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RELATIONSHIP BETWEEN ANAEROBIC ENERGY FORMATION AND MYOCARDIAL CONTRACTILITY DURING DISTURBANCE OF CORONARY PERFUSION

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Restriction of the blood and oxygen supply to the myocardium is accompanied by a switch from the aerobic to the anaerobic type of metabolism, which is regarded as an important compensatory mechanism maintaining the energy reserves of the myocardium under ischemic conditions. However, despite considerable activation of glycolysis and maintenance of a sufficiently high ATP level, myocardial contractility is reduced even in the earliest stages of ischemia. Many workers ascribe a decisive role in the change in myocardial contractility to a change in pH of the medium and, in particular, to lactate acidosis [14].

The object of this investigation was to study correlation between parameters of anaerobic metabolism in the heart tissues and the most informative parameters of myocardial contractility during a measured restriction of the coronary blood flow.

EXPERIMENTAL METHOD

Experiments were carried out on 50 dogs in which measured partial (by 70 and 90% for 30 min) restriction of the blood flow was carried out under conditions of closed-chest catheterization and autoperfusion of the circumflex branch of the left coronary artery [1]. The animals were anesthetized by intravenous injection of chloralose (80 mg/kg).

Myocardial contractility was studied by catheterization of the chambers of the heart and simultaneous recording of the intraventricular pressure and its rate of change (dp/dt), followed by calculation of various indices of contractility [9, 13]. After recording of the physiological parameters, part of the myocardium of the left ventricle was excised and placed in liquid nitrogen. The zone of ischemia and the myocardium at a distance from this zone were subjected to biochemical analysis, with quantitative determination of glycogen [10] and lactic acid [2], and of activity of glycolysis [8] and of phosphorylase [3]. Experiments with adequate perfusion (10 animals) served as the control. Multiple-factor correlation analysis was carried out with the Minsk-32 computer.

EXPERIMENTAL RESULTS

Reduction of the coronary blood flow by 70% was accompanied by a fall in the glycogen content in the zone of ischemia by one-third. An increase in the severity of the ischemia led to a more marked reduction in glycogen — to 54% of its initial level. Meanwhile, a considerable increase was found in glycolysis activity and in the lactic acid content — by 3-4 times compared with the control. Phosphorylase activity also increased in both groups of experiments,

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TABLE 1. Correlation between Some Parameters of Contractility and Carbohydrate Metabolism of the Myocardium

Parameter studied	Restriction of blood flow	Location of test object	dP/dt_{max}	$t-dP/dt_{max}$	$\frac{dP/dt_{max}}{IP}$	V_{CE10}	V_{CE40}	$t-V_{pm}$
Glycolysis	70%	Zone of ischemia	—	$r = +0,63$	—	—	—	$r = -0,79$
	90%	Zone of ischemia	$r = -0,63$	—	—	$r = -0,86$	$r = -0,66$	—
		Outside zone of ischemia	$r = -0,84$	—	—	—	$r = -0,75$	—
Lactic acid	90%	Zone of ischemia	—	—	$r = -0,79$	—	—	—
		Outside zone of ischemia	—	—	$r = -0,61$	—	—	—

to 150% of normal. Outside the zone of ischemia changes in carbohydrate metabolism were in the same direction, and differed only quantitatively from disturbances in the zone of perfusion. For instance, the glycogen content here was reduced by one-third in the case of 90% restriction of blood supply, whereas the lactic acid content was increased by 1.5-2.5 times.

Restriction of the coronary blood flow by 70 and 90% was accompanied by changes in contractility of the heart, as shown by a decrease of the intraventricular pressure in most cases on average by 15-20% (14.1 ± 3.9 and 19.7 ± 5.9%, respectively), a decrease in the rate of its rise on average by 20-25%, and a decrease in the calculated contractility indices. With the change from 70% to 90% restriction of coronary perfusion, the reactions were moderately aggravated.

