Inhalation Anesthetics and Myocardial Metabolism:
Possible Mechanisms of Functional Effects

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Heart muscle has two properties vital to organ function, automaticity and contractility. Tight controls are exerted on both for the regulation of cardiac function. The energy requirements of the membrane electrical events are minor, however, compared with those of the intracellular contractility mechanism. In consequence, it is unlikely that energy metabolism plays an important role in the effect of anesthetics on myocardial rate and rhythm. Inasmuch as the contractile process in the myocardium requires a large and continuous energy supply, interference in myocardial energy metabolism would appear to be a logical mechanism for the negative inotropic effect of anesthetics. For this reason, this review is not concerned with the metabolic processes involved in cardiac rate and rhythm, but considers the steps in myocardial metabolism at which anesthetics are likely to influence cardiac contractile function.

In the most recent publication on anesthetics and myocardial metabolism, the authors were able to refer to only one study of the effects of anesthetics on myocardial metabolism. Half of the section was devoted to adrenergic effects on myocardial metabolism and the effects of ethanol (hardly a typical anesthetic). Since then there has been more work on the effects of real anesthetics on myocardial metabolism, although at least as many questions are posed as are answered. More importantly, however, we have a much better understanding of the control and mechanisms of myocardial function and metabolism and the basic physiology of the contractile process.

It is worth noting that major contributions to our understanding of the subject have come from work on the perfused rat heart. Unfortunately, the rat heart differs from hearts of higher mammals in several aspects of myocardial function, including a very different intrinsic rate, maximal velocity of shortening and, perhaps most significantly, no increase in contractile force with increase in heart rate (the "rate treppe" or "staircase" effect). Most of the literature on the subject has resulted from in-culture studies of bathed isolated muscles (ventricular, papillary, and atrial) or perfused hearts from rats, dogs, cats, guinea pigs, frogs, and occasionally man. From such work in the perfused rat heart and cat papillary muscle, the direct negative inotropic effect of all potent inhalation anesthetics is apparent.

The lack of such an effect in man with cyclopropane, diethyl ether, or fluroxene is probably a result of centrally mediated sympathetic nervous stimulation. Most investigators have assumed that common mechanisms are involved, but in order to elucidate them, lower species and very artificial conditions must be utilized. The in-culture studies have measured myocardial arteriovenous substrate differences in animals of various types and, again occasionally, in humans. However, without myocardial (coronary) blood-flow measurements (which most of the early works did not have) this technique is less meaningful and, indeed, invalid, unless coronary blood flow is constant. Even with blood-flow measurements, synthetic and storage pathways cannot be measured without the use of tagged molecules. These problems of technique and transfer of data from species to species and from in vitro to in vivo should be noted.

Correlation of cardiac function and metabolism may best be reviewed by considering the points in the contraction cycle where they may be related. For this purpose, a schema of energetics in cardiac muscle is useful (fig. 1). The energy supply of the fasting heart is liberated primarily from fatty acids and...
from lactate delivered in the coronary blood, although glucose, pyruvate, acetate, and triglycerides can be used (fig. 1, 11, 14, 15). Anaerobic glycolysis occurs in the sarcoplasm (cytoplasm of the muscle), producing pyruvate, which under aerobic conditions is converted to acetyl Co-A (Ac-CoA). This acetyl Co-A and the substantially larger quantity from beta-oxidation of fatty acids enter the intramitochondrial tricarboxylic acid (TCA, Krebs) cycle, where the bulk of energy conservation as adenosine triphosphate (ATP) and creatine phosphate (CP) occurs. The mitochondrial electron-transport system, which transfers the hydrogen ions released in glycolysis and in the TCA cycle through the flavoproteins and cytochromes to oxygen, couples liberation and conservation of energy (fig. 1, 3). Obviously, oxygen delivery to the mitochondria is essential for TCA cycle function (fig. 1, 5). The critical links between the conservation of energy as ATP and its utilization by the contractile process are the ATPases, which are necessary for hydrolysis of ATP to support the energy-dependent processes in the contraction-relaxation cycle of heart muscle (fig. 1, 1 and 5), including actin–myosin interactions (fig. 1, 6), pumping of calcium into the vesicles of the sarcoplasmic reticulum, and mitochondrial function (fig. 1, 5). The central role of calcium in muscular contraction can be appreciated by noting that not only is actin–myosin binding controlled by sarco-

plasmic calcium (fig. 1, 6), but the ATPases are also under calcium-ion control (fig. 1, 5 and 7). According to current concepts, the link between the electrical depolarization of the cardiac cell membrane and the actual intracellular contractile process is also calcium-mediated (fig. 1, 7).

Energy liberation, conservation, and utilization are examined in more detail below. After each section, the effects of anesthetics are reviewed.

**Energy Liberation**

**Oxygen Supply**

Much of the basic theory of the mechanics and biochemistry of cardiac muscle has been based on work in white skeletal muscle, but there is a major metabolic difference between the muscle types.16, 17, 18 White skeletal muscle function is episodic, occurring mostly in short, high-velocity bursts, while red skeletal and cardiac muscles function at lower velocities and for longer periods. Consequently, white skeletal muscle can work anaerobically for appreciable periods, building up its energy reserve aerobically during rest. In contrast, the heart (and red skeletal muscle) is incapable of sustained anaerobic metabolism but must have oxygen for its energy demands. Anaerobic processes are much less efficient in energy liberation and conservation. For example, one mole of glucose yields only two high-energy phosphate bonds anaerobically,
while complete aerobic catabolism of one mole of glucose yields 15 such bonds. The continuous high-energy demands of cardiac muscle can be met only with aerobic metabolism. The activity of the TCA cycle, where most of the aerobic energy liberation occurs, is entirely within mitochondria. A graphic illustration of the difference in oxidative metabolism between white skeletal and cardiac muscle is seen in the distribution of mitochondria in the two muscle types (fig. 2). For these reasons, oxygen kinetics must be considered in relation to metabolism and contractile function.

**Oxygen Supply: Effect of Anesthetics**

Delivery of oxygen to heart muscle depends upon the oxygen content of the coronary arterial blood and the amount of that blood delivered to the muscle, i.e., the coronary blood flow. The ventilatory depression produced by most anesthetics can result in decreased oxygen concentration in arterial blood, but the depression can be easily controlled and should play no role in the problem being discussed. Although it is possible that anesthetics affect the oxyhemoglobin dissociation curve, the objective evidence is not convincing at present. It appears that if anesthetics interfere with the myocardial oxygen supply, the effect is probably on myocardial (coronary) perfusion.

The anesthetic most widely studied in this regard has been halothane, predominately in the dog. Philpart in Belgium, Eberlein in Germany, Saito in Japan, Weaver in England, and Bagwell and Merin in the United States have all reported strikingly similar dose-related decreases in myocardial blood flow and arterial blood pressure. While holding coronary perfusion pressure constant, Wolff et al. found increased coronary vascular resistance and decreased flow with halothane, as compared with diethyl ether. Employing an ingenious technique of counting radioactively tagged embolized microspheres in various organs postmortem, Amory and co-workers reported that coronary perfusion decreased in proportion to the decrement in cardiac output as the delivered halothane concentration increased in the monkey. Both Saito and Eberlein reported conflicting data on coronary A-V oxygen differences during halothane anesthesia. In their initial studies, both investigators indicated that A-V oxygen extraction increased with halothane, while their subsequent papers indicate there was no change or even a decrease.

Saito, Wolff, and Eberlein also tested diethyl ether in their animal preparations. With coronary perfusion maintained by a pump, Wolff's group noted that coronary vascular resistance decreased and coronary blood flow increased as the anesthetic was changed from halothane to diethyl ether. Concomitantly, aortic blood pressure increased. Saito and Eberlein also saw increased aortic pressure and/or cardiac output, together with increased coronary blood flow, with diethyl ether. Both authors commented on the decreased myocardial A-V oxygen difference. Saito et al. investigated methoxyflurane and cyclopropane as well. Both drugs decreased cardiac output and coronary flow, but the ratio of coronary flow to cardiac output increased with cyclopropane, as did with diethyl ether, while a decrease in the ratio was
seen with methoxyflurane and halothane. Both Saito and Eberlein thought that the
difference in coronary flow and oxygen extraction might be related to the sympathtomimetic
effects of diethyl ether and cyclopropane.

We have seen the same degree of myocardial function and blood flow depression with
methoxyflurane as with halothane. In contrast to the other investigators, however, with
the "sympathomimetic" anesthetic, fluroxene, we found dose-dependent decreases in aortic
blood pressure, myocardial blood flow and oxygen uptake (fig. 3). The only difference in
these measurements among the three anesthetics we studied was the significant decrease in
myocardial A-V oxygen extraction with fluroxene. The stroke work per unit of oxygen
consumed decreased with negative inotropic doses of all three anesthetics, while the
proportion of the cardiac output delivered to the left ventricle did not change (table 1).

In the reports reviewed above, it appears that myocardial blood flow and oxygen uptake
decreased in those instances where ventricular function (and work) was decreased (halothane, methoxyflurane, fluroxene) and increased where ventricular function increased (diethyl ether). Whether this is cause or effect is another problem, however. An estimate of the sufficiency of oxygen supply in relation to oxygen demand in the heart is needed. Some tissues, such as skeletal muscle and liver, are able to increase appreciably the amount of oxygen extracted from arterial blood when flow is diminished. In such tissues an increase in A-V oxygen difference indicates relative insufficiency. The primary mechanism for control of oxygen delivery to cardiac muscle, however, is a change in coronary vascular resistance and hence blood flow, because A-V extraction is very large at rest (fig. 1). Consequently, analysis of coronary arteriovenous oxygen difference alone is of limited value in assessing the adequacy of oxygen delivery to the heart.

