Three good reasons for heart surgeons to understand cardiac metabolism

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Summary

It is the principal goal of cardiac surgeons to improve or reinstate contractile function with, through or after a surgical procedure on the heart. Uninterrupted contractile function of the heart is irrevocably linked to the uninterrupted supply of energy in the form of ATP. Thus, it would appear natural that clinicians interested in myocardial contractile function are interested in the way the heart generates ATP, i.e. the processes generally referred to as energy metabolism. Yet, it may appear that the relevance of energy metabolism in cardiac surgery is limited to the area of cardioplegia, which is a declining research interest. It is the goal of this review to change this trend and to illustrate the role and the therapeutic potential of metabolism and metabolic interventions for management. We present three compelling reasons why cardiac metabolism is of direct, practical interest to the cardiac surgeon and why a better understanding of energy metabolism might indeed result in improved surgical outcomes:

(1) To understand cardioplegic arrest, ischemia and reperfusion, one needs a working knowledge of metabolism;
(2) hyperglycemia is an underestimated and modifiable risk factor;
(3) acute metabolic interventions can be effective in patients undergoing cardiac surgery.

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1. Introduction

One of the co-authors of this article posed the following question when seeing the first draft: 'Interesting title, but do you have a more exciting word for 'metabolism'?' As a practicing cardiac surgeon you may ask yourself: 'Why should I pay attention to metabolism?' Is understanding it really important for my part of patient care? The answer is 'Yes.' If you think what we do in the operating room is important for patient outcomes, if you think it is better to repair a mitral valve than to replace it, if you think it is better to use arterial grafts in a young patient with coronary artery disease instead of veins, then you should also care about metabolism. The impact of proper perioperative metabolic management on patient outcome may be just as big as the difference of the right choice in any of the examples mentioned.

The limited interest in metabolism in the surgical field may be due to the tremendous achievements in the area of myocardial protection that are taken for granted by most. Of note, cardiac surgeons have been in the spotlight of energy metabolism since the birth of cardiopulmonary bypass and the need for cardiac arrest through cardioplegia and/or hypothermia. The practical importance of how the heart generates ATP and transforms it into contractile activity is undeniable and extends well beyond the application of cardioplegia. Better understanding of these processes will allow us to improve results even further. We just have to look beyond the scope of cardioplegia and ischemia/reperfusion to broaden our appreciation and understanding of metabolism.

We will herein illustrate the practical role of metabolism in modern cardiac surgery and the possible impact on outcomes by posting three provocative statements. We are providing a basic review of the current knowledge with emphasis on the direct practical relevance of the individual topics discussed.
2. The three reasons

2.1. Reason 1: to understand cardioplegic arrest, ischemia and reperfusion, one needs a working knowledge of metabolism

There are several reasons why a heart slows or ceases its contractile activity. Whether it is done electively, by depolarizing the membrane with cardioplegic solutions, by decreasing energy demand through cooling or simply by the interruption of blood flow through intermittent cross-clamping, or whether it occurs accidentally through an occlusive thrombosis in an epicardial artery, all of them affect the way the heart muscle consumes substrates and makes ATP. Any modification to affect the consequences of such interruptions of contractile activity is directly linked to myocardial energy metabolism. Therefore, a short review of the basic principles of cardiac metabolism is in order.

2.1.1. Basic principles of cardiac energy substrate metabolism

Per gram tissue the heart consumes more energy than any other organ of the body. The human heart consumes up to 5 kg of ATP per day, i.e. 17 times its own weight. To do this the heart uses a variety of substrates supplied by the blood stream and has thus been termed a metabolic omnivore [1]. Under normal conditions, the heart generates 70% of its ATP from the oxidation of fatty acids, 10—30% from the uptake and oxidation of glucose and a small percentage from the oxidation of lactate, amino acids and ketone bodies [2]. All substrates compete for oxidation by the cardiac myocyte. This competition is based on certain regulatory processes important for the proper production of ATP [2].

