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Glucose-Insulin Therapy, Plasma Substrate Levels and Cardiac Recovery After Cardiac Ischemic Events

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Abstract
Introduction The potential usefulness of glucose-insulin therapy relies to a large extent on the premise that it prevents hyperglycemia and hyperlipidemia following cardiac ischemic events.
Methods In this review we evaluate the literature concerning plasma glucose and free fatty acids levels during and following cardiac ischemic events.
Results The data indicate that hyperlipidemia and hyperglycemia most likely occur during acute coronary ischemic syndromes in the conscious state (e.g. acute myocardial infarction) and less so during reperfusion following CABG reperfusion. This is in accordance with observations that glucose-insulin therapy during early reperfusion post CABG may actually cause hypolipidemia, because substantial hyperlipidemia does not appear to occur during that stage of cardiac surgery.
Discussion Considering recent data indicating that hypolipidemia may be detrimental for cardiac function, we propose that free fatty acid levels during reperfusion post CABG with the adjunct glucose-insulin therapy need to be closely monitored.
Conclusion From a clinical point of view, a strategy directed at monitoring and thereafter maintaining plasma substrate levels in the normal range for both glucose (4–6 mM) *and* FFA (0.2–0.6 mM) as well as stimulation of glucose oxidation, promises to be the most optimal metabolic reperfusion treatment following cardiac ischemic episodes. Future (preclinical and subsequently clinical) investigations are required to investigate whether the combination of glucose-insulin therapy with concomitant lipid administration may be beneficial in the setting of reperfusion post CABG.

Key words glucose-insulin therapy · free fatty acid · ischemia · reperfusion · CABG

Introduction

Ever since the introduction of glucose-insulin-potassium therapy in the setting of cardiac ischemic diseases [1], this technique has gone through alternating periods of varying attention. Although originally devised to prevent intramyocardial hypokalemia during ischemia and reperfusion, the therapy is nowadays mainly advocated to reduce hyperglycemia and hyperlipidemia which have been deemed to be present during the reperfusion period.

The first part of this review entails a critical appraisal of the literature concerning plasma substrate concentrations following reperfusion of ischemic cardiac events. We hope to convince the reader that, although plasma levels of free fatty acids (i.e., non-esterified fatty acids) and glucose may be elevated during reperfusion, this certainly is not always observed. Factors affecting substrate availability are highly influenced by the specific standard operation protocols used by the hospital (protocols for fasting, anesthesia techniques, heparin use, inotropic therapy), the anxiety of the organism (conscious versus anaesthetized) and the medical characteristics of the patient. The availability of substrates in the blood stream is a major determinant of myocardial metabolic activity. Metabolic treatment of the ischemic heart during reperfusion, therefore, can only be successful when it is based on accurate knowledge concerning the pre-

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treatment (=baseline) levels of circulating substrates of the patient.

The second part of this review is directed at how glucose-insulin therapy may affect substrate availability during reperfusion and how these changes may affect cardiac recovery following an ischemic episode through specific alterations in cardiac metabolism. From a clinical point of view, a strategy directed at keeping plasma substrate levels within the normal range (thus preventing both hyper- and hypoglycemia and hyper-*and* hypolipidemia) and at stimulation of glucose oxidation seems to hold the most promise for optimal treatment of the heart following cardiac ischemic episodes.

