structure and function [2]. Recent work has eluded to the fact that creatine supplementation may help improve insulin sensitivity in type 2 diabetes [105]. Interestingly, creatine has been found to increase antioxidants in skin, and can be protective against UV and other environmental damage [81].

Many positive effects have been documented with the use of creatine as a supplement, both in the healthy and the diseased state. However, care should be taken because the effect of creatine loading on skeletal muscle ergogenics may be negated by the intake of caffeine [140].

**Detrimental Effects of Creatine Supplementation**

Despite the positive observations detailed above, not all the evidence in the literature is encouraging. There have been reports of adverse effects of creatine supplementation. It has been found to bring about gastrointestinal stress and diarrhea [108]. Short-term, high-dose oral creatine supplementation increases the production and thus the excretion of potential cytotoxic compounds, methylamine, and formaldehyde, but does not have any detrimental effects on kidney permeability [110]. In addition, creatine supplementation exacerbates the allergic response of the lungs in mice [141].

Creatine supplementation has also been associated with atrial fibrillation and a rapid heart rate in a 30 yr old man who was admitted to the emergency room [66]. Clinicians could not find any reason for his condition, and when his medical history was examined it was revealed that he had been using creatine as a supplement. He was treated with anticoagulants. His heart rate stabilized and he was sent home 24 hrs later with no obvious adverse consequences.

Despite the negative effects of creatine, there are also studies that show no effect of creatine on endurance, power or recovery. Herda et al. [53] found that creatine supplementation did not increase
power output or muscle endurance. No increased power output or performance was found in tennis players [103]. Also, 7 days of creatine supplementation did not influence cardiac resistance to oxidative stress, alter heart rate or oxygen uptake responses to exercise in cyclists [68]. Similarly, 28 days of creatine supplementation did not improve sprint performance in endurance cycling [54].

**Proposed Mechanisms of Creatine Induced Cardiac Protection**

ATP is created in the mitochondrial by oxidative phosphorylation, and this ATP is then stored in the form of phosphocreatine (PCr) in the cytosol. In the inner membrane space in the mitochondrion a phosphate group is transferred from ATP to Cr, forming ADP and PCr. This reaction is catalyzed by the mitochondrial CK isoform (MiCK). PCr leaves the intermembrane space by diffusion and reaches the cytosol where it is used by cytosolic myofibrillar creatine kinases (MMCK) for the rephosphorylation of cytosolic ADP into creatine and ATP for use by ATPases for energy in cytosolic reactions. Such transfer of energy has been termed the phosphocreatine shuttle [8]. This also ensures that there is never an accumulation of ATP in the mitochondria, thus ensuring a gradient in the mitochondria for continuing ATP production [128]. This increased intracellular creatine potentially acts as a store of phosphate groups to be used during ATP synthesis as energy for the cell. See Figure 3.

![Figure 3. Schematic representation of the phosphocreatine shuttle model, adapted from [71]. During oxidative phosphorylation (OxPhos), ADP is converted to ATP when phosphocreatine in the mitochondrial intermembrane space, ATP donates a phosphate group to Cr and produces PCr. This reaction is controlled by mitochondrial creatine kinase (MiCK). ADP is released into the cytosol where myofibrillar creatine kinase (MMCK) produces ATP and Cr from ADP and PCr, and ATPase controls the reverse reaction.](image-url)

Brzezinska and colleagues [17] concluded that dietary Cr increased cardiac muscle high energy phosphate reserves and its oxidative potential in the rat model after 7 days of supplementation. Creatine supplementation has been shown to increase cardiac creatine reserves only slightly since initial total creatine concentrations are high [62]. They also showed that a minimum of 2 weeks of supplementation was required to raise muscle creatine levels. However, Boehm et al. [9] showed that there was no difference in total creatine transporter levels in cardiac muscle from rats after 6 weeks of
creatine supplementation, nor was there an increase in PCr or Cr in the heart tissue. McClung et al. [92] reported similar results after 3 weeks of supplementation. They found that although the Cr content of the heart tissue increased, total Cr (TCr), which is the sum of both Cr and PCr, did not increase.

These conflicting results may be a consequence of the animal model used, animal housing conditions, or the dosage of creatine used. In addition, the duration of study, the method of sacrifice and tissue extraction may have played a role. Then, too, there are other considerations such as the manner of feeding may also be a factor (e.g., intubation tube/ oral gavage).

