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The Myocardial Factor in Irreversible Hemorrhagic Shock

Alterations of Myocardial Performance of the Isolated Canine Heart Preparation following Irreversible Hemorrhagic Shock

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The functional capacity of the myocardium in irreversible hemorrhagic shock has been studied by several groups of investigators. Their experiments, however, were all conducted in intact animals. Consequently, no real separation was made between myocardial changes and the overall biochemical alterations which may occur in other parts of the body of the animal due to severe hypotension.

The purpose of this investigation, therefore, was to compare the myocardial performance of the isolated normal heart preparation with the heart previously subjected to irreversible hemorrhagic shock. The advantage of this preparation was the degree of control which could be exerted upon

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extrinsic factors, and particularly those related to vascular tone and vascular volume capacity. Circulating metabolic products resulting from ischemia during the period of severe hypotension were also excluded as factors affecting the myocardium.

Method

Dogs weighing between 17 and 25 kilograms were kept under light intravenous pentobarbital anesthesia. The trachea was intubated and positive pressure breathing was instituted with a mechanical respirator. Heparin was given in a dosage of 5 mgm/kg. body weight. The left femoral artery and vein were cannulated, and the femoral artery was connected to an overhanging reservoir. The animals were bled into the reservoir and the mean arterial pressure was allowed to fall rapidly to 35 mm. Hg. It was maintained at this level for 120 minutes. The reversal of blood flow from the reservoir into the animal's vascular space indicated the onset of the irreversible stage of hemorrhagic shock (11). Animals which did not show this characteristic change were excluded from the study. At the end of this period, the animals were re-infused through the femoral vein with the blood remaining in the reservoir.

The isolation of the heart was then begun. The animals were placed in the supine position and bilateral trans-sternal thoracotomy was made between the fifth and sixth ribs. The azygos vein was ligated and loops of heavy silk suture were placed around the superior and inferior vena cavae. Three or four pairs of intercostal arteries located distal to the subclavian artery were ligated and divided; the descending aorta was looped in this area with heavy silk suture. The subclavian and brachiocephalic arteries were dissected at the arch of the aorta and looped individually with heavy strands of silk suture. The main left pulmonary artery was then exposed and cannulated with a large catheter. This catheter was connected to outflow tubing allowing the right ventricular output, which consisted only of the coronary venous return, to drain by gravity to the bottom of an oxygenator. A large clamp was then applied to the remaining left hilar structures and this lung was

totally removed. Another large catheter was inserted into the proximal end of the thoracic aorta and connected to a second outflow tubing. This conduit permitted the left ventricular output to flow to a main reservoir. A third catheter was placed in the left atrium through its appendage and all the air was carefully exhausted before this was connected to an inflow tubing returning the total cardiac output to the heart.

At this stage the heart was ready for complete isolation. The ligatures around the left subclavian and brachiocephalic arteries and the superior and inferior vena cavae were tied in rapid succession and a large clamp was placed around the hilar structures of the right lung. Right pneumonectomy was then carried out.

In the control normal group, the heart was isolated in the same fashion except for the fact that the animals were not subjected to the two hour period of acute hypotension.

The total cardiac output transversed the circuit which is shown in Figure 1. This consisted of a bubble oxygenator, a reservoir with a 3,000 ml. capacity, and a roller pump. The volume of blood delivered into the left atrium was controlled by the pump, which was carefully calibrated prior to each experiment. The total cardiac output could, therefore, be varied as desired by changing the rotation of the pump. A Brown heat exchanger was inserted between the pump and the left atrium to maintain a blood temperature of 37° centigrade. An airfilled "Starling resistance" was placed on the left ventricular outflow tubing which allowed maintenance of a selected aortic pressure. An infusion pump permitted administration of drugs into the line returning to the heart. The circuit was primed with 3,000 ml. of whole fresh blood that was collected on the morning of each experiment. Three # 15 Teflon catheters were inserted into the left atrium through one of the small pulmonary lobular veins, into the left ventricle through its dimple, and into the aorta through its wall. These catheters were connected to three separate Statham AC strain-gauge transducers and simultaneous pressures were recorded from these three areas by means of a direct writing