The controversy over the relationship between extracellular lactate-pyruvate metabolism and intracellular oxygen supply has been widely discussed over the past decade in the anesthetic literature. Although there are serious objections to this use of the relationship, there is some basis for considering the

### Table 1. Myocardial Efficiency and Myocardial Blood Flow/Cardiac Output

<table>
<thead>
<tr>
<th>Efficiency</th>
<th>MAC</th>
<th>2-3 MAC</th>
<th>Per Cent Change</th>
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<tbody>
<tr>
<td>Left ventricular stroke work, left ventricular O₂ uptake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>7.35</td>
<td>3.82*</td>
<td>48</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>5.46</td>
<td>2.65*</td>
<td>51.4</td>
</tr>
<tr>
<td>Fluroxene</td>
<td>7.37</td>
<td>4.15*</td>
<td>45.6</td>
</tr>
<tr>
<td>Blood flow/cardiac output ratio (per cent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>1.52</td>
<td>1.52</td>
<td></td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>1.69</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td>Fluroxene</td>
<td>1.44</td>
<td>1.67</td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.01.

measurements in relationship to myocardial cellular hypoxia. The basic premise is inviting. With sufficient oxygen, glucose and lactate are converted to pyruvate, which is then hydrogenated to acetyl CoA, which enters the Krebs (TCA) cycle (fig. 4). The conversion of lactate to pyruvate is dependent on available oxidized nicotinamide adenine dinucleotide (NAD⁺). Hypoxia first blocks the terminal cytochrome in the mitochondrial electron-transport system (fig. 5). This results in a buildup of ADP and inhibition of the Krebs cycle with an increase in pyruvate. Hypoxia stimulates cellular membrane transport of glucose, and ADP stimulates glycolysis so even more pyruvate accumulates (fig. 5). Hypoxia converts NAD⁺ to NADH which, combined with the excess of pyruvate, drives the pyruvate-lactate reaction further toward lactate formation. In his original paper, Huckabee suggested that the lactate-pyruvate ratio in the blood reflected the NADH/NAD⁺ ratio (and hence oxygen availability) intracellularly. Objections to his theory include the effect of the membrane barriers between the two. In a carefully designed and executed study in the perfused rat heart, Opie and Mansford demonstrated that indeed there were major differences in extra- and intracellular levels of lactate and pyruvate, NAD⁺ and NADH, and alpha-glycerophosphate and dihydroxyacetone phosphate (one of the shuttle systems by which electrons can be transferred back and
Fig. 4. Aerobic myocardial metabolism (from Scheuer,\textsuperscript{14} with permission of author and publisher).

forth between cytoplasm and mitochondria).\textsuperscript{25}
However, they concluded that if the nutrition of the animal is normal and if no metabolic disease (diabetes) is present, extracellular lactate-pyruvate relationships reflect intracellular NAD\textsuperscript+ /NADH ratios quite well. Inasmuch as the extracellular lactate-pyruvate (L/P) ratios are supposed to be in equilibrium with the intracellular redox pair (NAD\textsuperscript+ /NADH), a steady state is necessary for any conclusions to be drawn from such ratios. While recognizing the problems inherent in use of this relationship, other authors have also felt that the estimate was useful at least qualitatively.\textsuperscript{14, 29, 40} It should be noted that this refers only to the total myocardial lactate-pyruvate kinetics, not "excess lactate" or "lactate/pyruvate ratio" alone. The adequately oxygenated heart extracts lactate in relation to the arterial level. Decreased lactate uptake in the face of a rising arterial concentration and/or decreasing pyruvate extraction suggests myocardial cellular hypoxia.

With this background, the effect of anesthetics on this relationship can be explored. In abstract form only, Bagwell reported that the dose-related decrease in contractile force and coronary blood flow produced by halothane was accompanied by negative "excess lactate" values, "indicating that coronary flow was adequate to supply the oxygen needed to maintain normal oxidative metabolism."\textsuperscript{25} In a poorly controlled study in open-chest dogs, Tajoli et al. noted no change in myocardial lactate and pyruvate extraction with 1 per cent halothane (vaporizer setting), compared with non-anesthetized animals paralyzed with d-tubocurarine.\textsuperscript{42} With 2 per cent halothane, myocardial extraction and arterial concentrations of both substrates increased. The same group reported similar findings with 1 and 3 per cent methoxyflurane.\textsuperscript{43} We have reported that the decrease in myocardial blood flow and oxygen uptake with 2–3 MAC (minimal alveolar anesthetic concentration) halothane or methoxyflurane was accompanied by decreases
or no change in myocardial excess lactate with maintenance of lactate uptake in relation to the arterial levels and blood flow (table 2). \(^{20,21}\) Similar hemodynamic effects of fluroxene were accompanied by very different lactate metabolism. \(^{22}\) Although the myocardial A-V oxygen difference decreased (fig. 3), the lactate data suggested cellular hypoxia with marked decrease in uptake and even production of lactate in spite of markedly increased arterial lactate values. However, if oxygen delivery actually had been impaired, it is unlikely that A-V extraction would have decreased, unless demand and uptake were uncoupled. Another possibility is the "sympathomimetic" effect of fluroxene. They has suggested that alterations in lactate metabolism seen in the whole body and in liver with diethyl ether and cyclopropane are related to sympathetic stimulation of glycolysis. \(^{23}\) Regan et al. have demonstrated such an effect with epinephrine \(^{44}\) but not with norepinephrine \(^{45}\) in the dog heart, so the question remains unresolved.

With reference to mechanisms of cardiac depression, Paradise and Griffith reported that high concentrations of halothane and anoxia produced equivalent ventricular depression in the perfused rat heart. The halothane depression was readily reversible and was accompanied by no change in perfusion rate (coronary flow), while the anoxic effects were less readily reversible and caused an increase in perfusion rate. \(^{46}\) They concluded that the mechanisms of depression were quite different.

In summary, inadequate oxygen delivery does not appear to be a primary mechanism in the myocardial depression produced by anesthetics. Decreased oxygen uptake is more likely a reflection of decreased demand, although the evidence available is less than conclusive.

**Substrate Utilization**

The mammalian heart is able to use a variety of fuels to satisfy its large and continuous energy demands. Depending on arterial levels,
oxygen availability, and the hormonal and enzymatic environment, glucose, fatty acids, ketones, lactate, pyruvate, triglycerides, and glycogen can provide heart muscle with energy. As mentioned in the previous section, the aerobic Krebs (TCA, citric acid) cycle is the most efficient energy-liberating mechanism available, but, with abundant oxygen, all of the above-mentioned substrates are able to enter into this ubiquitous metabolic pathway. Stated in simplest terms, the heart will extract energy from whichever of these substrates is presented to it in highest concentration. Obviously there are more complex control mechanisms as well.
Table 2. Myocardial Lactate Metabolism

<table>
<thead>
<tr>
<th></th>
<th>MAC</th>
<th>2-3 MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Halothane</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial (mg/100 ml)</td>
<td>24.88 ± 4.53</td>
<td>22.54 ± 2.65</td>
</tr>
<tr>
<td>A-V (mg/100 ml)</td>
<td>8.21 ± 1.52</td>
<td>10.67 ± 2.39</td>
</tr>
<tr>
<td>Uptake (mg/100 g/min)</td>
<td>3.18 ± 0.65</td>
<td>2.54 ± 0.75</td>
</tr>
<tr>
<td>Excess (mg/100 ml)</td>
<td>6.1 ± 2.08</td>
<td>-2.12 ± 2.05*</td>
</tr>
<tr>
<td><strong>Methoxyflurane</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial (mg/100 ml)</td>
<td>21.85 ± 3.67</td>
<td>17.88 ± 1.6</td>
</tr>
<tr>
<td>A-V (mg/100 ml)</td>
<td>10.44 ± 1.98</td>
<td>8.19 ± 0.84</td>
</tr>
<tr>
<td>Uptake (mg/100 g/min)</td>
<td>4.79 ± 1.23</td>
<td>2.04 ± 0.3*</td>
</tr>
<tr>
<td>Excess (mg/100 ml)</td>
<td>-2.18 ± 1.25</td>
<td>-1.49 ± 1.21</td>
</tr>
<tr>
<td><strong>Fluroxene</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial (mg/100 ml)</td>
<td>22.0 ± 3.3</td>
<td>41.3 ± 9.3*</td>
</tr>
<tr>
<td>A-V (mg/100 ml)</td>
<td>3.12 ± 1.5</td>
<td>0.96 ± 1.8 (3.9 neg)</td>
</tr>
<tr>
<td>Uptake (mg/100 g/min)</td>
<td>1.47 ± 0.17</td>
<td>0.20 ± 0.56</td>
</tr>
</tbody>
</table>

* P < 0.05.

**GLUCOSE**

Normally, transport of glucose across the myocardial cell membrane is the rate-limiting step in myocardial glucose metabolism. This transport is concentration- and insulin-dependent,23,24 The normal arterial glucose threshold of 60 mg/100 ml (below which there is no glucose uptake) is most likely a result of the insulin dependency,9,15 although lipid-glycolysis interactions may also play a role (see below). After cellular entry of glucose, the rate-limiting process governing glycolysis is the phosphofructokinase (PFK)-catalyzed conversion of fructose-6-phosphate to fructose-1,6-diphosphate (fig. 6).25 PFK activity is sensitive to the adenine nucleotides and citrate.26 When oxygen is plentiful, the TCA cycle keeps the ATP and citrate levels high, inhibiting PFK activity and glycolysis. Subsequent to any event interfering with TCA activity, both ATP and citrate levels decrease; adenosine diphosphate (ADP), adenosine monophosphate (AMP), and inorganic phosphate (Pi) concentrations increase; PFK is activated; glycolytic flux is accelerated. Alkalosis has been shown to increase glycolysis in the perfused rat heart, presumably by PFK activation, since optimal PFK activity occurs at pH 8.27 Hypoxia promotes glycolysis in several ways:28 cellular glucose transport is greatly increased by oxygen lack;29 TCA cycle activity is inhibited; ATP and citrate levels decrease; ADP, AMP, and Pi levels increase. Although increased work also stimulates glycolysis in skeletal muscle and in the perfused heart,28 the importance of this effect in cardiac muscle in vivo is yet to be determined.

In summary, myocardial glucose utilization is dependent on arterial glucose concentration and plasma insulin level. Hypoxia, or other interference with TCA cycle activity, alkalosis, and possibly increased cardiac work accelerate glycolysis.