Plasma substrate availability during cardiac ischemic events

Clinical factors affecting substrates

In the healthy, fed individual, blood glucose levels range between 4-6 mM (70–110 mg/100 dl) and free fatty acid (FFA) levels between 0.2–0.6 mM. However, in the peri-operative condition considerable changes in these substrate levels may occur as a consequence of the specific operation protocol. Patients scheduled for elective cardiac operations are usually requested to refrain from food intake 12–24 h before the operation. This fasting procedure results in low insulin levels (removing insulin-inhibition of lipoprotein lipase (LPL)), increased FFA concentration and decreased glucose concentration [2, 3]. The next confounding factor is the type of anesthetic regimen chosen. Many anesthetics differently affect plasma glucose and insulin levels, with minor effects on plasma FFA. We recently showed that, while pentobarbital and sufentanil-propofol were without effect on plasma glucose concentration, volatile anesthetics and α_2-agonists (e.g. xylazine, medetomidine) resulted in hyperglycemia and thus deregulation of glucose homeostasis [4]. Both anesthesia techniques based on the use of either opioids or volatile anesthetics are frequently used for the anesthetic management of patients undergoing cardiac operations. Furthermore, although cardiac operations necessitate the use of the anti-coagulation agent heparin, it has long been known that heparin can result in a several-fold increase in plasma FFA levels by inducing the release of hepatic and endothelial-bound LPL [5, 6]. This heparin-effect is often only present during the early reperfusion phase following by-pass operations, because heparin is usually quickly antagonized upon termination of the by-pass. Less well-known is the ongoing lipolysis in the sample due to the presence of this detached LPL, especially after the *in vivo* administration of heparin [7, 8]. Without special precautions, e.g. inhibition of ex vivo lipolysis with a potent lipoprotein lipase inhibitor [9], plasma FFA may be substantially overestimated by the lab. We believe that this aspect has often been neglected, resulting in an overestimation of FFA during conditions of heparin administration (usually early reperfusion). In addition, acute myocardial infarction in the conscious state and post-ischemic reperfusion are characterized by high levels of catecholamines from endogenous sources and/or from the inotropic support given by the clinician [10, 11]. These high levels of catecholamines have also been hypothesized to inhibit insulin secretion and to activate lipolysis of adipose tissue resulting in increased plasma FFA [12, 13].

Therefore, it appears that, in the peri-operative patient, the standard clinical treatment and applied biochemical determination of especially FFA are critical issues when reviewing substrate levels during reperfusion. Each surgical/anesthesia team should determine the metabolic profile associated with its perioperative protocols to determine if improvement in cardiac function may be anticipated with the use of metabolic support. To illustrate this important point, it is shown in Table 1 that certainly not all studies report increased FFA and glucose levels following ischemia. The table indicates that FFA levels are most likely to be elevated during conditions of acute coronary syndromes in the conscious state (e.g. acute MI, [14–16]). During conditions of actual reperfusion, such as following PTCA *after* acute MI [16–20] or after less severe ischemia, such as following CABG in the anaesthetized condition [21–24], FFA levels are less likely to be elevated.

It should be noted that, although elevated FFA levels have long been viewed as a risk factor, there is evidence that elevated glucose levels are also associated with increased risk [25, 26]. However, the table indicates that hyperglycemia is certainly not always present upon reperfusion and when it is present, the rise in plasma glucose is usually modest. An exception to this may be the diabetic patient [24] who is more likely to develop hyperglycemia. It therefore seems that, before embarking on standardizing the use of insulin therapy immediately following cardiac ischemic events on the premise of preventing hyperglycemia and hyperlipidemia, the metabolic profile of the patients and the clinical care treatment should be documented. Ideally, insulin therapy should only be given on indication of acutely monitored elevated glucose and/or FFA plasma levels. Alternatively, in a subset of each specific group of patients, together with the clinical care treatment given, the metabolic profile is characterized in terms of plasma glucose and FFA levels before a decision is made whether the whole group of patients is treated with insulin therapy. Only when hyperglycemia and hyperlipidemia are present should one use insulin therapy to combat these elevated circulating glucose and FFA levels.

Table 1 Glucose and free fatty acid (FFA) plasma levels (mM) determined before or during ischemia (pre-reperfusion, pre-R) and at reperfusion of the ischemic cardiac intervention as reported by several different studies

