Studies on Cardiac Lymph during Extracorporeal Circulation*

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Cardiac lymph in dogs was used to study the metabolism and state of the myocardium during extracorporeal circulation and various additional procedures. Changes in the flow characteristics, color and pH of lymph were noted, and corresponding samples of cardiac lymph and coronary sinus blood were analyzed for lactate concentration. Ventricular fibrillation led to higher lactate levels when compared to analyses of lymph and blood from a heart beating with sinus rhythm. Aortic occlusion at normothermia caused a pronounced and long-lasting elevation of lactates in the lymph, which also became blood stained, indicating capillary damage. Moderate hypothermia conferred a distinct but not complete protection against these effects. Coronary perfusion at normothermia appeared to be the preferable technique among those tested. We suggest that cardiac lymph reflects the state of the myocardium more accurately than do venous and arterial blood samples, and that lymph is a valuable medium for further studies on cardiac function and metabolism.

A number of procedures are claimed to be useful adjuncts in open heart surgery by providing a quiet and bloodless field, by protecting the heart from anoxic damage and by reducing the period of extracorporeal circulation. Considerable controversy, however, exists concerning the routine use of these procedures. Anoxic cardiac arrest is considered by some authors to be detrimental to myocardial function,1-4 while others are impressed with the apparent clinical safety of this procedure.4,5 Similarly, opinions differ on use of coronary perfusion during aortic occlusion, on the role of hypothermia in protection of the ischemic myocardium, and on whether the heart should be fibrillated or left beating in normal rhythm during surgery.

Most of the information on metabolic and functional changes occurring in the myocardium during extracorporeal circulation has been derived from studies on blood, either systemic or from the coronary sinus. The potential of cardiac lymph as an index of the cardiac "milieu interieur" has not been investigated until recently, undoubtedly because of difficulties inherent in cannulation of cardiac lymphatics. Our development of a reliable method of collection of cardiac lymph in dogs,6 has allowed subsequent studies which indicated that lymph is a very good indicator of the metabolic situation in the myocardium. In particular, we have been impressed with the sensitivity of cardiac lymph in demonstrating anoxic changes in the heart,7 and we believe that lymph is a more reliable parameter of such changes than coronary sinus blood.

The present experiments were designed to study the changes in cardiac lymph during cardiopulmonary bypass and certain procedures used commonly in open heart surgery.
Materials and Methods

Twenty-five adult mongrel dogs, weighing from 21 to 28 kg, were anesthetized with intravenous sodium pentobarbital (30 mg/kg), intubated, and ventilated with a Palmer respirator using a mixture of 96 percent oxygen and 4 percent CO₂. The heart was exposed through a left lateral thoracotomy and the pericardium opened widely. To delineate the cardiac lymphatics, one or two subepicardial injections of T 1824 dye were performed. The cardiac lymph node, which is the main recipient of cardiac lymph, was exposed between the innominate artery and the superior vena cava. All dye-stained lymphatics except one were carefully ligated, and cannulation was then performed by means of a specially designed cannula. This was kept in place by ligatures and traction sutures, and a stable flow of cardiac lymph was established.

Cannulation of vessels for cardiopulmonary bypass was performed peripherally, using the common iliac veins and the left external jugular vein. This method was chosen to reduce cardiac manipulations to a bare minimum and to avoid dislodgement of the lymph cannula. The superior and inferior vena cavae were encircled with tape and the azygous vein ligated, so that total bypass could be obtained. Venting of the left heart was achieved, whichever indicated, by a cannula inserted through the left atrial appendage. To reduce cardiac manipulation and to protect the lymph cannula, the coronary perfusion line was introduced into the supravalvular portion of the ascending aorta through the left subclavian artery in the chest. The aortic lumen could be occluded around this cannula, using a snare of umbilical tape. Catheters were inserted into the femoral vein and artery for infusions, blood gas sampling and continuous monitoring of blood pressure. The ECG was recorded throughout the experiments, and blood gas analyses were performed at regular intervals (Instrumentation Lab, Inc.).