Correlation between the changes in contractility thus revealed with changes in anaerobic oxidation is of great interest (Table 1). With 70% restriction of the volume of coronary perfusion (n = 14) significant positive correlation was found between the intensity of glycolysis and the following indices: $t - dp/dt_{max}$ (the time taken for dp/dt to reach its maximum), r = +0.63; t — Vpm (the time taken for the recorded rate of shortening of the contractile element to reach a maximum), r = +0.79.

A special feature of these indices, however, is their negative correlation with the contractile state of the myocardium. For this reason, these data can be considered to be in agreement with the results obtained in observations when the coronary blood flow was restricted by 90%. In nine experiments of this group, a high negative coefficient of correlation was found between the parameter dp/dt_{max} and the intensity of glycolysis in the zone of ischemia (r = —0.63) and outside the zone of ischemia (r = —0.84); negative coefficients also were found between the parameters Vce_{10}, Vce_{40}, and the intensity of glycolysis in the zone of ischemia (r = —0.86; r = —0.66), Veragut's index $\left(\frac{dp/dt_{max}}{IP}\right)$, and the lactate concentration in the zone of ischemia (r = —0.79) and outside the zone of ischemia (r = —0.61).

This relationship also was investigated in the experiments with 90% restriction of the coronary blood flow, to take into account the severity of disturbances of the contractile function of the heart. Lowering of contractility was estimated as moderate if the changes in the principal parameters did not exceed 10-15%. Experiments with a more severe disturbance of cardiac contractility and the single experiments in which the animals died were analyzed separately.

Experiments with more severe disturbance of contractile function were found to have a much greater increase in activity of phosphorylase, one of the principal glycolytic enzymes, in the zone of ischemia ($P < 0.01$). This was combined with a significantly greater increase in the intensity of glycolysis in the conventionally intact zone ($P < 0.02$). Dying animals differed from those which survived by a significantly greater fall in the glycogen level ($P < 0.02$) and by an increase in the lactic acid concentration in the zone of ischemia ($P < 0.02$), which was 10 times higher than in the animals with 70% restriction of the blood flow.

The presence of strong correlation between the parameters of anaerobic carbohydrate metabolism and changes in myocardial contractility in the presence of ischemia suggests that this dependence is not accidental but exists objectively. So far as the possible mechanisms of the effect of glycolysis metabolites on myocardial contractility are concerned, the role of lactate in the development of acidosis must be considered first. A pH shift is one of the most important causes of injury to the contractile system of the cell — of inhibition of the ATPase properties of actomyosin [7], of competition and displacement of Ca^{++} from its bonds with troponin [6], and of dissociation of actomyosin, with elution of the light chains of myosin into the bloodstream [12]. The action of hydrolysis products on myocardial contractility thus may take place through changes in the pH of the medium.

In recent years, an increasing number of investigations have been published which point to the possibility of a direct action of glycolysis metabolites, independent of pH changes, on energy metabolism and Ca^{++} transport. For instance, an investigation [5] showed that so-called undissociated lactic acid accumulates in myocardial ischemia and has a harmful action on mitochondria, causing them to swell and inhibiting oxidative phosphorylation. In experiments on the isolated perfused septum of the rabbit heart, addition of lactate (25 mM) to the perfusion solution, while its pH remained unchanged, reduced the force of isometric contraction, by the same degree as in experiments in which the Ca^{++} concentration in the perfusion fluid was reduced [11].

Similar investigations on vascular smooth muscles have shown that lactate modifies calcium metabolism, reducing the rate of liberation of Ca^{++} from Ca-binding sites of the membranes [4]. Lactate thus has a pH-independent relaxing effect on contractile proteins, acting on them through changes in calcium metabolism.

Activation of glycolysis, glycogen breakdown, and accumulation of lactic acid in the ischemized myocardium are thus the most important factors which reduce its contractility, and this result is brought about by two important effects of lactic acid: one pH-dependent, the other pH-independent.

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