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Review Article

Developmental Cardiac Metabolism in Health and Disease

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SUMMARY. **Cardiac metabolism changes in response to oxygen and substrate availability during development. The fetus is relatively more dependent on anaerobic glycolysis, using glucose as its major substrate during hypoxia, lactate when well-oxygenated. The mature heart is almost exclusively aerobic, with nonesterified fatty acids as the predominant substrate. During hypoxia and ischemia, shifting the heart to carbohydrate metabolism has oxygen-sparing effects. Blocking lipolysis or carnitine palmityl transferase activity prevents accumulation of potentially toxic long-chain esters during hypoxia/ischemia, thereby reducing the risk of electrophysiologic disturbance and membrane disruption. Knowledge of developmental cardiac metabolism may aid in the development of therapeutic strategies to preserve the myocardium during hypoxia and ischemia.**

KEY WORDS: **Cardiac metabolism — Developmental physiology — Hypoxia — Ischemia**

The heart is unique among organs in the amount of energy needed to maintain its mechanical work load. Less than 20% of resting myocardial oxygen consumption is used for basal metabolism and electrical activation, while 80% is used for pump functions. Taegtmayer has pointed out that the mature heart working against physiologic load uses oxygen at a higher rate than any other organ [58].

The heart is the first functional organ in the embryo, with myocardial contraction preceding placental gas-exchange in many species. The embryonic heart initially uses only anaerobic glycolysis to provide energy. However, myocardial work load rises rapidly with growth of the vascular bed. By late gestation, ovine fetal ventricular consumption of glucose and lactate represents 5–13% of net umbilical uptake, although the ventricles constitute only 0.5% of fetal body mass [14]. Glycolytic flux in the myocardium is very high throughout gestation, about twice that of the adult in both fetal rat and fetal guinea pig [27]. Complete oxidation of glucose and lactate begins with the establishment of maternal/embryonic gas-exchange. The percentage of glucose converted to lactate, rather than completely oxidized, varies greatly with both species and experimental conditions. In the aerobic Langendorff-perfused fetal guinea pig heart, about 75% of glucose is converted to lactate, only 20% completely oxidized. Fetal myocardial oxygen consumption in this species is reported as only one fourth that of the adult [48]. By contrast, Fisher and coworkers [14] found in the in vivo ovine heart that up to 60% of the carbohydrate consumed is lactate, and that myocardial oxygen consumption is very high and fully comparable to that of the adult. Recent studies in the fetal and neonatal pig by Werner and Sicard [65] have confirmed these findings, showing that lactate is the preferred substrate of the immature but well-oxygenated myocardium when arterial lactate concentrations are in the physiologic range.

In the mammalian fetus, carbohydrates are the major myocardial substrates, while amino acids are minor fuels. Oxygen availability determines whether lactate is produced or consumed [63]. Acidosis is a profound myocardial depressant in the fetus and newborn, as well as in the adult. Coronary blood flow in the fetus normally rises in response to acidosis, allowing removal of unmetabolized lactate from the myocardium when oxygen levels are too low to allow its complete oxidation [13]. Lactate is transported to the liver where it is recycled into glycogen by the enzymes of the Cori cycle (as shown in Fig. 1). Glycogenolysis then allows glucose to be released from the liver and transported to

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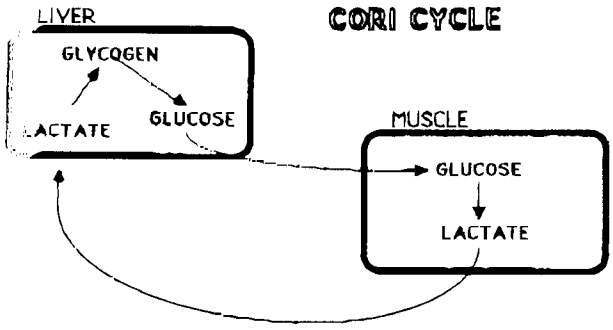

Fig. 1. The Cori cycle: lactate accumulation results in a fall in pH with depression of striated muscle contractility. When the circulation is intact, this can be prevented by arterial washout of lactate, with transport to the liver. The liver has a full complement of enzymes to reverse glycolysis and synthesize glycogen, allowing lactate to be recycled and eventually to be rereleased as glucose.

