The role of the liver in the development of lactic acidosis in low flow states

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Summary
The role of the liver in lactate metabolism in an experimental low flow state induced by cardiac tamponade was investigated in dogs.

Arterial and venous lactate, and pyruvate levels and arterio-venous oxygen content differences were measured for the liver, gut, forequarter and hind limbs. Cardiac output and regional blood flows were determined by electromagnetic flow probes.

The contribution of the liver to the development of lactic acidosis was found to be variable. When hepatic oxygen consumption was decreased, the liver was documented as the major site of lactate production with an associated increase in the lactate-pyruvate ratio of hepatic venous blood. In some experiments, however, the hepatic oxygen consumption was maintained, or even increased slightly; in these circumstances the liver was, in part, responsible for the development of lactic acidosis by impaired lactate consumption.

Introduction
It has been known since the beginning of this century, that tissue hypoxia leads to the production of lactic acid. This lactate leaves the cells and is distributed into the total body water. Lactic acid concentration in arterial blood may rise ten-fold in severe shock. In heavy exercise, the arterial lactate concentration may also increase to very high levels, but in contrast to shock, a rapid fall occurs when exercise is discontinued. The lactate concentration may even decrease, while the exercise continues (Rowell et al., 1966). It has been shown that 55 mM of lactate administered intravenously to a normal subject is cleared from the blood in about 30 min (Soffer, Dantes & Sobotka, 1938). Thus, it would appear that the prolonged hyperlactaemia in states of shock must reflect an imbalance between the production of lactate and its clearance. Which of these factors is the more important in the hyperlactaemia of shock is uncertain and in this context the question arises, which tissues are normally primarily responsible for removal of lactate from the blood and how do these tissues behave in low flow states and shock?

It is well known that heart muscle normally takes up lactate as a source of energy. Although this uptake of lactate may persist until a very low and critical level of coronary sinus oxygen saturation is reached (Lundsgaard-Hansen, 1966) the actual lactate uptake is too small to participate much in the overall lactate removal from the blood. There is evidence that the kidney is a potent organ for the removal of lactate. When renal blood flow is reduced, there is a proportionate reduction in net lactate uptake. But even with very low flow states, no net production of lactate could be observed (Levy, 1965).

Controversy exists concerning the ability of skeletal muscle to metabolize lactate (Pentecost, Reid & Reid, 1966). There is some evidence, however, that during exercise resting muscle groups (Harris, Bateman & Gloster, 1962) or the exercising muscle itself (Stainsby & Welch, 1966) may remove lactate from the blood. There is no evidence, however, that this occurs during low-flow states.

The most important organ concerned with the uptake of lactate from the blood appears to be the liver (Berry, 1967). Massive infusion of lactate fails
to produce a persistent hyperlactaemia unless hepatic function is grossly impaired (Berry & Scheuer, 1967). In abdominally eviscerated dogs the removal of lactate is impaired (Alpert, 1965) Rowell et al. (1966) concluded from their experiments in human subjects that approximately one-

half of the estimated total lactate production during exercise is removed by the liver.

Without giving direct proof, Schimassek (1965) from experiments with isolated perfused rat liver and Cain (1965) as well as Lundsgaard-Hansen (1966) from experiments with anaemic and hypoxic hypoxia in dogs concluded that liver function was of the utmost importance for the regulation of the blood lactate level and the lactate-pyruvate ratio. Finally in 1967 Berry & Scheuer showed in three dogs in which shock was produced by infusion of trimethaphan or by rapid arterial bleeding into a reservoir, that the hepatic vein lactate concentration exceeded the aortic concentration. Moreover, during the first 20 min of the period of shock the aortic lactate level was higher than that in the vena cava, suggesting that during this initial stage lactic acid production by skeletal muscle was not contributing to the rising arterial lactate level. During the recovery phase lactate uptake in the splanchnic bed took place.

**Personal experiments**

Our experiments were designed to investigate the effect of a consistently lowered cardiac output on regional flow, oxygen consumption, and metabolism of various parts of the body without decreasing the blood volume as in haemorrhagic shock. In order to produce a reversible form of cardiogenic shock cardiac tamponade was induced by the injection of oil into the pericardial sac. Seven acute experiments on mongrel dogs were successfully performed. The completed preparation is shown diagrammatically in Fig. 1.

In the thorax electromagnetic flow probes were placed around the superior and inferior vena cava outside the pericardium, and the azygos vein was ligated. The sum of the flows recorded by these two probes is the cardiac output minus the coronary flow. In the abdomen flow probes were fitted snugly around the inferior vena cava at its origin, the hepatic artery, and the portal vein. Hepatic blood flow was deduced from the combined flows of hepatic artery and portal vein, and gut flow by the portal vein alone. Catheters were placed in the superior vena cava, the pulmonary artery, the portal vein, the hepatic vein, the inferior vena cava at its origin, and in the lower aorta. The chest and abdomen were closed securely and the animal weaned from the respirator, the actual studies being carried out with the animals spontaneously respiring room air. Blood loss during operation was replaced by transfusion and during the experiment sample losses were replaced immediately by heparinized donor blood. After approximately 1–1½ hr of stabilization, control values were recorded. Blood samples from all sample sites were taken simultaneously, the maximal time difference being 1 min. Lactate and pyruvate were measured by an enzymatic method (Gloster & Harris, 1962; Hohorst, 1963). Oxygen content was calculated from oxygen saturation × capacity. Saturation was deduced from the dog blood dissociation curve (Bartels & Harms, 1959; Rossing & Cain, 1966) from oxygen tension and pH.

