Mechanisms of Activation of Cardiac Glycogen Phosphorylase in Ischemia and Anoxia

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ABSTRACT

The effects of ischemia and anoxia on cardiac adenosine 3',5'-monophosphate (cyclic AMP) concentration, glycogen phosphorylase activity ratio (−5'-AMP: + 5'-AMP), phosphorylase kinase activity ratio (pH 6.8:8.2), and myocardial contractility (left ventricular dP/dt) were studied in an open-chest rat heart preparation. Ischemia produced by termination of coronary blood flow increased cyclic AMP from 0.55 to 0.77 μmoles/kg in 5 seconds and phosphorylase from 0.14 to 0.57 in 20 seconds. Anoxia induced by breathing N₂ increased cyclic AMP from 0.50 to 0.62 μmoles/kg in 10 seconds and phosphorylase from 0.14 to 0.65 in 30 seconds. Phosphorylase kinase increased with ischemia but did not change with anoxia. Beta-receptor blockade with practolol prevented the rise in cyclic AMP and phosphorylase kinase but blocked the increase in phosphorylase only in ischemia. Myocardial contractility declined precipitously during the first 20 seconds of anoxia. Epinephrine (0.1 μg/kg) caused an increase in cyclic AMP comparable to that elicited by anoxia, and it produced an increase in dP/dt during N₂ breathing. These results suggest that in the intact working heart ischemia induces phosphorylase a formation through a cyclic AMP-dependent transformation of phosphorylase kinase; however, in anoxia phosphorylase a formation depends only on the regulation of the catalytic activity of phosphorylase kinase without conversion of this enzyme to its activated form. An increase in cyclic AMP during anoxia is not associated with a positive inotropic response even though such a response is obtained with epinephrine. Factors other than the elevation of myocardial cyclic AMP may be limiting in the control of both cardiac glycogenolysis and inotropic state.

KEY WORDS adenosine 3',5'-monophosphate phosphorylase kinase practolol glycogenolysis contractility epinephrine rat heart

The activation of glycogenolysis that occurs with ischemia and anoxia in the myocardium results from an increase in glycogen phosphorylase activity (1-4). The increase in enzyme activity occurs very rapidly, within approximately 10 seconds, and appears to be largely due to the conversion of the enzyme from the b to the a form (4-6). Epinephrine elicits activation of cardiac phosphorylase by a sequence of reactions beginning with the production of adenosine 3',5'-monophosphate (cyclic AMP) through the activation of adenylate cyclase (7-9). The mechanism of action of cyclic AMP appears to be the activation of protein kinase (10). This enzyme catalyzes the adenosine triphosphate-dependent transformation of phosphorylase kinase to its activated form. Phosphorylase kinase catalyzes the phosphorylation of phosphorylase b, converting it to phosphorylase a. Thus amplification is achieved through a series of reactions that result in rapid and intense glycogen utilization.

Ischemia in the nonworking heart causes an increase in myocardial cyclic AMP concentration and a subsequent formation of phosphorylase a by the release of norepinephrine from cardiac stores (6). However, it is not known if this mechanism is the sole or the major one responsible for phosphorylase activation in the ischemic working heart, i.e., a heart in which the myocardium continues to develop tension while coronary flow is interrupted. Since anoxia-induced formation of phosphorylase a in the heart is only slightly reduced by pronethalol, a β-adrenergic antagonist (4), or reserpine (3), activation of phosphorylase by oxygen deprivation appears to involve only minimal adrenergic participation. The mechanisms responsible for the activation of glycogenolysis in the anoxic working heart are not known.
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The purpose of this investigation was to compare the effects of ischemia and anoxia on the formation of cyclic AMP and the transformation of phosphorylase to their activated forms in the intact rat heart developing tension in situ with the objective of demonstrating cyclic AMP-dependent and cyclic AMP-independent mechanisms controlling glycogenolysis. Since it has been hypothesized that cyclic AMP participates in the control of the inotropic state of the heart (11-13), we also sought to correlate changes in cyclic AMP concentration during anoxia with measurements of the inotropic state of the myocardium.