Fig. 1 summarizes the basic regulatory processes of how the heart generates ATP through the use of energy providing substrates (for a detailed review see [2]). Glucose is transported across the plasma membrane through glucose transporters located in the plasma membrane [3]. If glucose uptake is increased, e.g. by insulin, catecholamines or by ischemia, more glucose transporters are recruited from intracellular vesicles [4]. Inside the cell glucose is phosphorylated to glucose-6-phosphate (G6P). Phosphorylated glucose enters the glycolytic pathway, is stored as glycogen, enters the pentosephosphate pathway, or enters the hexosamine biosynthetic pathway. The majority of G6P enters the glycolytic pathway and produces pyruvate. During glycolysis ATP and NADH2 are generated. Under normoxic conditions, pyruvate is transported into the mitochondria by the monocarboxylate transporter where the majority is decarboxylated to acetyl-CoA by the enzyme pyruvate dehydrogenase (PDH). PDH is the rate-limiting enzyme for glucose oxidation. PDH is an enzyme complex regulated through phosphorylation and dephosphorylation by the enzymes pyruvate dehydrogenase kinase (PDK) and PDH-phosphatase. PDK phosphorylates PDH, thereby reducing glucose oxidation [5]. Inhibition of PDK4, the predominant isoform in heart, is a commonly used pharmacological target to activate PDH and glucose oxidation (see Reason 3 and Table 1).

Fatty acids are mainly transported across the sarcolemma by fatty acid transporters (FATP, FAT/CD36) [6]. Following their import, fatty acids are esterified to Acyl-CoA. Acyl-CoA is then shuttled across the mitochondrial membranes through the carnitine-palmitoyl-transferase system (CPT1 and 2). Intramitochondrial acyl-CoA enters beta-oxidation resulting in the generation of acetyl-CoA and reducing equivalents to drive the respiratory chain (NADH2 and FADH2). Carnitine
funneled back into the matrix through the F0F1-ATPase, reducing equivalents (NADH2, FADH2) are oxidized in the generation of a proton gradient across the inner mitochondrial membrane (see[9,10] for review). The majority of protons are recruited and glucose uptake and oxidation is stimulated. The ATP-demand is a key regulator of fatty acid oxidation and is inhibited by malonyl-CoA. The concentration of malonyl-CoA is regulated through the enzymes acetyl-CoA carboxylase (ACC) and malonyl-CoA decarboxylase (MCD). High concentrations of acetyl-CoA activate ACC, resulting in malonyl-CoA production and inhibition of fatty acid oxidation [7]. Modulation of these enzyme activities is currently under investigation for therapeutic use [8].

The final product of almost all oxidizable substances is acetyl-CoA. Acetyl-CoA enters the citric acid cycle where it produces reducing equivalents, and generates CO2. All reducing equivalents (NADH2, FADH2) are oxidized in the respiratory chain (under normoxic conditions) and result in the generation of a proton gradient across the inner mitochondrial membrane, the driving force for ATP production (see [9,10] for review). The majority of protons are funneled back into the matrix through the F0F1-ATPase, which uses the energy to make ATP.

ATP-demand is a key regulator of fatty acid oxidation and substrate selection [11]. If ATP is not resynthesized readily AMP accumulates activating the AMP-activated protein kinase (AMPK), which acts as sensor for a decrease in energy charge of the cell. In general, AMPK activates ATP-production through inhibition of anabolic and activation of catabolic processes, acting as a ‘fuel gauge’ of the cell. In heart muscle, AMPK results in increases in both glucose and fatty acid oxidation [12,13]. AMPK is an important intracellular modulator of substrate utilization and may also serve as therapeutic target for pharmacological intervention. Substrate utilization and substrate preference of the heart can also be influenced through hormones from outside the cell.