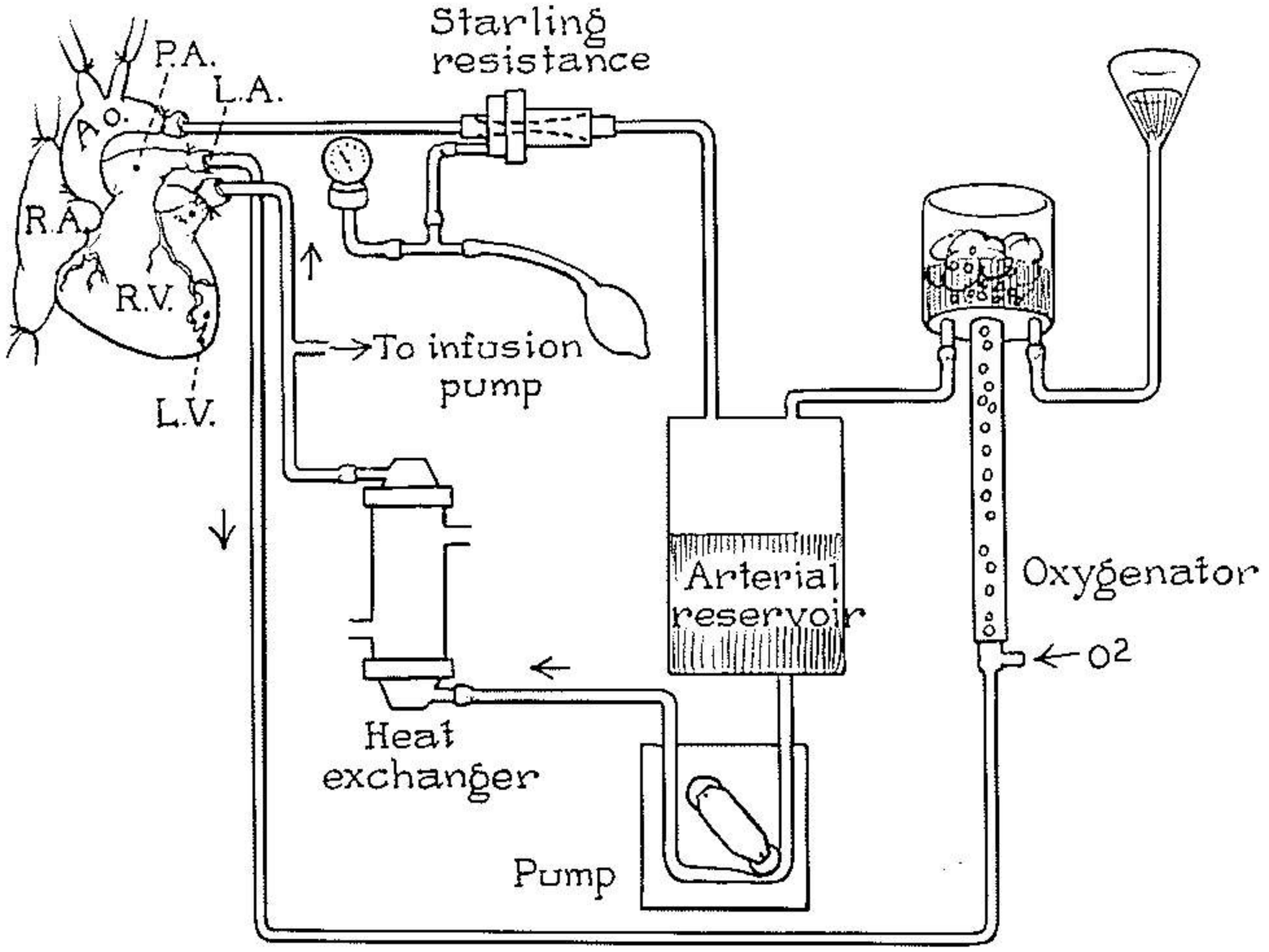


Fig. 1. Schematic diagram of the isolated canine heart preparation utilized to study the myocardial contractility in irreversible hemorrhagic shock. The venous blood from the right ventricle is oxygenated by the bubble oxygenator and flows into the arterial reservoir. Blood from this reservoir is pumped to the heart through the cannula placed in the left atrium.

4-channel Sanborn recorder. The tracings which are shown in Figure 2 are representative samples of aortic, left atrial, left ventricular and left ventricular end-diastolic pressures.

The maximum performance of the heart in each preparation was determined by increasing, stepwise, the stroke volume while the aortic pressure was maintained at a selected level. Figures 3 and 4 are tracings of a run from a control normal preparation in which gradual rises in left atrial and left ventricular end-diastolic pressures are demonstrated as the cardiac output was elevated from 300 ml. to 3,100 ml. The mean left atrial pressure was more easily obtained than the left ventricular end-diastolic pressure as illustrated by the tracings showing samples of both these pressures. Mean