the heart as required. In addition to receiving endogenous glucose from its liver, the fetal heart receives glucose almost continuously from the maternal circulation, with fetal glucose consumption bearing a linear relationship to maternal arterial glucose concentration. Recent data has shown that in addition to glucose, lactate is taken up in large quantities by the fetus, partly from the maternal circulation, but more substantially from the placenta which produces it in quantity from maternal glucose [10]. In order to ensure the availability of glucose and lactate, fetal liver and heart accumulate large quantities of glycogen. Glycogen is broken down during energetically unfavorable circumstances such as asphyxia, hypotension, or maternal starvation. The fetus and newborn are considered to be highly resistant to hypoxia in comparison to the adult [22–24]. Fetal and neonatal cardiac glycogen stores correlate with myocardial resistance to hypoxia [36]. In contrast, there appears to be less resistance to ischemia in the fetus and newborn when compared to the adult [6, 20, 68]. During ischemia, lactate produced in the heart cannot be removed, tissue pH falls, and contractility rapidly deteriorates. This emphasizes the importance of adequate coronary blood flow and of the Cori cycle in limiting the degree of myocardial acidosis when the inadequately oxygenated heart is producing rather than consuming lactate.

Neither free fatty acids nor ketone bodies are used in significant amounts as substrates in the immature heart. The fetal heart's ability to β-oxidize palmitate is only 10–30% that of the neonatal or adult heart [27], and much of that capability is used only to remodel lipid molecules needed for tissue accretion [7]. The reasons for limited β oxidation in the fetus are summarized in Table 1. Carnitine palmityl transferase activity is limited [60] and tissue carnitine concentrations are very low [47]. Transport of free fatty acids across mitochondrial membranes to the site of the β-oxidative enzymes is therefore limited. Enzymatic capacity for fatty acid synthesis is high in the liver and adipose tissue, while these same tissues are highly resistant to lipolytic agents both in vivo and in vitro [5, 26]. As a result, the concentration of long-chain fatty acids in coronary arterial blood is extremely low, and myocardial extraction is minimal.

Table 1. β oxidation in the fetus is limited

1. Liver and adipose tissue resist lipolysis
2. Tissue carnitine concentrations are low
3. Carnitine palmityl transferase activity is low
4. Mitochondria are few in number and immature
5. Respiratory chain activity is low

Similarly, although plasma acetate concentrations are high in fetuses of some species, oxidation of acetate in the fetal heart takes place at rates only 10% of those in mature hearts. Carnitine concentrations and carnitine acetyl transferase activity are both low in the fetal heart [62]. Unlike the heart, fetal brain is capable of rapid uptake and oxidation of ketone bodies, particularly during maternal starvation or diabetes [35, 45]. It is important to note that even in the mature heart, ketone bodies are incapable of maintaining myocardial contractility when they are the only myocardial substrate [57].

Werner and coworkers have reported that neither the fetal nor the neonatal pig heart maintains its ability to perform contractile work with either palmitate or octanoate as the sole substrate, even when oxidation of these substrates is documented. Contractility can be restored by adding glucose to the perfusion buffer [66, 67]. Therefore, it is clear that even when adequate concentrations of lipid substrates of any chain length are provided to the immature heart, myocardial contractility cannot be maintained by them alone.

The total oxidative capacity of the immature heart varies as a direct function of tissue oxygenation. The fetal heart has fewer mitochondria with a lower cristal density, and decreased concentrations and activity of the cytochromes and tricarboxylic acid cycle enzymes as compared to the adult heart [18, 27, 31, 41, 52, 53]. In contrast, activity of glycolytic enzymes and mitochondrial oxidative rates of glutamate and malate are increased in the fetus [3, 8, 22, 53, 64]. It is thought that certain amino acids such as glutamate and aspartate are partially oxidized as substrate during periods of hypoxia [50]. Taegtmayer calculated that anaerobic metabolism