The two main metabolically active hormones influencing energy substrate metabolism are insulin and the catecholamines (through both α- and β-receptor stimulation) [14–17]. Adrenergic hormones set the oxidative pattern of the cell towards ATP production, i.e. the full spectrum of substrate oxidation in the heart is activated. Glucose transporters are recruited and glucose uptake and oxidation is stimulated. Glycogenolysis is activated as well as lipolysis in peripheral fat cells and gluconeogenesis in the liver, increasing both glucose and fatty acid availability in the blood stream [15–18].

Insulin stimulates glucose uptake, glucose oxidation, glycogen synthesis and inhibits fatty acid oxidation. It does so by binding to its receptor on the plasma membrane and initiating a cascade of phosphorylation events, beginning with autophosphorylation of the inner portion of the receptor, followed by the insulin receptor substrate (IRS) 1 and 2, phosphatidylinositol-3-kinase (PI3K) and Akt (also known as PKB). Akt then mediates many of the metabolic effects. For the effect on glucose uptake, an additional pathway involving the protonocogene Cbl and the Cbl adaptor protein CAP and the small GTP binding protein TC10 needs to be activated [19]. Inhibition or dysfunction of any of these mediators can cause insulin resistance [20,21], which negatively impacts on cardiac surgery outcomes (see below for details).

The above described regulatory processes result in a perfect match of ATP production and ATP demand under normoxic conditions in the normal heart. Selection of substrates for ATP production is governed by their supply as well as intracellular factors, including ATP-demand [11]. However, it is important to realize that just as cardiac work influences energy substrate metabolism, energy substrate metabolism influences cardiac work.

2.1.2. Contractile function and energy substrate metabolism

The importance of the relationship between energy substrate metabolism and contractile function is just now being recognized on a larger scale [22]. It is considered a potential pathomechanism in heart failure and diabetes mellitus [23,24]. However, it may also bear a therapeutic option for the treatment of contractile dysfunction [2,22].

In 2002, Taegtmeyer [25] suggested the concept of the substrate switch where a shift from fatty acid to glucose oxidation improves ATP producing efficiency and thereby function in the failing heart. The concept has been tested by several investigators and is sound, if therapeutically exploited in the failing or postischemic heart [26–28]. Here, the shifting from fatty acid to glucose oxidation was associated with improved recovery of function after ischemia or increased contractility in the failing heart. However, in the context of heart failure, the concept of the substrate switch can be challenged, because the shift from fatty acid to glucose oxidation during the development of heart failure...
occurs late and is not associated with an improvement of contractile function [29,30]. Here, the observation may indeed signal a metabolic defect that results in the production of inadequate amounts of ATP, resulting in failure. Such a dysregulation may exist at the mitochondrial level, specifically at the level of a metabolic co-activator regulating mitochondrial biogenesis, fatty acid oxidation and respiratory capacity. This co-activator is termed PGC-1 (α and β), and has been implicated in the pathomechanism of heart failure and diabetes mellitus [31]. We [32] and others [29] have demonstrated that in the development of heart failure, contractile dysfunction is preceded by a down regulation of PGC-1α, and reduced fatty acid oxidation, suggesting a shortage in ATP-producing capacity as pathomechanism. Thus, mitochondrial dysfunction appears to play an important role in the genesis of heart failure and diabetes mellitus, both important risk factors in cardiac surgery.

Another interesting and therapeutically relevant observation in this context is the association of heart failure and insulin resistance. It is now becoming evident that heart failure can cause insulin resistance, and, vice versa, the insulin resistance can cause heart failure [33]. This is illustrated in studies demonstrating a high prevalence of insulin resistance and diabetes mellitus in heart failure populations on the one hand [34] and the high incidence of heart failure in patients with insulin resistance syndromes on the other hand [35]. We have observed cardiac insulin resistance in pressure overload heart failure in rats (unpublished observation 2008), which was correlated with decreased mitochondrial respiratory capacity. McQueen et al. [36] demonstrated in cardio-specific insulin receptor knockout mice that these hearts developed mitochondrial dysfunction suggesting the same link. Thus, we currently speculate that a decrease in insulin sensitivity of the heart may lead to impairment of mitochondrial respiratory capacity resulting in contractile dysfunction and heart failure.

