Distribution and Gradient of Lactate Between Blood and Heart Muscle.* (30068)

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It is widely accepted that the heart, unlike skeletal muscle, extracts lactate from its blood supply(1). Catheterization of the coronary sinus in the dog heart has demonstrated lactate extraction to depend on its arterial concentration(2). In myocardial anoxia associated with angina pectoris, myocardial infarction or hemorrhagic shock, venous lactate levels from the heart are often noted to rise above arterial levels(3). More recently, Huckabee(4,5) has attempted to quantitate cardiac anoxia from measuring the change in ratio of coronary arterial-venous difference of pyruvate to lactate. On the basis of the lactic dehydrogenase system (equations 1 and 2), Huckabee proposed that the relationship between pyruvate and lactate depends on the ratio of reduced (NADH) to oxidized nicotinamide adenine dinucleotide (NAD^+), where La, Lv, Pa and Pv are lactate and pyruvate levels in arterial and coronary sinus blood, respectively.

$$1.\ (Pv - Pa) + NADH \overset{LDH}{\rightleftarrows} (Lv - La) + NAD^+$$

$$2.\ (Lv - La) = (Pv - Pa) \times K\frac{NADH}{NAD^+}$$

In accordance with this concept, an increase in coronary arterial-venous blood difference of lactate not accounted for by a similar change in coronary arterial-venous difference of pyruvate would indicate an inadequacy of oxygen transport in the myocardium. The unaccountable lactate or "excess lactate" (ΔXL) could be calculated from equation 3.

$$3.\ \Delta XL = (Lv - La) - (Pv - Pa)(La/Pa)$$

Huckabee(6) assumed from observations made on lactate transport in the red cell, that entry of lactate from arterial blood into the cardiac cell was by simple diffusion and that blood levels of lactate are representative of the cellular concentration because they quickly achieve equilibrium with the cellular content.

In a study of the glycolytic metabolism of the dog's heart during hemorrhagic shock, levels of lactate in cardiac muscle could not be accounted for by the concentration of lactate or pyruvate in arterial or coronary sinus blood(7). On the basis of these observations, the distribution and gradient of lactate between blood and cardiac muscle was further investigated in the normal dog myocardium.

Methods. Experiments were performed in 23 mongrel dogs anesthetized with 30 mg/kg of sodium pentobarbital. From a midline ventral neck incision, the trachea was exposed and connected to a respiratory pump carefully regulated to avoid changes in blood pH. The chest was opened in the left 5th interspace and the heart was suspended in a pericardial cradle. Arterial concentrations of lactate were determined in samples drawn from an indwelling needle in the right femoral artery. Venous concentrations were determined in blood drawn from a catheter placed in the coronary sinus *via* the left external jugular vein. Both arterial and venous blood samples were drawn simultaneously in cold, lightly oiled Tuberculin syringes and quickly injected into tubes containing iced 10% trichloroacetic acid. Duplicate cardiac muscle samples, weighing approximately 500 mg, were taken from predetermined areas of the heart and quickly frozen in liquid N_2. The excision of muscle to its immersion in liquid N_2 averaged approximately 4 seconds in all experiments. The frozen muscle was trimmed of fat, weighed and homogenized in a Potter-Elvehjem tube containing iced 0.6 N perchloric acid. With minor modifications, levels of lactate in blood and cardiac muscle samples were analyzed according to the method

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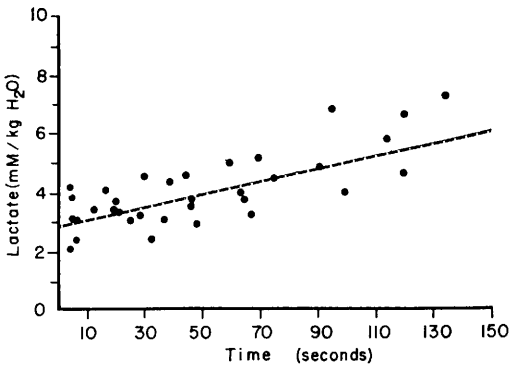

FIG. 1. Lactate levels of 34 duplicate left ventricular apical samples from 8 dogs subjected to varying periods of anoxia. The interrupted line represents the calculated sample regression line to the plotted values.

of Barker and Summerson(8). Concentration of lactate was expressed in millimoles per kilogram of water; water content was determined for every blood and muscle sample.

