CARDIAC LYMPH AND LYMPHATICS

EXPERIMENTAL OBSERVATIONS AND CLINICAL SIGNIFICANCE

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SCIENTIFIC EXPERIMENTATION WAS John Hunter's way of life, and nowhere is its value better illustrated than in the field of cardiac surgery, which has seen phenomenal advances thanks to experimental work in the laboratory. In an oft-quoted letter to his good friend Edward Jenner in 1775 John Hunter wrote these famous words—'Why think? Why not try the experiment?' It is therefore appropriate that this lecture should deal with experimental work on a subject that was of great interest to both John and William Hunter—namely, the lymphatics, or 'absorbents', to use the Hunterian term.

Since lymph originates from the intercellular fluid, it is a step closer to the cells than blood. Cardiac lymph may therefore be expected to reflect closely the changes occurring in heart muscle in health and in disease. Unfortunately, this subject has been a long-neglected one, and it is only in recent years that there has been an appreciation of the possible significance of the cardiac lymph and lymphatics in heart disease. The cardiac lymphatics have been shown to be affected in rheumatic heart disease[1]. Recent experimental work has suggested that lymphatic obstruction may produce functional as well as pathological changes in the heart, some not unlike those seen in rheumatic and other affections of the heart[2, 3].

The story of the discovery of the cardiac lymphatics is practically as old as that of the discovery of the lymphatic system itself. On 30th October 1651 Olaus Rüdbeck, of Sweden, observed for the first time lymphatic 'glands' receiving afferent vessels from the heart in a dog. In 1692 Nuck used mercurial injections to demonstrate the lymphatics in the dead heart—a method which fell into disuse until nearly a century later, when William Hunter and his assistant Cruikshank in England, and Mascagni in Italy, employed this technique to give the first detailed account of the superficial cardiac lymphatics, with relevant illustrations.

The method of injecting coloured substances into the myocardium of the living heart was introduced by Albrecht in 1887. Using this technique

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Aagaard, in 1924, was able to demonstrate the subepicardial, myocardial, and subendocardial lymphatic plexuses. The most exhaustive study of the morphology of the cardiac lymphatics was not made until 1939, when Patek[4] established beyond doubt the presence of intercommunicating lymph capillary networks in the subendocardial, myocardial, and subepicardial layers of the ventricles. He was unable, however, to demonstrate lymphatics in the atrial muscle or atrioventricular valves. A year later Drinker and his colleagues[5] succeeded in cannulating a lymphatic vessel leaving the heart in a dog and studied the flow rate and partial composition of cardiac lymph. Nothing more was attempted until the late fifties, when Miller and his colleagues[2, 3] in Chicago provided the stimulus for further work on this subject. They produced chronic lymphatic obstruction of the dog heart and reported marked pathological changes in the myocardium and endocardium in consequence. Their suggestion that lymphatic obstruction may be of significance in the aetiology of certain cardiac disorders focused the attention of clinicians and research workers on the subject of cardiac lymph and lymphatics. Since then anatomical studies of the cardiac lymphatics have been carried out with hydrogen peroxide[6, 7] and dye injection techniques[8, 9, 10] on the beating dog heart.

The present study was undertaken at the Institute of Medical Sciences, Pacific Medical Center, San Francisco. Its main purpose was to evaluate the use of cardiac lymph as a parameter of myocardial behaviour and to assess the functional and pathological changes in the heart following lymphatic obstruction. To achieve this a preliminary study of the anatomy of the cardiac lymphatic drainage into the mediastinum, as well as a baseline study of the flow characteristics and composition of normal cardiac lymph, was essential. Thus the project was divided into five sections: (A) anatomical studies of the lymph drainage of the heart; (B) the flow and composition of cardiac lymph; (C) the effect of anoxia on cardiac lymph; (D) cardiac lymph during extracorporeal circulation; and (E) functional and pathological changes in the heart following chronic cardiac lymphatic obstruction.

Lymph drainage of the heart

Methods. Anatomical studies were conducted on 35 anaesthetized adult mongrel dogs. The heart was exposed through a left anterolateral thoracotomy in the fourth intercostal space. The pericardium was opened and small amounts of Evans blue (T 1824) were injected at multiple sites into the myocardium of all the four chambers through a 27-gauge needle. Care was taken to avoid contamination of the pericardial cavity by the dye. Ten dogs were killed and a detailed and meticulous mediastinal dissection performed to outline the extracardiac course of the lymphatics. In some cases attempts were made to demonstrate lymphatics in the mitral and tricuspid valve leaflets in the beating heart, employing the technique described by Miller *et al.*[3] Tissue specimens from the myocardium and valves were processed for microscopical examination.

Results. A dense network of subepicardial lymphatics was demonstrated immediately after dye injection. These converged on to larger vessels, supplied with valves, which coursed alongside the coronary vessels in the atrioventricular sulcus and terminated in the left tracheobronchial node. The efferents from this node, usually two or three in number, ran diagonally upwards across the trachea and behind the innominate artery to enter the 'cardiac node' situated between the superior vena cava and the innominate artery (Fig. 1). Efferents from this lymph node ran upwards towards the neck to join the right lymphatic duct.