Substrate	Pre-reperfusion	Reperfusion	Study
Glucose	n.r.	n.r.	**pre-reperfusion (pre-R)**: AMI patients within 24 h of MI; no
FFA	0.5–2.1	n.r.	prior administration of heparin or catecholamines. [14]
Glucose	12	n.r.	**pre-R**: AMI-patients selected with arterial FFA levels > 0.8 mM
FFA	1.2	n.r.	(~50% of MI patients); no heparin used. [15]
Glucose	n.r.	n.r.	**pre-R**: ST-elevation MI < 12 h of symptom onset; **R**: 24 h after
FFA	0.8±0.4	0.4±0.2	PTCA of the AMI-patients; heparin n.r. [16]
Glucose	7.9	6.7	**pre-R:** ST-elevation MI < 6 h of symptom onset; **R**: 24 h after
FFA	n.r.	n.r.	PTCA/thrombolysis of the AMI patients; heparin n.r. [17]
Glucose	5.9±0.8	4.4±0.4	**pre-R**: baseline control dogs; **R**: 24 h after 3 h LAD occlusion;
FFA	0.4±0.1	0.8±0.2	heparin n.r., no inotropics. [18]
Glucose	5.7±1.4	not sign.	**pre-R**: baseline open-chest pigs; **R**: 30–90 min after 11 occlusions of 1–2
FFA	0.4±0.2	versus pre-R	min of left main coronary artery; 300 IU/kg heparin, no inotropic. [19]
Glucose	3.8±0.4	3.7±0.2	**pre-R**: baseline open-chest pigs; **R**: 60–90 min reperfusion after 90 min
FFA	0.4±0.1	0.3±0.1	low-flow LAD occlusion; no heparin or inotropics. [20]
Glucose	9.6±2.4	8.4±2.0	**pre-R**: before crossclamp in 30 CABG patients; **R**: 10 min reperfusion;
FFA	0.4±0.2	0.4±0.2	3 mg/kg heparin, no inotropics [21]
Glucose	5.5±0.5	6.3±1.0	**pre-R**: before crossclamp in 21 CABG patients; **R**: 2 h reperfusion;
FFA	0.4±0.1	0.4±0.2	no inotropics. [22, 23]
Glucose	9.8±0.2	13.8±0.3	**pre-R**: before crossclamp in 141 diabetic CABG patients; **R**:
FFA	0.7±0.1	0.6±0.1	6 h reperfusion; + inotropics. [24]

CABG coronary artery bypass grafting, *AMI* acute myocardial infarct, *PTCA* percutaneous transluminal coronary angioplasty, *n.r.* not reported

Glucose-Insulin therapy and substrate availability

Because plasma substrate availability may limit metabolism to a large extent [27, 28], any change in substrate availability instigated by insulin therapy will result in shifts in the major cellular metabolic pathways involved in the generation of ATP, i.e., glycolysis and glucose oxidation and fat oxidation. The administration of large amounts of insulin will decrease circulating glucose through activation of GLUT transporters that facilitate cellular glucose uptake and inhibition of hepatic gluconeogenesis. The increased risk of developing temporary periods of hypoglycemia is one of the well-known adverse effects of insulin therapy [29]. Insulin therapy is therefore almost always combined with glucose administration to prevent hypoglycemia. As a result of this increased cellular glucose uptake, glucose-insulin therapy will increase glycolysis and glucose oxidation. Insulin will also reduce plasma FFA concentrations, resulting in decreased fatty acid oxidation, promotion of TAG storage and possibly hypolipidemia. This lowering of lipids is mainly due to insulin-mediated inhibition of the hormone-sensitive lipase in adipose tissue, the determining enzyme for whole-body lipid fuel availability [30] and insulin-induced CD36-mediated increase in FFA uptake [31]. Interestingly, the developing of hypolipidemia with glucose-insulin therapy has received far less attention in current clinical practice as compared to hypoglycemia [32]. This probably stems from the premise that fatty acids are commonly believed to be elevated at reperfusion and that any decrease in fatty acid metabolism is always associated with improved cardiac recovery from ischemia. However, we now know that hyperlipidemia is not always present at reperfusion (see above), and that too little fatty acid oxidation can be detrimental for cardiac recovery (see below). In the following paragraphs, the insulin-mediated changes in the three major ATP-generating pathways (increased glycolysis, increased glucose oxidation, decreased fatty acid oxidation) are discussed in relation to cardiac recovery from ischemia. It is well documented that the potential usefulness of GIK certainly also leads to non-metabolic mechanisms such as the activation of cell survival pathways leading to cardioprotection through reduction in apoptosis [33–36] and reduced inflammatory (22) and neurohumoral responses (11). However, in this review we focus primarily on the GIK effects on plasma substrate levels and metabolic pathways.