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Fig. 6 (left and below). Pathways of energy liberation and conservation (adapted after Davies,27 with permission of author and publisher).
GLYCOGEN

Carbohydrate stored as glycogen can be utilized by the heart, although its physiologic role in the heart is relatively unimportant compared with fast (white) skeletal muscle. Cardiac glycogen is synthesized only from glucose because of the absence of fructose 1,6-diphosphatase, which is necessary for the reversal of the glycolytic pathway if pyruvate, lactate or acetyl CoA is to be a glycogen precursor (fig. 6). Insulin stimulates glycogen synthesis, so the fed state favors glycogen buildup. Since cardiac glycogen has been shown to be lower in fed than in fasted hearts, by inference glycogenolysis must be more active in the fed heart as well. The main control point of glycogenolysis is at the phosphorylase system. Catecholamines would be expected to increase glycogenolysis by their known ability to activate phosphorylase through adenyI cyclase and cyclic AMP (see below), but the complexities of adrenergic effects on cardiac metabolism obscure this effect in the intact animal. The whole subject of glycogenolytic control in the heart is unclear at the present. As Opie has stated, "There is no established role for glycogen in the normal cardiac cycle. It is only in extreme conditions such as anoxia that cardiac glycogen is mobilized..." °

LACTATE

Myocardial lactate usage appears to be regulated by two factors, the arterial level of lactate, and the integrity of pyruvate degradation and oxidative metabolism in the TCA cycle and in the mitochondria (see above). At high arterial concentrations, lactate can provide a substantial contribution to myocardial energy liberation.

PYRUVATE

If pyruvate dehydrogenase is not inhibited and if the entry of acetyl Co-A into the TCA cycle is not impaired, heart muscle will use as much pyruvate as it is given. Hypoxia and fatty-acid metabolism can cause both of the above effects and hence are the most common circumstances in which pyruvate use is decreased. Glucose and fructose have been shown to activate pyruvate dehydrogenase and facilitate pyruvate oxidation. The contribution of pyruvate to the cardiac energy supply is minor, however, because of the low circulating arterial levels (0.5–2.0 mg/100 ml).

FRUCTOSE

Myocardial transcellular transport of fructose is insulin-independent, but otherwise its degradation is similar to that of glucose. It appears that fructose is used by the heart only in the absence of other fuels.°

FATTY ACIDS

There can be little doubt that free (non-esterified) fatty acids (FFA, NEFA) are important myocardial fuels. Myocardial extraction of saturated fatty acids is inversely proportional to chain length, but the predominant NEFA in the plasma of mammals, the 16-carbon palmitic acid and the 18-carbon oleic acid, are preferentially used over any of the shorter-chain saturated acids. NEFA travels in the blood bound to albumin. As the albumin–NEFA molar ratio approaches unity, myocardial fatty acid extraction decreases. Except in extreme hypolipidemia, however, the ratio is unimportant in vivo. Transcellular transport appears to be a physical, non-energy-dependent process with a threshold of 0.07 to 0.35 mm, depending on the species. There are at least two intracellular binding sites, a high-affinity locus which is freely exchangeable with the TCA cycle, and a larger, low-affinity site which exchanges more slowly. There is some evidence that NEFA form triglyceride fatty acids (TGFA) before being oxidized, which might account for the low-affinity sites. Nevertheless, TGFA must be hydrolyzed to NEFA and thence, by beta oxidation, to acetyl Co-A before being oxidized. It appears that carnitine (beta-hydroxy gamma-trimethyl ammonium butyrate), which is present in high concentration in heart muscle, is essential for efficient transfer of fatty acid–Coenzyme A complex into the mitochondria for TCA-cycle degradation. Oxidation and uptake of NEFA are more closely related than with any other substrate in the heart, although there are other intracellular pathways for NEFA. NEFA oxidation can account for as much as 90 per cent of myocardial oxygen consumption.
TRIGLYCERIDES

Fat absorbed from the gut is transported primarily as lipoprotein-bound triglyceride fatty acids (TGFA) and broken down to NEFA in the liver. Because TGFA are such a rich energy source, oxidation of 5 mg per minute (less than 10 per cent of the total TGFA passing through the heart) could provide the total cardiac energy requirements. Consequently, quantitation of TGFA extraction in vivo has proven difficult, although it has definitely been shown in the perfused heart. Carlson and co-workers recently demonstrated TGFA uptake in resting man by a combination of chemical and radioisotopic measurements. The physiologic import remains unclear. TGFA are also formed from plasma NEFA and are the primary lipid storage form in the heart. They are unquestionably a fuel in the perfused heart. Crass has recently reported that endogenous TGFA oxidation is inversely related to the exogenous NEFA concentration presented to the working perfused rat heart, while the presence of glucose in the perfusate has little effect. It appears that endogenous lipids are utilized only in extremely stressful situations, in a manner similar to the endogenous carbohydrate, glycogen.

KETONES

Acetoacetate and beta-hydroxybutyrate are the principal circulating ketones in plasma and can be utilized by perfused and in-situ hearts. Uptake depends on arterial level. As ketone uptake increases, NEFA uptake and glucose uptake decrease. Except in severe starvation or diabetic ketosis, however, arterial levels are low and myocardial ketone utilization is minimal.

PROTEINS

Although some amino acids may enter into the TCA cycle and liberate energy for cardiac function, this probably only occurs in extreme substrate deficiency (starvation, etc.).

CARBOHYDRATE–LIPID INTERACTION

I have described some of the interactions between fuels in cardiac muscle in the previous sections. In a series of studies on rat skeletal and cardiac muscle, Randle and co-workers evolved the concept and mechanisms of the "glucose-fatty acid cycle." The cycle is based on the inhibitory effects of glucose and insulin on release of NEFA from adipose tissue and on the reciprocal inhibition of glycolysis and pyruvate oxidation in muscle by fatty acids. During carbohydrate deprivation (starvation, hypoinsulinemia, diabetes mellitus), NEFA oxidation is enhanced because the normal stimulation of triglyceride synthesis and the depression of lipolysis in adipose tissue by glucose and insulin are absent. The decreases in plasma glucose and insulin depress cellular membrane transfer of glucose into muscle (including the heart). Further, even in the presence of insulin, the elevated NEFA levels decrease the insulin stimulation of membrane glucose transport, suppress glucose phosphorylation by hexokinase, suppress glycolysis by inhibiting PFK (see above for mechanism), and depress pyruvate entry into the TCA cycle by inhibiting pyruvate dehydrogenase. All of these interactions effectively inhibit glycolysis, and the last interferes with lactate and pyruvate oxidation as well. Although most of the work in perfused and in-situ hearts suggests that lipids, ketones and lactate decrease glycolytic flux, there is some evidence that glucose can depress utilization of the other substrates. Olson pointed out as early as 1963 that the multifactorial controls on cardiac fuel utilization made generalizations about the primacy of one fuel over another dangerous. Although it is generally believed that heart muscle preferentially utilizes lipids, particularly NEFA, the evidence is not conclusive.

HORMONAL EFFECTS ON MYOCARDIAL ENERGY METABOLISM

Adrenergic

The sympathetic nervous system plays an important role in controlling myocardial function in awake and anesthetized animals. Although the metabolic effects of adrenergic stimulation have been difficult to categorize, particularly from species to species, increased circulating NEFA levels are a universal manifestation of sympathetic nervous activity. Stimulation of adipose tissue lipolysis is a
constant and well-documented effect of sympathetic (or catecholamine) stimulation which is held to be responsible for the elevated NEFA levels. In an exhaustive review, Himms-Hagen concluded that most of the effects of adrenergic stimulation on lipid metabolism of organ systems could be explained primarily by the increased arterial levels of NEFA. However, glycogenolysis is augmented by sympathetic stimulation, predominantly through activation of glycogen phosphorylase (see below), but also from PFK stimulation. (Both effects are believed to be beta receptor-mediated.) Another systemic effect of sympathetic stimulation could also affect myocardial metabolism. Porte has demonstrated that sympathetic stimulation suppresses pancreatic insulin release through an alpha receptor effect. As discussed before, such an effect would tend to decrease myocardial glucose utilization and favor lipid uptake. However, several investigators have shown myocardial metabolic effects of epinephrine and norepinephrine which are independent of these systemic effects. Regan and coworkers demonstrated that epinephrine stimulated myocardial glycogenesis and decreased NEFA extraction, but that norepinephrine increased glucose and lactate extraction without changing NEFA utilization. Both catecholamines increased TGCA uptake. However, Cowley et al. noted increased NEFA oxidation with intracoronary injection of norepinephrine. Claviano and Masters found that intracoronary norepinephrine stimulated glucose, lactate and NEFA uptake; 1.0 mg/kg propranolol (a large dose) given prior to infusion of norepinephrine markedly decreased NEFA uptake while interfering minimally with carbohydrate metabolism. In a combined in-vivo and in-vitro study, the same authors produced suggestive evidence that the mechanism of the increased NEFA uptake with norepinephrine involved obligatory esterification of circulating NEFA to TGCA before oxidation (see previous section). According to their hypothesis, beta-adrenergic stimulation would cause activation of a lipoprotein lipase necessary for hydrolyzing TGCA back to NEFA before oxidation of the NEFA could proceed. Beta-adrenergic blockade with propranolol would block this event. Evidence for such a lipase system in the heart has been provided by the work of Christian et al.

The metabolic interactions between carbohydrates and lipids probably control the overall metabolic effect of catecholamines on the heart in vivo. If the lipid supply is great, NEFA oxidation will be high and the feedback from the TCA cycle via ADP, AMP, P_i and citrate will depress PFK activity and decrease glycolysis. There may be pyruvate output as well because of decreased pyruvate dehydrogenase activity. With decreased NEFA supply, the sympathetic stimulation of glycogenolysis via phosphorylase activation and of glycolysis by PFK stimulation predominate. So there appear to be both direct effects of adrenergic stimulation on myocardial metabolism, probably mediated through glycogenolysis and lipolysis, as well as systemic effects producing increased circulating NEFA, again through lipolysis in adipose tissue as well as through hyperglycemia from hepatic glycogenolysis. The concomitant suppression of pancreatic insulin release would favor lipid uptake by the in-situ heart.

In the intact animal, the increase in myocardial oxygen consumption seen with catecholamine administration has been noted to be greater than that dictated by the isotropic effect. In a series of experiments, Mjols reported that myocardial oxygen consumption was increased in association with elevated NEFA levels, independent of ventricular function changes. By blocking lipolysis with nicotinic acid, he could decrease the elevation of myocardial oxygen uptake produced by beta-adrenergic stimulation without changing the hemodynamic effects. Recently his laboratory has demonstrated that the effect of increased afterload (aortic pressure) on myocardial oxygen consumption was also dependent in part on fatty-acid metabolism. Other studies have suggested that elevated NEFA levels can depress ventricular function and cause ventricular arrhythmias. Apparently, NEFA are capable of interfering with myocardial oxygen utilization and ventricular function, possibly by a detergent effect on membranes.