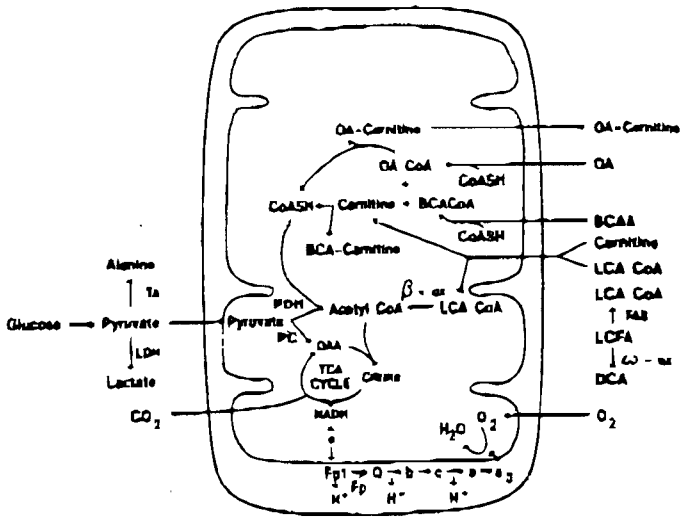

Fig. 2. A summary of oxidative metabolism in the mature cardiac mitochondria. *a*, a_3, *b*, *c*, cytochromes; *BCAA*, branch chain amino acid; *BCACoA*, branch chain acyl-CoA; *CoASH*, coenzyme A; *β-ox*, β oxidation; *BCA-carnitine*, branch chain acyl carnitine; *DCA*, dicarboxylic acids; *e*, electron; *Fpl*, flavoprotein; *FAS*, fatty acid synthetase; *LCA CoA*, long-chain acyl-CoA; *LCFA*, long-chain fatty acid; *OA*, organic acid; *LDH*, lactate dehydrogenase; *ω-ox*, ω oxidation; *OAA*, oxaloacetate; *PC*, pyruvate carboxylase; *PDH*, pyruvate dehydrogenase; *Q*, coenzyme Q; *TCA*, tricarboxylic acid cycle; *TA*, transaminase. (Reprinted with permission from Pierpont ME, Tripp ME (1986) Abnormalities of intermediary metabolism. In: Pierpont ME, Moller JH (eds) *Genetics of cardiovascular disease*. Martinus Nijhoff)

of amino acids could add about 16% to the ATP produced in the formation of lactate from anaerobic glycolysis alone [56]. The mitochondrial enzymes, noted to be more active in the fetus, are those that are active in amino acid oxidation during periods of hypoxia.

The fetus is relatively more dependent on glycolysis for energy production than is the adult. Su and Friedman [55] found that fetal rabbit atrial strips were able to maintain contractility after blockade of the tricarboxylic acid cycle, but were dramatically affected by iodoacetate, a glycolytic blocker. Conversely, strips from adult hearts tolerated iodoacetate without significant effect, but ceased contraction after dinitrophenol or other blockers of oxidative metabolism [55]. During oxygen deprivation, anaerobic ATP production can approach 43% of the aerobic production in the fetus, compared to only 18% in the adult [51]. When glycogen stores are adequate, and coronary perfusion is maintained, the fetal heart remains relatively resistant to hypoxia. Low plasma lipid concentrations and resistance to lipolysis limit the toxic buildup of unmetabolized acyl esters, seen in mature ischemic hearts. However, resistance to hypoxia and ischemia in the fetus as in the adult remains ultimately a function of tissue pH and of ATP and creatine phosphate (CrP) stores. Contractility falls when acidosis ensues and concentrations of ATP and CrP decline.

During the perinatal period, myocardial metabolism changes from a carbohydrate-based system of energetics with enhanced capacity for anaerobic glycolysis to an almost exclusively aerobic metabolism predominantly using free fatty acids as substrate. Figure 2 summarizes the major metabolic pathways used by the mature heart. The total oxidative capacity of the heart rises markedly within hours of birth [53]. The number, crystal density, and enzyme activity of mitochondria rise as a direct function of arterial and tissue PO_2 [40, 41]. Continuous glucose and lactate infusion from the umbilical circulation abruptly stops, and the activity of gluconeogenic enzymes rises. Tissue carnitine levels rise shortly before birth in some species, with suckling in others. The lipid and carnitine content of milk results in both increased availability and rate of oxidation of long-chain fatty acids [63]. Lipolytic activity also rises dramatically, with the activity of lipoprotein lipase rising sixfold one day postnatally in the neonatal rat [9]. While the age at which the neonatal myocardium converts to predominant fatty acid oxidation is species-dependent (in part as a function of the lipid and carnitine content of maternal milk), it is always accomplished well before weaning, and continues for the rest of the life span.