Though this was the pattern in the majority of the dogs, anatomical

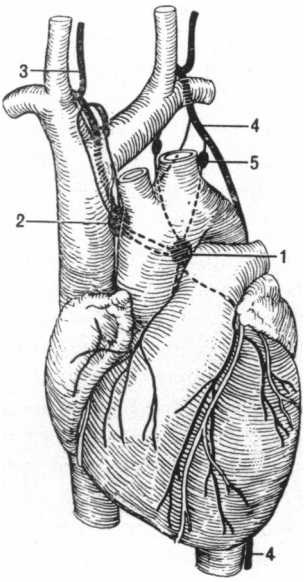

Fig. 1. Schematic diagram of lymphatic drainage pathways in the dog heart. (1) Tracheobronchial lymph node. (2) Cardiac node. (3) Right lymphatic duct. (4) Thoracic duct. (5) Posterior mediastinal node.

variations were found in nearly a third of the animals. Quite frequently a couple of efferent vessels from the tracheobronchial node entered small paratracheal nodes at the apex of the chest, sometimes completely bypassing the cardiac node. In a few cases several small vessels were seen communicating directly with the thoracic duct. The frequent presence of such anatomical variations in lymph drainage makes it essential, in all experiments involving total cardiac lymph obstruction or collection of all the cardiac lymph, for the lymphatic pathways to be studied first in each animal. Otherwise some of the cardiac lymph may escape analysis or lymph originating elsewhere may be included.

In 4 dogs it was possible to demonstrate the presence of fine lymphatic vessels in the wall of the atria, the main difficulty, as with the valves,

being the injection of dye into these thin structures in a beating heart. Very delicate lymphatic vessels were also demonstrated on the atrial surfaces of the mitral and tricuspid leaflets.

Flow and composition of cardiac lymph

Methods. A standard technique was developed[11] to expose, dissect, and cannulate an afferent lymph vessel joining the cardiac node between the superior vena cava and the innominate artery. All the other lymph vessels demonstrated by dye injection were ligated, thus ensuring a total collection of all the heart lymph. This was carried out on 15 anaesthetized adult mongrel dogs, 10 of which were ventilated with a mixture of room air and oxygen (5 l./min), while the remainder were maintained on room air alone.

The dye-stained cardiac lymph collected during the first 15 minutes was discarded. The clear lymph following this was collected in heparinized tubes for estimation of electrolytes. Protein and lactate estimations were also performed, the latter by a spectrophotometric method of high sensitivity described by

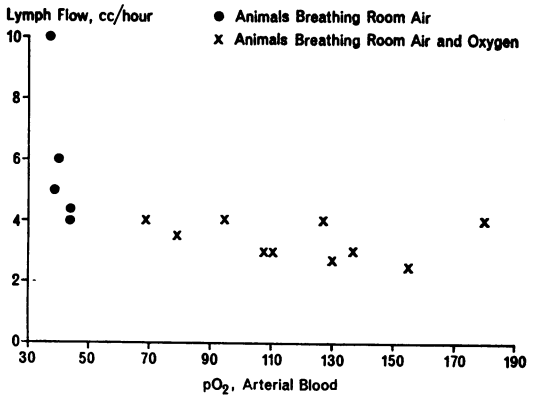

Fig. 2. Relationship between cardiac lymph flow and arterial oxygen tension.

Mattenheimer[12]. The pH of the lymph specimens was determined with an Instrumentation Laboratories gas analyser. Corresponding blood samples taken from the coronary sinus were analysed for electrolytes, proteins, pH, and lactate.

Results. *Lymph flow.* The rate of flow of cardiac lymph in dogs breathing room air and oxygen varied from 2.5 to 4 ml/hr (mean 3.3 ml/hr). Flow rates of more than 5 ml/hr were observed in dogs breathing room air alone (Fig. 2). Differences due to anaesthetic agents and rapid fluid infusions, which are known to affect the flow of lymph[13], were eliminated by keeping these two factors constant in all the experiments. The only significant factor found to alter cardiac lymph flow was the oxygen tension (Po_2) in arterial blood, a low Po_2 being always associated with a high lymph flow.

Electrolytes and proteins. The average chloride and sodium values tended to be higher and the potassium values lower in cardiac lymph than in coronary sinus blood. All the protein fractions were present in cardiac lymph but in different proportions from those in plasma. The albumin : globulin ratio was consistently higher in cardiac lymph than in plasma.

pH. In all well-oxygenated dogs the pH of cardiac lymph was consistently on the alkaline side (8.0 or higher).

