The homeostasis of plasma glucose levels is essential for survival of the mammalian organism. Since blood glucose concentration is maintained within a narrow range, glucose is a most reliable substrate for energy production in the heart. The importance of glucose metabolism via glycolysis is well appreciated in ischemic and hypertrophied heart muscle, but aerobic glucose metabolism for support of lysis is well appreciated in ischemic and hypertrophied heart. The importance of glucose metabolism via glycolysis is well appreciated in ischemic and hypertrophied heart muscle, but aerobic glucose metabolism for support of normal contractile function has received less attention, mainly because of the well-known fact that fatty acids are normally the predominant fuel for cardiac energy production. We have drawn attention to the heart as a true "omnivore," i.e., an organ that functions best when it oxidizes different substrates simultaneously. In light of this concept, we wish to reexamine myocardial glucose metabolism and its relevance to the human heart. In recent years, the tools of molecular and cellular biology have provided new insight into the mechanisms of glucose transport and phosphorylation. Glycogen metabolism has come into greater focus. The regulation of glycolysis is more accurately defined, and the effects of second messengers on myocardial glucose utilization are better known. In view of this background, 2 well-known clinical concepts of myocardial glucose metabolism require critical reevaluation: (1) the diagnostic concept of metabolic support for the postischemic heart and (2) the therapeutic concept of metabolic support for the posts ischemic heart with glucose, insulin, and K⁺ (GIK).

Regulation of Glucose Metabolism in Normoxic Heart

The simple sugar d-glucose is the most abundant organic molecule in nature. Glucose for the heart is derived either from the bloodstream or from intracellular stores of glycogen (Figure 1). The transport of glucose into the cardiomyocyte occurs along a steep concentration gradient and is regulated by specific transporters. Intracellular glucose is rapidly phosphorylated and becomes a substrate for the glycolytic pathway, glycogen synthesis, and ribose synthesis. After entering the glycolytic pathway, glucose is ultimately broken down to pyruvate (Figure 1), which, in turn, is a substrate for further metabolic pathways. Glucose uptake, defined as glucose transport and phosphorylation, is measured as the product of glucose extraction (percentage) × arterial concentration of glucose × flow. Measurements of net glucose uptake and lactate release by the arteriovenous differences have been extensively used in humans to assess glucose metabolism, but measurements in vivo are not as precise as in isolated hearts. In the latter, glucose metabolism can be directly assessed by labeled tracers and analogues. For instance, glucose uptake may be measured by the detrition rate of [2-3H]glucose, and glycolytic flux may be measured by the detrition rate of [3-3H]glucose or [5-3H]glucose. Similarly, glucose oxidation may be measured by the release of 14CO₂ from [14C]glucose. Glycogen may also be labeled with the same tracers. Dual- or triple-labelling techniques allow precise measurement of the relative amounts of glucose derived from glycogen compared with glucose derived from extracellular sources. The quantitative determination of glucose uptake by the glucose tracer analogue 2-deoxyglucose or FDG is based on the assumption that, unlike glucose 6-phosphate, 2-deoxyglucose 6-phosphate and FDG 6-phosphate are irreversibly trapped in the tissue and are neither subject to further metabolism nor subject to dephosphorylation. The 3-compartment model of Sokoloff et al. and the graphic analysis of Patlak et al. are commonly used to quantify the rates of myocardial glucose uptake from dynamic measurements of radioactivity in a region of interest. Under steady-state conditions, the accumulation of tracers is linear and follows zero-order kinetics. Since the affinity of glucose transport is higher and that of hexokinase is lower for deoxyglucose than for glucose, Sokoloff et al. introduced a lumped constant (LC) to calculate rates of glucose uptake from tissue activity in the brain. However, derivation of this formula for tracer kinetic analysis of glucose uptake in the heart is flawed by a trivial solution, and LC decreases significantly with insulin or after addition of another substrate together with glucose. Combining upper and lower limits for LC with the ratio between unidirectional and steady-state FG uptake rates allows the prediction of individual LCs and, hence, the quantification of myocardial glucose uptake by a simple tracer kinetic model.