Adenyl Cyclase-Cyclic AMP

Investigation of the glycogenolytic effect of epinephrine in the liver led to the original
elucidation of the adeny1 cyclase–cyclic AMP mechanism by Sutherland and co-workers.\textsuperscript{93} One of the more widely publicized attempts to relate myocardial function and metabolism has been concerned with this interaction between adrenergic stimulation and intracellular cyclic AMP activity. The concept of cyclic AMP as a “second messenger” in translating hormonal effects from blood to intracellular foci has been generally accepted (fig. 7).\textsuperscript{94} The hormone stimulates the elaboration of adeny1 cyclase, an enzyme found almost exclusively in membrane systems. In the presence of adequate magnesium, adeny1 cyclase catalyzes the breakdown of adenosine triphosphate (ATP) to adenosine-3',5'-monophosphate (C-AMP) plus pyrophosphate (PP\textsubscript{i}); C (cyclic)-AMP is then broken down to 5'AMP in the presence of magnesium in a reaction catalyzed by the enzyme phosphodiesterase. The methyl xanthises (caffeine, theophylline, etc.) are phosphodiesterase inhibitors. In the original work of Sutherland, the effect of epinephrine on glycogenolysis was shown to be through activation of adeny1 cyclase, producing increased cyclic AMP levels intracellularly.\textsuperscript{95} The cyclic nucleotide in turn stimulated phosphorylase \textit{b} kinase, which catalyzed the conversion of the inactive glycogen phosphorylase \textit{b} to the active phosphorylase \textit{a} (fig. 8). Phosphorylase \textit{a} promoted the degradation of glycogen to glucose-1-phosphate.\textsuperscript{96} C-AMP also stimulates a glycogen synthetase kinase, which converts the synthetase from the active \textit{I} form to the inactive \textit{D} form.\textsuperscript{96} This action, combined with the insulin-suppressing effect of sympathetic stimulation, effectively stops glycogen synthesis. Initially, an attempt was made to correlate the phosphorylase activation and the consequent glycogenolysis in the heart with the positive inotropic effects of beta-adrenergic stimulation,\textsuperscript{97} but several studies demonstrated the dissociation between phosphorylase activation and increased contractility.\textsuperscript{98, 99} These observations directed attention to the release of cyclic-AMP as the intracellular mediator in a number of hormonal actions. Sutherland’s group defined four criteria for acceptance of cyclic AMP as a “second messenger” of any hormone\textsuperscript{94}: 1) activation of adeny1 cyclase in subcellular preparations; 2) appropriate change of cyclic AMP levels in the intact organ in response to the hormone; 3) poten-
Fig. 8. Myocardial glycogen metabolism (from Mayer, with permission of author and publisher).

The pharmacologic action of the hormone by phosphodiesterase inhibitors; 4) production of hormonal action by exogenous cyclic AMP. These criteria have been satisfied for the catecholamine activation of liver and cardiac glycogen phosphorylase and for the ACTH-stimulated synthesis of adrenal cortical steroids. The cyclic nucleotide appears to mediate a number of other metabolic reactions as well. Stimulation of phosphofructokinase (PFK) and the lipase of adipose tissue, and decrease in pancreatic insulin secretion, have all been shown to correlate with at least three of the criteria. Although phosphorylase activation is not the mediator of beta-adrenergic inotropy, the criteria of Sutherland appear to have been satisfied for cyclic AMP as the mediator. There are still some doubts about the mechanisms, however. It is possible that the inotropic effect of cyclic AMP is not mediated through energy metabolism but rather through an effect on the calcium-accumulating properties of the sarcoplasmic reticulum (discussed in a later section). Although Sutherland's group suggested that adenylyl cyclase might be the beta receptor, it is apparent that the enzyme mediates many other hormonal activities. Even in the heart, glucagon, histamine and the prostaglandins stimulate adenylyl cyclase and cyclic AMP outside the beta receptor mechanism. Apparently, hormone receptors are located in the cell membrane, but are distinct from adenylyl cyclase, which is activated by several types of receptors. Whether the adenylyl cyclase-cyclic AMP system is the true mediator of the inotropic effect of various hormones or not, it appears to play an important role in the regulation of myocardial contractile function.

Insulin

Within the decade of the discovery of insulin, all manner of marvelous effects were ascribed to exogenous administration of the hormone, including cardiac inotropic action. Although insulin certainly increases myocardial glucose extraction in the dog and man, intracoronary glucagon-free insulin pro-
dues no inotropic effect in healthy dogs. The positive inotropic effect noted in earlier studies was probably a result of glucagon contamination and/or the sympathetic activation resulting from uncontrolled hypoglycemia. As I have noted, oxygen lack promotes glucose uptake and glycolysis. There has been adequate documentation of the dependence of the hypoxic and ischemic heart on glycolysis. Since insulin exerts a major controlling effect on myocardial glucose utilization, the combined use of GIK (Glucose to combat the hypoglycemia, Insulin, and potassium K) to prevent hypokalemia) in ischemic heart disease seemed logical. The early work of Sodi-Pallares was directed mainly at arrhythmia prevention, but there was little objective evidence of improvement in cardiac function by GIK infusion until the publication last year of studies in the dog and man. The animal study indicated that GIK significantly reduced the area of infarction and prevented the arterial hypotension and tachycardia produced by ligation of a coronary artery. GIK (with glucagon-free insulin) produced impressive positive inotropic effects in a group of patients with severe left ventricular failure presumed to be caused by ischemic heart disease. An interesting facet of the latter study was the positive inotropic effect of GIK in the control group of patients with functional heart murmurs and no indication of cardiac failure or ischemic heart disease. No hypoglycemia was reported, although only two blood samples were taken. NEFA levels were not reported, so there is little objective information as to whether sympathetic excitation was produced by the insulin. The glucose-fatty acid cycle influence cannot be evaluated, either. The mechanism is obscure. To my knowledge, this is the only reported study in the well-oxygenated intact heart where a positive inotropic effect of insulin has been seen without obvious extraneous causes (drug effects, glucagon contamination, hypoglycemia), although a previous review by the same group intimated that insulin and glucose produced beneficial effects in non-ischemic heart failure, without citing adequate documentation. GIK may well prove to be beneficial in ischemic heart disease, either by increasing the cardiac energy supply or by decreasing the deleterious effects of NEFA. However, Opie has cautioned against widespread acceptance of the technique without proper control trials. Although the major effect of insulin on carbohydrate metabolism is probably through acceleration of membrane glucose transport, recently the hormone has been shown to increase pyruvate oxidation in beating heart cells in culture, presumably by activating pyruvate dehydrogenase.

Other Hormones

The myocardial metabolic and functional effects of thyroid hormone are difficult to separate from the sympathetic excitation which accompanies hyperthyroidism. It would appear that the hormone does have a direct inotropic effect on cardiac muscle, perhaps mediated through cyclic AMP. The metabolic effects have been reported to include increases in circulating NEFA and in oxidative metabolism, both of which would fit with this finding. The physiologic role of glucagon lies in its control of carbohydrate metabolism in the liver. In pharmacologic doses, which far exceed the physiologic amounts secreted by the pancreas, the drug can be a potent inotropic agent, although clinical results have been confusing. The hormone is presumed to act through the adenyl cyclase-cyclic AMP system. In view of the marked variability in the therapeutic effects of glucagon, it is of interest that Epstein and co-workers could correlate the functional effect of glucagon in cat and human papillary muscles with the adenyl cyclase response, even though the inotropic and cardiac metabolic effects have been clearly dissociated. The positive inotropic effect of the prostaglandins has also been postulated as depending on adenyl cyclase. Discussion of this protein group of compounds is beyond the scope of this paper.

Effect of Anesthetics

Halothane and Methoxyflurane

Most of the published work on the effects of anesthetics on myocardial metabolism has dealt with energy liberation. In a series of papers based on experiments utilizing atrial muscle strips, initially from rats and subsequently from man (obtained during cardiac surgery), Paradise et al. have demonstrated...
an interesting correlation between metabolism and function. Gimeno et al. had shown that stimulated rat atrial strips could function using glucose, fructose, lactate, pyruvate, acetate, mannose, or butyrate. The highest tensions could be achieved with 16.5 mM glucose, indicating a preference for that substrate by rat atria. Using this information, Paradise and Ko demonstrated that the decrease in developed tension produced by halothane in the stimulated rat atrial preparation could be partially reversed by pyruvate and lactate but not by glucose in any concentration; thus a block in the conversion of glucose to pyruvate was indicated (fig. 9). Inasmuch as one of the prime controls of glycolysis is phosphofructokinase (PFK), this appeared to be a likely site for the block. Shaw and Stadie had demonstrated in skeletal muscle that PFK was inactivated in bicarbonate-free media. Ko and Paradise could see no effect of either glucose or fructose in their bicarbonate and substrate-free medium, confirming that PFK was also inactivated in rat atria. However, the demonstration that fructose (in addition to pyruvate, lactate and acetate) could partially reverse the negative inotropic effect of halothane suggested that PFK was functioning in the halothane-depressed atrium. Consequently, the block must be above the PFK step at the uptake of glucose into the cell (fig. 9, A); the phosphorylation of glucose (fig. 9, B); or the isomerization of glucose-6-phosphate to fructose-6-phosphate (fig. 9, C).

In a separate publication, the same authors confirmed that atrial contractility in a 5-mM glucose medium could indeed be depressed by a bicarbonate-free bath. The fact that the depression could be partially reversed by pyruvate, lactate, and acetate, but not by glucose or fructose, suggested that PFK inhibition was involved. Contractile depression by citrate, a known inhibitor of rat heart PFK, could also be reversed by pyruvate and lactate but not by fructose. However, acetate was relatively ineffective, while glucose was most effective in this preparation. Thus, glucose appeared to be able to influence contractility in the perfused rat atrium in some fashion that bypassed the crucial PFK step. Decreasing calcium ion concentration produced decreases in developed tension, but were only minimally reversed by the highest glucose concentration, negating the idea that the citrate effect involved chelation of calcium. Thus, the glycolytic mechanisms in stimulated rat effect were still somewhat obscure. It is important to note that all this evidence is circumstantial, for no glycolytic intermediates were measured at any time in these studies.