Lactate. The mean lactate concentrations in cardiac lymph were significantly higher than in coronary sinus blood (Fig. 3). Pyruvate estimations were not carried out owing to the technical difficulty of collecting the quantities of lymph needed for such tests. Besides, recent

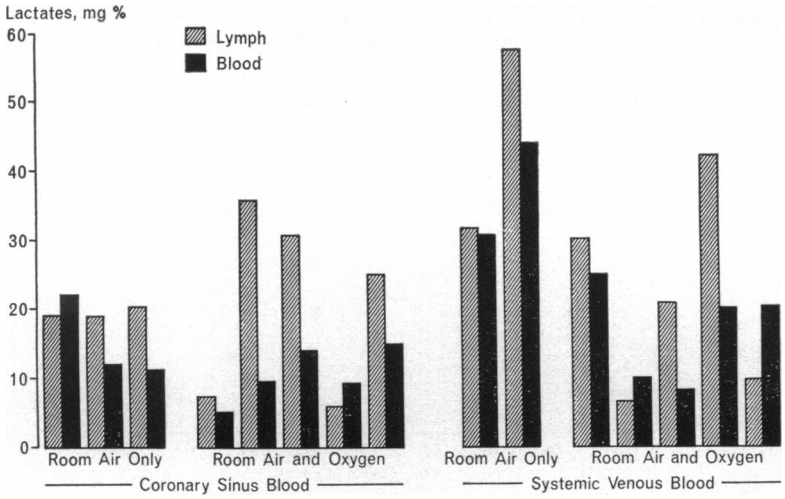

Fig 3. Lactate concentrations in cardiac lymph and blood.

work[14] has shown that the lactate level alone serves as a good indicator of oxygen deficit and that neither the pyruvate level nor the lactate : pyruvate ratio is more reliable.

Effect of anoxia on cardiac lymph

Blood is one step away from the tissue cells, with the interstitial fluid and lymph intervening. For this reason it is believed that the validity of blood lactate and pyruvate levels as true indicators of the intracellular state of oxygenation is open to doubt[15]. The same argument has been advanced against relying on the electrolyte levels in the blood as reflecting the electrolyte state in the myocardium[16]. The consistently higher level of lactate found in cardiac lymph than in coronary sinus blood suggests that lymph may perhaps provide a more sensitive

indicator of changes in myocardial oxygenation. To test this hypothesis a set of experiments were devised to study the changes in cardiac lymph resulting from oxygen lack.

Methods. Cardiac lymphatic cannulation was carried out on 15 anaesthetized dogs and the first hour's collection of lymph was used to determine baseline flow rates and lactate concentrations. Generalized anoxia was then produced in 10 of the dogs by stopping the respirator and clamping the endotracheal tube. As soon as cardiac arrest occurred the dog was resuscitated by oxygenation, cardiac massage, and correction of acid–base problems. The cardiac lymph was collected for another 2–3 hours and analysed for lactate. Corresponding samples of blood from the coronary sinus were also analysed. The arterial blood gases were monitored throughout the experiments.

In 2 dogs generalized hypoxia was induced by ventilation with a mixture of 10% oxygen and 90% nitrogen. Cardiac arrest did not occur in either.

In 3 others the left anterior descending coronary artery was occluded for an hour, producing localized myocardial anoxia. The occlusion was released after this period and both lymph and coronary sinus blood analysed for lactate during the next 2–3 hours.

Results. The most noticeable change was in the flow rate and colour of the cardiac lymph. Both generalized hypoxia and anoxia produced a sharp rise in the lymph flow rate. This was noticeable within 5 minutes of the anoxic episode and continued for 1½ hours, after which it started to decline slowly. Even 3 hours after the anoxic episode the lymph flow rate was still higher than the pre-anoxia level. The cardiac lymph also became grossly blood-stained in the dogs subjected to anoxia, and the blood-staining persisted during the next 3 hours right up to the end of the experiments. The blood-staining was either absent or very faint in the dogs subjected to generalized hypoxia.

In the dogs with occlusion of the anterior descending coronary artery the lymph remained clear and the flow rate practically stable during the period of occlusion. Immediately after restoration of coronary perfusion the lymph became grossly blood-stained and the flow rate rose steeply, both the changes persisting during the rest of the experiment.

The lactate concentration increased sharply in both cardiac lymph and coronary sinus blood during the first hour after anoxia, the lymph showing the higher readings. The blood value thereafter decreased, reaching baseline level within 1–2 hours. The pattern of change in cardiac lymph was markedly different; the lymph lactate level remained high for 2 hours or more before starting to decline slowly, and remained considerably above the baseline level in all the dogs at the end of the experiments (Fig. 4).

Discussion. Hypoxia and anoxia have been reported to produce increased flow and protein concentrations in cervical[17], pulmonary[18],

and thoracic duct lymph[19]. Two possible causes of the increased flow have been postulated; one is increased capillary filtration pressure resulting from complex cardiovascular reactions in response to oxygen lack[20] and the other is increased capillary permeability due to endothelial damage[21]. The changes seen in cardiac lymph suggest that both these mechanisms must be operating, depending on the degree and duration of oxygen lack. The blood-staining must surely indicate damage to the capillary endothelial cells.