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Regulatory Steps of Glucose Metabolism

**Glucose Transport**

The transporters regulating the uptake of glucose belong to the GLUT family and constitute a system of stereospecific and saturable transport/countertransport. The isoform that is predominantly expressed at the surface of adult cardiomyocytes is GLUT 4, the insulin-sensitive transporter also found in adipose tissue. In addition, the cardiomyocyte expresses the GLUT 1 transporter, which is presumably independent of insulin action and predominant in fetal myocardium. Both transporters have a \( K_m \) for glucose (ie, the concentration of glucose at which the rate of transport is half-maximal) that is in the range of plasma glucose concentrations under fasting conditions. The normal heart also expresses a low amount of GLUT 3, which has a \( K_m \) below the normal plasma glucose concentration. Stimulation of glucose transport is exerted by a recruitment of transporters from intracellular stores to the plasma membrane, resulting in an increased maximal velocity of transport.

**Hexokinase**

Glucose phosphorylation by hexokinase is the first regulatory step that commits glucose to further metabolism (Figure 1). Two different isozymes of hexokinase are present in the heart, hexokinases I and II. Hexokinase I is predominant in the fetus and newborn heart, whereas the insulin-regulated hexokinase II is predominant in the adult heart. The reasons for this genetic shift are not known. Hexokinase is present in the cytosolic fraction of the cell but also binds to the outer mitochondrial membrane. This attachment also suppresses inhibition of hexokinase by glucose 6-phosphate. Insulin shifts the control strength of glucose uptake from glucose transport to phosphorylation. Control strength is defined as the ratio of the change in enzyme activity on the change in the pathway flux.

**Glycogen Metabolism**

Although the bulk of glucose 6-phosphate enters the glycolytic pathway (Figure 1), glucose 6-phosphate is also a substrate for glycogen synthesis. The dynamics of glycogen turnover have recently been investigated, and cycling of glucose moieties in and out of glycogen has been proposed as a control site for myocardial glucose metabolism. Glycogen occupies about 2% of the cell volume of the adult and 30% of the cell volume of the fetal and newborn cardiomyocyte. Unlike liver and skeletal muscle, heart muscle increases its glycogen content with fasting. This observation is consistent with the general principle that fatty acids, the predominant fuel for the heart during fasting, inhibit glycolysis more than glucose uptake, thereby rerouting glucose toward glycogen synthesis. Glycogen stores are also increased by insulin, from the simultaneous stimulation of glucose transport and glycogen synthase activity. Net glycogen synthesis also occurs when lactate is the predominant fuel for the heart.

A variable amount of exogenous glucose cycles through glycogen before entering the glycolytic pathway. The cycling of glucose through the glycogen pool is substrate dependent. In isolated working rat heart perfused with glucose as sole substrate, a small part of extracellular glucose taken up by the cell is incorporated into glycogen before entering the glycolytic pathway, whereas this incorporation rate is significantly greater in vivo, when hormones and competing substrates are present. At the other end of the spectrum, glycogen is rapidly broken down when glycogen phosphorylase is stimulated by epinephrine or glucagon. Glycogen phosphorylase is the main regulator of glycogenolysis and one of the best-studied enzymes. It is activated by phosphorylation, either by cAMP-dependent protein kinase or by Ca\(^{2+}\)-activated phosphorylase kinase. Glycogen breakdown is also rapidly stimulated during sudden increases of heart work. Glucosyl moieties coming from glycogen breakdown are preferentially oxidized rather than converted to lactate. As a result, there is a dichotomy between glucosyl units coming from extracellular glucose, which are metabolized into lactate, and glucosyl units coming from glycogen, which are oxidized. After the addition of epinephrine (in the presence of physiological concentrations of fatty acids), the extra energy requirements are initially met by glycogenolysis and then by a sustained increase in the rate of glucose oxidation.
6-Phosphofructo-1-Kinase

The first regulatory site that commits glucose to the glycolytic pathway is at the level of 6-phosphofructo-1-kinase (PFK-1), catalyzing the phosphorylation of fructose 6-phosphate to fructose 1,6-bisphosphate (Figure 1). Because of a complex allosteric regulation, conversion of fructose 6-phosphate into fructose 1,6-diphosphate is a rate-limiting step of glycolysis. ATP, citrate, and protons are negative allosteric effectors, whereas AMP and fructose 2,6-diphosphate are positive effectors. Fructose 2,6-diphosphate is the main activator of PFK-1 in normoxic heart. The concentration of this effector increases when glycolytic flux is stimulated and decreases when the heart oxidizes competing substrates.

GAPDH catalyzes the transformation, by oxidation and phosphorylation, of glyceraldehyde 3-phosphate into 1,3-diphosphoglycerate. As is the case with most dehydrogenases, GAPDH is inhibited by high concentrations of NADH and protons.