The extracorporeal circuit utilized a medium-sized Temp-control disposable bubble oxygenator, equipped with roller pumps. The circuit was primed with 1,500 ml of fresh ACD blood obtained from healthy donor dogs, and 1,000 ml of 5 percent dextrose in 0.2 percent normal saline. Heparin (30 mg per 500 ml of ACD blood) and 100 ml of 7.5 percent sodium bicarbonate (89.2 mEq) were added to the prime. The dogs were heparinized (3 mg/kg body weight) prior to insertion of canulas. The extracorporeal system delivered an average flow of 2,000 ml per minute at a pressure averaging 120 mm Hg, and allowed for either partial or total cardiopulmonary bypass with venting of the left heart and coronary perfusion when indicated. The coronary perfusion line was driven by a separate pump. Calculated flow into the proximal part of the ascending aorta was 250 ml per minute at a pressure of approximately 200 mm of Hg. The experimental set-up is depicted in Figure 1.

The dogs were divided into five groups:

Group A (eight animals)

These were subjected to partial and total cardiopulmonary bypass at normothermia for periods ranging from 30 minutes to one hour, with the heart beating.

Group B (five animals)

After initiation of bypass, the heart was electrically fibrillated for periods of 30 minutes. This was achieved by using a battery delivering a current of 1-5v, through crocodile clips attached to the right and left atrial appendages. The left heart was decompressed with a left atrial vent. The heart was then defibrillated with AC shock and bypass maintained for another 30 minutes.

Group C (four animals)

Following total bypass and left atrial venting, the ascending aorta was occluded for 15 minutes at normothermia. Due to surface cooling by exposure to room air, the temperature was usually at 35°C during this procedure. Following release of the aortic clamp and restoration of heart action by electric shock, bypass was continued for another 30 minutes.

Group D (four animals)

The blood was cooled to 30°C on extracorporeal circulation, and the experiment carried out as in Group C.

Group E (four animals)

Bypass was initiated and the aorta occluded at normothermia with simultaneous coronary perfusion of oxygenated blood. At the end of 15 minutes, the aortic clamp was released and the coronary perfusion stopped.

During all the experiments, cardiac lymph and coronary sinus blood were sampled simultaneously at regular intervals and analyzed for concentrations of lactate. Before and after bypass, coronary sinus samples were obtained by direct puncture. During total bypass, samples were taken from the right atrium, since all the blood entering the right chambers was considered as coronary venous blood. Lymph and blood specimens were immediately mixed with a measured amount of cold perchloric acid, and the lactate concentrations determined by an enzymatic spectrophotometric method. As explained in a previous study,7 pyruvate determinations in cardiac lymph were neither feasible nor believed to yield additional information. Changes in the flow rate, evidence of blood staining and the pH values of cardiac lymph were noted at different stages of the experiments.

Results

Group A: Bypass at Normothermia with a Beating Heart

During cardiopulmonary bypass, there was no significant change in the flow rate of cardiac lymph. On total bypass, the flow of lymph tended to decrease slightly. Blood staining of the lymph was never noticed either during or after perfusion. Arterial blood gas analyses showed a moderate respiratory alkalosis in all the dogs during bypass. This was noted in all the experimental groups. The pH of cardiac lymph was consistently at very

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Figure 1. Diagrammatic sketch of the experimental set-up used for studies of cardiac lymph during extracorporeal circulation.
alkaline levels (8.0 or more), which has been established as normal in dogs.7 Shortly after the start of bypass, the lactate concentration in coronary sinus blood showed a sharp rise and continued to climb steadily during the whole period of extracorporeal circulation. Maximum values were obtained immediately after termination of the bypass. Initial sharp rise of lactates was not seen in cardiac lymph. Instead, the rise was slow but steady and usually exceeded the blood levels before the end of bypass (Fig 2). Maximum values were seen immediately after bypass, following which there was a slow decline. This trend of a slow, steady rise in lactate concentrations during bypass was noticed during all the experiments.