The sensitivity of cardiac muscle to lack of oxygen is well appreciated and documented. But the prolonged trend of changes in the cardiac lymph following anoxia suggests that myocardial damage from anoxia, even of short duration, may be far more profound than has previously been suspected from studies of the blood under such conditions. Thus

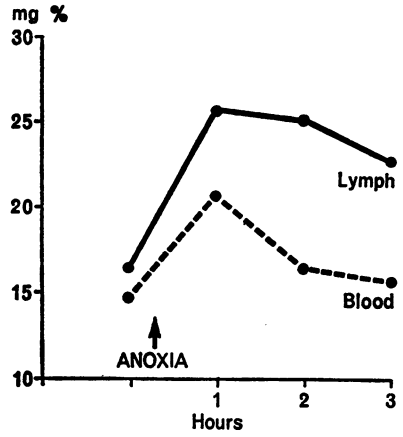

Fig. 4. Trend of changes in lactate concentrations in cardiac lymph and coronary sinus blood during and after anoxia.

it appears that even after a very brief cardiac arrest and adequate resuscitation, the status quo in the myocardium is not restored for a considerable period of time, although the usual blood readings may not indicate anything abnormal and the patient appears to have made a satisfactory clinical recovery from the episode.

These observations also confirm that changes in the cardiac lymph, particularly its colour, flow rate, and lactate content, can be used as sensitive indices of changes in the myocardium during and after periods of oxygen deficit. It would also seem that in this respect cardiac lymph is a far more sensitive and accurate indicator than coronary or systemic blood.

Cardiac lymph during extracorporeal circulation

Most of our present information about the changes in the heart during bypass have come from studies of blood. In spite of these studies

there are still several practical problems which remain unsolved or about which there is no unanimity of opinion. Thus anoxic cardiac arrest is considered by many to be detrimental to myocardial function[22], while others are impressed with the apparent clinical safety of this procedure[23]. Differences of opinion exist about the use of coronary perfusion during aortic occlusion, on the role of hypothermia during extracorporeal circulation, and on whether the heart should be fibrillated or left beating during bypass and surgery. As cardiac lymph had proved to be a very sensitive indicator of myocardial damage due to anoxia, it was logical to use it to study the changes in the myocardium during bypass and the above-mentioned procedures.

Methods. Adult mongrel dogs weighing 21–28 kg were anaesthetized and a stable flow of cardiac lymph was established. The external jugular vein and the external iliac vessels were cannulated for bypass (Fig. 5). This reduced manipulations in the vicinity of the heart to a bare minimum, preventing dis-

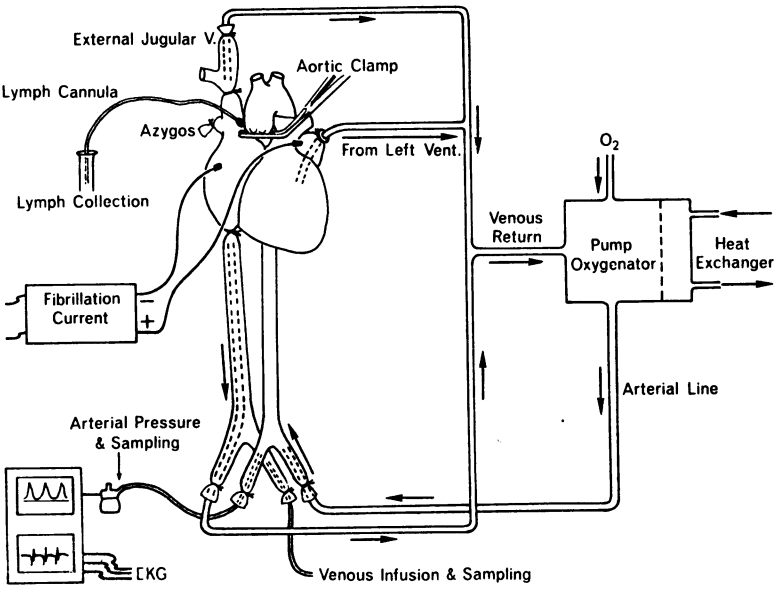

Fig. 5. Schematic diagram showing the experimental set-up for cardiopulmonary bypass and lymph cannulation.

lodgement of the lymph cannula. The superior and inferior venae cavae were encircled with tapes and the azygos vein ligated before lymph cannulation, so that total bypass could be achieved whenever indicated. A cannula inserted through the left atrial appendage served as a left heart vent. To avoid disturbing the lymph cannula the coronary perfusion cannula was introduced into the supravalvular portion of the ascending aorta through an opening made in the left subclavian artery in the chest. The aortic lumen could be occluded around this

cannula by means of a snare. Catheters were inserted into the femoral vein and artery for infusions, blood gas sampling, and continuous monitoring of blood pressure.