Under normal circumstances, about two-thirds of the energy used by a well-oxygenated mature heart is supplied by the β oxidation of free fatty acids. The remaining third is generally provided by the complete oxidation of glucose, although lactate, amino acids, and ketone bodies can be oxidized as well [46]. Relative coronary arterial concentrations strongly influence which myocardial substrate is predominant at any given time [29]. When substrates are present in normal physiologic concentrations, the resting mature well-oxygenated heart tends to use free fatty acids in preference to other substrates. When a substrate is present to physiologic excess in a normal heart, it tends to become the predominant myocardial energy source at that time. During fasting, the predominant myocardial substrates are free fatty acids, with a myocardial respiratory quotient (RQ) ratio of 0.7 [16]. After a carbohydrate feeding, glucose becomes the major substrate, with the RQ ratio rising to 0.9–1.0 [17]. Drake and coworkers found lactate to be extracted

Table 2. Adverse effects of long-chain acyl esters

1. Accumulation of amphiphiles with detergent properties
2. Inhibition of adenine nucleotide translocase
3. Inhibition of Na^+–K^+ ATPase
4. Inhibition of glycolytic enzymes
5. Ca^{2+} release from mitochondria; retention by SR
6. Depression of oxidative phosphorylation

SR, sarcoplasmic reticulum.

preferentially by the myocardium of dogs in which lactate was present in elevated concentrations [12]. Spitzer and coworkers [54] documented a tenfold rise in the contribution of ketone bodies to myocardial energy production from 3% to 38% in dogs with acute severe alloxan-diabetes. This correlated with a rise in arterial ketone bodies from 69 at baseline to 976 μM with diabetes [54].

In addition to the effect of arterial substrate concentrations on myocardial extraction, there is also inhibition of myocardial use of alternate substrates by the predominant substrate at a given time [15, 46]. Free fatty acids exert their inhibitory effect on carbohydrate fuels at three major sites: (1) glucose entry, (2) hexokinase-phosphofructokinase, and (3) pyruvate dehydrogenase [46]. The mechanisms through which carbohydrate fuels inhibit metabolism of free fatty acids are more controversial and incompletely defined. Glucose, lactate, pyruvate, and ketone bodies have all been shown to decrease β-oxidative rates under certain experimental conditions [4, 21, 35, 58]. Forsey and coworkers [15] found that ketone bodies inhibited the metabolism of both oleate and octanoate, and might therefore directly inhibit β oxidation. In contrast, pyruvate, lactate, and lactate plus glucose inhibited oleate oxidation but not that of octanoate. Oleate differs from octanoate in requiring carnitine for transport across mitochondrial membranes [15]. They postulated that pyruvate and/or lactate inhibit the oxidation of oleate by preventing either the activation of the acyl groups or the transport of these groups across mitochondrial membranes. Given the equilibrium characteristics of carnitine acetyl transferase, diffusion of acetyl-CoA from the mitochondria to the cytoplasm could result in the formation of acetyl-carnitine, limiting the availability of carnitine for transport of long-chain acyl groups [44]. Alternatively, malonyl-CoA, now known to be present in the heart and an active inhibitor of carnitine acyl transferase, could slow β oxidation in spite of normal activation [39].

The fetal/neonatal heart is so dependent on carbohydrates that myocardial contractility declines within minutes when either palmitate or octanoate is provided as sole substrate [66]. In the well-oxygenated mature heart, substrate availability is rarely a significant problem. A significant exception to this is the poorly understood inability of the myocardium to maintain contractility when ketone bodies are the sole substrate. This apparently occurs because certain intermediates of the tricarboxylic acid cycle are provided in inadequate amounts [57]. With this exception, the normal mature heart contracts poorly only when oxidative phosphorylation is disturbed by hypoxia, ischemia, acidosis, or metabolic toxins. Once this occurs, however, the nature of available substrate becomes critical. To paraphrase Lionel Opie, if myocardial oxygenation is impaired, free fatty acids are detrimental to the heart, while carbohydrates, particularly glucose, are beneficial [43].