**Group B: Bypass at Normothermia with a Fibrillating Heart**

Cardiac lymph flow was considerably diminished during fibrillation, averaging less than 50 percent of the flow during bypass and sinus rhythm. After defibrillation, the flow increased sharply, exceeding the baseline values, and remained so for the rest of the experiment. During the first 15 minutes of fibrillation, the lymph remained clear. Following this period, it was noted to become faintly blood stained and remained so after defibrillation and throughout the experimental period. Lactate concentrations showed a steep rise during fibrillation, and this pattern persisted until after termination of bypass. Coronary sinus blood showed the same pattern as in group A, with slightly elevated values. However, there appeared to be no significant elevation of lactates in the blood during fibrillation (Fig 3).

**Group C: Anoxic Cardiac Arrest at Normothermia**

A sharp decrease in cardiac lymph flow occurred immediately after aortic occlusion. Release of the aortic clamp was followed by a copious flow of lymph, which was frankly blood stained (Fig 4). The increased flow, as well as the blood staining, persisted until the end of the experiment. The pH of cardiac lymph did not change during the period of aortic occlusion. After release of the aortic clamp, however, the pH value showed a sharp but transitory drop, and soon returned to the original alkaline values. The pH of arterial blood, on the other hand, stayed within normal limits throughout the experiment (Fig 5). Lactate concentrations in lymph and blood specimens showed a maximum rise during the period of anoxic arrest, and continued to climb...
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Figure 5. pH of cardiac lymph during extracorporeal circulation and aortic occlusion. Steadily until the termination of the experiment (Fig 6). These values were the highest recorded in the whole series of studies performed.

Group D: Anoxic Cardiac Arrest at Hypothermia

Changes in the flow rate of lymph were similar to those recorded in group C. Following release of the aortic clamp, the lymph was invariably stained, but very faintly as compared to the heavy staining after normothermic arrest. The other significant difference was the pattern of lactate concentrations (Fig 6). This followed the general trend in group A, with a steady but slow rise during bypass, but remained at considerably lower levels than in group C with signs of return to baseline values after termination of bypass.

Group E: Aortic Occlusion with Coronary Perfusion

Cardiac lymph was clear throughout the experiment, and no significant changes in flow occurred. The lowest lactate concentrations in the whole series were recorded in this group (Fig 7).

A diagram of the mean values for cardiac lymph lactate concentrations (Fig 8) gives a comparison of the results in the different experiments conducted.

Discussion

Use of blood to assess the metabolic state of the myocardium has several drawbacks. The bloodstream is several steps away from the myocardial...
cell and therefore cannot accurately reflect the intracellular events. Samples of coronary sinus blood are also open to the criticism that they may reflect regional differences in the myocardium. Finally, any sample of arterial or venous blood taken during cardiopulmonary bypass will necessarily also reflect the whole body perfusion rather than myocardial events alone.

Cardiac lymph is virtually free from these drawbacks. It originates from the interstitial spaces surrounding the myocardial cells and is therefore closer to the intracellular level. In a previous study of cardiac lymph, coronary sinus blood and systemic arterial blood, it was demonstrated that anaerobic myocardial metabolism, as expressed by lactate concentrations, can be detected by analysis of the lymph even when the blood lactate concentrations are normal. By induction of short-lasting myocardial anoxia, it was also suggested that cardiac lymph was a sensitive index of anoxic effects upon myocardial cells and capillaries. This assumption was based upon:

a) Pronounced blood staining of the lymph, which contained numerous red cells by microscopy. This was taken as evidence of long-lasting and perhaps permanent damage to the coronary capillaries, induced by the anoxic episode.

b) A striking post-anoxic increase in lymph flow which was ascribed partly to local hemodynamic changes, partly to increased capillary permeability.

c) A pronounced increase in lactate concentrations of the cardiac lymph during and after the anoxic episode; an increase which was far more pronounced and long-lasting than the corresponding changes in arterial as well as in coronary sinus blood.