A medium-sized Temptrol disposable bubble oxygenator equipped with De-Bakey roller pumps was used for cardiopulmonary bypass. The circuit was primed with 1,500 ml of fresh acid-citrate-dextrose dog blood and 1,000 ml of 5% dextrose in 0.2% normal saline. An average flow rate of 2 l./min at an average pressure of 120 mm Hg was maintained. The coronary perfusion line was driven by a separate pump with a calculated flow of 250 ml/min at an average pressure of 200 mm Hg.

Results. *Group 1 (8 dogs).* These were subjected to partial and total bypass at normal temperature for ½–1 hour, with the heart beating. The flow rate of cardiac lymph tended to decrease slightly during total bypass, but otherwise remained stable. The lymph remained clear during and after bypass. There was a slow but steady rise in lymph lactate concentration during bypass, the maximum values being seen immediately after the end of perfusion, following which there was a slow decline back to baseline values. Moderate respiratory alkalosis was present in all the dogs during bypass.

Group 2 (5 dogs). After initiation of bypass the heart was fibrillated electrically for 30 minutes, with decompression of the left heart by a left atrial vent. The heart was then defibrillated with AC shock and bypass continued for another 30 minutes. The cardiac lymph flow decreased by more than 50% during fibrillation. It remained clear for the first 10–15 minutes, after which it became faintly blood-stained and remained so to the end of the experiment. After defibrillation and restoration of the heart beat the lymph flow increased sharply, exceeding the baseline flow rate, and remained so even after bypass was discontinued. The steep and persistent rise in the lactate concentrations of cardiac lymph during and after fibrillation is shown in Figure 6.

Group 3 (4 dogs). After initiation of total bypass at normal temperature and left atrial venting the ascending aorta was clamped for 15 minutes. After the release of the clamp and restoration of heart action bypass was continued for another 30 minutes. Aortic occlusion coincided with a sharp decrease in cardiac lymph flow. Release of the occlusion was immediately followed by a copious flow of lymph which was frankly blood-stained, both these changes persisting till after bypass and the end of the experiment. The highest and sharpest rise of lactate concentrations in lymph in the whole series was recorded in these dogs (Fig. 7).

Group 4 (4 dogs). The same experiment was performed as in Group 3 but with the blood cooled to 30°C during the period of aortic occlusion. Though the lymph flow changes were essentially similar to those seen in Group 3, the blood-staining was very faint. The lactate

concentrations rose slowly and steadily during bypass but remained at significantly lower levels than in Group 3 (Fig. 7).

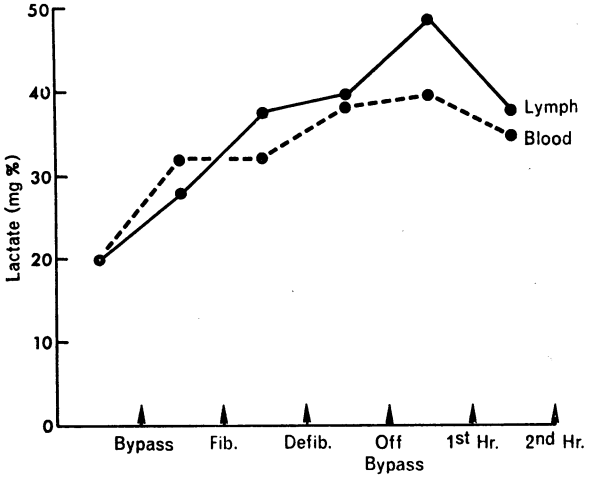

Fig. 6. Lactate concentrations in cardiac lymph and blood during bypass and fibrillation (Fib.).

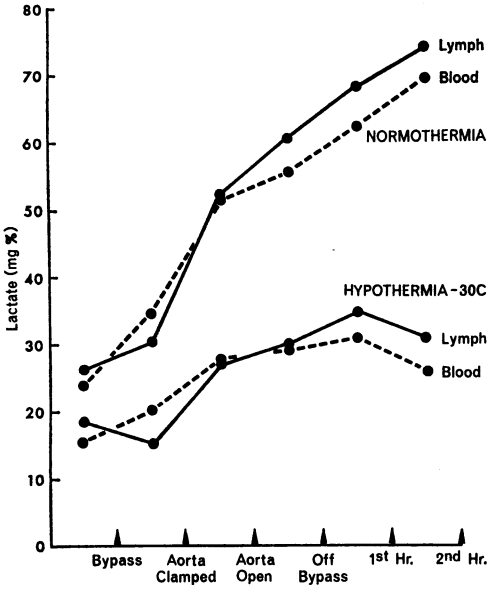

Fig. 7. Changes in lactate content of cardiac lymph and blood during and after anoxic cardiac arrest at normothermia and moderate hypothermia.

Group 5 (4 dogs). The aorta was occluded for 15 minutes at normal temperature with simultaneous coronary perfusion. No significant changes were noticed in the flow rate of cardiac lymph, which re-

mained perfectly clear throughout the experiment. The lactate concentrations in lymph were the lowest recorded in the series (Fig. 8).