Continuing their studies with atrial appendages from children (taken at cardiac surgery) with a variety of heart diseases, the same investigators demonstrated some differences between the human and rat atrial preparations. Higher glucose and calcium concentrations were necessary to maintain developed tension in the human atria. The human preparation was also less stable than the rat-heart preparation, deteriorating in 60 minutes. Maximum developed tension required 30 mM glucose in the human heart, as contrasted to 16.5 mM glucose in the rat heart. The human atria depressed by a lack of substrate responded very well to 20 mM glucose and pyruvate, but there was little reversal of the depressed tension by lactate, fructose, or acetate, in contrast to results seen with the rat atria. In human atria halothane produced a contractile depression qualitatively similar to that seen in the rat. With the information from the previous studies available, only glucose and pyruvate were tested in the human preparation. As in the rat, glucose had no effect on the halothane-depressed tension. Pyruvate not only reversed the depression but produced increases of as much as 50 per cent above the control non-anesthetized state, although the results were extremely variable. Consequently it appeared that a block in glycolysis qualitatively similar to that seen in the rat was contributing to the depressed tension produced in human atria by halothane. The demonstration that decreased tension could be produced by halothane in a glucose-free medium indicated that a block in glucose uptake (fig. 9, A) or in phosphorylation (fig. 9, B) was not an essential feature of the glycolytic interference produced by the anesthetic. The source of this glycolytic substrate blockade in a glucose-free medium presumably was glycogen (fig. 9, D), with block at the hexose
isomerase conversion of glucose-6-phosphate to fructose-6-phosphate (fig. 9, C).

Ko and Paradise had recognized several problems inherent in transferring the results of in-citro rat-atria experiments to the intact animal. The halothane concentrations producing 50 per cent depression in developed tension in all the prior experiments were of the order of the minimal anesthetic alveolar concentrations (MAC), which have been shown to produce little direct myocardial depression in the intact animal. In addition, the predominate fuel for the heart in the fasting state has been assumed to be fatty acids, (fig. 9, E), not the carbohydrates involved in these experiments. Technical problems prevented the use of fatty acids in their preparation. Starved rat hearts had been shown to have increased amounts of storage lipids (TGFA). The authors reasoned that these atria would use TGFA and be less sensitive to the glycolytic blocking effect of halothane. The results indeed showed that more halothane (10.8 mg/100 ml) was needed to produce a 50 per cent decrement in developed tension in starved than in fed rat atria (6.5 mg/100 ml). Thus, in the in-citro situation, where presumably lipids were being used for the energy requirements of the atria, more halothane was necessary for equivalent depression, thereby approximating the in-citro situation. The rat atrial model was also used for methoxyflurane, where an effect qualitatively similar to that seen with halothane was observed. The reversal of the methoxyflurane tension depression produced by pyruvate and fructose was even less complete, however, than that seen with halothane. In human atrial appendages obtained from patients during cardiopulmonary bypass, developed tension was markedly increased by pyruvate alone in the absence of anesthetics. As in human atria exposed to halothane, pyruvate completely reversed the tension depression produced by methoxyflurane. In contrast, only a small increment in pentobarbital-depressed tension was produced by pyruvate.

Most recently, Morrow and Paradise reported...
decreases in rat atrial $^{14}$C-labeled glucose uptake without change in pyruvate or fructose uptake by low halothane doses (0.25–1.0 mM). Higher concentrations (1.0–2.0 mM) decreased uptake of all three substrates, confirming the observations that the isolated glycolytic block was produced by the low anesthetic doses.

The conclusions from the above studies were that halothane and methoxyflurane decrease atrial developed tension by a block in glycolysis before the PFK-catalyzed conversion of fructose-6-phosphate to fructose-1,6-diphosphate, but that pentobarbital has a different mode of action. The doses of the volatile anesthetics producing this effect were considerably lower than the concentrations producing negative inotropic responses in vitro. In atria where endogenous lipids were a significant fuel, the effect disappeared and higher anesthetic doses were needed for depression of contractility. The differences between the substrate effects in rat and human atria observed in these studies might be expected, but one wonders how “normal” these hearts from patients on cardiopulmonary bypass were and whether this also influenced the results. Other investigators have not been able to demonstrate a positive inotropic effect of either pyruvate in halothane-depressed cat papillary muscle or acetate in halothane-depressed dog hearts in situ. Thus, the relevance of the nicely demonstrated correlation between metabolism and function in rat and human atria remains puzzling.

At about the same time, our laboratory was working with intact closed-chest dogs. The left ventricle, aorta, right atrium and great cardiac vein were catheterized fluoroscopically. Temperature, hydration and ventilation were maintained constant during MAC and 2–3 MAC halothane anesthesia. Myocardial NEFA uptake decreased significantly with the negative inotropic effect of the high halothane concentration. There was no appreciable myocardial glucose uptake until the arterial concentration reached 100 mg/100 ml in spite of the previously-demonstrated myocardial threshold in the dog (and man) of 60 mg/100 ml. The decrease in glucose uptake appeared to be greater in the depressed hearts. Lactate was utilized and uptake was well maintained in the depressed hearts, while pyruvate uptake declined. The effects of higher arterial glucose levels (213–363 mg/100 ml) on myocardial glucose uptake demonstrated that uptake did not follow arterial levels, as in the normal dog, but resembled uptake in the diabetic dog. Plasma immunoreactive insulin (IRI) levels during halothane anesthesia did not follow blood glucose levels, and were lower during anesthesia than before anesthesia in a different group of dogs (unpublished data). Finally, glucagon-free insulin produced a positive inotropic effect and increased glucose uptake in the halothane-depressed heart in our intact dog preparation (fig. 10). As reported above, insulin’s primary action in the heart is to stimulate transcellular glucose transport. At this point in the experiments of Paradise and Ko, membrane glucose transport (fig. 9, A) was still a likely site for the glycolytic block produced by halothane in rat atria. Consequently, the effect of halothane in both studies might be to impede membrane transport of glucose. Our low IRI levels combined with the observation of a diabetic glucose-tolerance curve induced by halothane in the dog suggest that a decrease in the pancreatic insulin response to glucose might be responsible for our findings. This blunted insulin response has been confirmed in man with halothane and methoxyflurane.

As mentioned previously, methoxyflurane produced hemodynamic changes similar to those produced by halothane in our dog model. Arterial concentration and myocardial uptake of fatty acids decreased during methoxyflurane-induced cardiac depression, as did uptake of both pyruvate and lactate. Although there was little glucose uptake in either control or depressed hearts, arterial levels were in the low range where minimal uptake might be expected. However, plasma IRI levels were very low during methoxyflurane anesthesia (unpublished data), so that decreased transcellular glucose transport remains a possible mechanism (as with halothane). The effect of insulin on the methoxyflurane depressed heart has not been tested, however.

As Paradise has pointed out, the block in the hexose isomerase step of glycolysis (fig. 9, C) should have been present in our
control animals anesthetized with MAC anesthesia. Thus, this metabolic defect cannot be responsible for the dose-dependent negative inotropic effect of anesthetics, for the block in glycolysis is virtually complete at in-vivo anesthetic concentrations which produce little if any myocardial depression. In addition, only half of the tension reduction produced by anesthetics in the rat atria or less could be reversed by substrates (the human atria behaved differently with pyruvate only). Insulin also produced less than 50 per cent reversal in the intact dog. If interference in glycolytic metabolism by anesthetics is important in the in-vivo clinical situation, the myocardial fuel source must be predominantly glucose. (Although glycogenolysis could also be interrupted, myocardial glycogen stores are rapidly exhausted in the working heart.) There are two major circumstances which favor the use of glucose as the primary energy source in the heart: high arterial levels of glucose (accompanied by appropriate insulin secretion) and hypoxia (see above). Although infusions of glucose commonly accompany surgical anesthesia, there is abundant evidence that insulin levels are low and NEFA levels are high under these conditions. Consequently, a shift to carbohydrate predominance seems unlikely. Hopefully, myocardial hypoxia during surgical anesthesia is rare. As mentioned above, the halothane- and methoxyflurane-depressed dog heart seemed to be well oxygenated. It is possible, however, that the dependence of stimulated rat atrial strips on glucose reflected a relative hypoxia. Brown and co-workers were able to observe light-microscopic changes indicative of poor perfusion of rat ventricle strips and atrial strips more than 16–20 cells wide. Intrinsic contractility and oxygen uptake of the rat heart are considerably greater than in larger mammals. Rat-heart-muscle preparations are very prone to diffusion hypoxia. The rapid rate of stimulation of the rat atrial preparation (300/min) could well lead to hypoxia of the inner core of the muscle and the predominance of anaerobic glycolysis. However, there must be well-oxygenated portions in the outer layers for the pyruvate, lactate, and acetate to liberate energy aerobically and reverse the depression. Recall that any process decreasing TCA cycle activity will also stimulate glycolysis. It may well be that some of the effects of anesthetics on oxidative metabolism...
to be discussed later could contribute to a shift to glycolytic predominance.

The major advantage of the use of myocardial A-V differences in the intact animal is the minimal derangement in physiology produced (compared with perfused hearts, etc.). This advantage is largely lost when an acute experiment using thoracotomy for catheter placement is used. If metabolism and function are to be correlated, both must be measured. In the other published works on the effects of halothane and methoxyflurane on myocardial substrate uptake in the dog, no measure of cardiac function was made. The preparation was an acute thoracotomy without temperature, acid-base, or anesthetic dose measurements. No estimate of coronary blood flow was made. Consequently, it is impossible to correlate the findings in any meaningful fashion.