The full elucidation of the aspects discussed above potentially provides the surgeon with new, metabolic tools to either improve contractile function of failing hearts before surgery, which should translate directly into reduced operative mortality, or to improve recovery of hearts after ischemia during reperfusion. In order to assess the potential impact of these metabolic interventions, it is helpful to review the metabolic changes during ischemia and reperfusion.

2.1.3. Metabolic changes during ischemia and reperfusion

If the continuous supply of oxygen is diminished or interrupted (hypoxia or ischemia), the fine tuned balance of ATP-production from the various substrates is disturbed. Depending on the degree of hypoxia or the type of ischemia (low-flow or total) substrate selection changes [37—39]. During hypoxia or low-flow ischemia glucose uptake increases. The limited oxygen availability leads to a shift in glucose metabolism from oxidation to lactate production, i.e. glycolysis switches from the ‘aerobic’ to the ‘anaerobic’ state. The increase in glycolytic rate is induced by activation of phosphofructokinase through increasing AMP-levels, thus stimulating AMP-activated protein kinase [12]. Due to limited oxygen availability, oxidation of fatty acids and glucose is decreased [40].

During total ischemia, glycogen is quickly degraded resulting in a temporary increase in glycolysis [40]. Glucose uptake cannot be increased due to limited supply. The glycolytically produced ATP during ischemia is mainly used to maintain ion pump function of the plasma membrane [41]. If total ischemia continues, glycolysis comes to a stop because lactate and protons accumulate and NAD⁺ cannot be regenerated. Contractile function ceases for a variety of reasons, including lack of ATP and intracellular acidosis. If total ischemia continues, cell death is inevitable. In the human heart, irreversible damage begins after 40—60 min of ischemia [42,43] while in rat heart irreversible damage already starts at 30 min [44]. Such irreversible damage develops first in distal areas of the coronary perfusion bed (endocardial infarction), and, as time goes on, it spreads like a ‘wavefront’ to the epicardium [45].

Shorter or less severe phases of ischemia do not necessarily result in necrosis but may result in apoptosis. Apoptosis is an alternative form of cell death, defined as organized, i.e. programmed cell death. Apoptosis is characterized by an ordered sequence of intracellular events culminating in the break-up of nuclear DNA (see [46] for a detailed review). Ischemic arrest during cardiac surgery induces apoptosis and interventions to inhibit apoptosis have been shown to improve recovery after cardioplegic arrest [47]. However, there is still debate whether the amount of apoptosis induced by cardioplegic arrest is causally involved and whether the small amounts are relevant [48,49], since the severity of ischemia during cardiac surgery is usually rather mild compared to a true infarct.

Short-term ischemia or milder, low flow ischemia almost always cause contractile dysfunction. It is readily conceivable, that a lack of sufficient ATP-production during ischemia results in immediate impairment of contractile function. However, ischemia-induced contractile dysfunction often remains when blood flow and ATP production are restored. It can be found without evidence of continuing ischemia or cell death in one of two ways, either myocardial stunning or myocardial hibernation. Myocardial stunning is defined as temporary contractile dysfunction as a result of short episodes of ischemia or hypoxia which is reversible upon adrenergic stimulation [50]. Stunning is the most frequent cause when reversible dysfunction is observed after cardioplegic arrest. Myocardial hibernation is a chronic down regulation of contractile activity as a response to repeated or chronic states of low-flow myocardial perfusion [51]. It is the morphological substrate behind positive viability tests in akinetic or dyskinetic myocardium. In both cases metabolic changes have been described but are not in the front row of current concepts explaining the mechanisms (for review see [49]).