Pyruvate kinase catalyzes the transformation of phosphoenolpyruvate into pyruvate. Pyruvate kinase, which constitutes an irreversible step of glycolysis in heart muscle, may increase glycolytic flux, because it is stimulated by fructose 1,6-diphosphate, the product of PFK-1. PFK-1 thus synchronizes several glycolytic reactions, allowing an acceleration of the glycolytic pathway without accumulation of the glycolytic intermediates.

Fate of Pyruvate

Pyruvate enters the mitochondria via a monocarboxylate carrier. In the mitochondrial matrix, pyruvate becomes an intermediate at a branch point for several metabolic pathways (Figure 2). Most of pyruvate produced either from glycolysis or from exogenous lactate is oxidized to acetyl coenzyme A (acetyl-CoA) by the pyruvate dehydrogenase complex (PDC) and fed into the Krebs cycle. Pyruvate can also replenish Krebs cycle intermediates through its transformation into oxaloacetate by pyruvate carboxylase or malic enzyme. This mechanism of replenishment in a metabolic cycle is also termed anaplerosis. Oxidative decarboxylation of pyruvate to acetyl-CoA by the PDC commits pyruvate to oxidation. The PDC is a mitochondrial multienzyme complex that is regulated by its substrates and products and by phosphorylation/dephosphorylation (Figure 3). Pyruvate dehydrogenase (PDH) kinase, which inhibits the PDC, is stimulated by acetyl-CoA and NADH (produced mainly by fatty acid oxidation) and inhibited by pyruvate (produced from glucose and lactate), whereas PDH phosphatase, which activates the PDC, is mainly stimulated by Ca²⁺.

Integrative Mechanisms Regulating Glucose Metabolism

Long-Chain Fatty Acid Metabolism

The inhibition of glucose oxidation by fatty acids is a well-known phenomenon of mammalian metabolism. Its mechanisms were defined in the isolated perfused heart, and the results gave rise to the formulation of the “glucose–fatty acid cycle.” Glucose may also inhibit fatty acid oxidation, as follows. The transfer of the fatty acyl moieties into mitochondria, where β-oxidation occurs, is catalyzed by carnitine palmitoyltransferases (CPT-1 and CPT-2). The rate of fatty acid oxidation is controlled by their rate of transfer into the mitochondria through CPT-1 (Figure 4). This latter step is inhibited by malonyl-CoA, formed from acetyl-CoA by acetyl-CoA carboxylase (ACC). Conditions that increase the production of acetyl-CoA from pyruvate (as an increased concentration of glucose or lactate or the addition of insulin) stimulate the production of malonyl-CoA and thereby inhibit the β-oxidation. Such a mechanism leads to the suppression of fatty acid oxidation by glucose or lactate and is reinforced by the fact that high plasma levels of glucose and insulin decrease the concentration of circulating fatty acids.

The Krebs Cycle

The Krebs cycle is perhaps the best example for the paradigm of efficient energy transfer through metabolic cycles, which includes the recycling of CO₂ and H₂O. Without the recycling of H₂O, ATP production by the Krebs cycle would be 60%
less than with recycling (6 versus 15 moles of ATP per mole pyruvate oxidized). Under normoxic conditions, pyruvate is not only decarboxylated but also carboxylated to oxaloacetate and malate (Figure 2). This mechanism allows both a "reefading" of Krebs cycle intermediates and a recycling of CO₂ produced from the action of dehydrogenases. Fixation of CO₂ is particularly important during prolonged oxidation of fatty acids and ketone bodies, which can "unspan" the Krebs cycle by the sequestration of coenzyme A. The potential contribution of substrates to anaplerosis has given rise to the distinction between glucose and lactate, which produce both acetyl-CoA and oxaloacetate, and fatty acids or ketone bodies, which produce only acetyl-CoA. The need for anaplerosis may explain why glucose uptake is never completely inhibited in hearts perfused with fatty acids.

**Malate-Aspartate Shuttle**

This shuttle, first discovered in the liver, is also of major importance for the heart. Several of the intermediates presented in Figure 4 participate in the transfer of reducing equivalents from cytosol to mitochondrion. The malate-aspartate shuttle operates through 2 carriers, the dicarboxylate carrier, which exchanges malate and 2-oxoglutarate, and the aspartate/glutamate shuttle, which exchanges these 2 amino acids. The net effect of the malate-aspartate shuttle is the transfer of hydrogen ions from the cytosol (where they are produced) into the mitochondrion (where they are consumed by the electron transport chain for oxidative phosphorylation). These carriers thus preserve the ionic balance between the cytosol and mitochondria. Such a mechanism may be of particular importance during postischemic reperfusion, when protons produced by ATP breakdown need to be carried into the mitochondria (see below).