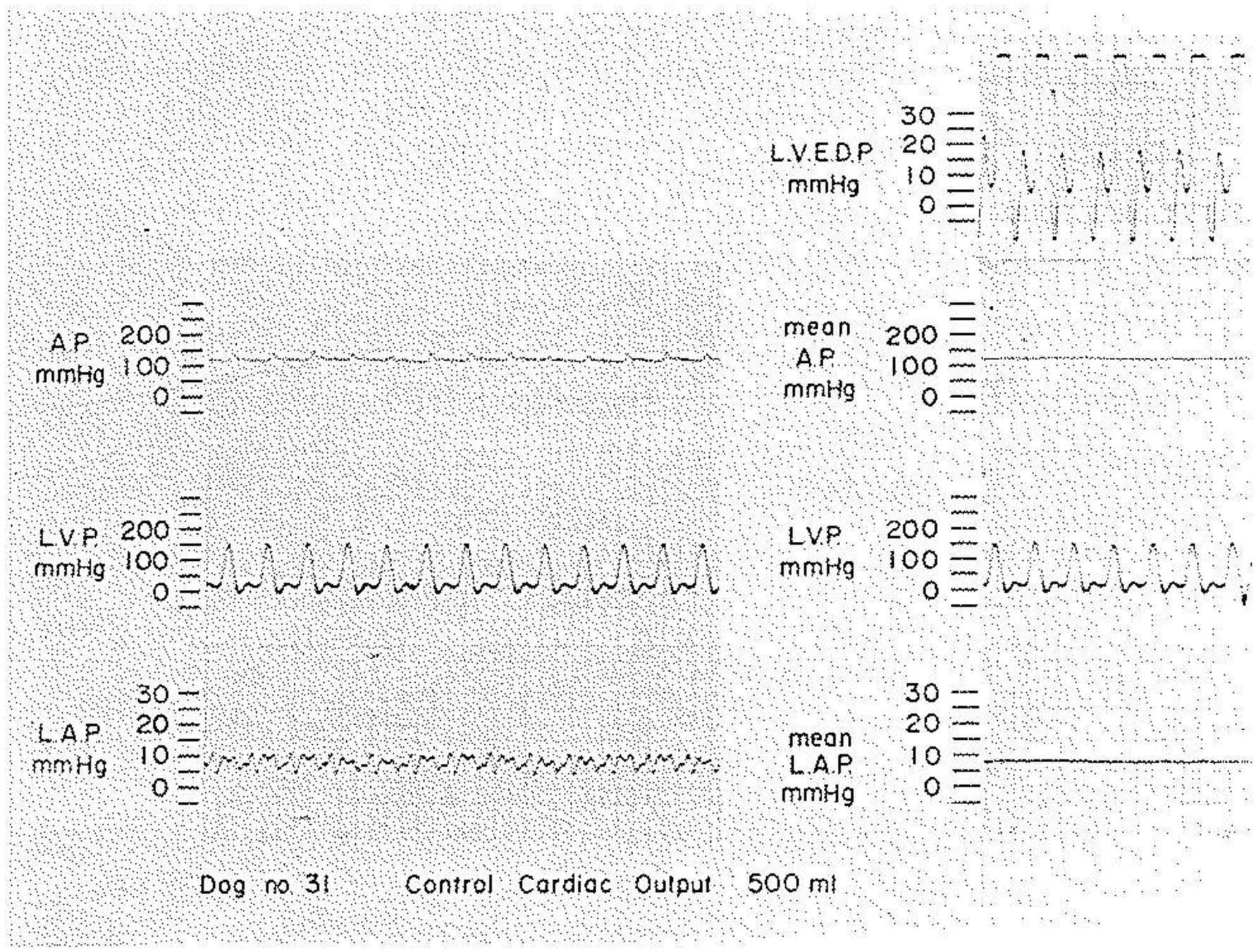


Fig. 2. Tracings of the pressures taken from a control normal preparation.

left atrial pressure in cm. of H2O was, therefore, plotted against the left ventricular stroke work in Gram Meter to construct left ventricular function curves. Left ventricular stroke work (L.V.S.W./G.M.) was calculated from the following formula:

$$\text{L.V.S.W./G.M.} = \frac{(\text{Cm. H2O M.A.P.-Cm. H2O M.L.A.P.}) \times \text{Stroke Volume}}{100}$$

M.A.P.: Mean aortic pressure, M.L.A.P.: Mean left atrial pressure
G.M.: Gram meter

Results

Figure 5 shows one of the left ventricular function curves obtained from several isolated heart preparations in the control group. The left ventricular function curves of all the preparations in this group were identical in configuration and location. This is shown in Figure 6 where four such curves