In 8 of the 23 dogs, acute myocardial anoxia was produced by sudden clamping of the pulmonary artery. Cardiac muscle from the apical region of the left ventricle was analyzed for lactate for periods of anoxia ranging from 4 to 135 seconds. In 9 of the remaining 15 dogs acting as controls, muscle samples from the right and left atrial appendages were taken simultaneously with samples from the base, from the area between the base and apex (midportion) and from the apex of the right and left ventricles. Prior to excision of the muscle samples, arterial and coronary sinus blood was drawn for lactate analysis. The remaining 6 dogs, which varied in weight from 13 to 25 kg, were infused by vein for 30 minutes with 200 ml of a 1/6th M neutral racemic sodium lactate† containing an equal mixture of L and D lactates. Muscle from the apex of the left ventricles was taken 15 minutes after the infusion was completed, longer periods of waiting resulted in a gradual decline of arterial lactate levels. Mean arterial blood pressure in lactate-treated dogs was monitored with a Hg manometer connected to the right femoral artery. Anaerobic samples of coronary sinus and arterial blood were checked for changes in pH before and after infusion of lactate. To prevent the coagulability of blood, all dogs were given 2.5 mg/kg of Heparin (sodium).

Results. Fig. 1 represents a plot of 34 duplicate left ventricular muscle samples from the apical region of 8 dogs after inducing acute myocardial anoxia from clamping the pulmonary artery. It can be noted that the relationship between duration of anoxia and endogenous production of lactate appears to be linear. By linear regression analysis, a sample regression line was determined from the plotted values(9). Aside from illustrating the well-accepted thesis of lactate production by the anoxic myocardium, extrapolation of the regression line to the ordinate gave the concentration at zero time or the *in vivo* concentration of lactate in the left ventricle. The value of 2.8 mM/kg H_2O of muscle lactate at the intercept was 48% greater than the level found in arterial blood (1.89 mM/kg H_2O) and 120% higher than in coronary sinus blood (1.27 mM/kg H_2O) of 9 dogs acting as controls. The "goodness of fit" of the calculated regression line to the plotted values was highly significant ($P < .001$).

Fig. 2 gives average levels of arterial and coronary venous blood lactate for 9 control dogs. In the same figure, average lactate concentrations with standard errors are given for right and left atrial appendages and for base, midportion and apical regions of the right

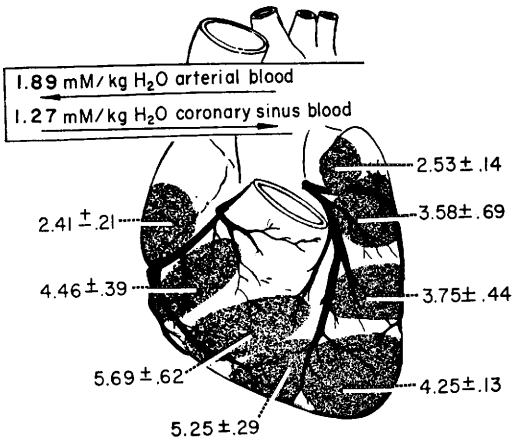

FIG. 2. Average lactate levels and standard errors of arterial and coronary sinus blood, together with levels found in the base, midportion and apex of the right and left ventricles in 9 dogs.

† Generously supplied by Baxter Laboratories, Morton Grove, Ill.

TABLE I. Levels of Lactate in Arterial and Coronary Venous Blood and in Right and Left Ventricular Muscle of Normal Dogs Compared to Dogs Infused with Sodium Lactate.

	Blood (mM/kg H_2O)		Ventricular apex (mM/kg H_2O)	
Control	Arterial	Coronary sinus	Right	Left
No.	9	9	9	9
Mean	1.89	1.27	5.25	4.25
S.E.	± .17	± .14	± .29	± .13
Infusion*				
No.	6	4	6	6
Mean	10.83	9.50	5.20	4.28
S.E.	± 1.83	±1.57	± .25	± .40
P	<.001	<.001	>.50	>.50

* 200 ml of 1/6 M neutral sodium lactate infused in a period of 30 min by vein.

and left ventricles. Although samples from atria and ventricles were taken simultaneously, the concentration of lactate was found to vary markedly in different regions of the myocardium. Levels in the base, midportion and apex of the right ventricle were found to be consistently higher than the corresponding base ($P<.001$), midportion ($P<.01$) and apex ($P<.005$) of the left ventricle. Concentration in the right and left atria did not differ significantly ($P>.50$). A gradient in lactate was observed to occur from the base to the apex of the heart, although levels in the midportion area of either ventricle were not significantly different from their respective apex.