Methods

OPEN-CHEST HEART PREPARATION

Male albino Sprague-Dawley rats weighing 225-325 g were obtained from local suppliers and maintained on nonmedicated Purina chow ad libitum in rooms with a lighting sequence of 12 hours light and 12 hours dark. The rats were anesthetized with sodium pentobarbital (25 mg/kg, ip) and α-chloralose (50 mg/kg, ip). In addition all rats received atropine sulfate (1 mg/kg, ip) to suppress vagal responses in the heart. Body temperature was maintained at 37 ± 1°C. Aortic blood pressure was continuously recorded from a saline-filled cannula inserted in the left common carotid artery with a Statham P23Db strain-gauge manometer. The left jugular vein was cannulated for the administration of drugs.

Acute bilateral adrenalectomy was performed in all experiments to eliminate the influence of adrenal catecholamines. The chest was opened, and the rat was ventilated with 95% (X-5& 2CO2) with 5% O2 via a tracheal cannula with a Harvard respirator (model 673) at 80/min. Proper lung inflation was ensured by a side tube connected to the inspiratory cannula that was submerged in a 15-cm column of water. The beating hearts were frozen in situ by compressing them into thin (1-2 mm) wafers with silver clamps precooled in liquid nitrogen 0-120 seconds after the onset of either ischemia or anoxia (14).

Ischemia was introduced in the open-chest heart by techniques producing either a working or a nonworking preparation. In the working preparation the base of the heart was cross-clamped with a hemostat. This maneuver terminated coronary blood flow and maintained a constant ventricular volume by occluding ventricular inflow and outflow. Consequently, the myocardium continued to develop tension by contracting against a constant afterload. In the nonworking preparation the descending aorta and the inferior vena cava were severed cephalad to the diaphragm. Aortic pressure fell to zero within 2-3 seconds. Anoxia was produced without manipulation of afterload by substitution of the respiratory gas (95% O2-5% CO2) with 100% N2.

In several rats in which N2 breathing was introduced, arterial oxygen tension (P02) was recorded by a micro-oxygen electrode (IBC multi-purpose differential oxygen analyzer, model 145-071). The electrode was inserted into the aorta via a common carotid artery so that arterial blood flow was not restricted. The response of the electrode to changes in P02 was determined in saline bubbled with O2. When the P02 was changed abruptly from 300 to 1-2 mm Hg, the electrode recorded the change exponentially and required 15 seconds to indicate a decrease in P02 to 10 mm Hg.

In some open-chest preparations intraventricular pressures were recorded through an 18-gauge stainless steel cannula (1 cm in length) filled with heparinized degassed saline inserted through the cardiac apex into the left ventricle. The cannula and the pressure transducer (Pitran pressure transister, model PT22) had a frequency response of 250 Hz. Left ventricular dP/dt was derived from the peak intraventricular pressure signal by resistance-capacitance differentiation. All pressure and dP/dt data were recorded directly on magnetic tape at 15 ft/min (Hewlett-Packard magnetic recorder system, model 395S) and played back at 3.75 ft/min on a multichannel oscillograph (Sanborn series 7700 recorder).

ANALYTICAL PROCEDURES

Tissue Preparation and Extraction.—Cardiac muscle samples were stored at −65°C prior to analysis. The entire ventricles were finely powdered by percussion with a stainless steel mortar and pestle. The samples and the pulverization apparatus were previously cooled in liquid nitrogen. The powdered samples were transferred to screw-cap glass vials and stored at −65°C until they were assayed. Approximately 10 mg of the powdered muscle was weighed and transferred to a Duall homogenizing tube (size 20, Kontes Glass Co.) in a room at 20°C. Fifty to one hundred volumes (based on sample weight) of an ice-cold solution containing 20 mM K-Pi, 4 mM ethylenediaminetetraacetate, 20 mM β-glycerophosphate, and 20 mM β-mercaptoethanol (pH 6.8) was quickly added; the mixture was homogenized at 0°C. The homogenization was performed in 1-2 minutes with a motor driven pestle at a speed of 100-200 rpm. The homogenate was centrifuged at 3000 g for 20 minutes, and the supernatant fluid was assayed immediately for phosphorylase and phosphorylase kinase.

Another 35-40-mg portion of the powdered muscle was transferred to a Duall homogenizing tube (size 20); it was homogenized and extracted as described elsewhere (15) for assay of cyclic AMP.