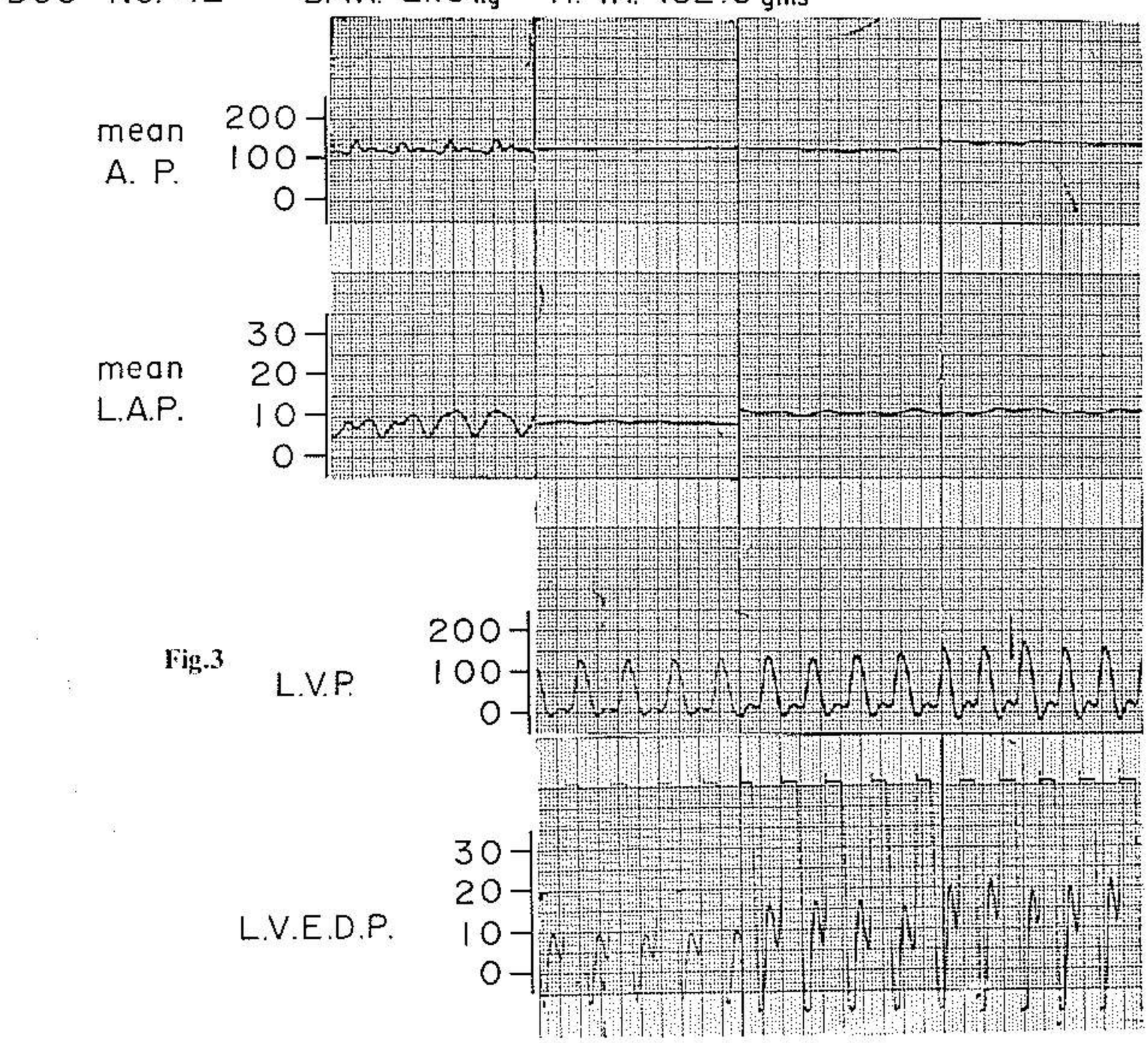


Fig.3

Figs. 3 & 4. Pressure tracings taken to study the maximum left ventricular work as the cardiac output is gradually increased from 300 ml. to 3,100 ml. The left atrial pressure rises as the cardiac output is increased during the run.

have been plotted, as well as curves obtained from hearts in the shock group.

In the isolated heart preparation, the performance characteristics of the heart could only be examined by studying the maximum cardiac output and the aortic pressure, and thereby the maximum work performed by the left ventricle. The highest cardiac output which was delivered by the heart in this preparation was 4,580 ml. and the maximum mean aortic pressure was in excess of 200 mm of Hg. The average for the maximum left ventricular

minute work was 3.8 kg. for each 100 grams of heart tissue.

The myocardial contractility of the isolated heart preparation in animals subjected to hemorrhagic shock and reaching the irreversible stage was studied in a similar manner. In these animals, the myocardium showed a severe degree of deterioration in its functional capacity. The altered myocardial contractility can be seen in Figure 6 where eight composite left ventricular function curves are presented from the shock group, and showing a marked displacement to the right as compared to similar curves of the control normal group.