Increased glycolysis

The non-oxidative breakdown of glucose to pyruvate or lactate, i.e. glycolysis, is commonly increased in the post-ischemic heart [37–39]. In addition, important cardiac pathologies such as hibernation, hypertrophy and heart failure are associated with increased glycolytic activity, probably as a result of recurrent episodes of limited oxygen supply [40–42]. The use of glucose-insulin therapy will

further enhance post-ischemic glycolysis, provided that hypoglycemia does not occur. The functional benefit of increased glycolysis is in keeping with the observation that the heart requires glycolysis during early reperfusion [43, 44]. Although glycolytically produced ATP only amounts to ∽ 2% of total ATP production in the presence of oxygen, this ATP seems to be preferentially used for membrane functions allowing recovery of ionic homeostasis (preventing Ca^{2+} overload) during early reperfusion. In addition, acidification at the moment of reperfusion may be beneficial, because it inhibits mitochondrial permeability transition pore opening [45].Thus, increased glycolysis during reperfusion is protective in conditions of recurrent ischemia and reperfusion. However, increased glycolytic flux during zero-flow ischemia is detrimental [46] and may result in increased acidification during ischemia. Finally, the post-ischemic increase in glycolysis will also slow down cellular energy transfer [47–49] and may decrease the rate of maximal, sustainable oxidative phosphorylation [50, 51].

It therefore seems that increasing glycolysis during reperfusion with glucose-insulin therapy will protect against reperfusion damage at the expense of slower energy transfer. Because it is unlikely that delayed energy transfer will be detrimental for the heart during acute reperfusion, increasing glycolysis during reperfusion seems to entail an overall protective effect against reperfusion damage.

Increased glucose oxidation

Although increased glucose oxidation is not always observed following ischemia [27, 37, 52], most studies have shown that the activation of glucose oxidation in the reperfusion phase improves the recovery of cardiac performance [53, 54]. Thus glucose-insulin therapy will be beneficial through activation of this pathway, provided that no hypoglycemia occurs that may actually decrease glucose oxidation. In addition, the therapy will reduce hyperglycemia, a risk factor that has been shown to contribute independently to poor recovery [55].

Currently, the two most prevailing hypotheses explaining the protection offered by increased glucose oxidation involves increased mechanical efficiency and decreased proton load, respectively. With respect to the former, it has recently been shown that oxygen consumption for the same amount of work increased considerably (from 10% at high work to 48% at unloading conditions) when switching from a predominantly glucose metabolizing condition to a predominantly fatty acid metabolizing condition in *in vivo* pigs [56]. This decreased efficiency with increased fatty acid oxidation may be explained by a fatty acid induced decreased P:O ratio in addition to uncoupling of oxidative consumption and futile, energy-consuming cycling of fatty acids in and out the intracellular triglyceride pool [56]. The second hypothesis is associated with the so-called coupling of glycolysis with glucose oxidation, i.e. when pyruvate produced by glycolysis is subsequently oxidized in the TCA cycle, the proton production from hydrolysis of glycolytically-produced ATP is zero [27]. However, if glycolysis is uncoupled from glucose oxidation, and pyruvate is not oxidized further, there is a net production of two protons from each glucose molecule metabolized. Such may occur with increased fatty acid metabolism. Fatty acids inhibit glucose oxidation more than glycolysis and glycolysis more than glucose uptake, indicating that with increasing fatty acid oxidation the rate of glycolysis increasingly deviates from that of glucose oxidation, resulting in the uncoupling of glycolysis from glucose oxidation [57]. The resulting acidosis may then cause decreased contractility and increased calcium overload during the reperfusion period. Increased glucose oxidation will then prevent ongoing acidosis during the early reperfusion period, thereby improving recovery of mechanical performance. However, this theory is not without controversy. It has been shown that insulin-glucose administration in an isolated heart model improved functional recovery compared with the administration of dichloroacetate (DCA) which is a direct stimulant of carbohydrate oxidation, whereas DCA had a greater impact on increasing glucose oxidation [58]. In that study it was found that the protection was not associated with increased coupling of glucose oxidation to glycolysis. A recent study examining mechanical recovery following low-flow ischemia in GLUT1-overexpressed mice hearts reached similar conclusions [59]. An uniform mechanistic, cellular, explanation for the advantageous effects of increasing glucose oxidation is therefore currently lacking.