During the control period the mean arterial blood pressure was 137·6 ± 14 mmHg. The cardiac output (minus the coronary flow) was 76 ± 29 ml/kg/min. This figure for cardiac output is low compared with values quoted for the awake animals but in this experiment values are reduced, partly because the coronary flow is not included and also undoubtedly because of the effects of anaesthesia and operation. The total oxygen consumption during the control period was 4·5 ± 0·45 ml/kg/min.

This relatively normal oxygen consumption in the presence of a reduced cardiac output results in an increased arteriovenous oxygen content difference, 6·16 ± 0·94 volumes per cent. Thus it would seem
that the preceding operation did not result in a restriction of the peripheral oxygen supply and this is further supported by the arterial lactate of 1.0 ± 0.28 mM/l and the lactate – pyruvate ratio of 11.3 ± 1.8 during the control period, both these results being within the normal range.

The regional distribution of blood flow during the control period is shown in Fig. 2. The actual values as a percentage of the cardiac output (minus the coronary flow) were as follows: superior vena cava 31.7%; thoracic inferior vena cava 68.3%; hepatic flow 30.5% (hepatic artery 8.3% and portal vein 22.2%); and the inferior vena cava at its origin in the abdomen 9.8%. These values for the regional distribution of flow are in good accordance with the results given by other authors. Assuming a coronary blood flow of 8% of the cardiac output then the hepatic flow in this series would be 28% and the inferior vena cava at its origin would be 9% of the total cardiac output.

With cardiac tamponade there was a fall in the cardiac output (minus the coronary flow) to 25 ± 4 ml/kg/min. The mean femoral arterial pressure fell to 59% of the control value. There was no large change in the relative distribution of blood flow although the superior vena cava flow, as a percentage of cardiac output, increased slightly and the inferior caval flow (in the thorax) correspondingly decreased. The flows given as a percentage of the values obtained during the control period were as follows: cardiac output (minus coronary flow) 33%; superior vena cava 37%; inferior vena cava (in the thorax) 30%; hepatic flow 32.7% of control (portal vein 32.1% and hepatic artery 34.1%). The reduced flow in the inferior vena cava in the thorax was due to a decrease in hindquarter muscle flow (inferior vena cava in the abdomen) rather than to a reduction in hepatic flow. The calculated renal flow during this time also showed a relatively greater reduction.

A significant decrease in oxygen consumption occurred in the region drained by the inferior vena cava (hindquarter) 30 min after maximum cardiac tamponade. The flow was reduced from a mean value of 8 to 1.9 ml/kg/min and the oxygen consumption from 0.63 to 0.34 ml/kg/min. At this time there was some, but only a small lactate output from this area, the mean value being 1.5 µM/kg/min.

Throughout the experiment the oxygen consumption of the area drained by the portal vein did not change and there was no lactate production in this region. The response of the liver both with regard to oxygen consumption and lactate production was different. The mean oxygen consumption during the control period was 0.89 ± 0.46 ml/kg/min. In three dogs, this was reduced to approximately 50% of the control value, whereas in the other animals the oxygen consumption increased somewhat above the control value during the period of cardiac tamponade. The handling of lactate by the liver closely corresponded to changes in hepatic oxygen consumption, and the results may be summarized as follows:

Firstly, in those animals where liver oxygen consumption did not fall there was no lactate production. However, the ability of the liver to clear lactate was considerably impaired, or even totally absent.

Secondly, a decrease in the oxygen consumption of the liver was associated with lactate production. The lactate–pyruvate ratio in the hepatic venous blood increased at the same time providing further evidence of hepatic tissue anoxia (Schroeder et al., 1968).

Thirdly, during the recovery phase after release of cardiac tamponade, the liver was the only area of all those studied where lactate was consistently removed from the blood. During this time, the oxygen consumption of the liver significantly rose above the control values.

Figs. 3 and 4 serve to illustrate these points. Thus it may be concluded that the liver appears to play a vital role in the development of hyperlactaemia in low flow states either by failing to clear lactate from the blood or by actual lactate production. The contribution of the liver to the lactic acidosis relates to hepatic oxygen consumption and as oxygen consumption decreases so does the liver’s ability to metabolise lactate. Thus an impairment of hepatic function appears necessary for an increasing systemic lactic acidemia.
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Fig. 3. Diagram of the results obtained in dog 1. The lines represent the lactate balances of the various areas. The columns represent the lactate–pyruvate (L/P) ratio of the hepatic venous blood (on the left-hand side) and the oxygen consumption of the liver (on the right-hand side). A decrease of the oxygen consumption of the liver during cardiac tamponade is accompanied by lactate production and an increased L/P ratio in hepatic venous blood. On release of the tamponade the oxygen consumption increases, the L/P falls to within the normal range, and there is a small net lactate removal by the liver.

Fig. 4. In contrast to dog 1, the hepatic oxygen consumption increases slightly during cardiac tamponade. The L/P ratio in hepatic venous blood remains within the normal range. The liver takes up lactate but not in sufficient quantity to prevent a rise in the arterial lactate concentration. On release of the tamponade, however, there is a marked increase in hepatic lactate consumption.
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