Chemical Assays.—Glycogen phosphorylase was measured by the production of glucose-1-phosphate in the absence and the presence of 5’-AMP (16). One unit of phosphorylase is defined as the amount of enzyme that produces 1 μmole of glucose-1-phosphate from glycogen per minute at 30°C. The results were expressed as the ratio of phosphorylase activity without AMP to phosphorylase activity assayed with AMP. An increase in the ratio indicates an increase in the conversion of phosphorylase b to phosphorylase a, which is physiologically more active. Phosphorylase kinase was assayed using the modification by Drummond and Duncan (17) of the method of Krebs et al. (18). The
activity of the enzyme was measured by the production of phosphorylase $a$ from crystalline skeletal muscle phosphorylase $b$. The results were expressed as the ratio of phosphorylase kinase activity measured at pH 6.8 to that measured at pH 8.2. An increase in the activity ratio of phosphorylase kinase indicates transformation to the activated (phosphorylated) form of the enzyme. Cyclic AMP was assayed by the method of Wasila et al. (19), which is based on the activation of skeletal muscle protein kinase.

Materials.—L-Epinephrine bitartrate (Winthrop) and d,l-practolol (Ayerst Laboratories) were prepared fresh daily in a 0.9% (w/v) sodium chloride solution containing 0.2% (w/v) sodium metabisulfite. Nucleotides were obtained from P-L Biochemicals or Boehringer Mannheim Corporation. All enzymes used for the phosphorylase kinase and phosphorylase assays and the $\gamma$-32P-ATP synthesis were from Boehringer Mannheim Corporation. Carrier-free (32P) inorganic phosphate was purchased from Schwarz Bio-Research. Phosphorylase $b$, containing less than 2% of the $a$ form, was prepared as described by DeLange et al. (20).

Statistical Methods.—Statistical analyses were performed using Student’s t-test for paired or unpaired observations. A probability of $< 0.05$ was accepted as a significant difference.

Results

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In the working heart ischemia produced an increase in the myocardial concentration of cyclic AMP and an activation of cardiac phosphorylase (Fig. 1). The cyclic AMP concentration increased from 0.55 to 0.77 μmoles/kg 5 seconds after the termination of coronary blood flow; it then rapidly returned to control concentrations. The control phosphorylase activity ratio was 0.14 and increased to 0.34 after 10 seconds of ischemia and to 0.57 after 20 seconds of ischemia. Total phosphorylase activity ($a + b$) ranged from 14 to 18 units/g for all hearts studied and did not change during ischemia. The activation of phosphorylase followed the elevation in cyclic nucleotide by 5 seconds. This activation persisted throughout the ischemic period unlike the transient activation observed in response to epinephrine infusion (21). Practolol (5 mg/kg, iv) prevented the increase in cyclic AMP concentration and the phosphorylase $a$ formation. This dose of practolol did not appreciably influence aortic blood pressure (100-125 mm Hg), heart rate (300-400/min), or myocardial contractility.

In the nonworking heart ischemia elicited an increase in the cyclic AMP concentration from 0.50 to 0.62 μmoles/kg in 20 seconds (Fig. 2). After this initial increase and a return toward control, the myocardial cyclic nucleotide concentration increased again and remained elevated. The phosphorylase activity ratio increased from 0.14 to 0.34 20 seconds after the initiation of ischemia by whole rat circulatory arrest and increased further after...
60-120 seconds of ischemia. Again practolol blocked the elevation in myocardial cyclic AMP and the formation of phosphorylase a.

The phosphorylase kinase activity ratio increased with ischemia from a control of 0.08 to 0.16 in the working heart and to 0.12 in the nonworking heart (Fig. 3). The activity of phosphorylase kinase was highest at the time when the concentration of cyclic AMP was increased. Total phosphorylase kinase activity determined at pH 8.2 ranged from 95 to 120 units/g for all hearts and was not altered by ischemia. The transformation of the enzyme to its activated form was prevented by practolol. The β-adrenergic antagonist did not influence the control kinase activity ratio.