Irrespective of the effects of ischemia on the cardiac cell, reperfusion of the ischemic myocardium is the prerequisite for any potential return of contractile function. However, reperfusion itself can cause additional damage, also known as reperfusion injury [52]. The importance of reperfusion injury has been discovered by reduction of ischemic damage with interventions applied only during reperfusion. The mechanisms of reperfusion injury are still hotly debated. Current
suggestions involve the influence of neutrophil granulocytes or free radicals, direct endothelial damage as well as changes in intracellular calcium homeostasis [53—58]. The severity and duration of reperfusion injury is dependent on the type and duration of ischemia and is also dependent on the conditions of reperfusion. It is possible to metabolically influence reperfusion injury. This has been done successfully and repeatedly by supplementation of cardioplegic solutions with metabolically active ingredients (see [53] for a detailed review). The most widely applied technique in this aspect is the ‘terminal hot shot’, where warm blood cardioplegia enriched with glutamate and aspartate as reperfusion supplements is given at the end of a phase of cardioplegic arrest just before the cross-clamp is removed [59]. It is interesting to note that the practically applied treatments for reperfusion injury all share a tight time limit. They are all given at the end of a cardioplegia protocol and are limited to a few minutes. It appears that this therapeutic window has not yet been fully explored.

If reperfusion occurs early enough, full recovery of function is possible. Metabolic processes (i.e. substrate oxidation and ATP-production) usually recover quicker than contractile function [22]. Fatty acid oxidation, for instance, is rapidly restored upon reperfusion [60]. We already mentioned above that a delay in the return of fatty acid oxidation and an increase in early glucose oxidation contributes to the speed and the degree of functional recovery [22,30] (substrate switch). And here it becomes interesting for the practicing surgeon. Substrate switching can be pharmacologically induced and has been shown to reduce ischemia/reperfusion injury [30], increase recovery of function after ischemia [61,62] and may even delay the onset of contractile dysfunction during the development of heart failure [63]. The shift in substrate oxidation towards glucose is associated with more efficient ATP generation, i.e. significantly less oxygen is used per ATP generated. This is mainly due to the fact that carbohydrates carry more oxygen for their own oxidation than fatty acids. Lopaschuk et al. [28] additionally suggested that an increase in pyruvate consumption through elevated glucose oxidation decreases the proton load generated during oxygen shortage. Irrespective of the exact mechanisms, these effects are attractive to the cardiac surgeon, because they could be and partially are being exploited for patient care today (see Reason 3). Understanding the mechanism might help our understanding of ischemia/reperfusion and our ability to improve the heart’s tolerance to withstand it.

2.1.4. Myocardial protection through cardioplegia; how does it work?

Every organ is able to withstand a certain time period of interrupted substrate and oxygen supply without suffering irreversible injury. This time period is termed ‘ischemia tolerance’. The main principle of myocardial protection is the extension of ischemia tolerance through the reduction of metabolic activity. This can be done by reducing energy consumption through applying hypothermia, or by reducing energy demand through arresting the contractile apparatus with cardioplegia. From a didactic standpoint, cardioplegic solutions can be separated into ‘intracellular’ and ‘extracellular type’ solutions, based on their electrolyte composi-tions. Extracellular type solutions arrest the heart based on high potassium or magnesium content or both. Intracellular type solutions arrest the heart based on low sodium content. The classic intracellular type of solution is Bretschneider’s solution, the classic extracellular type is St. Thomas cardioplegia. Blood cardioplegia (all variants) belongs to the group of extracellular type solutions. The principle action of conventional cardioplegia (i.e. the clinically used solutions) is the depolarization of the cell membrane and the complete electrical arrest of the myocyte [64,65]. A new concept combines the application of adenosine with lidocaine resulting in hyperpolarization of the heart [66]. While the initial results of this concept are promising [66], further experiments need to be conducted.