A considerable decrease in the maximum left ventricular minute work

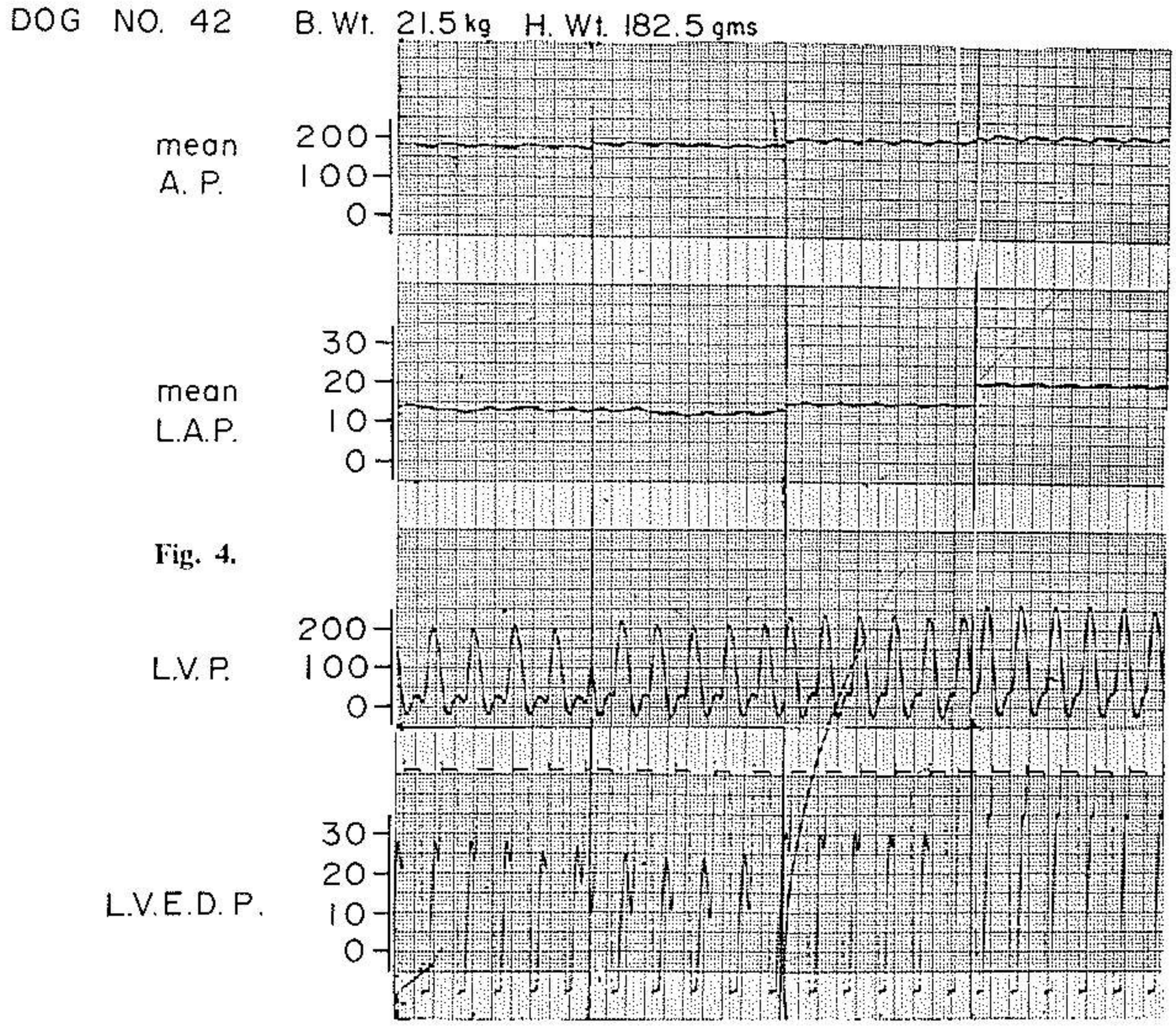


Fig. 4.