**Determinants of Myocardial Glucose Uptake**

**Substrate Supply**

Quantity and quality of substrate supply to the heart are determined by the dietary state and physical activity of the body as a whole. Long-chain fatty acids are the major substrates for the heart. With fasting, fatty acids and triglycerides are released from the adipose tissue and enter the circulation. Fatty acids are taken up by the cardiac cell to be degraded to acetyl-CoA. Oxidation of acetyl-CoA begins with the formation of citrate, which is the first intermediate of the citric acid cycle. By an allosteric feedback mechanism, citrate inhibits glycolysis at the PFK-1 step. Inhibition of glucose metabolism by fatty acid oxidation was first observed in isolated perfused heart muscle and also occurs in vivo. As already stated, fatty acids inhibit glucose oxidation more than glycolysis and glycolysis more than glucose uptake. Glucose becomes the main substrate for oxidative metabolism of the heart when fatty acid levels are low and when the concentrations of glucose and insulin are high, as in the postprandial state. We have already mentioned that glucose decreases rates of long-chain fatty acid oxidation, most likely at the level of CPT-1 through the production of malonyl-CoA by ACC. Other substrates are lactate and ketone bodies. The uptake and utilization of these substrates by the heart is a function of their blood concentration. Isotopic studies in vivo have shown that the heart takes up lactate in spite of net lactate release. There are 2 separate nonexchanging pools of lactate in the isolated glucose-perfused rat heart. Lactate contributes significantly to the supply of carbons for the tricarboxylic cycle and may replace all other substrates (including glucose), especially after exercise. Ketone bodies are produced from the catabolism of fatty acids in the liver, and their plasma concentra-
Glucose Metabolism in the Ischemic and Reperfused Heart

Glucose assumes a central role for energy production in the ischemic heart, when lack of oxygen induces a shift to anaerobic metabolism with rapid stimulation of glucose uptake, glycogenolysis, and glycolytic flux.\(^{75,78}\) The relative contribution of glucose to energy production is highly dependent on the severity of ischemia. In moderate ischemia (reduction of coronary flow by 75%), glucose uptake remains unchanged, while glucose extraction increases and metabolism of glucose is directed from oxidation to lactate production.\(^{77}\) In severe ischemia, myocardial glucose extraction is inversely related to coronary flow,\(^{78}\) until the degree of ischemia becomes so severe that glycolysis is inhibited by the accumulation of its products.\(^{79}\) Once glycolysis is inhibited, glucose uptake progressively decreases, while protons, Na\(^+\), and Ca\(^{2+}\) continue to accumulate.\(^{80-82}\) The decline of glucose uptake during prolonged severe ischemia may be attenuated by various interventions protecting the heart against ischemic injury, such as an increase of the extracellular glucose concentration or the addition of insulin.\(^{82-86}\) The stimulation of glucose uptake by moderate ischemia is additive to that induced by insulin.\(^{87}\) These interventions promote glucose uptake to meet the increased demand for glucose moieties as an energy source. These conditions also stimulate glycogen synthesis.\(^{81,88}\)

The controversy over whether the effects of glucose during ischemia are beneficial or deleterious is most likely the result of the different models used to investigate glucose metabolism and the different parameters measured by the investigators. A clear distinction must be made between glucose uptake, glycolysis, proton production, and glucose oxidation, on one hand, and between the different models of ischemia, on the other hand. Two models are mainly used to investigate heart metabolism during ischemia/reperfusion, the model of no-flow ischemia and the model of low-flow ischemia. Both models are not fully representative of the situation in vivo. In the first model, the heart is usually perfused in a working mode, and coronary flow is commensurate with the work performed. With ischemia, the flow is totally interrupted, so that all the metabolic end products accumulate in the heart. In the model of low-flow ischemia, the heart is perfused at constant coronary flow. Ischemia is induced by decreasing the coronary flow to such a value that the heart cannot further sustain its contractile activity. During low-flow ischemia, residual flow thus allows for a washout of metabolic end products. In such a model, it is possible to impose longer periods of ischemia, so that the damage induced by ischemia is only partly irreversible.\(^{80}\) In the model of low-flow ischemia, glucose uptake and glycolysis are accelerated, and both lactate and protons may be extruded. In the model of no-flow ischemia, glucose uptake is interrupted, glycolytic flux is supported by glycogen breakdown, and metabolic end products accumulate in the cytosol, where they not only amplify ischemic injury but eventually also shut down glycolysis.\(^{89}\)