**Fluroxene and Diethyl Ether**

The hemodynamic effects of high concentrations of halothane and methoxyflurane in the intact dog are similar and resemble those of halothane in man. The cardiovascular effects of fluroxene have recently been shown to be quite different in man, however. Cardiac output and myocardial function remained stable at 3-4 MAC. As mentioned before, Skovsted and Price reported that the drug behaved like diethyl ether and cyclopropane in the cat, causing increased sympathetic nervous activity. As the explosion hazard is less than with cyclopropane or diethyl ether, we chose to study fluroxene as a representative of the non-cardiac-depressant, sympathomimetic anesthetics in our dog model. To our surprise the hemodynamic effects were entirely similar to those seen with halothane and methoxyflurane (fig. 11). Unlike the latter drugs, fluroxene produced significant metabolic acidosis in our dogs at both MAC (6.5 per cent) and 2-3 MAC (13.8 per cent) (fig. 12). Although it appeared that much of the acidosis was lactic in origin (fig. 13), there was no difference in arterial lactate levels between the animals anesthetized with 73 per cent nitrous oxide and those anesthetized with low concentrations of fluroxene, although MAC fluroxene produced significant metabolic acidosis compared with nitrous oxide (unpublished data). Of the arterial substrate changes between the low and high fluroxene concentrations, only glucose was statistically insignificant (fig. 13). The most striking aspect of the myocardial A-V differences seen with fluroxene was the low extraction of all substrates (table 3). As with halothane, even with high arterial glucose levels there was virtually no
glucose uptake. Negative A-V differences for the other three substrates were seen for the first time in our laboratory with fluroxene. It is tempting to ascribe these effects to sympathetic stimulation. We saw no cardiovascular evidence of such stimulation, however. In addition, fatty-acid levels were not increased by fluroxene in this study, and, in fact, were decreased by higher concentrations. Consequently, we have no objective evidence of sympathetic stimulation in the dog by fluroxene. It is difficult to attribute the high coronary venous pyruvate and lactate levels to increased glycolysis in the face of little or no glucose uptake. This study points up the speculations that are necessary to explain changes in myocardial metabolism on the basis of myocardial A-V differences without more explicit data on concentrations of the metabolic intermediates. One conclusion appears certain, however. There is a marked difference between the myocardial metabolic effects of fluroxene and halothane in the dog.

The pioneering study of Galla et al. on the effects of diethyl ether on myocardial substrate utilization in the dog demonstrated a shift in myocardial extraction from predominantly lipid in the awake fasting animal to predominantly carbohydrate during ether anesthesia.\textsuperscript{255} This was primarily a function of substrate availability, as glucose, lactate and pyruvate arterial levels increased markedly, while NEFA concentrations decreased. No measurements of myocardial blood flow, body temperature, pH, or blood gases were reported. Only animals in which mean aortic blood pressure exceeded

![Graph of acid-base values with MAC (6.5 per cent) and 2-3 MAC (13.8 per cent) fluroxene.]

![Graph of arterial substrate concentration with MAC (6.5 per cent) and 2-3 MAC (13.8 per cent) fluroxene.]

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Fig. 12. Acid-base values with MAC (6.5 per cent) and 2-3 MAC (13.8 per cent) fluroxene.

Fig. 13. Arterial substrate concentration with MAC (6.5 per cent) and 2-3 MAC (13.8 per cent) fluroxene.
100 torr were used, and no estimate of myocardial function was made. Consequently the significance of the study to mechanisms of anesthetic myocardial depression is questionable.

Miscellaneous

Measurement of myocardial A-V oxygen and substrate extraction remains the major method of estimating the effects of various interventions on myocardial metabolism in man, although it suffers from the same limitations as in lower animals. More and co-workers have extensively studied patients undergoing open-heart surgery using this method. The authors did not report data from either unanesthetized patients or anesthetized patients not subjected to operation, so no information about the effects of anesthetics alone is available. It is interesting that the insulin response to the massive hyperglycemia produced by the pump prime and the lesser hyperglycemia in the postoperative period was less than might have been predicted. There was suggestive evidence that insulin administration might have improved postoperative cardiac function in association with decreasing ketosis.

Several anesthetics, including chloralose, urethane, diethyl ether, and chloroform, have been reported to have no consistent effect on rat-heart glycogen content. The concentrations of gaseous anesthetics were completely uncontrolled, however, so it is difficult to draw conclusions from the study.

Brown and Crout have suggested that interference in energy liberation could not be an important feature in the negative inotropic effects of anesthetics because they could see papillary muscle depression by anesthetics after pharmacologic blockade of all energy-liberating pathways. Conclusions drawn from these "poisoned" papillary muscles are somewhat suspect. Although it is probable that the basic mechanism of the negative inotropic effect of anesthetics is not an interference in energy liberation, available evidence is not sufficient to prove or disprove this possibility. Radioactive tracer studies of carbohydrates and lipids in both perfused and in situ hearts correlated with evidence of functional depression by anesthetics are necessary. If, indeed, energy liberation is involved, then the energy stores of the heart should be depleted. Tissue levels of ATP and CP must

<table>
<thead>
<tr>
<th>Table 3. Myocardial Substrate Metabolism</th>
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<tbody>
<tr>
<td>Fluroxene, Alveolar</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>MAC 6.5 Per Cent</strong></td>
</tr>
<tr>
<td><strong>MAC 13.6 Per Cent</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
</tr>
<tr>
<td>Arterial (mg/100 ml)</td>
</tr>
<tr>
<td>$A-V$ (mg/100 ml)</td>
</tr>
<tr>
<td>Uptake (mg/100 g/min)</td>
</tr>
<tr>
<td><strong>103 ± 11</strong></td>
</tr>
<tr>
<td><strong>-4.3 ± 2.9 (6/9 neg)</strong></td>
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<tr>
<td><strong>-2.17 ± 1.66</strong></td>
</tr>
<tr>
<td><strong>161 ± 32</strong></td>
</tr>
<tr>
<td><strong>14.4 ± 21.4 (7/9 neg)</strong></td>
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<tr>
<td><strong>5.51 ± 7.7</strong></td>
</tr>
<tr>
<td><strong>Non esterified fatty acids</strong></td>
</tr>
<tr>
<td>Arterial ($\mu$Eq/l)</td>
</tr>
<tr>
<td>$A-V$ ($\mu$Eq)</td>
</tr>
<tr>
<td>Uptake ($\mu$Eq/100 g/min)</td>
</tr>
<tr>
<td><strong>492 ± 54</strong></td>
</tr>
<tr>
<td><strong>53.4 ± 26 (2/8 neg)</strong></td>
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<tr>
<td><strong>2.39 ± 1.8</strong></td>
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<tr>
<td><strong>159 ± 29</strong></td>
</tr>
<tr>
<td><strong>14 ± 6.4 (2/8 neg)</strong></td>
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<tr>
<td><strong>0.44 ± .21</strong></td>
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<tr>
<td><strong>Lactate</strong></td>
</tr>
<tr>
<td>Arterial (mg/100 ml)</td>
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<tr>
<td>$A-V$ (mg/100 ml)</td>
</tr>
<tr>
<td>Uptake (mg/100 g/min)</td>
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<tr>
<td><strong>22.0 ± 3.3</strong></td>
</tr>
<tr>
<td><strong>3.12 ± 1.6 (2/9 neg)</strong></td>
</tr>
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<td><strong>1.47 ± 0.77</strong></td>
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<td><strong>41.3 ± 0.3</strong></td>
</tr>
<tr>
<td><strong>0.96 ± 1.8 (3/9 neg)</strong></td>
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<tr>
<td><strong>0.20 ± 0.56</strong></td>
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<tr>
<td><strong>Pyruvate</strong></td>
</tr>
<tr>
<td>Arterial (mg/100 ml)</td>
</tr>
<tr>
<td>$A-V$ (mg/100 ml)</td>
</tr>
<tr>
<td>Uptake (mg/100 g/min)</td>
</tr>
<tr>
<td><strong>1.1 ± 0.17</strong></td>
</tr>
<tr>
<td><strong>0.16 ± 0.20 (2/9 neg)</strong></td>
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<tr>
<td><strong>0.09 ± 0.11</strong></td>
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<tr>
<td><strong>1.76 ± 0.20</strong></td>
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<tr>
<td><strong>0.27 ± 0.12 (2/9 neg)</strong></td>
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<tr>
<td><strong>0.11 ± 0.04</strong></td>
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* $P < 0.05.$
also be measured and correlated with the decreased contractility (see below).

**Energy Conservation**

**Mitochondrial Metabolism**

For more detail on this subject, the reader should consult the review in the Symposium devoted to oxidative phosphorylation. I will briefly review some aspects which I feel are pertinent to the anesthetic effects which have been reported to occur in the heart. As the heart is an aerobic organ and oxidation of substrates takes place within the mitochondria, the mitochondria would be a likely locus for drug effects. Some aspects of mitochondrial metabolism have been discussed above, as TCA cycle activity is located in the organelle. Specific studies of mitochondrial function usually focus on changes in oxygen consumption. One of the TCA cycle intermediates is introduced into the medium containing the mitochondrial preparation, and oxygen uptake is measured. The addition of ADP activates the high-energy phosphorylation mechanism and oxygen uptake accelerates markedly (state 3). Decrease in state 3 oxygen consumption indicates interference with the electron-transfer chain. The location of such a block can be deduced by using different TCA cycle intermediates as substrates (fig. 6A). If the inhibition is before the cytochrome system, oxygen uptake using succinate as a substrate will not be affected, while the glutamate, beta-hydroxybutyrate, etc., oxygen uptake will be decreased. In a like fashion, by using substances known to affect specific enzymes in the transport chain (e.g., rotenone), the locus of action of a drug can be more precisely identified. When TCA substrates are added in the absence of ADP, oxygen uptake is slow (state 4). Increase in oxygen uptake during state 4 mitochondrial respiration is indicative of loss of respiratory control (or uncoupling). Either a block in the electron-transport chain or uncoupling can interfere with the conservation of energy as high-energy phosphates. Another aspect of mitochondrial function which may be related to cardiac metabolism and function is the active transport of cations by the mitochondrial membrane. The physiologic import of cation transport may relate to control of transcellular flux, intracellular compartmentalization, or metabolism. The importance of compartmentalization of calcium in myocardial function is well established. The effect of anesthetics is considered in detail in the discussion of energy utilization.