During hypoxia, β oxidation of free fatty acids slows, while glycolysis is accelerated. The biologic wisdom of this is evident. For each molecule of oxygen consumed, palmitate oxidation produces 5.7 high-energy phosphate bonds compared with 6.3 from glucose oxidation; thus, glucose oxidation is relatively more efficient when oxygen availability is more limited than that of substrate. Unfortunately, lipolysis may continue during hypoxia or ischemia, even when β oxidation is essentially halted. The resulting unmetabolized lipids can exert an inhibitory effect on carbohydrate metabolism, limiting production of high-energy phosphate bonds from glycolytic pathways. In addition, they can accumulate as non-esterified fatty acids and long-chain acyl-CoA and carnitine esters. These amphiphilic esters in high concentrations are known to accumulate during ischemia and to exhibit multiple toxicities summarized in Table 2 [11, 30]. The clinical expression of these toxic effects is destabilization with ventricular dysrhythmias, and a rapid decline in myocardial contractility well before tissue high-energy phosphate compounds are totally depleted [11].

Metabolic Strategies in Hypoxia and Ischemia

Myocardial preservation during hypoxia and ischemia should be improved by therapeutic measures which optimize high-energy phosphate bond production while decreasing myocardial energy consumption. The following strategies are supported by clinical experience and/or experimental data in animals and in humans.

Improve Oxygenation Whenever Possible

Maintain hemoglobin concentrations and cardiac output within the normal range to maximize oxygen transport. Anaerobic glycolysis yields only a net of

two ATP molecules per molecule of glucose converted to lactate. Complete aerobic oxidation of 1 molecule of glucose produces 36.

Decrease Myocardial Oxygen Requirements

Decrease myocardial oxygen requirements using exercise restriction, avoidance of psychological stress, sedation, and pharmacologic afterload reduction. In the context of surgical ischemia, hypothermia with or without the use of cardioplegic agents reduces myocardial energy requirements to minimal levels.

Increase Coronary Blood Flow

Increase coronary blood flow to increase oxygen and substrate transport and to remove excessive carbon dioxide, lactate, and other toxic metabolites. This can be accomplished with coronary vasodilators and maintenance of an adequate cardiac output.

Correct Acidosis

Correct acidosis using hyperventilation, bicarbonate, or tromethamine acutely to preserve myocardial metabolic functions and contractility.

Provide Carbohydrate as Substrate

Maintaining normoglycemia with adequate oral intake or intravenous infusion is the least controversial approach to specific metabolic management of myocardial hypoxia and ischemia. However, many investigators argue that glucose should be provided in optimal, not minimal, amounts. Both GIK (glucose, insulin, potassium) regimens and hypertonic glucose infusions have been studied in patients with myocardial infarction and in animals with acute ischemia [33]. Myocardial oxygen consumption consistently decreases on an exclusively carbohydrate regimen, but improvement in clinically significant parameters of myocardial function has been more difficult to document. GIK regimens have been reported to protect the ischemic heart from ventricular dysrhythmias. It is not clear whether this is due to the resultant transport of potassium into the myocardium, to the suppression of fat metabolism, or to an actual substrate effect on myocardial energetics [43]. Improved left ventricular function and decreased hospital mortality have also been reported in GIK-treated patients. Complications of the regimen have included pulmonary congestion, phlebitis, and hypoglycemia [43]. In spite of the widespread clinical impression that hypoglycemia impairs myocardial function in infants [1], there has been no recent experimental research examining GIK or other carbohydrate regimens as a means of improving myocardial function in hypoxic or hypotensive (ischemic) newborns.

Diphosphofructose has been administered experimentally and clinically in an attempt to bypass the phosphofructokinase block in glycolysis induced by acidosis in shock and ischemia. These studies have been extremely controversial since it is generally thought that diphosphofructose, like other phosphorylated compounds, cannot cross cellular membranes. Lazzarino and coworkers [34], however, showed a rise in intra-erythrocyte diphosphofructose levels when whole blood was incubated with 1,6-diphosphofructose (DFP). This effect was not observed when blood was incubated with fructose and 2M phosphate. They postulated that DFP might act as an intracellular metabolic regulator from an extracellular site [34]. Markov and coworkers [38] compared the effects of glucose and DFP infusions during hemorrhagic shock and subsequent retransfusion in anesthesized dogs. While arterial pH dropped more rapidly in the DFP group because of lush lactate production during shock, normalization of blood pressure after retransfusion was more rapid in the DFP group. All eight DFP-treated dogs survived, while all six glucose-treated dogs died within 24 h. DFP-treated animals sacrificed at the end of the 3-h period of oligemia had higher myocardial ATP and CrP concentrations when compared to the glucose-treated group [37]. A small group of patients with hemorrhagic shock also showed improved survival when treated with DFP infusion compared to equimolar glucose infusion. Markov [37] reported reduced left ventricular end diastolic pressures and increased dP/dt in dogs with acute myocardial ischemia after DFP infusion. This again correlated with an elevated tissue lactate and relative preservation of ATP and CrP levels in DFP-treated animals compared with untreated ischemic controls [19]. Recently, Zhang and coworkers [69] were able to reproduce these results in dogs subjected to acute ligation of the left anterior descending coronary artery. Eight DFP-treated animals had less ST segment elevation, and maintained a normal cardiac output in all cases for the 4 h of the study. In contrast, during the same period the eight untreated animals all had ST segment elevation, and the mean cardiac output fell from 2.5 L/min to 1.4 L/min. Likewise, the serum creatine kinase isoenzymes were unchanged from controls in the DFP group, but significantly elevated in the untreated infarcted group [69]. Given the augmented glycolytic capabilities of the fetus and newborn, and their relative