CARDIAC OUTPUT	2000	2400	2750	3100
STROKE VOLUME	14.2	15	17.1	19.3
L.V.S.W./G.M.	30.8	32.5	42.5	49.8

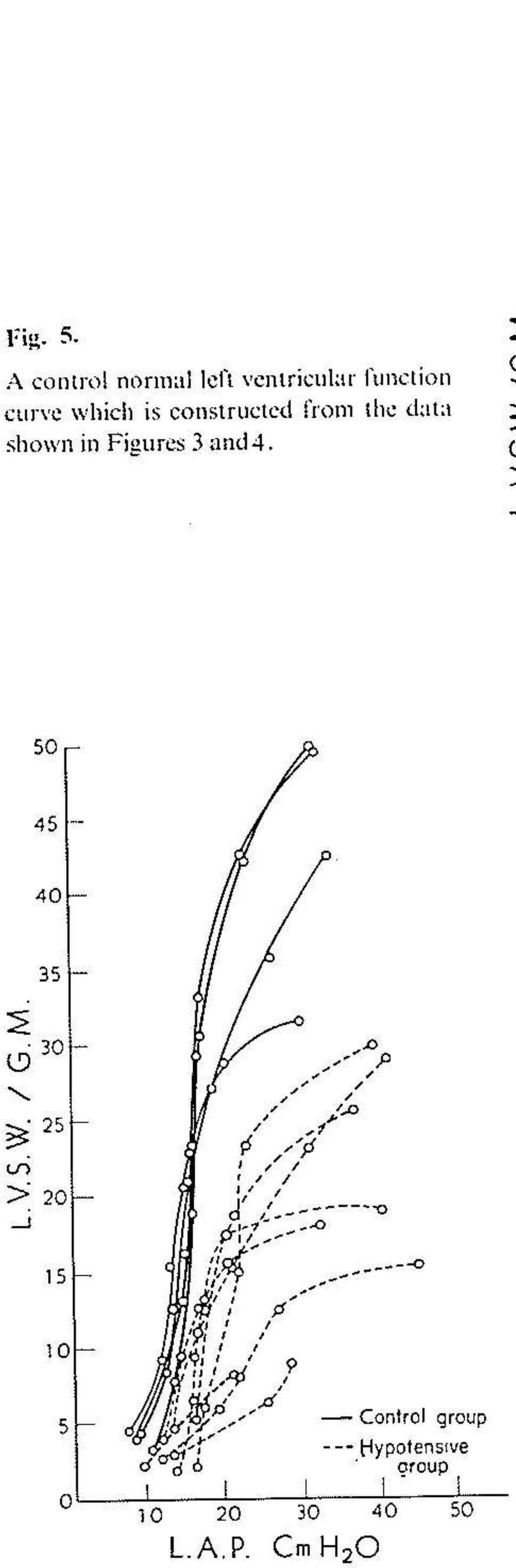


Fig. 5.

A control normal left ventricular function curve which is constructed from the data shown in Figures 3 and 4.