**High-energy Phosphates**

The energy liberated from the fuels discussed in the previous sections is conserved (stored) as high-energy phosphate compounds. In muscle, ATP and CP are the predominate storage forms (fig. 14) and exist in a reversible equilibrium. Energy derived from glycolysis and oxidation is transferred to the high-energy phosphate bond of ATP. Hydrolysis of ATP by an ATPase enzyme frees the energy for use in contraction–relaxation, metabolism, etc. CP serves as a reservoir for the high-energy phosphate, replenishing the ATP, which is the direct source of energy during muscular activity. Consequently, ATP levels vary minimally and CP levels are more labile in heart muscle. The enzyme creatine phosphokinase (CPK) catalyzes rephosphorylation of ADP to ATP via CP (fig. 14). The ADP produced by energy release
in muscle can also replenish ATP without further supply from the mitochondrial transport system through myokinase (fig. 14). This enzyme appears to be activated by rather large decreases in ATP, which do not occur in cardiac muscle under normal conditions.\textsuperscript{109,122} Consequently, this system functions only during very low energy availability states. From figure 14 it is apparent that the relationship between ATP synthesis from the heart’s energy sources and ATP hydrolysis by the ATPases will determine the level of ATP and CP in the heart. If there is interference with synthesis (hypoxia, a block in energy liberation or conservation), and if ATPase activity is not affected, ATP and CP concentrations decrease. If ATPase activity is depressed without a change in ATP synthesis, ATP and CP concentrations rise. Either event can result in decreased myocardial contractility, although there is evidence that the heart can function satisfactorily with a 50 per cent reduction in high-energy phosphate stores.\textsuperscript{11}

**Effect of Anesthetics**

To date there have been only two publications of the effects of anesthetics on cardiac mitochondria. Taylor and co-workers reported the effects of halothane on conformational changes in beef-heart mitochondria.\textsuperscript{124} They hypothesized that the electron-microscopic picture of the mitochondrial membrane indicates the energy state of the mitochondrion.\textsuperscript{125} Halothane induced beef-heart mitochondria to assume an orthodox non-energized structure seen when mitochondrial oxygen uptake is uncoupled from high-energy phosphate production. Close to 100 per cent of the mitochondria were “uncoupled” with 4 per cent halothane, and the proportion of mitochondria in this state decreased as the halothane dose was lowered. It should be noted, however, that there is controversy as to the validity of the relationship of mitochondrial structure and energy state.\textsuperscript{126} Harris et al. noted that halothane reversibly depressed NAD-linked electron transport (fig. 6A) in beef-heart mitochondria in a dose-dependent manner.\textsuperscript{127} With succinate as a substrate there was minimal depression at equivalent concentrations. Uncoupling was not seen until very high concentrations (>2 mM) of anesthetic were used, and it was irreversible. The same workers reported similar findings with methoxyflurane, fluoroxyne, chloroform, and diethyl ether, although the latter two depressed succinate-linked respiration as well. (The authors did not specify whether these studies were carried out in beef-heart or rat-liver mitochondria.) It is interesting that the same findings were reported for halothane and methoxyflurane in mitochondria from rat skeletal muscle, although the proportions of red and white muscle studied were not specified.\textsuperscript{128} Miller also noted inhibition of NADH-linked mitochondrial electron transport in pigeon, rabbit, beef, and rat hearts by halothane, methoxyflurane, and chloroform, with minimal effects on non-
NADH-linked succinate respiration. Unlike Harris, he found no effect of fluroxene on the NADH-linked electron-transport system, although Nahrwald and Cohen showed a dose-related depression of state 3 oxygen uptake by fluroxene in rat-liver mitochondria.

If the effects of anesthetics on electron transfer and oxidative phosphorylation are related to the negative inotropic effect of anesthetics, the levels of ATP and CP in cardiac muscle would be expected to be decreased (if ATPase activity remains unchanged). The only documentation of these levels, to my knowledge, has been in a study of rat hearts. ATP and ADP levels were unchanged by diethyl ether and halothane. High concentrations of ether decreased CP levels, but no data on CP were reported for halothane. Unfortunately, anesthetic dose was poorly controlled and not measured. Respiratory acidosis undoubtedly occurred with the higher anesthetic doses. The “quick-freeze” technique was not employed for the measurement of the high-energy phosphates, so the values are suspect.

In summary, it appears that inhalation anesthetics do interfere with NADH-linked oxidative phosphorylation in the heart but affect succinate-mediated, non-NADH-linked mechanisms minimally. The mechanistic significance of this remains to be determined.

Energy Utilization

The precise way in which cardiac muscle uses the energy liberated and stored is not fully understood. Again, much of the basic work has been done in skeletal muscle and carried over to cardiac muscle, although there are substantial functional and metabolic differences. There can be little doubt that the process of contraction of all muscle involves the making of “cross bridges” between the actin thin filaments and the myosin thick filaments according to the Husleys’ sliding-filament theories. A detailed discussion of the mechanochemistry of cardiac contraction is beyond the scope of this paper.

Contractile Proteins

During diastole, the filamentous contractile proteins, actin and myosin, are dissociated.

Fig. 16. Schematic representation of actin-tropomyosin–tropinin complex (from Katz, with permission of author and publisher).
The current postulate holds that the regulator proteins, troponin and tropomyosin, are responsible for this inhibition of the actin-myosin cross-bridge formation (fig. 15). Tropomyosin is a long, rod-like protein wound around the actin alpha helix in the opposing grooves (fig. 16). It serves as a framework for the active component of the complex, troponin, and probably participates passively in the cross-bridge inhibition. Troponin is bound to tropomyosin every 400 angstroms along the helix. This active protein has several components, whose structure and function are not entirely clear. Schematically, they may be equated to tropomyosin binding, calcium sensitivity, and cross-bridge inhibition (fig. 17). During diastole, the sarcoplasmic calcium ion concentration is very low (<10⁻⁷ M) and the troponin–tropomyosin complex inhibits cross-bridge formation (fig. 18). As systole develops, calcium ion concentration rises to a maximum of 10⁻⁵ M at the time of greatest muscle shortening (fig. 19). The calcium ions are bound to the troponin–tropomyosin complex, releasing the inhibition of cross-bridge formation, and the myosin head attaches to the actin binding site, pulling the filaments toward the middle of the sarcomere (shortening). The ATPase necessary for the hydrolysis of the conserved high-energy phosphate is thought to lie on the myosin head (fig. 17). The activity of myosin ATPase is markedly increased by the actin–myosin association and by the increase in calcium ion concentration. This activation leads to splitting of the Mg-bound ATP to ADP and Pi. Relaxation (dissociation of the actomyosin cross-bridge) is promoted by a rapid decrease in sarcoplasmic calcium ion, with calcium release from the troponin and inhibition of cross-bridge formation again (fig. 20).

**Calcium**

As oxygen is necessary for TCA-cycle activity, so calcium is essential for the muscle contraction–relaxation cycle. There is little doubt that the link between sarcolemmal electrical depolarization and the formation of the actomyosin cross-bridges is dependent on calcium through the transverse sarcotubules and the longitudinal sarcoplasmic reticulum (SR) (fig. 21). In skeletal muscle, the source of the sarcoplasmic calcium increase in systole
and the reservoir to which it returns during diastole is this SR.\textsuperscript{190} There is still some controversy about whether the same can be said for cardiac muscle.\textsuperscript{191} Skeletal muscle can contract quite nicely in a calcium-free medium, recycling the intracellular calcium, but cardiac muscle is dependent on extracellular calcium for continuing contractility.\textsuperscript{192} The sarcoplasmic reticulum in skeletal muscle is more highly developed, has a higher calcium capacity, and is more intimately associated with the myofibrils than that in cardiac muscle (fig. 21).\textsuperscript{191} As noted previously, cardiac-muscle mitochondria are more numerous and more closely applied to the myofibrils than those in skeletal muscle. Cardiac mitochondria possess the requisite calcium-accumulating ability to clear the sarcoplasm of calcium during diastole, so they could participate in calcium compartmentalization during relaxation.\textsuperscript{192, 193} However, the bulk of the evidence at present suggests that the SR is the major calcium-accumulating mechanism in normal function.\textsuperscript{194–196} The origin of the activating calcium in systole still has not been positively identified in the heart,\textsuperscript{197} although the SR is the prime candidate.\textsuperscript{187, 192, 194} Chidsey’s scheme of calcium movement in the myocardium is probably as good a conception as we have (fig. 22).\textsuperscript{195} In the normal heart at rest, calcium is present in the extracellular fluid, the SR, and the mitochondria, but not in the sarcoplasm. Membrane excitation increases calcium permeability, and extracellular calcium influxes. This calcium triggers the release of a different intracellular calcium pool (probably from the SR), actin–myosin cross-bridging occurs, and the sarcomere shortens. At the beginning of relaxation (diastole), calcium is rapidly removed from the sarcoplasm, probably into the SR, but possibly into another site (mitochondria), cross-bridging is inhibited, the sarcomere returns to resting length, and the cycle recurs. Whatever the ultimate calcium compartmentalization turns out to be, there seems to be little question that sarclemmal calcium transport plays a more important role in excitation–contraction coupling in cardiac than in skeletal muscle.\textsuperscript{196}

The active clearance of the sarcoplasmic calcium during early diastole is energy dependent.\textsuperscript{192} ATP hydrolysis, catalyzed by calcium-dependent ATPases, fuels the calcium-pumping of both the SR and mitochondria. So calcium mediates excitation–contraction coupling, removes the troponin–tropomyosin
inhibition of actomyosin cross-bridge formation, and activates the ATPases involved in energy utilization for the cross-bridge reaction and the active processes involved in relaxation.

**(Acto)myosin ATPase**

In excess of 70 per cent of the total cardiac energy utilization is concerned with the work done and tensions developed by the contractile proteins. Consequently, the ATPase activity of these proteins is a major determinant of energy utilization. The ATPase activity appears to be a basic property of myosin. Actin has no physiologically important activity. Barany has demonstrated that myosin ATPase activity is directly related to the maximum shortening velocity of many types of muscles from a variety of animals, including the very slow ileofibularis of the tortoise, the intermediate cat soleus and rat soleus, and the very rapid mouse extensor digitorum longus. Cardiac myosin falls in the slower group of red muscles. The calcium sensitivity of cardiac myosin ATPase is probably conferred by the tropomyosin–troponin complex, as it is not present in myosin ATPase or deactivated (without tropomyosin and troponin) actomyosin. Consequently, the physiologically active, calcium-regulated ATPase is the associated actomyosin form. Decrease in this activity could impair the energy utilized for the contraction–relaxation cycle and decrease contractility.

**Effect of Anesthetics**

Although there have been three studies of the effects of anesthetics on (acto)-myosin ATPase, for various reasons the results cannot be considered definitive. Luchi and Kritcher administered nitrous oxide (probably in hypoxic concentrations), diethyl ether, and cyclopropane to dogs, excited the hearts, and measured myosin ATPase activity. They found no change, but during the prolonged extraction of the protein, it is likely that the drug effects were lost, particularly considering that these are gaseous anesthetics. In addition, they were measuring myosin ATPase rather than the actomyosin enzyme, so they could not characterize the effects of the anesthetics on calcium sensitivity, which may be important in drug mechanisms. Brodkin et al. looked at actomyosin ATPase activity of rat-heart muscle as influenced by halothane. They dosed the protein in vitro, but neither mentioned the partition problem nor measured the drug concentration, so their dose calculations are suspect. The calcium-concentration effect was not tested, and, in fact, was not considered, for they did not buffer calcium in their reaction mixture. In addition, there was probably some contaminant mitochondrial ATPase activity. They needed large doses of halothane (40–100 mM) to see a decrease in ATPase activity, so, aside from the problems in technique, the pharmacologic significance of their findings is doubtful. Although Cormack and Craythorne demonstrated a dose-dependent decrease in cardiac myofibrillar ATPase from cat hearts by methoxyflurane, they did not consider the effect of calcium either. They documented significant mitochondrial ATPase contamination in their preparation (27 per cent). Their reported methoxyflurane concentrations were high (10–40 mM), and they did not consider the partition problem in dosing. There has been no satisfactory documentation of the effects of anesthetics (particularly those with negative inotropic effects) on actomyosin ATPase, the enzyme governing most of the energy utilization during cardiac contraction.