In Table I average control values of arterial and coronary venous lactate together with levels found in the right and left ventricular apex of 9 control dogs are compared with 6 dogs infused with 200 ml of ⅙th M sodium lactate solution. Fifteen minutes after the infusion, the elevation in arterial and coronary venous lactate averaged 10.83 and 9.50 mM/kg H_2O, respectively. The marked increase in blood lactate was not accompanied by a significant change in lactate concentration of the right or left ventricle. Changes in mean arterial blood pressure and blood pH in the infused dogs were minimal.

Discussion. The distribution of lactate in the walls of the heart parallels a recent report on the increasing concentration of glycogen found from the base of the heart to the apices of the right and left ventricles(10). The gradient of myocardial glycogen was postulated to be related to the distribution of the Purkinje fibers within the ventricular walls. In the reported experiments, the distribution of lactate was found to be similar to that of glycogen in the ventricles. However, it is unlikely that levels of lactate can be correlated with the conduction tissue of the heart since the gradient was observed to begin from the atria, an area of myocardium devoid of conducting tissue. There is the possibility that lactate distribution may vary according to metabolic energy requirements of the different muscular components of the cardiac chambers.

The assumption that the mechanism of lactate transport from blood to cardiac muscle involves a process of simple diffusion is not supported by the reported experiments. The *in vivo* concentration of lactate in cardiac muscle appears to be higher than in arterial blood, indicating that passage of this anion may not follow a concentration gradient. Although administration of exogenous lactate caused an almost 6-fold increase in lactate levels of blood perfusing the heart, lactate concentration of the right or left ventricle remained unchanged. Coronary venous lactate levels that were postulated by Huckabee(5) to be in equilibrium with the tissue concentration failed quantitatively to indicate the tissue lactate.

The use of a racemic sodium lactate solution for increasing the concentration gradient of lactate between heart and blood may be questioned. It would have been preferable to infuse L-lactate, since this isomer is more efficiently utilized than D-lactate in the reductive synthesis of carbohydrates(11). On this basis an increase in myocardial concentration of the D-form could have occurred in dogs infused with the racemic mixture. However, simultaneous administration of both isomers did not raise cardiac muscle lactate, suggesting that both L- and D-lactates were utilized by the dog myocardium.

The reported experiments demonstrated that a marked difference in lactate concentrations can be encountered in different areas of the myocardium (Fig. 2). These observations lead to the conclusion that blood from the coronary sinus cannot be considered a

homogenous venous sample for the entire heart since determination of the steady-state levels of lactate showed the apices of the myocardium to contain almost double the atrial concentration. The implication of such a distribution raises serious questions on attempting to assess lactate metabolism of the heart from levels present in coronary sinus blood.

Summary. The concept that blood lactate is in equilibrium with myocardial concentrations of this substrate could not be demonstrated in the anesthetized dog. A factor questioning the existence of an equilibrium was the distribution of lactate found in the walls of the heart. Levels in right and left atria were markedly different from those found in the base, midportion and apex of the right and left ventricles. Although administration of sodium lactate by vein raised arterial lactate almost 6 times control, right and left ventricular muscle concentrations remained unchanged. The linear relationship observed between the duration of myocardial anoxia and lactate production by cardiac muscle made possible the calculation of the *in vivo* myocardial lactate level, a value significantly higher than the level present in arterial blood. The entry of lactate into the myocardial cell may therefore be governed by a mechanism of active transport rather than simple diffusion.

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Effect of Chronic Hypoxia on the Pulmonary Circulation of Cats.* (30069)

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In the cat, acute hypoxia causes an increase in pressure in the pulmonary artery (1-6). The increase is due to a constriction of pulmonary vessels caused by a local but unknown effect of hypoxia on the pulmonary vessels. This study reports the effect of chronic hypoxia on the pulmonary circulation of the cat.

Methods. Nitrogen was added to room air and the mixture was introduced into a 15-cubic-foot box at 15 to 20 L per minute. The oxygen content of the atmosphere in the box was checked at least once weekly with a Pauling oxygen meter (accuracy, within 1%) and ranged from 9 to 11%; carbon dioxide content was negligible. Temperature in the box was maintained at 72°F.

Cats varying in age from 2 weeks to 2 years were kept in the box for 3 weeks to 10 months; the chamber was opened daily for 5 to 10 minutes for cleaning and feeding.

The cats were removed from the box at intervals, exposed to room air for ½ to 1 hour, and then anesthetized with sodium pentobarbital (20 mg/kg). A catheter, intro-

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