Based upon these observations and conclusions, we consider it likely that cardiac lymph at present is a better medium for evaluation of myocardial and vascular changes during cardiopulmonary bypass and certain cardiac surgical procedures.

To establish a baseline for evaluation of the various auxiliary procedures, the first experimental series was designed to determine the lactate concentration pattern during extracorporeal circulation alone (group A). The results show a slow, progressive rise in lactate concentrations of lymph and blood which represents the changes induced by the cardiopulmonary bypass situation. This baseline pattern itself does not necessarily indicate any degree of myocardial anaerobism. A similar increase in lactate concentrations of arterial blood has been reported during cardiopulmonary bypass, and can be ascribed to factors present during perfusion which are known to increase the lactate levels. Of these, the most common are the presence of respiratory alkalosis, and the glucose load from the priming solution, both of which were present during our experiments.

Ventricular fibrillation provides a quiet field for open-heart surgery, and has been advocated as a safe method in the presence of coronary perfusion. This is supported by Senning, who reported that myocardial oxygen consumption during extracorporeal circulation did not differ in beating and fibrillating hearts. Other studies, however, have indicated that fibrillation does increase oxygen consumption as compared to the beating state and can be a factor in producing myocardial necrosis. The present experiments indicate that fibrillation does produce changes in capillary permeability, as shown by the faint blood staining of the lymph, as well as increased anaerobic metabolism.

In the experiments with anoxic cardiac arrest, changes in cardiac lymph were quite striking. The lymph became frankly blood stained, indicating severe damage to the capillary endothelium, and the steep rise in lactates during and after aortic occlusion attested to a pronounced anaerobic metabolism in the myocardium. Another important feature was the progression of changes even two hours after the termination of the extracorporeal circulation. This pattern must be considered indicative of long-lasting, and perhaps permanent damage to the myocardium, and was induced by only 15 minutes of anoxic arrest. Indeed, ultrastructural studies have demonstrated cellular damage in the myocardium after 20 minutes of cardiac anoxia during open-heart surgery. It should be kept in mind that the "safety" of a surgical procedure is often assessed by the ability of the heart to take over circulation after bypass, or the immediate survival rate. This is indeed a rough measure, since plain survival does not necessarily mean that temporary or permanent damage to the myocardium has not occurred.

Moderate hypothermia did not decrease the lymph wash-out after the release of the aortic clamp. This is in accordance with our previous observations and indicates that the postocclusion wash-out of lymph is dependent mainly on hemodynamic changes in the capillary bed. The faint staining of the lymph indicated that even at hypothermia, some damage to the endothelium of the capillaries had occurred. However, a distinct protective effect from anaerobiosis was apparent from the lactate concentration curves.

In animals subjected to satisfactory coronary perfusion, all evidence of capillary damage and
myocardial anaerobism was absent. It therefore
seems justified to conclude that continuous perfu-
sion of the coronary arteries is the method of choice
to protect the myocardium during cardiac anoxia,
provided the perfusion pressure is kept within
normal range.20 The apparent safety of anoxic
cardiac arrest4,5 is not supported by this study,
which seems to confirm other reported results based
on investigations of changes in blood and ultra-
structure.19 The duration of anoxic cardiac arrest in
our experiments was timed to fall well within the
reported "safety range" of coronary ischemia in
dogs.5

The present study also indicates that a beating
heart is preferable to fibrillation during bypass
surgery and that moderate hypothermia offers a
significant degree of protection against anoxic dam-
age and anaerobic metabolism.

The pH of cardiac lymph was observed to fall
sharply immediately following periods of anoxia,
normothermic cardiac arrest. At the same time, the
ECG and blood gas readings remained normal. This
supports our view that cardiac lymph is a better
parameter than blood for studying several aspects
of myocardial cell metabolism and myocardial cir-
culation. We believe that it will prove to be a very
useful medium for future investigations in the
laboratory, and that attempts should be made to
extend this approach to clinical medicine as well.

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