Lain et al. studied the effects of chloroform, halothane, diethyl ether and pentobarbital on one of the enzymes thought to control cardiac relaxation, the sarcoplasmic reticulum (SR) ATPase. They also measured SR calcium uptake. Partition factors were considered in calculating dose, but the partition coefficients for their reaction mixtures were not measured, nor was anesthetic concentration. Chloroform and halothane decreased SR calcium uptake and ATPase activity in a dose-dependent manner. The halothane effect was not seen until concentrations higher than those shown to produce depressed contractility (from other investigators’ work) were reached, whereas the concentration ranges for depression of both contraction and calcium uptake were similar for chloroform. Diethyl ether had no effect at concentrations which depressed contractility by 80 per cent in a heart–lung preparation (again, reported by other investigators). The decrease in calcium uptake produced by chloro-
form and halothane was clearly related to decreased SR ATPase activity. Pentobarbital, on the other hand, uncoupled ATP hydrolysis from calcium uptake. Although calcium uptake was decreased by increasing doses of pentobarbital, ATPase activity actually increased slightly. Thus, the higher the pentobarbital dose, the more ATP had to be split per unit of calcium taken up by the SR. The same group of investigators also reported that amobarbital decreased calcium uptake by increasing calcium binding by SR membrane phospholipids. This could be reversed by ouabain without affecting ATPase activity.
Nayler and Szeto confirmed Lain’s and Hess’ findings and, in addition, suggested that pentobarbital altered sarcolemmal membrane distribution of calcium. Although there have been no more studies of anesthetic effects on cardiac SR, it is of interest that halothane and diethyl ether have been shown to decrease skeletal muscle SR calcium uptake in a dose-dependent manner. Halothane also decreased ATPase activity. Although diethyl ether stimulated SR ATPase activity, this action was attributed to increase in calcium ion concentration in the reaction mixture, rather than to a direct effect of the anesthetic. Lain and Nayler postulated that decreased calcium uptake during diastole in the SR would result in a smaller pool available for release during systole. Although this mechanism may be valid in skeletal muscle, in view of the lack of knowledge concerning the source of the rapid rise in sarcoplasmic calcium during systole in cardiac muscle, such a mechanism is purely speculative.

Haugard and co-workers hypothesized along the same line in regard to the mitochondria. They had noted that oligomycin decreased mitochondrial calcium uptake and retarded relaxation in rat hearts. Miller and Hunter reported that halothane, methoxyflurane, and chloroform markedly inhibited calcium uptake by mitochondria from pigeon and beef hearts in association with the depression of NADH-linked electron transport. Fluroxene depressed neither electron transport nor calcium uptake by the mitochondria. The in-citro studies demonstrating direct myocardial depression by all inhalation anesthetics did not include fluroxene, although it has been assumed that the drug behaves like diethyl ether and cyclopropane (which were tested). Sohn et al. reported that fluroxene, like other anesthetics, depressed peak developed tension in rat trabeculae carneae in a similar dose-dependent fashion. Maximum shortening velocity (Vmax) was maintained until very high drug doses were reached, however. Fluroxene appeared to depress the intact dog heart (see above), but no direct measure of contractility was made. Miller hypothesized that the inhibition of calcium uptake in cardiac mitochondria by drugs which produced myocardial depression in intact animals and man suggested a mechanistic connection. If, indeed, fluroxene does not produce direct myocardial depression, then the lack of inhibition of myocardial calcium uptake by fluroxene strengthens this hypothesis. Whether or not fluroxene has a direct action on myocardial contractility different than that of the other anesthetics, coupling the effects on mitochondrial calcium transport and contractility would mean that the mitochondria play an important role in decreasing the sarcoplasmic calcium concentration during diastole and increasing it during systole. The current weight of evidence suggests that SR is more likely to be involved in the calcium...
kinetics of the normal contraction-relaxation cycle.

Malsch et al.\textsuperscript{211} and Price and Davidson\textsuperscript{212} have demonstrated the importance of extracellular calcium ion concentration in the negative inotropic effect of halothane on kitten papillary muscle. Malsch's group also reported that relaxation was prolonged during halothane washout, although others have failed to note an effect of halothane on relaxation.\textsuperscript{212} If anesthetics did affect SR (or mitochondrial) calcium uptake, then relaxation should be interfered with, inasmuch as this would be the mechanism most likely to be governed by this activity. Price's work merely states that the mechanism(s) by which halothane depresses contractile force is calcium dependent, and allows no further speculation about intracellular events.

Thus, there is suggestive evidence that inhalation anesthetics can affect ATPase activity of the calcium-accumulating sarcoplasmic reticulum and mitochondria in heart muscle. The significance of this in relation to the negative inotropic effect must remain obscure until the kinetics of the calcium flux in the contraction-relaxation cycle is defined. There is no valid information about the effect of anesthetics on the ATPase activity of the contractile proteins.

Overview

Inasmuch as myocardial metabolism has been reviewed in the framework of energy liberation, conservation and utilization, it may be helpful to consider where the most likely loci for the effects of inhalation anesthetics may be. Olson\textsuperscript{214} and Fleckenstein\textsuperscript{215} have proposed that heart failure, whether spontaneous (pathologic) or induced (pharmacologic, as with anesthetics), occurs from a defect in energy supply (liberation or conservation) or utilization.

Supply

Factors resulting in an insufficient supply of the cardiac muscle energy sources ATP and CP include: 1) defective oxygen delivery from a) arterial hypoxemia, b) ischemia or c) interferences with transport (carbon monoxide); 2) chemicals which interfere with oxidative and glycolytic phosphorylation (cyanide, 2,4-dinitrophenol, fluoroacetate).\textsuperscript{215} 1a) Arterial hypoxia does not play a role in the negative inotropic effect of anesthetics. 1b) Although anesthetics have not been demonstrated to interfere primarily with oxygen transport, an effect on oxyhemoglobin dissociation has not been ruled out. 1c) There is increasing evidence that myocardial-tissue oxygen delivery may depend more on capillary distribution than on coronary blood flow.\textsuperscript{216,217} We have no information about the effect of anesthetics on the cardiac precapillary sphincters which control capillary distribution. 2) Anesthetics can uncouple oxidative phosphorylation, but only at high concentrations, and irreversibly. The reversible partial inhibition of cardiac mitochondrial electron transport associated with anesthetics has not been shown to have a functional effect. If mitochondrial depression interfered with NEFA oxidation, however, then during anesthesia the heart would depend on glycolysis for energy liberation.\textsuperscript{77} In consequence, the interference in glycolysis demonstrated by Paradise and co-workers\textsuperscript{129-141} and the block in transcellular glucose transport suggested by our laboratory\textsuperscript{143} might prove to be important. More precise studies of the latter effects using radioactive tracers are necessary. Definitive investigation of the effects of anesthetics on lipid metabolism is also needed. As an example, inhibition of NEFA oxidation in pathologic failure of guinea-pig hearts has been shown to result from a defect in carnitine (thus interfering with mitochondrial fatty-acid-CoA transport).\textsuperscript{218} Such studies should be done with anesthetics. Decreases in tissue concentrations of CP and possibly ATP and increases in ADP and P\textsubscript{i} should also be documented, for confirmation of a defect in energy supply.

Utilization

Fleckenstein maintained that defects in energy utilization in heart failure involved interference with calcium metabolism.\textsuperscript{215} His criteria for such a statement included: 1) a negative inotropic effect manifested by decreased isometric tension in vitro and decreased stroke volume in vivo coupled with increased diastolic volume; 2) no impairment of membrane electrical activity; 3) decreased myocardial oxygen demand; 4) complete and
rapid reversal of all other signs by exogenous calcium; 5) normal or increased myocardial high-energy phosphate content. He documented all of these for several barbiturates and beta-adrenergic antagonists. The positive inotropic effect of digitalis glycosides and catecholamines in these depressed hearts was attributed to calcium release, which seems a likely possibility.\textsuperscript{194,219} All of these criteria have been at least suggested for inhalation anesthetics except the high-energy phosphate content. However, it is interesting to recall that when inhalation anesthetics and barbiturates have been tested in the same system (atrial glycolysis\textsuperscript{125} and SR calcium uptake\textsuperscript{203}), the metabolic effects have been different. Although the negative inotropic effect of inhalation anesthetics may well involve an effect on calcium fluxes in heart muscle, at the present time, calcium seems to be implicated in almost any process one looks at. As in the case of oxygen, there is still no firm evidence as to cause and effect.

Defective lipid-facilitated membrane calcium transport has been suggested as a mechanism for the inotropic effects of various beta antagonists by Nayler's group.\textsuperscript{220} They failed to correlate inotropic effects with actomyosin ATPase activity in the same study. As was the case with the anesthetic investigations of actomyosin ATPase activity,\textsuperscript{200,201} no measure of calcium response was made. Honig and Reddy have shown that beta antagonists specifically shift the calcium response of actomyosin ATPase by affecting the troponin–troponyosin complex.\textsuperscript{221} As mentioned before, this is a possible site for anesthetic effects and needs to be investigated in proper fashion.

At the beginning and throughout this review, I have noted that the transfer of data from species to species, from \textit{in vitro} to \textit{in vivo}, and from skeletal muscle to cardiac muscle must be critically analyzed. I will end by citing a tantalizing bit of very preliminary evidence high-lighting these cautions. There can be no doubt that halothane produces a dose-dependent negative inotropic effect on cardiac muscle, \textit{in vitro} and \textit{in vivo}. Strobel (Strobel, G. E., personal communication) has noted in a very preliminary way that halothane produces a dose-dependent positive inotropic effect on frog skeletal muscle \textit{in vitro}. C'est la vie!

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