Glucose Uptake

The mechanisms leading to the stimulation of glucose uptake in ischemia have recently been reviewed.\(^{90}\) The induction of ischemia or hypoxia is rapidly followed in various experimental models by a recruitment of both GLUT 4 and GLUT 1 transporters from intracellular stores to the plasma membrane.\(^{91-94}\) and if oxygen deprivation is prolonged, the transcription of glucose transporters is also modified.\(^{95-97}\) In any event, the net result is an increase in the maximal velocity of glucose transport. Glucose uptake progressively and irreversibly decreases during ischemia, despite a maintained substrate supply.\(^{80}\) This “metabolic exhaustion” of glucose uptake happens before irreversible ischemic injury is observed in isolated heart preparations\(^{80}\) and results from inhibition of glycolytic activity by the combined effect of ionic disturbances (such as accumulation of protons), the inability to
extrude the products of glycolysis (such as lactate), and the
damaging effects of oxygen-derived free radicals on enzymes
and membrane phospholipids. Also, cGMP increases in the
ischemic heart because of an activation of NO synthase, the
product of which stimulates cGMP production. Addition of
cGMP analogues or NO donors to perfused hearts decreases
glucose uptake and glycolytic flux. Thus, cGMP probably downregulates glucose uptake during ischemia, as
the addition of NO synthase inhibitors to ischemic heart stimulates glucose metabolism and improves the resistance
against ischemia.

Glycolytic Flux
Stimulation of glucose transport by ischemia is coupled to accelerated glycolytic flux. Such acceleration is explained by
a reversal of Pasteur’s effect, which is the inhibition of glycolysis by ATP. The acceleration of glycolytic flux is attributed to an activation of PFK-1 by both an increase of
AMP, an activator of PFK-1, and a decrease of ATP, an
inhibitor of the enzyme. The change in the ratio of these 2
nucleotides constitutes the mechanism of PFK-1 activation by ischemia, since no change of fructose 2,6-diphosphate and
citrate concentration is observed in this condition. Stimulation of glycolytic flux may also be due to a translocation of
hexokinase, but this possibility has not yet been investigated.
In no-flow ischemic conditions, however, the overall glyco-
lytic flux may be limited by GAPDH, through an inhibition
by the accumulation of lactate and protons, although no
allosteric control of GAPDH by lactate has been found in a
purified enzyme preparation. Glycolysis during ischemia seems particularly important in providing a residual production
of ATP. Such production sustains the activity of ATP-
requiring enzymes, mainly the sarcolemmal Na+/K+-ATPase and the sarcoendoplasmic Ca2+-ATPase.

Glycogen Metabolism
Glycogen breakdown during ischemia and the stimulation of
glycogen phosphorylase by cAMP are long recognized but
still incompletely understood. Several studies have postulated a “toxic” effect of glycogen breakdown in ischemic heart that is due to an accumulation of protons and lactate and have suggested the beneficial consequences of depleting the gly-
cogen stores before an ischemic episode. Many other
studies, however, have shown that protection of the heart against ischemic injury is related to glycogen availabil-
ity. The absolute amount of glucose moieties arising from glycogen is not negligible at the onset of ischemia. In
isolated perfused hearts subjected to low-flow ischemia, glycogen breakdown provides, during the first 15 minutes,
about 60 μmol glucose equivalents per gram dry weight, whereas during the same period, glucose uptake offers about
35 μmol glucose per gram. In the same model, ischemic contracture begins when glycogen breakdown stops and,
concomitantly, the rate of glucose uptake decreases. En-
hanced utilization of extracellular glucose during ischemia
does not increase the absolute rate of glycolytic flux but
prevents the participation of glycogen stores to this flux, thereby limiting ischemic damage and contracture. These
data indicate that cellular homeostasis in the ischemic heart is
better preserved as long as glycogen is present and available
for energy production. The exact mechanism by which glycogen protects the ischemic heart remains to be
determined.