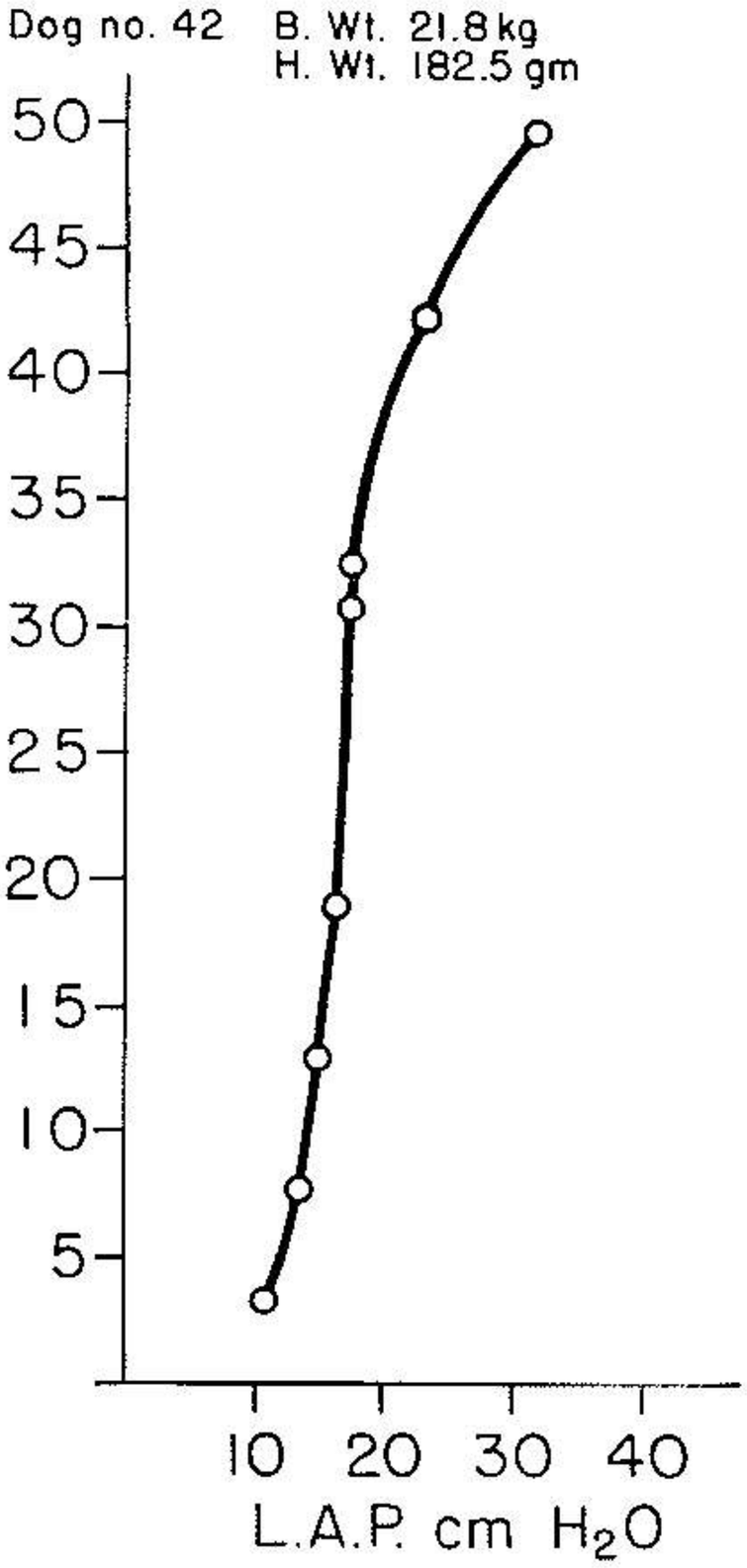


Fig. 6.

Composite 12 left ventricular function curves from four control normal preparations, and eight preparations from animals subjected to two hours period of hemorrhagic shock reaching the irreversible stage prior to the isolation of the heart.

in the shock group is shown in Table I, presenting the data collected from 16 isolated heart preparations. In the control group, the work performed by the left ventricle for each minute was between 3.1 and 5.8 Kg. for each 100 grams of heart tissue. Values for the group of hearts subjected to two hours of hemorrhagic shock prior to their isolation were between 0.5 and 2.5 Kg. for each 100 grams of heart tissue.

Norepinephrine was infused at the rate of four micrograms per minute to determine the positive inotropic response of myocardium in both groups. Figure 7 shows marked increase in myocardial contractility in a control normal preparation. Such a positive response, as seen in Figure 8, was also observed in the control normal preparations even when signs of left ventricular failure were observed after the experiment had continued for periods of three or four hours. In contrast, Figures 9 and 10 show the limited myocardial response to such an infusion in two preparations in the shock group.