Discussion. The cardiac lymph changes during anoxic cardiac arrest clearly point to severe damage to the capillary endothelium in the myocardium, as well as to pronounced anaerobic metabolism. The progression and persistence of these changes must be regarded as indicating long-lasting and perhaps permanent damage to the myocardium, even though the anoxic arrest period was only 15 minutes, which is reported to be within the 'safety range' for dogs[23]. The so-called safety of a surgical procedure is often assessed from the ability of the heart to take over after bypass or the immediate survival rate. This is evidently an unsatisfactory method of assessment, as such 'safe' procedures may well produce long-lasting changes in the myocardium which cannot be

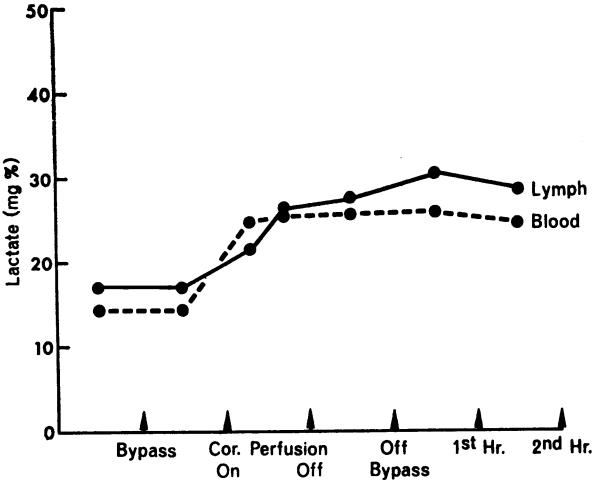

Fig. 8. Influence of coronary perfusion during bypass on lactate content of cardiac lymph and blood.

appreciated by the usual battery of tests, most of them conducted on blood. Ultrastructural studies[24] have demonstrated cellular damage in the myocardium after 20 minutes of anoxic arrest during clinical open-heart surgery. The apparent clinical safety of anoxic arrest, as reported by some, is not supported by our findings in cardiac lymph. The study also indicates that a beating heart is preferable to fibrillation during bypass surgery and that moderate hypothermia does confer a significant, though not complete, degree of protection against anoxic damage to the heart muscle.

Changes in the heart following chronic cardiac lymphatic obstruction

Methods. In 22 adult dogs the cardiac lymph drainage was studied and all the lymph vessels leaving the heart were divided between ligatures. The cardiac

node was dissected out and excised after ligation and division of all the vessels entering and leaving it. The dogs were killed at intervals of 1–36 weeks and histopathological studies of cardiac tissue carried out. In 14 of these dogs haemodynamic data were collected before lymphatic obstruction and again at the second operation. Six dogs were subjected to 'sham operations'—thoracotomy and injection, dissection, and identification of the cardiac lymphatics, which were left intact. The haemodynamic data included heart rate, arterial blood pressure, left atrial pressure, left ventricular systolic and diastolic pressures, and the maximum rate of rise of intraventricular pressure (dp/dt). Cardiac output was measured by the Cardiogreen dilution technique at three different levels of left atrial pressure. The stroke volume and the left ventricular work (g/m) were calculated and ventricular function curves constructed.

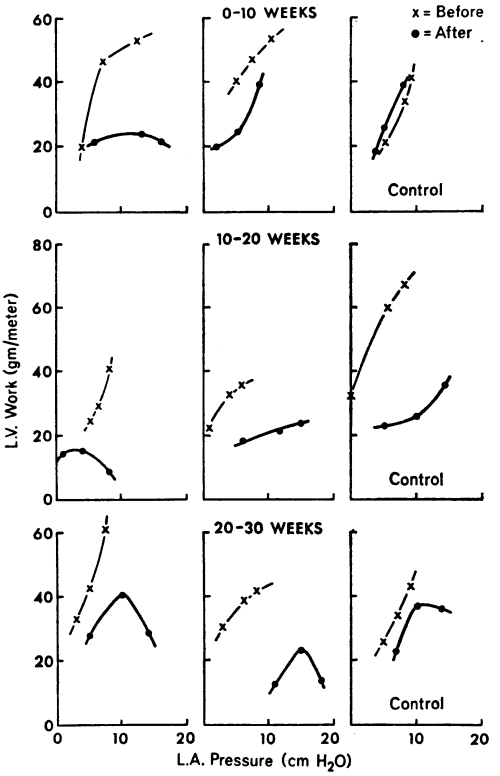

Fig. 9. Changes in ventricular function curves following cardiac lymphatic obstruction.

Haemodynamic changes. The ventricular function curves were depressed in all dogs after cardiac lymphatic obstruction, as well as in those controls which were evaluated more than 10 weeks after the initial operation. The control dogs evaluated within the first 10 weeks showed no significant changes in their ventricular function curves (Fig. 9).

A significant reduction in maximum dp/dt was also observed in the majority of animals with cardiac lymphatic obstruction (Fig. 10) and was definitely more marked than in the controls.