Another intriguing characteristic of glycogen metabolism in ischemic heart disease is the accumulation of glycogen in hibernating heart. Hibernating myocardium represents a
chronically dysfunctional myocardium that has most likely been subjected to repetitive episodes of ischemia but is still
capable of improving contractile function after reperfusion.
To prevent irreversible tissue damage, the myocardium
adapts the ventricular performance to the reduction of oxygen
delivery. Indirect evidence supports a deregulation of glyco-
gen metabolism in the hibernating heart, and several groups
of investigators have reported that glycogen content in this
tissue is dramatically increased. However, it is also characterized at PET by an increased signal of FDG, corresponding to glycogen accumulation in the same regions. The increased FDG signal in hibernating myocardium could thus be related to a stimulation of glucose uptake
for glycogen synthesis, although this remains to be demonstrated. Interestingly, the accumulation of glycogen and other
morphological alterations seen in hibernating tissue are also
found in unloaded myocardium and in fetal heart, suggesting that hibernation may induce a reliance on glucose for
energy provision similar to that observed in fetal heart.

Glycogen and Ischemic Preconditioning
Although the exact mechanism of preconditioning is most
probably multifactorial, many studies have demonstrated an attenuation of glycolytic activity in preconditioned hearts. Preconditioning decreases glycogen breakdown as well as the accumulation of hexose 6-phosphates and lactate during no-flow ischemia. Because the duration of protection by preconditioning is also related to the time course of postis-
chemic glycogen recovery, the data, when taken together,
show that protection by ischemic preconditioning reduces glycogen breakdown, therefore attenuating the accumulation of metabolic end products and the development of intracel-
lar acidosis. The slower decline of both pH, and high-
energy phosphates in preconditioned hearts during no-flow ischemia is in agreement with this hypothesis. Most of the
preconditioning protocols are performed on models of no-
flow ischemia; this further illustrates the importance of
limiting the accumulation of glycolytic end products in the
absence of residual coronary flow. The controversies about
preconditioning may in part result from the variety of the
models used and parameters measured. Because of the
incomplete understanding of the mechanisms underlying
ischemic preconditioning, it is quite impossible to gauge the
relative importance of glucose metabolism in this condition.

Glucose Metabolism at Reperfusion
Both severity and duration of ischemia determine not only the
extent of the metabolic and ionic derangements but also the
return of function at reperfusion. The biochemical features of
the postischemic heart are both similar and different from
those of the ischemic heart. As for the ischemic heart, many
uncertainties exist about the role of glucose as substrate
during reperfusion. Again, such uncertainties may result from the different experimental models. The 2 models described above for the ischemic heart (no-flow ischemia and low-flow ischemia) are also those used to investigate the effects of reperfusion. In the model of no-flow ischemia, the ischemic episode is relatively short (\( \approx 30 \) minutes), and the functional recovery at reperfusion is mainly determined by both the extent of accumulation of metabolic end products during ischemia and the substrate availability at reperfusion. In the model of low-flow ischemia, the ischemic damage is partly irreversible because of the longer episode of ischemia (usually \( \geq 1 \) hour). The functional recovery at reperfusion is thus mainly determined by the extent of irreversible ischemic damage. After brief episodes of ischemia (up to 20 to 30 minutes), oxidative metabolism rapidly returns, well before contractile activity is restored.\(^{123-126}\) Stimulation of glucose oxidation at the onset of reperfusion improves and accelerates functional recovery, whereas inhibition of glucose utilization induces a strong impairment of postischemic contractility.\(^{127-129}\) When glycolysis is stimulated in reperfused myocardium, the cytosolic accumulation of \( \text{Ca}^{2+} \) decreases.\(^{128}\) Because pharmacological interventions that prevent \( \text{Ca}^{2+} \) accumulation in reperfused myocardium also decrease the severity of stunning,\(^{130}\) it is reasonable to assume that ATP produced from glycolysis is used preferentially to support the activity of ion pumps. The efficiency of this ionic homeostasis is further improved by stimulating the PDC,\(^{131}\) which reduces the accumulation of protons brought by glycolysis during ischemia. The breakdown of ATP produced from glycolysis induces a net production of protons that are consumed by the PDC. When glycolysis is not coupled to glucose oxidation, the resulting accumulation of protons stimulates the \( \text{Na}^-\text{-H}^- \) exchanger at reperfusion.\(^{132}\) As a result of the accumulation of \( \text{Na}^+ \), the \( \text{Na}^-\text{-Ca}^{2+} \) exchanger is stimulated, eventually leading to \( \text{Ca}^{2+} \) overload and reperfusion injury.\(^{133}\) By activating the PDC, such accumulation can be limited, and functional recovery is improved.\(^{89}\) Paradoxically, fatty acid oxidation is favored at reperfusion by a decrease of malonyl-CoA, thus relieving the inhibition of CPT-1.\(^{134}\) The decrease of malonyl-CoA results from the inhibition of ACC by a specific AMP-dependent protein kinase activated by the AMP accumulation during ischemia.\(^{134,135}\) The beneficial effect of pyruvate at reperfusion\(^{136}\) and the fact that the utilization of fatty acids instead of glucose strongly impairs the efficiency of the reperfused heart\(^{129,137}\) suggest that the anaplerotic pathway is also stimulated at reperfusion. Finally, glucose at reperfusion is also required to rebuild glycogen. The best protection to the reperfused heart should be brought by a combination of stimulated glycolytic flux, activated PDC, increased glycogen storage, and anaplerosis of the Krebs cycle. This hypothesis has yet to be tested.