In general, the literature suggests that treatment aimed at stimulation of glucose oxidation while normoglycemia is maintained (i.e. without the concomitant development of hyperglycemia or hypoglycemia) seems to be promising and safe with respect to improved cardiac function in the post-ischemic period.

Decreased fatty acid oxidation

At the moment, the prevailing opinion is that increased fatty acid oxidation during the reperfusion period is detrimental to the functional recovery of the heart. However, although some studies demonstrate that increasing FA oxidation is associated with decreased functional recovery in the reperfusion phase [57, 60, 61] other studies showed unaltered [62] or even improved recovery with increased FA oxidation [37, 63]. It has been suggested that the effects of lipids are primarily detrimental when present at high levels during the ischemic period, but not during reperfusion [64]. That FA oxidation during reperfusion can

be protective is also supported by studies showing decreased functional recovery of hearts from fatty acid transporter-knockout animals that lack the sarcolemmal fatty acid transporter CD36 [65], a similar observation as found for GLUT4-knockout animals [66]. Recently, Tuunanen et al [67] demonstrated that acute depression of plasma FFA by acipimox, an inhibitor of lipolysis, depressed cardiac work in healthy and diseased humans with additional decreases in cardiac efficiency for heart failing patients. Acipimox decreased FFA concentrations from 0.6 mM to 0.1 mM. Interestingly, the very few studies examining the effect of insulin therapy on FFA levels also indicate that this therapy may reduce FFA to similar levels. Addo et al [16] reported FFA levels of 0.2 mM with GIK therapy in patients undergoing primary percutaneous coronary intervention (without taking into account sample lipolysis). We recently demonstrated FFA levels around 0.1 mM with insulin therapy following CABG procedures [23]. These low FFA levels are commensurate with the observation that FFA concentrations are often not increased during reperfusion (see "Plasma substrate availability during cardiac ischemic events" section above). From these observations it may be hypothesized that there exists a requirement for a minimal concentration of plasma FFA for the heart in order to perform optimally. As for glucose, the data suggest that the prevention of hypolipidemia as well as hyperlipidemia during reperfusion may be an important consideration of any metabolic therapy, including the glucose-insulin therapy.

Finally, one complicating factor concerning FA effects that may explain some of the controversy is that there are "good" and "bad" fatty acids. Especially the saturated fatty acids such as palmitate appear to be detrimental, even inducing apoptosis [68], whereas other fatty acids (mainly (poly)unsaturated fatty acids) appear to be beneficial in the reperfusion period [69]. Future preclinical studies have to demonstrate the potential beneficial effect of the combination of glucose-insulin therapy with additional lipids on myocardial energy balance, infarct size and mechanical function following ischemia and reperfusion. Due to the ambiguity of the cardiac functional effects of changes in FA metabolism, clinically directed manipulation of FA metabolism must be executed with great care.

Summary

In the peri-operative patient, the standard clinical treatment and applied biochemical determination of especially plasma FFA are critical issues when reviewing substrate levels during reperfusion. Each surgical team should determine the metabolic consequences of its perioperative protocol to determine if improvement in cardiac function may be anticipated with the use of metabolic support. FFA levels are most likely to be elevated during conditions of acute coronary syndromes in the conscious state (e.g. acute MI) and less so during reperfusion post CABG. Consequently, GIK therapy in conditions of CABG may result in hypolipidemia that can potentially limit the beneficial effects of this therapy. Whether hypolipidemia is disadvantageous during post CABG reperfusion awaits further pre-clinical and subsequently clinical studies. At the moment, monitoring of FFA levels during GIK therapy, as is commonly performed for glucose levels, is strongly recommended.

From a clinical point of view, a strategy directed at monitoring and thereafter maintaining plasma substrate levels in the normal range for (glucose 4–6 mM; FFA 0.2–0.6 mM), and at stimulation of glucose oxidation, seems to hold the most promise for optimal metabolic reperfusion treatment following cardiac ischemic episodes.

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