In brain tissue from rats, creatine administration stops the inhibition of the Na\(^+\)/K\(^+\) ATPase pump in a model of metabolic disease [119]. Under basal conditions the Na\(^+\)/K\(^+\) ATPase pump uses ATP to remove Na\(^+\) and increase intracellular K\(^+\), thus maintaining ion homeostasis in the cellular environment. During ischemia, the Na\(^+\)/H\(^+\) exchanger becomes activated in response to intracellular acidosis [106] which causes protons to leave the cell down its concentration gradient. The resulting influx of Na\(^+\), occurring as a result of a reduction in ATP and thus a reduction of Na\(^+\)/K\(^+\) pump activity, causes the intracellular accumulation of Na\(^+\). The pump is inhibited and thus the membrane potential is negatively affected.

Zhu et al. [153] reported that creatine supplementation reduced caspase-induced cell death cascades. Caspases are signalling proteins in cells inducing apoptosis, or programmed cell death, and they are termed “executioner proteins.” The cascade includes signalling molecules which activate post transcriptional changes in effector caspases which, then, cause apoptosis in the cell. Active caspase-3 and cytochrome c were found to decrease in neurons after creatine supplementation.

The expression of the insulin dependent glucose transporter, GLUT4, increases in rat and human skeletal muscle with creatine supplementation [65,104], as does AMP-activated protein-kinase (AMPK) phosphorylation [22]. AMPK is involved in the regulation of fuel supply and energy-generating pathways in response to the metabolic needs of the organism. It is activated in response to hormonal signals and stressors such as strenuous exercise, anoxia, and ischemia which increase the AMP/ATP ratio. Ceddia and Sweeney [23] have also observed decreased lactate production and increased glucose oxidation with creatine supplementation. Other researchers have also shown increased glycogen storage in skeletal muscles in humans during creatine supplementation [31,120], thus promoting the storage of energy reserves for use when required.

From the above research findings it would seem that creatine supplementation increases both the energy reserves and the mobilization of energy reserves in the heart and, therefore, would leave it better prepared to withstand an ischemic event. Increased phosphate for regeneration of ATP stores, increased glycogen for energy, as well as increased GLUT4 for glucose uptake and glycolysis during an ischemic event would be expected to afford protection against ischemia and reperfusion injury.

**Creatine Supplementation and Exercise in Laboratory Studies**

**Effects of Exercise and Creatine on Infarct Size**

Reduction in infarct size with exercise was reported as far back as the 1970s [93]. Infarct size was reduced in exercised rats that were subjected to 48 hrs of *in vivo* coronary artery occlusion. This benefit may have been partly related to increased myocardial vascularity that was observed [93]. Melling et al. [96] found decreased infarct size in the ex vivo heart excised after 24 hrs of acute exercise (60 min of treadmill running) and subjected to regional ischemia, with an increase in HSP70, possibly providing the protection. Brown et al. [15] showed decreased cardiac infarct sizes after
treadmill run training in rats trained for a 1 hr a day for 20 weeks. Exercise training also induced a reduction in infarct size in vivo in rats subjected to an 8-week swimming regime 3 hrs per day, 5 days per week [152].

Although De Waard and Duncker [32] reported that exercise in mice using voluntary wheel running for 8 weeks reduced post-MI mortality and reduced LV dysfunction, it did not reduce infarct size. In fact, the thickness and area of infarct worsened in the exercise trained group. Infarct size was reduced in the brain after 3 weeks of creatine supplementation in an induced stroke model in mice [112]. This was independent of levels of Cr, PCr or ATP, which were found to be unaltered in the brain tissue. The same group found that life-long creatine administration failed to decrease infarct size in the brain after an induced stroke, suggesting that adaptive mechanisms could occur which compromise the beneficial effects of creatine. Data from Rawson et al [117] implied that oral creatine supplementation does not reduce skeletal muscle damage or improve functional recovery after hypoxic resistance exercise. These data illustrate that information on the effect of creatine supplementation and exercise in regards to infarct size in various organs are contradictory, some showing protection while others failed to show such benefits.

