There has been an increased interest on the part of surgeons in metabolism of the heart since the perfection of techniques for operating within the cardiac chambers. The use of cardiopulmonary bypass, inflow occlusion without bypass, hypothermia, and pharmacological agents for the induction of cardioplegia have required a better understanding of normal myocardial metabolism and the alterations induced by these techniques.

It is well known that the myocardium utilizes lactate during periods of mild to moderate hypoxia, while at the same time lactate is produced by the skeletal muscle. During this period, the respiratory quotient of the myocardium remains lower than 1. Katz and associates have shown that the heart is able to increase its efficiency (work performed per unit of oxygen used) when the oxygen supply to the heart becomes relatively inadequate, as in hypoxia or at very high work levels. These investigators postulated that in order to make this increase in efficiency possible, a spontaneous change must occur in myocardial metabolism when hypoxia reaches a certain point. The present investigation was carried out in order to define more accurately this spontaneous change in myocardial metabolism and to determine whether a shift to predominantly anaerobic metabolism is responsible for this change.

Methods

Twelve mongrel dogs were anesthetized with intravenous pentobarbital, 25 mg./Kg. of body weight, and respiration was maintained with a Bird ventilator via a cuffed endotracheal tube. A thoracotomy was performed through the right fourth intercostal space and a cardiac catheter inserted into the coronary sinus via the right atrium. A suture placed about the proximal coronary sinus was tightened to prevent leakage around the catheter. The femoral artery was cannulated and arterial blood pressure monitored with a strain gauge. Samples of blood from the femoral artery and coronary sinus were drawn at intervals during ventilation with room air or 100 per cent oxygen. Samples were also obtained during periods of hypoxia produced by ventilation for up to six minutes with 90 per cent nitrogen and 10 per cent oxygen, 95 per cent nitrogen and 5 per cent oxygen, and 100 per cent nitrogen. In additional experiments, samples were obtained during periods of respiratory arrest lasting up to five minutes. Succinyl choline was administered intravenously to produce respiratory paralysis, and the ventilator was disconnected. Oxygen and carbon dioxide content were determined manometrically. The lactate content of the blood was measured according to the technique of Barker and Summerson and the pyruvate as described by Friedemann and Haugen. These blood samples were precipitated in chilled trichloroacetic acid within 30 seconds after being drawn. Excess lactate was calculated from the measured blood lactate and pyruvate, using the formula of Huckabee, and represents that lactate produced by anaerobic metabolism alone. The difference between arterial and coronary sinus excess lactate concentration was calculated to indicate the production or removal of excess lactate per L. of coronary blood. Values for lactate pyruvate and excess lactate are expressed in mEq./L. Similarly, the oxygen uptake and carbon dioxide production of the heart were calculated as the arteriovenous difference of the contents of these gases, measured per L. of coronary blood. The respiratory quotient was calculated as the ratio of carbon dioxide production to the oxygen uptake.

Results

Figure 1 illustrates the calculated respiratory quotient plotted against the arterial oxygen content of 35 blood samples drawn before and during periods of hypoxia. In addition, the production or removal of excess lactate is plotted against the arterial oxygen content. After the production of hypoxia, the content of oxygen in arterial blood fell, and the re-
Respiratory quotient of the heart rose. At no time in these experiments did the hematocrit of arterial blood fall below 33 per cent. Most of the determinations revealed that with an oxygen content of arterial blood of 9 ml. or more per 100 ml. of blood, the respiratory quotient was less than 1, the lowest value recorded being 0.33. When the oxygen content fell below 9 ml./100 ml. of blood, however, the respiratory quotient became greater than 1. The highest value, that of 6.6, was recorded when the arterial oxygen content was 0.8 ml./100 ml. of blood. Correlation between the production of excess lactate and falling arterial oxygen content was also noted. This metabolite was removed from the coronary circulation when the oxygen content of arterial blood was maintained above 9 ml./100 ml. of blood; that is, lactate was utilized when the respiratory quotient remained less than 1. During periods of hypoxia, with a low arterial oxygen content, excess lactate accumulated and paralleled the rise in the respiratory quotient. Thus, under these experimental conditions, the heart functioned at least partially anaerobically when the arterial oxygen content became less than 9 ml./100 ml. of blood, and this action was accompanied by a carbon dioxide production greater than the oxygen uptake.

Figure 2 illustrates the amount of oxygen taken up by the myocardium per unit of coronary blood flow plotted against the oxygen content of arterial blood. The solid line indicates 100 per cent oxygen utilization, a theoretical value which would occur if all of the oxygen delivered were taken up by the myocardium. The dotted line indicates the average oxygen uptake at varying levels of arterial oxygen content. Oxygen utilization is defined as the oxygen uptake expressed as a percentage of the available oxygen delivered. It may be seen, then, that oxygen utilization, expressed as a percentage, remains the same at all levels of arterial oxygen content. Thus, in these experiments, hypoxia did not increase the utilization of oxygen per unit of coronary blood flow. Furthermore, it is shown that anaerobic metabolism occurs in the myocardium, even though all of the available oxygen is not utilized.

The effect of ventilation for four minutes with 100 per cent nitrogen is shown in figure 3. During the period of maximum hypoxia, the respiratory quotient rose to 6.6, and excess lactate was produced at the rate of 2.3 mM/L.
of coronary blood flow. At the same time, 3.1 ml. of carbon dioxide were produced, compared to an oxygen uptake of 0.5 ml., resulting in a carbon dioxide excess of 2.6 ml./100 ml. of coronary blood. Excess lactate, expressed in mM/100 ml., was converted to its oxygen equivalent by multiplying by 11.2. Thus, the oxygen equivalent of the excess lactate produced under these conditions of severe hypoxia was 2.6 ml./100 ml. of coronary blood, identical with the carbon dioxide excess. When the animal was ventilated with 100 per cent oxygen, aerobic metabolism resumed, excess lactate was removed, and the respiratory quotient dropped below 1.