ANOXIA

In the working heart anoxia caused an increase in cyclic AMP concentration and an activation of phosphorylase (Fig. 4). Cyclic AMP increased significantly from a control value of 0.50 μmoles/kg to 0.62 μmoles/kg, 10 seconds after the substitution of 100% N₂ for 95% O₂-5% CO₂ and returned to control values at 15 seconds. This return was followed by another increase that occurred after 120 seconds of N₂ breathing. An increase in the phosphorylase activity ratio from 0.14 to 0.43 followed the transient elevation of cyclic AMP by 5 seconds. Thirty seconds after the onset of N₂ breathing the ratio increased to 0.65 and remained elevated. Practolol prevented the increase in cyclic AMP but did not have any effect on the formation of phosphorylase a. This finding is in contrast with that observed during ischemia, since enzyme activation was completely prevented by β-receptor blockade during ischemia. During anoxia the phosphorylase kinase activity ratio did not differ from control (Fig. 3), indicating that no covalent transformation of the enzyme occurred with N₂ breathing. Total phosphorylase and phosphorylase kinase activities were not altered by anoxia or by practolol.

Abruptly changing the respiratory gas mixture from 95% O₂-5% CO₂ to 100% N₂ caused the arterial Po₂ to decrease from 250-300 to 15 mm Hg in 15 seconds. The fall in arterial blood Po₂ was slower than the response time of the electrode. Thus the Po₂ of coronary arterial blood fell precipitously during the time that cyclic AMP concentration was augmented and the conversion of phosphorylase b to a was initiated.

Effects of ischemia and anoxia on phosphorylase kinase activity ratio in the rat heart in vivo. Ischemia was produced by either clamping the base of the heart (working) or by sectioning the abdominal aorta and the inferior vena cava (nonworking). Anoxia was produced by respiration with 100% N₂ (working). Samples for phosphorylase kinase determination were taken at the time of peak cyclic AMP concentration 5-20 seconds after onset of ischemia or anoxia. See legend of Figure 1 for further explanation.

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Epinephrine caused an increase in myocardial cyclic AMP concentration, phosphorylase kinase transformation, and phosphorylase a formation in the open-chest preparation (Table 1). The concentration of cyclic AMP increased from 0.50 to 0.64 μmoles/kg 10 seconds after a bolus intravenous injection of epinephrine (0.1 μg/kg). The phosphorylase activity ratio increased twofold above control levels 15 seconds after injection. No significant change in phosphorylase kinase was observed. The elevations in both the cyclic AMP concentration and the phosphorylase activity ratio produced by this dose of epinephrine were similar to the initial increases in cyclic nucleotide and enzyme activity elicited by ischemia or anoxia. Epinephrine (1.0 μg/kg) caused a greater increase in the concentration of cyclic AMP and a marked augmentation of phosphorylase kinase and phosphorylase activity ratios. Practolol alone did not influence control cyclic AMP, phosphorylase kinase, and phosphorylase but did prevent the elevation of these three biochemical parameters following the administration of epinephrine.

**ANOXIA AND MYOCARDIAL CONTRACTILITY**

During the first 20 seconds of N₂ breathing in the open-chest preparation myocardial dP/dt decreased from 4800 to 2600 mm Hg/sec (Fig. 5). The small increases at time zero are artifacts of switching the respiratory cannula and performing injections. In the preparation ventilated with 95% O₂-5% CO₂, a bolus injection of epinephrine (0.1 μg/kg) produced an increase in dP/dt from 4800 to 6000 mm Hg/sec. When epinephrine (0.1 μg/kg) was injected 8 seconds after the introduction of anoxic respiration, a significant increase in dP/dt above that caused by N₂ breathing alone was observed between 12 and 20 seconds. There was a greater increase in dP/dt during anoxia with the administration of epinephrine (1.0 μg/kg) 8 seconds after the onset of N₂ breathing.

**Discussion**

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In both the working and the nonworking ischemic heart, the increase in cyclic AMP concentration and the concomitant transformation of phosphorylase kinase to its activated form that occurred in 5-20 seconds were followed by an increase in phosphorylase a (Figs. 1-3). A low dose of epinephrine (0.1 μg/kg) caused a similar increase in cyclic AMP concentration and a similar formation of phosphorylase a (Table 1). The β-adrenergic antagonist, practolol, prevented the increase in cyclic AMP, the transformation of phosphorylase kinase, and the formation of phosphorylase a produced by either ischemia or epinephrine. Therefore, these results confirm that the observed increase in cyclic AMP is of sufficient magnitude to be largely if not totally responsible for the transformation of phosphorylase kinase and the activation of phosphorylase found in the ischemic working heart. These results are essentially in agreement with those of Wollenberger et al. (6).