**Effects of Exercise and Creatine on Post Ischemic Cardiac Function**

Zhang et al. [152] found that after 8 weeks of free loading swim training 3 hrs per day, 5 days per week, left ventricular systolic pressure (LVSP) improved in rats subjected to regional ischemia in vivo. Demirel et al. [29] found an improved myocardial LVDP and rate pressure product (RPP) recovery after 5 days of treadmill exercise training for 20 min per day. This was associated with an increased HSP72 expression and antioxidant enzyme activity, showing beneficial effects of short term exercise. Lennon et al. [80] found that moderate (55% VO$_2$ max) and high intensity treadmill training provided protection against 20 min of global ischemia as reflected by enhanced recovery of cardiac output (Q) and cardiac work, while RPP recovery, heart rate and coronary flow were no different from controls. Burelle et al. [19] also found that treadmill training for 10 weeks (4 days per week) protected isolated hearts against reperfusion injury when using Q as the end point. They found the hearts from exercise trained animals had higher glucose and palmitate oxidation rates before and after ischemia and lower glycolysis rates at these times.

Cardioprotection against ischemia and reperfusion damage was seen in hearts from exercised rats in males but not females [136]. The female’s hearts displayed better recovery of LVDP than the hearts of males, but not better than their control, post-ischemic values. It was postulated that the female heart was possibly already maximally protected by estrogen and could, therefore, not be further protected by exercise training. Starnes et al. [130] found low intensity training (55-60% VO$_2$ max) did not improve cardiac recovery of heart work after 20 min global ischemia and reperfusion. Brown et al. [15] found no LVDP or CF differences under baseline conditions, and although LVDP was greater immediately after ischemia in trained hearts, LVDP had decreased to values comparable to those of control hearts by the end of reperfusion. One study by Mancardi et al. [88] has shown that stressful forced exercise using treadmill training is detrimental to the ischemic heart, increasing infarct size and decreasing LVDP recoveries in the heart.

Many of the studies that have documented cardioprotection with exercise training have used different end points to assess reperfusion myocardial viability. These end points include coronary flow (CF), active tension, LVDP recovery, Q, cardiac work recovery, and infarct size) [16,78,118,152]. This is possibly because these groups looked at the effects of regional [16,152] or low flow ischemia [78,118] on these parameters, while no study has been documented on total global ischemia. The exercise models used were also different. Zhang et al. [152] used swim training similar to our model and
Brown et al. [16], Reger et al. [118] and Le Page et al. [78] used treadmill training. These differences in model may have led to different results.

Bowles and Starnes [12] and Lennon et al. [80] looked at Q and cardiac work recovery and found that it was increased. However, considering that Q is a function of both aortic output (AO) and coronary flow (CF), the increased Q may have been due to an increase in CF without an increase in AO. Myocardial function (pressure and stroke work) was preserved by creatine infusion in a model of coronary artery bypass grafting. Creatine infusion for 10 min during CAL and 10 min of reperfusion increased myocardial cellular ATP levels during ischemia and reperfusion in the treated animals [149]. Creatine supplementation in cardioplegic solution during heart surgery also resulted in better post surgery left ventricular work [133].

Interestingly, Thorelius [135] showed that creatine phosphate in a cardioplegic solution led to better stroke work after aortic valve surgery even though no increases in myocardial ATP or PCr levels were observed. Yet, creatine supplementation (1% body weight in powdered rat chow) for 21 days did not provide cardioprotection during global ischemia (which was induced until ATP was completely depleted in the heart) in rats [107]. Here the Langendorff perfusion apparatus was used and mechanical functional measured was HR multiplied by systolic pressure. The time taken to restore function to normal after ischemia was similar in untreated and creatine supplemented hearts.

**Effects of Exercise and Creatine on Biochemical markers**

A combination of swim training and creatine supplementation for 2 months in hypertensive rats increased mitochondrial creatine kinase (CK$_{Mi}$) expression [44]. Increased CK$_{Mi}$ expression in the myocardium is characteristically associated with hypertrophy. Hypertrophy in hypertensive hearts is associated with increased risk of cardiac death that is not characteristic of exercised hearts. Pressure overload and coronary artery disease both caused increased CK expression in a study by Ingwall and co-workers [61]. This anomaly has not been addressed in either study.

In a study by McClung et al. [92], chronic exercise stress in rats induced a significant decrease in cardiac-muscle total RNA. A loss of cardiac RNA results in a decrease in muscle protein which is detrimental to mechanical function of the heart. Creatine supplementation, in conjunction with the same exercise stress, corrected this attenuation and resulted in values of RNA that were comparable to those of control animals.

**CONCLUSION**

The majority of scientific evidence supports a positive outcome after the use of creatine and exercise. However, there is also evidence suggesting that the “positive outcome” is not always the case. This conflicting information in the literature supports the need for more research to be done before this supplement can be regarded as safe or marketed as an effective treatment for clinical conditions and a miracle supplement for sportsmen and women.
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