**Glucose and Insulin as Substrates for Postischemic Heart**

Substrate metabolism and contractile function are inseparable features of normal cardiac physiology. Reperfusion of ischemic myocardium is accompanied by a separation of substrate oxidation and contractile function. Prominent among the derangements responsible for functional impairment of postischemic myocardium is cellular \( \text{Ca}^{2+} \) overload, and ATP derived from glycolysis appears to play an important role for the restoration of \( \text{Ca}^{2+} \) homeostasis. The effects of glucose and insulin on restoration of contractile function are not entirely surprising in light of earlier clinical and experimental findings. After the effects of glucose and insulin on the ECGs of acutely ischemic dog hearts had been determined, a clinical role for GIK as a therapeutic agent was proposed in the 1960s.\(^{138}\) The rationale was that such a “polarizing treatment” reverses loss of intracellular \( K^+ \) during acute ischemia. Although the exact mechanisms for the effects of glucose and insulin in the ischemic myocardium are not known, it seems reasonable to assume that they enhance membrane stability.\(^{104,138}\) Shortly after, it was also observed that GIK decreases the infarct size after coronary artery ligation in dogs, lessens ultrastructural damage, and improves global contractile function of the heart.\(^{139}\) The infusion of GIK was shown to reduce the frequency and duration of ventricular arrhythmias and to improve the survival of patients after myocardial infarction.\(^{139,140}\) Similarly, beneficial effects on ejection fraction and survival were observed when GIK was administered in conjunction with a thrombolytic agent\(^{142}\) or when GIK was given to patients with myocardial infarction and non–insulin-dependent diabetes mellitus.\(^{143}\) Most recently, a meta-analysis of all placebo-controlled trials of GIK treatment in acute myocardial infarction has shown an overall mortality reduction of \( 28\% \).\(^{144}\) A large prospective, randomized study of GIK as an adjunctive therapy to thrombolysis and/or restoration of blood flow in acute myocardial infarction has not yet been undertaken, probably for the following reasons. First, it was pointed out that the phosphorylation of glucose in glucose 6-phosphate actually uses ATP and draws on an already limited supply of the high-energy phosphates.\(^{79}\) Second, it was suggested that depletion of glycogen before ischemia reduces lactate production and improves contractile function with reperfusion.\(^{79}\) Third, in the postischemic myocardium, there is an imbalance between glycolysis on the one hand and glucose oxidation on the other.\(^{131}\) It has been argued that postischemic contractile dysfunction is caused by impaired glucose oxidation and cytosolic proton accumulation, and agents that enhanced glucose oxidation in the postischemic heart also seem to improve contractile function.\(^{89}\) Although this line of reasoning seems of compelling logic, glycolysis is also an adaptive emergency mechanism that can prevent deleterious myocyte deenergization.\(^{127,145}\) Thus, the use of metabolic support during both ischemia and reperfusion should complement other pharmacological interventions aimed at the restoration of normal pump function of the myocardium. Moreover, the different experimental data summarized in the previous section have shown that fatty acid metabolism is stimulated at reperfusion. This may be harmful for the heart, because it decreases functional performance and alters membrane stability.\(^{17}\) One of the beneficial effects of the GIK solution is the reduction of circulating free fatty acids. We have proposed that such treatment also promotes glucose oxidation, thereby limiting proton accumulation by replenishing the tricarboxylate cycle.\(^{146}\) The short-term infusion of GIK (up to 48 hours) has been used very effectively in patients with refractory left ventricular failure after hypothermic ischemic arrest of the heart for revascularization surgery.\(^{147,148}\) In these patients, the adminis-
tration of GIK (a solution of 50% d-glucose containing 80 U of regular insulin and 100 mEq KCl) lowered the plasma concentration of free fatty acids, decreased systemic vascular resistance, raised the cardiac index, and increased urine output. The need for inotropic drugs, the time on the intra-aortic balloon pump, and the stay in the intensive care unit were all significantly reduced. Most important, there was a significant decrease in both short-term and long-term mortality in patients receiving GIK. These results have recently been corroborated in a larger (but nonrandomized) group of 322 patients treated at the Texas Heart Institute (Houston, Tex) and in a smaller (but randomized) study at Boston University (Boston, Mass).149,150