With a nonworking dog heart made ischemic by severing the aorta, these investigators reported an increase in cyclic AMP and phosphorylase activation within a few seconds after the onset of ischemia. However, in their experiments the cyclic nucleotide concentration increased to a level twice that of control, and the elevation was maintained for 20–30 seconds. We observed a more transient,

### TABLE 1

| Effect of Epinephrine and Practolol on Cyclic AMP Concentration, Phosphorylase Kinase, and Phosphorylase Activity Ratios in the Myocardium of the Working Rat Heart |
|---------------------------------|------------------|------------------|
|                                 | Cyclic AMP (μmol/kg) | Phosphorylase kinase (pH 6.8/8.2) | Phosphorylase a (AMP/–AMP) |
| Control                         | 0.50 ± 0.01        | 0.08 ± 0.01      | 0.14 ± 0.01 |
| Epinephrine (0.1 μg/kg)         | 0.64 ± 0.03*       | 0.10 ± 0.02      | 0.28 ± 0.02* |
| Epinephrine (1.0 μg/kg)         | 1.75 ± 0.15*       | 0.14 ± 0.02*     | 0.73 ± 0.03* |
| Practolol (5 mg/kg)             | 0.46 ± 0.05        | 0.08 ± 0.01      | 0.13 ± 0.01 |
| Practolol (5 mg/kg) and epinephrine (1.0 μg/kg) | 0.52 ± 0.06       | 0.09 ± 0.01      | 0.16 ± 0.03 |

Epinephrine was administered intravenously as a bolus (0.2 ml) to the working open-chest rat heart preparation ventilated with 95% O₂-5% CO₂. The myocardial cyclic AMP concentration and the phosphorylase kinase activity ratio were determined 10 seconds after the administration of epinephrine. The phosphorylase activity ratio was determined 15 seconds after injection of the catecholamine. All values represent the mean ± 1 SE of at least four hearts.

*P < 0.05.
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Effect of anoxia and epinephrine on myocardial contractility (dP/dt) in the working rat heart in vivo. Nitrogen breathing (diamonds) was introduced at time zero. Epinephrine was injected intravenously (0.1 μg/kg, 0.2 ml) at time zero (circles with dots) except during N₂ respiration when it was injected after 8 seconds of anoxia at 0.1 μg/kg (triangles) and 1.0 μg/kg (dots). The data were obtained from oscillograph tracings reproduced from magnetic tape recordings of the actual experiments. All data were normalized to the mean dP/dt for all experiments at —4 seconds. Each point represents the mean of at least five experiments. Single asterisks denote significant differences (P<0.05) from —4 seconds. Double asterisks indicate significant differences (P<0.05) between anoxia in the presence and the absence of epinephrine at the same time intervals. Bars represent ±1 se.

Figure 5

Phosphorylase activation in anoxic hearts was not prevented by β-receptor blockade. If anything it was slightly augmented. In addition, anoxia did not produce a transformation of phosphorylase kinase to its activated form. These findings support the hypothesis we have previously proposed that the mechanism of enzyme activation may be different in anoxia compared with that in ischemia (4, 5). Since N₂ breathing caused conversion of phosphorylase b to a that was independent of stimulation of adrenergic receptors and cyclic AMP formation, it is difficult to assign a role to the cyclic nucleotide. The apparent nonadrenergic component of phosphorylase a formation in the anoxia studies suggests that the covalent modification of phosphorylase is a result of an increase in the catalytic activity of the nonactivated form of phosphorylase kinase and that mediators other than cyclic AMP such as Mg²⁺, Ca²⁺, or an alkaline shift in pH may be involved.

Free Mg²⁺ has been shown by Villar-Palasi and Wei (24) to stimulate the nonactivated form of phosphorylase kinase. They proposed that small changes in the intracellular concentration of free Mg²⁺, for example when the ratio of Mg²⁺ to ATP exceeds 1, could significantly change the activity of the enzyme and thereby be responsible for the in vivo activation of phosphorylase during muscle
contraction. The myocardial concentration of ATP begins to decline within 15 seconds of N₂ breathing (4). Therefore, during anoxia it is possible that the ratio of Mg²⁺ to ATP exceeds 1 and that the free Mg²⁺ concentration is sufficient to increase nonactivated phosphorylase kinase activity.

