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Can lessons learned about preventing cardiac muscle death be applied to prevent skeletal muscle death?

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Historical significance

In 2017, 200 million people worldwide were living with disability due to fractures.[1] Soft tissue damage and prolonged tourniquet application as a result of these injuries can lead to limb dysfunction, paralysis, and even amputation.[2] While ischaemia often causes the initial insult, reperfusion leads to a second-hit, intense inflammatory response that can cause muscle apoptosis and necrosis in what has been termed the ischaemia-reperfusion (IR) injury.[3] Other causes of skeletal muscle IR injury include elective or emergent tourniquet use, acute or chronic compartment syndrome, and vascular injury requiring repair.[4] Preventing IR injury has been an area of interest in cardiology after myocardial infarction (MI) but has not been aggressively pursued in the orthopaedic realm.

Glucose-insulin-potassium (GIK) gained acceptance in the cardiac literature for the treatment of cardiac IR injury in the 1960 s.[5-9] Since its introduction, many clinical studies have evaluated its utility in patients with MI to minimize IR injury, but recommendations on its use remain mixed. Concurrent meta-analyses of very similar early data came to completely different conclusions; one stated that GIK may have an important role in reducing mortality after acute MI,[10] while another explicitly recommended against GIK[11] citing the Polish-Glucose-Insulin-Potassium (Pol-GIK) trial, which was prematurely terminated after noticing higher mortality in GIK patients.[12] Subsequent well-designed randomized controlled studies published after these meta-analyses only showed a benefit of GIK in specific subgroups. The Estudios Cardiológicos Latinoamérica (ECLA) study demonstrated mortality reduction in a reperfusion-treated subgroup[13] and the Glucose-Insulin-Potassium Study-I (GIPS-I) found a mortality reduction in a reperfusion-treated subgroup who presented without heart failure.[14] Alternatively, a meta-analysis of the CREATE-ECLA study and the OASIS-6 GIK trial, together the largest analysis of GIK in MI patients with over 25,000 subjects, found that GIK has no effect on any clinically important end points through 30 days following MI.[15] But the interest in GIK never waned, and a newer study looking at GIK as a treatment for suspected MI found that early, out-of-hospital administration of GIK lowered cardiac arrest rates, in-hospital mortality, one-year mortality, and heart failure hospitalization within one year, although it did not affect progression to MI or improve 30 day survival.[16,17]

While the definitive benefit of GIK in MI patients remains controversial, GIK continues to be popular in cardiothoracic surgery practice, where it demonstrated positive results after valve arthroplasty surgery in the 1970 s.[18] Since then, subsequent studies including a recent meta-analysis of all randomized controlled trials using GIK in cardiac surgery supported this finding, suggesting that GIK can decrease the risk of perioperative MI, the need for inotropic support, and can increase postoperative cardiac index.[19,20]

Interestingly, although skeletal muscle and cardiac muscle undergo similar IR injuries, no studies have evaluated GIK's use in skeletal muscle injury. In fact, a large meta-analysis of GIK use in critically ill patients explicitly noted that study populations in the literature are limited to MI or cardiovascular surgery patients, with no data on trauma patients.[21] A logical question that arises is, given the similar mechanisms of injury, can GIK play a prophylactic and protective role in reducing musculoskeletal IR injury?

Interrelated mechanisms of GIK in cardiac and skeletal muscle

Several mechanisms have been described for the theoretical benefit of GIK in myocardium. These include anti-arrhythmic effects through membrane stabilization, increased

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glycogen content, reduction of free fatty acids (FFAs) and reactive oxygen species (ROS), improved glucose utilization, and increased growth hormone/factor production. Interestingly, these mechanisms may similarly help reduce IR injury in skeletal muscle.

Anti-arrhythmic effects. The anti-arrhythmogenic properties of GIK were the first proposed benefit of GIK in myocardium.[5-9] Studies demonstrated that the insulin in GIK can improve potassium uptake from the myocyte by increasing Na/K-ATPase and hyperpolarizing the myocardium.[22] This has been proposed to lead to cell stabilization and decreased atrial and ventricular arrhythmogenicity in damaged myocardium.[23-27] After ischaemia or trauma in skeletal muscle, dysregulation of the same Na/K-ATPase and by association Ca-ATPase occurs due to adenosine triphosphate (ATP) depletion. Subsequent aberrant electrochemical gradients lead to destabilized cell membranes, increased electrolyte permeability, and excess intracellular calcium, which altogether cause an increase in intracellular calcium-mediated proteolytic enzyme activity and thus myocyte degradation.[28] Increasing insulin-stimulated Na/K-ATPase activity may stabilize the skeletal muscle cell membrane and limit this destructive cascade.