Another experiment is illustrated in figure 4. This animal was ventilated with 100 per cent oxygen, following which apnea was induced and maintained for four minutes. After two minutes of apnea, the oxygen content of arterial blood fell to 5.8 ml./100 ml. of blood, and the respiratory quotient rose to 2.1. Nevertheless, excess lactate was still being removed, but at a much reduced rate. A possible explanation of this fact is the demonstration by Huckabee that lactate and pyruvate diffuse through the cell membrane somewhat more slowly than oxygen and carbon dioxide. After four minutes of respiratory arrest, the oxygen content of arterial blood fell to 0.2 ml./100 ml. of blood. Accumulation of excess lactate, the anaerobic metabolite, was again demonstrated, and calculation of its oxygen equivalent indicated that 2.3 mM/L were produced, which was identical to the difference between the carbon dioxide production and the oxygen uptake.

Discussion

These experiments have indicated that the myocardium removes excess lactate under these experimental conditions before the production of hypoxia. Coronary inflow occlusion has been shown by others to result in the accumulation of lactic acid in the myocardium. Carter and Sabiston demonstrated that under such circumstances, there is a depletion of the glycogen content of cardiac muscle, indicating the presence of anaerobic glycolysis. Our data show that a marked degree of anaerobic metabolism develops in the canine heart when the arterial oxygen content falls below 9 ml./100 ml. of blood. This observation suggests the development of an insufficient arterial oxygen supply to the heart, in spite of the fact that an increase in coronary blood flow occurs with falling arterial oxygen content. Thus, it may be assumed that if the hemoglobin content of the blood falls below a level at which 100 per cent oxygen saturation would correspond to an arterial oxygen content of less than 9 ml./100 ml. of blood, the oxygen supply to the canine heart becomes inadequate, even with the entire body at rest. A theoretical nomogram could be constructed for each value of hemoglobin, indicating a certain minimum oxygen partial pressure that must be present in the ventilatory mixture in order to insure a satisfactory oxygen supply to the heart.
Cardiac efficiency is defined as the amount of work done by the heart per unit of oxygen consumed. Katz and associates noted that cardiac efficiency increased with decreasing oxygen content in arterial blood. Laurent and coworkers determined that an increase in cardiac work resulted in increasing cardiac efficiency, so that the highest efficiency was measured at the highest work levels. A "spontaneous change" was postulated in myocardial metabolism, permitting an increase in work obtained from a given amount of oxygen supplied. Our data indicate that this increase is due to the sudden release of anaerobic energy which results when the oxygen supply becomes inadequate. If part of the energy which is used by the heart to perform work during hypoxia stems from anaerobic metabolism, the cardiac efficiency, by definition, is increased. This increase was illustrated in the two experiments shown in figures 3 and 4. When the oxygen content of arterial blood fell below 1 ml./100 ml., the oxygen uptake of the heart approached zero. Nevertheless, the heart continued to beat and produced an excess of carbon dioxide for a period of several minutes. Obviously, the heart was working almost completely anaerobically. This observation was confirmed by the fact that the oxygen equivalent of the pyruvate, which was anaerobically converted to lactate, was identical to the carbon dioxide production of the heart. Cardiac efficiency under such circumstances approaches infinity. The time limit of this process is most probably a result of the accumulation of organic acids in the myocardium itself.

Summary

Calculation of excess lactate removal and production, together with the arteriovenous difference of oxygen and carbon dioxide content of the coronary circulation, was performed during normal ventilation, induced hypoxia, and apnea in dogs. During ventilation with 100 per cent oxygen or room air, excess lactate was removed by the canine heart and continued to be removed until the arterial oxygen content fell to an average.
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level of 9 ml./100 ml. of arterial blood. Below this level, excess lactate was produced by the heart, indicating a shift to anaerobic metabolism. The heart continued to work anaerobically, and its efficiency was increased since little, if any, oxygen was utilized. During severe hypoxia, the oxygen equivalent of the excess lactate produced was equal to the carbon dioxide produced. The heart, still performing work, was functioning completely anaerobically.

References

References

Book Review

Myocardosis: Pathogenesis, Clinical Aspects and Therapy with Recent Investigations Concerning the Principles of Metabolic Electrocardiography, Ferdinand Wuhrmann, M.D., with the collaboration of Serge Niggli, M.D., and translated by Harvey T. Adelson, M.D. Springfield, Illinois, Charles C Thomas, 1959, 228 pages. $10.50.

This monograph is the English translation of the German edition of Die Myokardose. The etiological factor for the syndrome of myocardosis is predominantly a shift of the serum proteins. This proteinemic myocardosis, which is almost always an accompanying symptom of an underlying disease and is rarely a disease entity by itself, is a functional, humoral occurrence at the outset, a functional metabolic injury of the heart. It can result in irreversible anatomical changes, particularly nonspecific myocardial fibrosis in cases where the deranged state persists for an extended period of time, namely over many years or when additional traumatic events occur."

The chapters on the symptomatology of the myocardosis syndrome and examples of clinical courses are complete. However, the metabolism of the myocardium is covered in only five pages. The chapter on therapeutic problems includes the use of liver extracts and heart muscle extracts. More space should have been devoted to these agents to explain the rationale for their use.
Anaerobic Metabolism of Heart
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