From a practical perspective, one needs to distinguish blood cardioplegia from crystalloid cardioplegia. Countless studies have addressed potential differences between blood and crystalloid cardioplegia (reviewed in [67,68]), but the results do not support recommendation of one technique over the other. Further investigations looked at the composition or the temperature of cardioplegia, others at the direction of delivery [69,70]. None of them has achieved a true breakthrough. Instead, they have contributed to the generation of a large armamentarium of cardioplegic techniques which are utilized by the individual surgeon according to his/her experience. Large, prospective, randomized multi-center trials are missing and the only study with acceptable evidence is a recent meta-analysis demonstrating significant advantages (less postoperative low output syn-drome and early CK-MB release) of blood cardioplegia compared to crystalloid, but no survival advantage [71]. Today, a plethora of different solutions is available (e.g. more than 160 different solutions are used to arrest and protect the heart for heart transplantation in the United States alone [72]). The importance of differences in composition and routes of applications may thus be questioned, bringing us back to the two main principles, which are shared by most cardioplegic techniques: reducing energy consumption by cardioplegic arrest and reducing energy demand by hypothermia.

The advances in the field have been tremendous and the results of cardiac surgery have reached a level that seems difficult to improve. Yet, cross-clamp times still matter. A large analysis was performed by us on 30,000 patients in the Toronto General Hospital database having undergone cardiac surgery with blood cardioplegic arrest between 1990 and 2003. We found that cross-clamp time is an independent predictor of mortality [73]. In other words, even during protected ischemia, the above described detrimental processes of ischemia/reperfusion still occur. Thus, it is important to realize, that the dangers of ischemia may be delayed but are not overcome.

2.2. Reason 2: hyperglycemia is an underestimated and modifiable risk factor

Hyperglycemia develops when the effect of the body’s insulin on adipose tissue and muscle is impaired (i.e. decreased insulin sensitivity or increased insulin resistance). During cardiac surgery, every patient develops some degree of insulin resistance [74]. It is the common notion that this
insulin resistance is due to stress-induced release of cortisol and other stress hormones such as epinephrine or norepinephrine. These hormones stimulate gluconeogenesis in the liver, activate glycogenolysis of most cells and inhibit insulin action. The result is hyperglycemia. These mechanisms are independent of the presence of diabetes, but they aggravate a pre-existing state of insulin resistance [74]. Therefore, even non-diabetic patients demonstrate various degrees of hyperglycemia during and after cardiac surgery [74—76].

There is now strong evidence that perioperative hyperglycemia is associated with poor outcome in patients undergoing cardiac surgery [77,78]. The Portland group [77] demonstrated that the degree of postoperative hyperglycemia in patients with diabetes mellitus undergoing cardiac surgery is independently correlated with operative mortality and morbidity. This finding is consistent with the pathophysiological concept that diabetes mellitus aggravates perioperative insulin resistance, suggesting that those patients with the most severe insulin resistance are at the greatest risk. If insulin resistance is involved in this mechanism, it appears reasonable to assume that hyperglycemia is also a risk factor in non-diabetic patients. Indeed, van den Berghe et al. [79] demonstrated in a landmark study that establishing euglycemia in intensive care patients (the majority of patients were non-diabetics) after any type of surgery (65% cardiac) significantly reduces morbidity and mortality (Fig. 2) [79]. The reduction of blood glucose from an average of 153 ± 33 mg/dl to 103 ± 19 mg/dl in patients staying in the ICU for more than 5 days resulted in a 47% reduction in mortality and similar reductions in the need for therapeutic interventions. A subanalysis of this trial focusing on patients undergoing cardiac surgery showed a more than 50% survival benefit of glucose control, which was maintained after 4 years of follow-up [80]. In addition to this prospective randomized trial, we demonstrated in a retrospective databank analysis that the peak glucose level during cardiopulmonary bypass is an independent predictor of mortality in both diabetic and non-diabetic patients undergoing cardiac surgery [81]. Thus, hyperglycemia (and possibly insulin resistance) appears to be involved in the mechanisms of these detrimental effects, which in turn is independent of the presence or absence of diabetes.