The rationale for the use of glucose and insulin as therapeutic agents is based on the considerations described in the first part of this review. In the ischemic heart, a protection against ischemic damage can be afforded as long as ATP is produced and protons are eliminated. The GIK solutions increase glucose uptake in the ischemic heart and probably allow for a higher rate of ATP production from glycolysis. Such ATP production inhibits ATP-dependent K⁺ channels of the plasma membrane and prevents changes of membrane potential that could lead to severe arrhythmias.151 Glycogen synthesis is also stimulated by increasing the production of glucose 6-phosphate, leading to a “glycogen loading” similar to that described above in isolated heart preparations.146 Several clinical reports stress the importance of preoperative glycogen loading for improvement of myocardial protection during cold cardioplegia and reperfusion.152

Unresolved Issues

Many issues of glucose metabolism in the heart remain unresolved, especially with respect to the heart in vivo. Examples include the exact triggering mechanism inducing increased glucose extraction at the onset of ischemia. Although many effectors (ATP, phosphocreatine, Ca²⁺, AMP, and glucose 6-phosphate) have been implied, none of them seems to be the exact mechanism. Also, we have described above the ionic imbalance occurring during ischemia/reperfusion, but the real contribution of glycolysis in the production of protons remains to be measured. Experiments using NMR spectroscopy have provided tantalizing glimpses at changes in protons and Na⁺ and Ca²⁺ concentrations but yielded no quantitative measurements on the source and fate of these ions. If proton overload induces an accumulation of Na⁺, then a stimulation of the Na⁺,K⁺-ATPase during ischemia/reperfusion should prevent Ca²⁺ accumulation. The inhibition of GAPDH by protons and/or lactate is still controversial, because no clear conclusion could be made from experiments using purified enzyme preparations.45 The regulation of glucose transporters also remains largely unknown. Besides their recruitment to the plasma membrane, glucose transporters could also be regulated by covalent modifications, such as phosphorylation or binding of regulatory proteins. Moreover, their mechanism of trafficking between intracellular stores and plasma membrane is largely unknown. Another topic awaiting further resolution is the compartmentation of ATP. Because ATP is used for many purposes in the heart (eg, contraction, Ca²⁺ reuptake and other ionic pumps, protein phosphorylation, and glycolysis), it is possible that a real compartmentation of high-energy phosphates exists. Also of interest is the increasing awareness of the importance of phosphorylation signaling pathways, which are intimately intertwined with enzyme regulation. Proteins such as mitogen-activated protein kinases, AMP-dependent protein kinase, cAMP-dependent protein kinases, cGMP-dependent protein kinases, protein kinase C, Jun NH₂-terminal kinase, and many others are now familiar terms, and the future will tell us more about the role of phosphoprotein phosphatases.

Of growing interest is the study of intercellular communication, mainly that between the cardiomyocyte and the endothelial cell. Metabolic effects of many intercellular mediators, such as NO, cAMP, cGMP, adenosine, endothelin-1, bradykinin, and interleukins, are now under investigation. Last, the tools of molecular biology will help to define the long-term regulation of metabolism at the transcriptional level. It is very likely that clinical situations such as hibernation, heart failure, hypertrophy, chronic ischemic heart disease, and cardiomyopathies induce a shift in the genetic expression of metabolic enzymes, contractile proteins, and oncogenes. A better understanding of these alterations may help to prevent them and could provide potential targets for gene therapy.

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Glucose for the Heart


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Glucose for the Heart


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