Increased glycogen content. In all ischaemic muscle, ATP production preferentially occurs through glycolysis. Increased glycogen, the storage form of glucose, allows glycolysis to continue to produce ATP when the body's glucose stores are exhausted, which could help reduce damage from the ischaemic arm of an IR injury. In fact, myocardia with increased glycogen stores have been shown to continue to produce ATP and creatine triphosphate during anaerobic conditions.[23] Since the insulin from GIK may increase glycogen content in myocardium through upregulated glycogen synthetase activity, GIK may improve myocardial tolerance to ischaemia.[27,29-31] Similarly, in the only study done on GIK in skeletal muscle, GIK was also shown to limit glycogen depletion during ischaemia.[32] GIK may thus lend the same survival benefit to ischaemic or damaged skeletal myocytes.

Reduction of free fatty acids and reactive oxygen species. While insulin may stabilize cell membranes and increase the body's capacity for ATP production, the transient post-ischaemia insulin resistance, subsequent hyperglycaemia, and systemic lipolysis that occur after MI cause different problems—they increase FFA levels, which in turn increases ROS.[24] During the reperfusion arm of an IR injury, hyperglycaemia and increased ROS can increase myocardial oxygen requirements for the production of ATP, reduce myocardial contractility, and increase cardiac cell membrane damage.[33-36] Alternatively, the insulin in GIK can reduce post-ischaemia hyperglycaemia and inhibit hormone-sensitive lipase and mitochondrial acetyl-CoA-carboxylase, thus directly inhibiting FFA oxidation and the production of ROS.[37] This has been suggested to be beneficial not only in those with cardiac injury, but the critically ill as a whole.[38] In skeletal muscle, high levels of ROS that occur after myocyte ischaemia have also been linked to increased cell damage and apoptosis by raising intracellular calcium.[39] Overall, the mitigation of post-ischaemia hyperglycaemia and ROS production by GIK is likely to be beneficial to both cardiac and skeletal myocytes.

Improved glucose utilization. GIK is suggested to improve myocardial glucose metabolism and ATP production by increasing the expression of glucose transporters, Na-K-ATPase turnover, and the rate of glycolysis through the stimulation of hexokinase and 6-phosphofructokinase.[31] These effects have been shown to improve cardiac contractility even in markedly damaged myocardium.[40,41] Insulin has the same effect on skeletal muscle expression of glucose transporters and on the enzymes involved in glycolysis.[42-44] Thus, GIK may also improve glucose metabolism and ATP production in ischaemic or otherwise damaged skeletal muscle.

Increased growth hormone/factor production. GIK, and insulin specifically, has positive effects on the synthesis of growth hormones and growth factors.[45] It has been proposed to inhibit post-ischaemic apoptosis in myocardium through increased insulin-like growth factor-1 (IGF-1),[46] and can even be anabolic in the critically ill, catabolic patient.[38,47] Insulin is also known to increase skeletal muscle protein synthesis, possibly through a similar pathway as in cardiac muscle, although its exact mechanism remains unclear.[48-50]

Outlook

Despite the clear biochemical pathways that support GIK as a therapy for skeletal muscle IR injury, very little has been published on its use in musculoskeletal trauma, elective orthopaedic surgery, compartment syndrome, or vascular injury. Only one study on an animal model found that GIK decreases glycogen depletion in skeletal muscle during fasting,[32] but did not address its effect on muscle injury. Considering the body of work in cardiac muscle and the analogous cellular mechanisms, GIK may lend a prophylactic and therapeutic benefit to traumatized skeletal muscle cells by improving skeletal muscle membrane stability, glycogen content, glucose transportation, and protein synthesis, as well as by reducing ROS production. If effective, GIK could speed up recovery after musculoskeletal injury, and thus decrease its associated morbidity and mortality. GIK is therefore an attractive therapy for a host of in vitro, animal model, and human trials aimed at improving the treatment of skeletal muscle IR injury.

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