While the evidence that perioperative hyperglycemia negatively affects outcome in cardiac surgery is excellent (class 1B), the evidence that treating hyperglycemia especially intraoperatively improves outcome is not as strong. For the postoperative setting, Van den Berghhe [79] made the first step, followed by a more recent prospective randomized study by Lazar’s group in Boston [78]. The investigators demonstrated a short- and long-term survival benefit for diabetic patients receiving a mixture of glucose-insulin-potassium to establish euglycemia after cardiac surgery. However, the establishment of euglycemia during CPB has not shown the expected benefit. A recent single center randomized study on 400 routine coronary bypass patients demonstrated no survival benefit of intensive insulin treatment [82]. Surprisingly, the study found slightly higher mortality and stroke rates in the insulin treatment group (not significant). Whether this observation is treatment associated is not clear. The study is rather small and the fraction of patients with high risk low. Further assessment of this question is needed. In the meantime, it still appears advisable to at least treat extreme degrees of hyperglycemia during CPB and to establish euglycemia after CPB by applying insulin (even in higher doses) or withholding glucose infusions. This is especially true in patients with longer intensive care unit stays. Even if hyperglycemia cannot be avoided by insulin administration, some of the negative side effects of hyperglycemia (e.g. increased leukocyte adherence to the endothelium) may be counteracted by increasing the levels of circulating insulin [83]. A recent evidence-based review of the practice of cardiopulmonary bypass recommends the establishment of perioperative euglycemia (i.e. including euglycemia during cardiopulmonary bypass) for all patients and rates the evidence as class 1 [84]. However, when aggressively treating hyperglycemia, one needs to be aware of the risks. The application of even extreme doses of insulin (up to 500 IU/h) does not cause any detriment per se [74]. Treatment associated hypoglycemia may be dangerous [85], even though the reports on this complication are scarce. In this context, consider the well-known effect of hyperglycemia on stroke and cerebral ischemia (common complications of cardiovascular surgery [86]). If the results of the van den Berghhe trial [79] translate to the specific management of all patients undergoing cardiac surgery, the impact of this minor modification may be staggering.

Here, it may be the time to remember the previously mentioned concept of extending the therapeutic window for reperfusion injury. Reducing glucose levels by increasing glucose oxidation or inhibiting fatty acid oxidation during or at the end of CPB and continuation of this treatment in the postoperative period would extend the therapeutic window of reperfusion and may serve two possibly distinct therapeutic purposes, establishing euglycemia and ameliorating reperfusion injury. First steps have been taken in this direction but the potential is far greater (see below).

2.3. Reason 3: acute metabolic interventions can save lives

The concept of treating contractile dysfunction and ischemic conditions of the heart metabolically is not new. Insulin was the first metabolic ‘drug’ that was suggested to be
used to treat heart disease only a few years after its discovery [87]. However, insulin has never found a place in the armamentarium of drugs used to treat heart failure. Since then, many drugs have been developed and tested. Table 1 shows a list of these drugs and their effects. Many of them have been developed as anti-diabetic drugs and their effects on the heart have been investigated later. One of these drugs is etomoxir, an inhibitor of CPT1. Etomoxir has started out very promising in an initial small, non-randomized study, where treatment with the drug improved symptoms of heart failure [88]. Later, the drug was withdrawn from the market due to side effects on the liver demonstrated in a randomized trial [89]. Other investigators had already shown that prolonged inhibition of muscle CPT1 promotes intramyocellular lipid accumulation and insulin resistance [90]. In contrast, another drug, trimetazidine, also an inhibitor of fatty acid oxidation, is a commonly prescribed anti-angina pectoris medication in France [91,92] and ranolazine, another partial fatty acid oxidation inhibitor, is currently being tested for its effects on heart failure in the MERLIN trial [93]. Irrespective of the individual mechanism of action, all drugs listed in Table 1 have two things in common. They all induce a substrate switch from fatty acids to glucose, and there is currently no visible effort to seriously test their effects in the acute setting of cardiac surgery. But they should be tested for the following three reasons. First, a substrate switch is capable of improving myocardial efficiency. It is generally accepted that operative mortality is inversely related to perioperative risk. Second, because the drugs improve the efficiency of ATP-production they may reduce catecholamine requirements. Third, the desired drug effect (e.g. the inhibition of fatty acid oxidation) is dependably inducible in the acute setting. Long-term application of these drugs in the setting of heart failure or the chronic treatment of angina may not guarantee the drug effect witnessed in the acute setting. It is therefore likely, that the chronic inhibition may be overcome or decreased in effectiveness if the time for transcriptional responses is available. Accordingly, metabolic modulation such as therapeutic induction of a substrate switch should belong in the field of cardiac surgery and should be embraced by surgeons.