No significant changes in the electrocardiogram or serum enzyme levels were noticed, as reported by Foldi and Braun[25].

Discussion. The reduction in maximum dp/dt must be assessed with caution in view of the various factors which are known to affect such readings[26] and which could not be controlled during these experiments. Functional abnormalities have been observed in the postoperative period after heart transplantation, and interruption of lymph pathways has

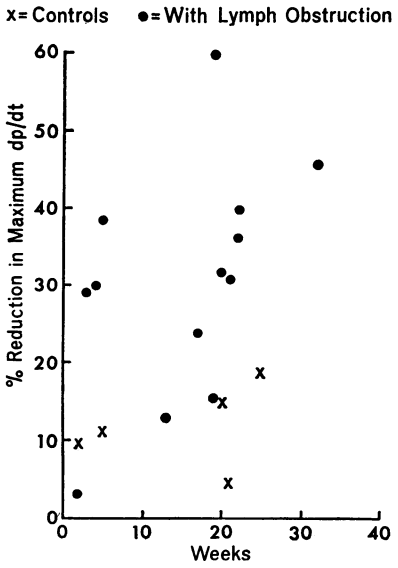

Fig. 10. Changes in maximum dp/dt in dogs with cardiac lymphatic obstruction.

been one of the reasons suggested[27]. The changes in ventricular function curves in the first 10 weeks after lymphatic obstruction would appear to support this theory.

Pathological changes. No evidence of cardiac enlargement, pericardial effusion, or gross cardiac failure was found in any of the dogs. Surprisingly, no collateral or aberrant lymph pathways could be demonstrated. The presence of lymphovenous communications was suspected, but could not be confirmed. In the majority of dogs with long-standing cardiac lymphatic obstruction the atrioventricular valve leaflets were found to be thickened and irregular, with a waxy appearance. In vivo injection of dye into these leaflets demonstrated a far more extensive network of lymph capillaries than is found normally

(Fig. 11). However, gross endocardial thickening and subendocardial haemorrhage, as reported by Miller *et al.*[2], were not observed in this series.

Microscopically, significant changes appeared to be confined to the atrioventricular valves and, to a slight extent, the endocardium. These consisted of dilated interstitial spaces and lymph capillaries during the first 3 weeks. In more chronic lymph obstruction, thickening of the valve leaflets became apparent and was quite marked after 12 weeks. The thickening was caused by loose mesenchymal connective tissue and

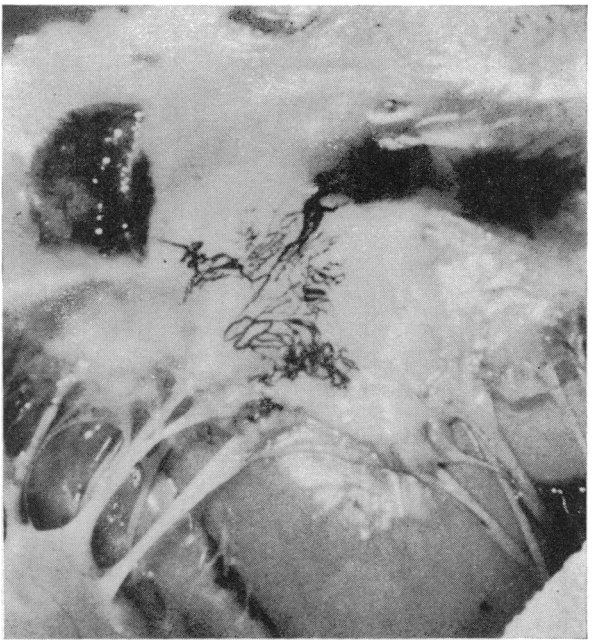

Fig. 11. Preparation showing the extensive network of lymph vessels on the atrial surface of the mitral valve in a dog with lymphatic obstruction of the heart.

also by accumulation of an amorphous 'myxoid-like' substance which was faintly basophilic on staining with haematoxylin and eosin and stained positively with Alcian blue (Fig. 12). The same changes, along with some degree of fibrosis, were sometimes found in the subendocardial layer, though these were patchy in distribution and far less pronounced than in the valve leaflets.

Discussion. Occasional deposits of myxoid are known to occur in old dogs, but never to the extent observed in this series. Moreover, these dogs were young and no such lesions were present in the controls.

These findings may have some clinical significance. Myxomatous degeneration of the mitral valve has been recognized as a cause of isolated acquired mitral regurgitation[28]. Similar changes have been shown to cause mitral insufficiency and cardiac failure in dogs, with increased susceptibility to endocarditis and to rupture of the chordae tendineae[29]. Electron microscopical studies have demonstrated that rheumatic heart lesions are associated with deposits of acid mucopolysaccharides, similar to the 'myxoid' seen in these experiments, in the endocardium.