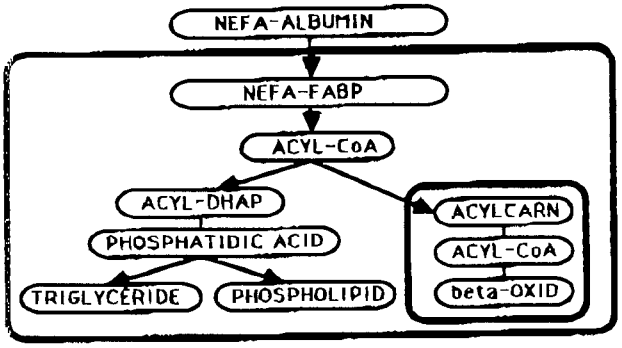

Fig. 3. The disposition of nonesterified fatty acids on entry into the cell. Fatty acids are rarely "free" (i.e., unbound). In plasma, they are noncovalently bound to albumin; in the cytoplasm, to fatty acid binding protein. Once activated as an acyl-CoA compound, a fatty acid can be shunted into biosynthetic pathways for triglycerides or phospholipid. Alternatively, they can be transesterified to acyl carnitine, traverse mitochondrial membranes, and undergo β oxidation. *beta-oxid*, β oxidation; *DHAP*, dihydroxyacetone phosphate; *FABP*, fatty acid binding protein; *NEFA*, nonesterified fatty acids.

tolerance of hypoxia, it is not clear whether DFP would improve tolerance further.

Activate the Enzyme Pyruvate Dehydrogenase

Activating the enzyme pyruvate dehydrogenase favors complete aerobic oxidation of glucose, rather than lactate production.

Dichloroacetate (DCA) activates pyruvate dehydrogenase, stimulating the aerobic metabolism of glucose by diverting pyruvate into the tricarboxylic acid cycle. This activation also tends to inhibit fatty acid oxidation. Granot and Steiner [19] treated 17 dogs with both DFP and DCA prior to induction of hemorrhagic shock and subsequent retransfusion. Mean arterial pressure, cardiac index, arterial pH, and lactate levels were all better during recovery when compared with untreated controls. Six of nine treated dogs recovered, while all eight untreated dogs died. Wargovich and coworkers [61] acutely administered DCA alone to nine patients with coronary artery disease and stable angina during cardiac catheterization. Stroke volume and cardiac index rose. Left ventricular efficiency (defined as left ventricular work divided by myocardial oxygen consumption) increased from 24% at baseline to 32% after DCA [61]. Similar studies have not been reported in immature animals or in infants or children.

Block Lipolysis

Blocking lipolysis decreases the concentrations of long-chain fatty acids and their CoA and carnitine esters which otherwise accumulate in the hypoxic or ischemic myocardium.

β blockade: while it is known that administration of β blockers can improve patients with ischemia, and may improve patients with congestive cardiomyopathy, it is not clear that the mechanism in any way relates to the ability of these agents to block lipolysis. Since myocardial oxygen consumption is reduced by the reduction in inotropic state alone, it is difficult to assess β blockade in this context.

Nicotinic acid analogues: the drug, 5-fluoro-3-hydroxymethylpyridine, an nicotinic acid analog, was administered to patients within 5 h of onset of myocardial ischemia. In those patients in whom nonesterified fatty acid levels dropped into the normal range in response to the drug, none developed ventricular tachycardia; whereas 80% of those in whom nonesterified fatty acid concentrations remained elevated in spite of the drug developed ventricular tachycardia [49].