Yet, the published studies on the impact of metabolic drugs (with the exception of insulin) are easily counted. Trimetazidine has been assessed in one randomized controlled trial. The study included only low-risk patients with normal ventricular function and demonstrated no beneficial effect [94]. This observation is not surprising since the outcome of these patients is already so good that efforts to further improve it have to be backed by randomized trials that are prohibitively expensive. Interestingly, a randomized trial of trimetazidine application in patients with heart failure demonstrated a drug specific improvement of contractile function, and attested best efficacy for patients with low ejection fraction [92]. Other non-randomized studies demonstrate less troponin T release after coronary bypass grafting with trimetazidine [95] and reduced oxidative stress [96]. There are no reports on studies using any of the other drugs (except insulin) listed in Table 1 in the setting of cardiac surgery.

More interest has been demonstrated in the use of insulin in the treatment of cardiovascular disease, specifically the use of glucose, insulin and potassium. Over the last four decades, interest has waxed and waned for this treatment regimen. The intended reasons for its use have changed from the belief that it replenishes lost potassium during infarction (Soli-Pallares; ‘polarizing solution’) [97], to increasing glucose consumption by supplying and aiding its uptake through delivery of insulin [98], to direct action of insulin on contractile function [61], and most recently to the ability to establish postoperative euglycemia [78]. The suggested intracellular mechanisms include effects such as increased anaerobic ATP production, glycogen loading, repletion of depleted energy cycles by anaplerosis, reduction of FFA oxidation and increased efficiency of ATP production from glucose oxidation [74]. The results are as different and as colorful as the intended purposes. However, in the surgical setting, insulin is a powerful drug. Fig. 3 demonstrates the impact of GIK on postoperative contractile function from a recent meta-analysis [75]. Though limited in its ability to stimulate glucose consumption by perioperative insulin resistance [74], it is still effective in establishing euglycemia [78,79] and may exert a direct effect on postischemic myocardial contractile function [99]. We have recently reviewed this field in detail [74]. Using insulin to establish postoperative euglycemia is classified as class 1 evidence for reducing perioperative mortality [79,84]. Other drugs and therapeutic concepts targeted at specific metabolic sites should be tested for their ability to do the same.

3. Conclusions

The generation of contractile function is linked to the metabolism of energy producing substrates. Metabolism can be slowed by arresting the contractile apparatus (e.g. through cardioplegia) and vice versa, contractile function slows when metabolism is halted (e.g. through ischemia or metabolic toxins). Cardioplegia extends ischemia tolerance, but this extension is not indefinite. Several ‘metabolic
windows’ remain that can be therapeutically exploited, including the induction of substrate switching, extending the treatment of reperfusion injury beyond the scope of minutes, and preoperatively addressing mitochondrial defects or optimizing substrate supply. Several tools are already out there. All it takes is us, the practicing cardiac surgeons, to make better use of it.

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