Ca²⁺ is required for myocardial phosphorylase kinase activity (25), and increases in the concentration of this cation of about 1 μM produce a marked elevation in activity of partially purified cardiac phosphorylase kinase (26). We have previously shown that catalytic activity of cardiac phosphorylase kinase is controlled by the extracellular concentration of Ca²⁺ (27). Enhanced influx of this ion has been shown by Bauer et al. (28) to occur in smooth muscle during hypoxia. Therefore, an increase in free Ca²⁺ may be responsible for the apparent enhanced activity of phosphorylase kinase in the anoxic myocardium.

Hydrogen ions have a marked effect on phosphorylase kinase activity at physiological pH. Drummond and his colleagues (25) have shown that in cardiac muscle extracts an elevation in pH of 0.5 units in the range of 7.0 to 8.0 results in more than a twofold increase in enzyme activity. In a series of contractions skeletal muscle first becomes alkaline because of hydrolysis of creatine phosphate (29). Since anoxia causes a rapid hydrolysis of cardiac creatine phosphate (4, 5), it is conceivable that the myocardium becomes slightly alkaline. Dog myocardial interstitial pH increases more than 0.05 pH units approximately 30 seconds after changing the respiratory gas from 20% O₂ to 10% O₂ (30). However, coronary ischemia has an opposite effect on intercellular pH presumably because the washout of lactic acid and other acid metabolites is limited (30), even with rapid hydrolysis of creatine phosphate in the ischemic myocardium (5, 31). Therefore, alkalosis resulting from creatine phosphate hydrolysis could participate in regulating phosphorylase kinase activity. In fact any one of the above mediators singly or in combination may be responsible for enhancing the activity of nonactivated phosphorylase kinase in cardiac anoxia and thereby promote covalent phosphorylase modification.

Both ischemia and anoxia caused a sustained conversion of phosphorylase b to a for at least 2 minutes. This phenomenon confirms earlier studies (4, 5) and is unlike the transient activation of the cardiac enzyme that occurs with continuous epinephrine infusion (21). Inhibition of phosphorylase phosphatase, the enzyme that catalyzes the conversion of phosphorylase a to b could be involved. Haschke and colleagues (32) have shown reversible inhibition of phosphorylase phosphatase when phosphorylase is activated in a concentrated protein-glycogen complex from rabbit muscle. The phosphatase was inhibited by 80% when the free Ca²⁺ concentration was 0.3 mM, a concentration causing maximal rapid activation of phosphorylase in the complex. Therefore, Ca²⁺ could participate in the inhibition of phosphorylase phosphatase and in the regulation of phosphorylase kinase activity in the anoxic heart.

We have not performed studies for longer than 2 minutes to determine if phosphorylase remains activated. However, Cornblath et al. (3) have shown that the activity of phosphorylase b increases after several minutes of anoxia, presumably due to the marked elevation of AMP and inorganic phosphate that occurs under such conditions (33, 34). This observation suggests that the activation of glycogenolysis in the anoxic heart is governed by a continuum of mechanisms, first by the formation of phosphorylase a and then by either a persistence of this form of the enzyme, an increase in phosphorylase b activity, or both.

**Anoxia and Myocardial Contractility**

The rapid, steady decline in dP/dt observed in the anoxic working heart at a time when cyclic AMP concentration was increased appears to represent a dissociation between the intracellular content of the cyclic nucleotide and the inotropic state. These results could be explained by the supposition that, as a consequence of anoxia, the control of contractile state by cyclic AMP is disrupted. However, when a low dose of epinephrine was administered during N₂ breathing, an increase in dP/dt was observed. This dose of the catecholamine elicited an increase in cyclic AMP comparable in magnitude to that observed during anoxia. Although creatine phosphate was almost completely hydrolyzed during the first 20 seconds of anoxia (4, 5), the availability of high-energy phosphate apparently was not limiting and the preparation was still capable of an increase in contractility. These results do not refute the hypothesis that the positive inotropic effects of catecholamines are mediated by intracellular cyclic AMP (35) but project the possibility that the nucleotide is not the sole mediator of changes in cardiac contractility. It may be simplistic to visualize only one mechanism responsible for controlling contractility when myocardial glycogen...
metabolism is regulated at several levels by a variety of mechanisms.

References


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