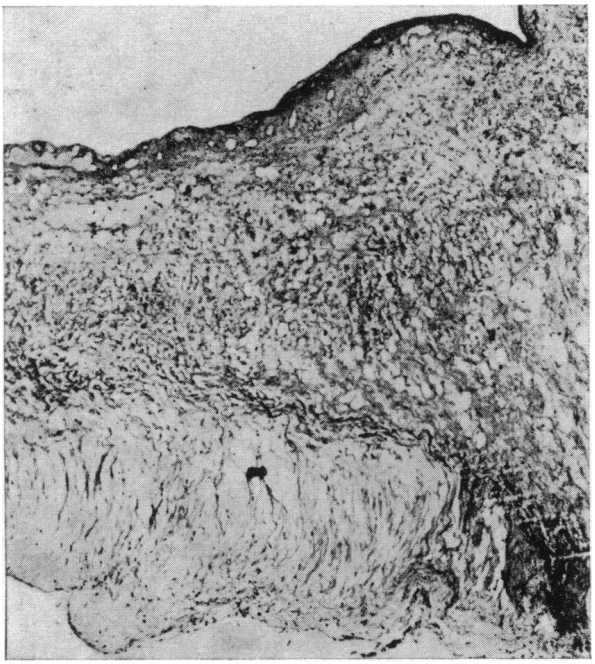

Fig. 12. Microscopic appearance of a section through the mitral valve leaflet, showing deposition of 'myxoid' and connective tissue following lymphatic obstruction.

The absence of collateral lymph pathways was puzzling. Lymphatic regeneration occurs after transection or ligation of lymph vessels[30]. After resection of a length of lymphatic, however, lymph flow can be established only through the opening up of preexisting collateral channels[31]. It is possible that in the heart a substantial amount of lymph is drained through lymphovenous communications, which are known to start functioning under the stress of increased lymph pressure or volume[32]. This may also explain the absence of gross and progressive changes in the myocardium and endocardium even after long-standing

lymphatic obstruction. A thorough investigation of lymphovenous communications in the heart is long overdue.

Conclusions

Cardiac lymph appears to provide a very sensitive indicator of anoxic changes in the myocardium. Such changes can be appreciated in cardiac lymph even when the usual blood studies present an apparently satisfactory picture. The use of blood to assess the metabolic state of the myocardium has several drawbacks. The blood stream is a step away from the heart cells. Any arterial or venous blood sample used for analysis during bypass will necessarily reflect the state of whole body perfusion rather than local changes in the myocardium alone. Even samplings of coronary venous return are unsatisfactory, as they may reflect regional differences in the heart muscle, depending on the site of sampling. Cardiac lymph is virtually free of these defects.

It also appears that lymphatic obstruction impairs myocardial activity by producing changes in structure and function. It is tempting to surmise that some form of lymphatic dysfunction may be of significance in rheumatic and other forms of heart disease. Unfortunately, observations on laboratory animals need not always be applicable to man, and we have yet to study the normal lymphatic drainage of the heart of man in detail, for want of a satisfactory method of demonstrating these lymphatics post mortem. Now that the attention of research workers has been drawn to this field, no doubt satisfactory techniques will be developed and the results may provide new insight into the working of the heart and the diseases affecting this most fascinating muscle in the human body.

ACKNOWLEDGEMENTS

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PRIMARY F.R.C.S. COURSE IN BIRMINGHAM

A COURSE FOR candidates taking the Primary F.R.C.S. Examination will be held at the Birmingham Medical School on each Wednesday from 2.30 to 7.00 p.m., from 10th January to 6th June 1973.

The syllabus will include lectures, tutorials, and demonstrations in anatomy, physiology, general pathology, bacteriology, immunology, and pharmacology. The course will not replace systematic reading in these subjects.

All those attending the course will meet at the Medical School at 2.00 p.m. on Wednesday 10th January for a preliminary discussion of arrangements before the first lecture.

Refreshments during the 4.30–5.00 p.m. break can be taken in the canteen in the New Block of the Medical School.

A trial examination consisting of multiple choice and written essay questions will be held on the last afternoon, 6th June, to be taken by all those who have attended the course.

The course fee is £21 and the number of places available is limited to 20. Applications should be made to Professor A. G. W. Whitfield, Director, Board of Graduate Studies, The Medical School, Birmingham B15 2TJ, and should be accompanied by the names of two referees.

FINAL F.R.C.S. COURSE IN BIRMINGHAM

THIS COURSE IS run every Thursday from 2.30 until 7.00 p.m. and is held in turn at the various Birmingham hospitals. The next term will be from 11th January to 26th April 1973. There will be a four-day intensive course from 30th April to 3rd May 1973 designed for those candidates who are taking the English F.R.C.S. at this time.

A fee of £15 will be charged for each term and an additional fee of £10 for the four intensive days in May.

Applications should be made to Professor A. G. W. Whitfield, Board of Graduate Studies, The Medical School, Birmingham B15 2TJ, enclosing the course fee. It is hoped that those signing on for this course will attend regularly.