N-6-allyl-*N*-6-cyclohexyladenosine (PAA) was administered to open-chest dogs which were then submitted to a wide range of hemodynamic loads. PAA administration resulted in a shift to glucose and lactate metabolism, and away from nonesterified fatty acid extraction. It also resulted in a 14% decrease in myocardial oxygen demand for a given external workload [28]. While promising in mature hearts, blocking lipolysis would be unlikely to be helpful in the fetus and newborn in whom lipolysis is physiologically very limited.

Block the Enzyme Carnitine Palmityl Transferase (CPT) I

Blocking the enzyme CPT in animals with myocardial ischemia decreases long-chain acyl-CoA and acyl-carnitine concentrations, which are consistently elevated in this setting, by promoting the synthesis of nontoxic triglycerides (see Fig. 3). CPT blockers oxfenicine and phenylalkyl oxirane carboxylic acid (POCA) improve reperfusion systolic pressure, dP/dt, cardiac index, and partially prevent depression of the maximum diastolic potential, amplitude, and phase O maximum velocity of the cardiac action potential in the acutely ischemic rat or swine heart. Available studies correlated hemodynamic and electrophysiologic improvement, with decreased tissue concentrations of long-chain CoA and carnitine esters [32, 42]. In contrast, blockers of mitochondrial enzymes of β oxidation (such as 4-bromocrotonic acid) cause hemodynamic deterioration which correlates with a rise in tissue long-chain CoA and carnitine esters [42]. Human studies of CPT I blockers are not yet available. Although

many blockers have been synthesized, many are irreversible, and many have multiple toxicities. CPT deficiency exists clinically and is characterized by a skeletal myopathy with rhabdomyolysis during stress and heavy exercise [2, 25]. Thus CPT blockade could only be envisioned as a short-term therapy, using reversible blockers during acute myocardial compromise. Since β oxidation is not a major cardiac energy source in the fetus and newborn, this strategy would not be expected to be helpful in those age groups.

To summarize, in the fetal or neonatal heart, in which β oxidation does not contribute significantly to myocardial substrate metabolism, the best metabolic strategy for improving myocardial function in the hypoxic/ischemic myocardium is to provide as much glucose or lactate and oxygen as possible, while maintaining maximal coronary perfusion. In the mature heart capable of β oxidation, these strategies remain valid. In addition, deliberately intervening to shift cardiac metabolism from lipid to carbohydrate utilization by activation of pyruvate dehydrogenase, or by blockade of either lipolysis or of CPT I, appears to have beneficial effects. In situations where reliance on anaerobic metabolism is unavoidable in the short term, DFP has been proposed as a means of circumventing the acidosis-induced block in the glycolytic pathway, while providing an easily used substrate. Since, however, DFP is not capable of crossing biological membranes, it is difficult to understand its utility in clinical situations. Ketone bodies might also be considered as an alternate substrate in ischemia, since they are known to inhibit β oxidation when present in substantial quantities. However, since ketone bodies alone are not capable of maintaining myocardial contractility, glucose or another carbohydrate substrate must also be available.

Thomassen and coworkers [59] recently reported on myocardial substrate preference in coronary artery disease (CAD) patients with stable angina pectoris. They measured myocardial uptake or release of free fatty acids, glucose, lactate, citrate, glutamate, and alanine in 64 patients with coronary disease and in 21 controls both at rest and during coronary sinus pacing at 135–150 beats/min. Resting myocardial uptake of free fatty acids was 50% lower in CAD patients than in controls, whereas uptake of glucose and lactate were twice as high. Glutamate uptake and alanine release were also higher in the CAD patients. The stress of pacing resulted in a further decrease in fatty acid uptake and an increase in glucose uptake and in the production of lactate in 40 of 64 CAD patients [59]. Thus, it appears that the in vivo hypoxic/ischemic human heart with normal substrate availability relies less on lipid metabolism and more heavily on carbohydrate and amino acid metabolism than the normal heart. In this response, the mature heart reverts to substrate utilization patterns more typical of the fetus and newborn. The effects of pharmacologically exaggerating this protective response in both the developing and mature heart would appear to be a fruitful topic for future research. Increased understanding of myocardial metabolism throughout development could lead to improved strategies for preserving myocardial structure and function during hypoxia and ischemia.

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