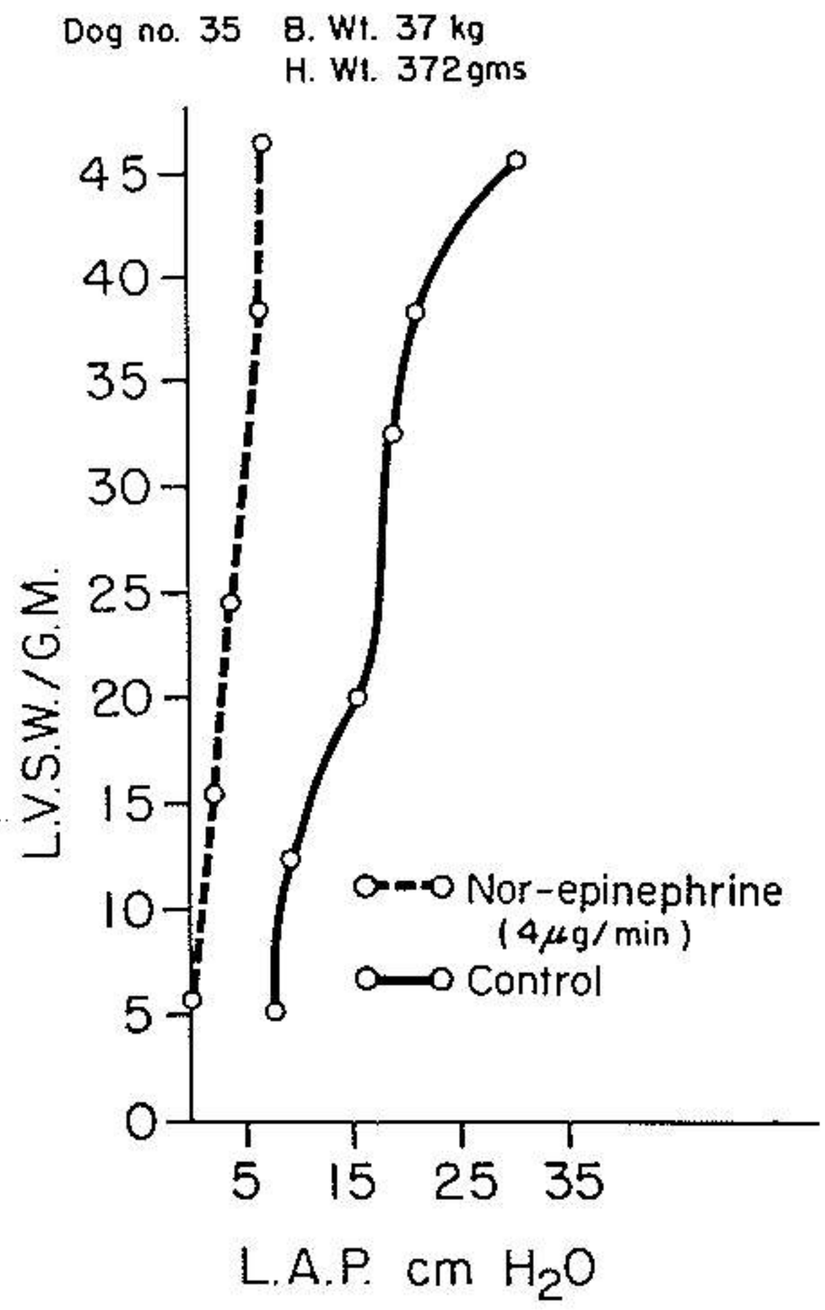


Fig. 7.

Displacement of the left ventricular function curve to the left, showing the positive inotropic effect of norepinephrine in an isolated normal heart preparation.

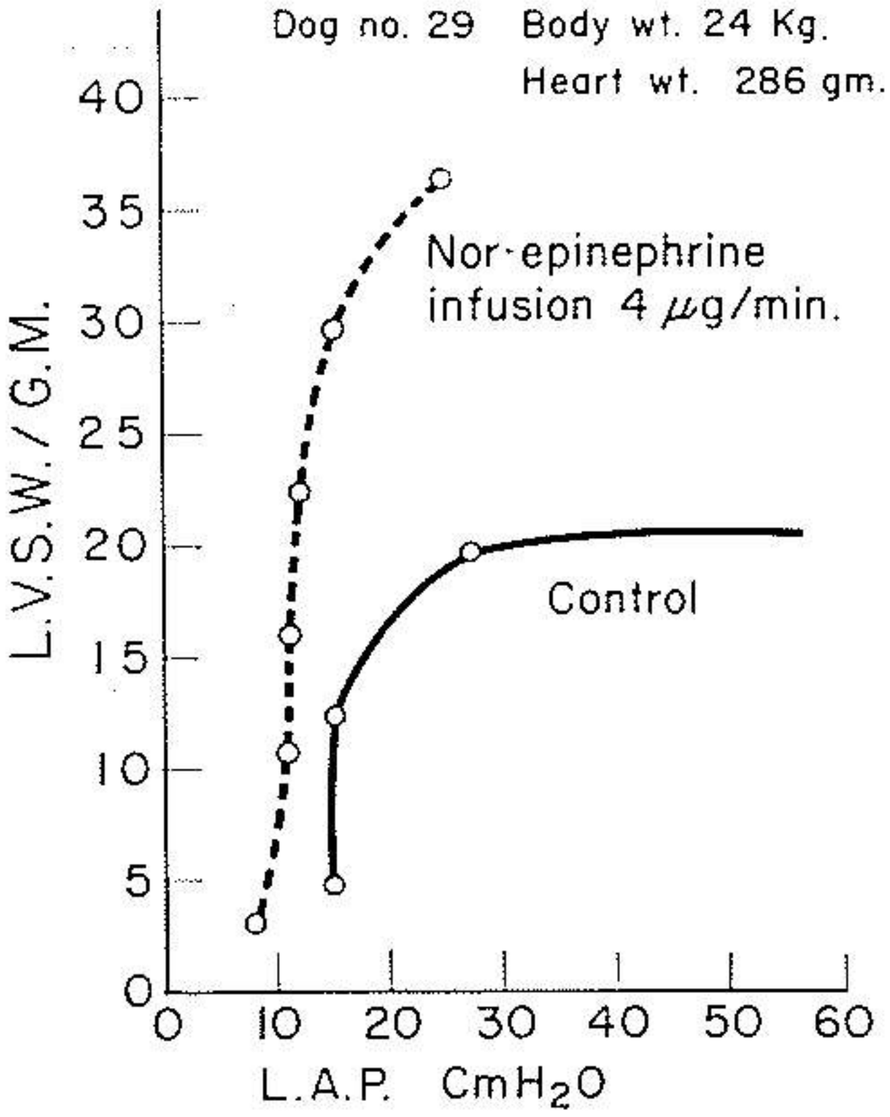


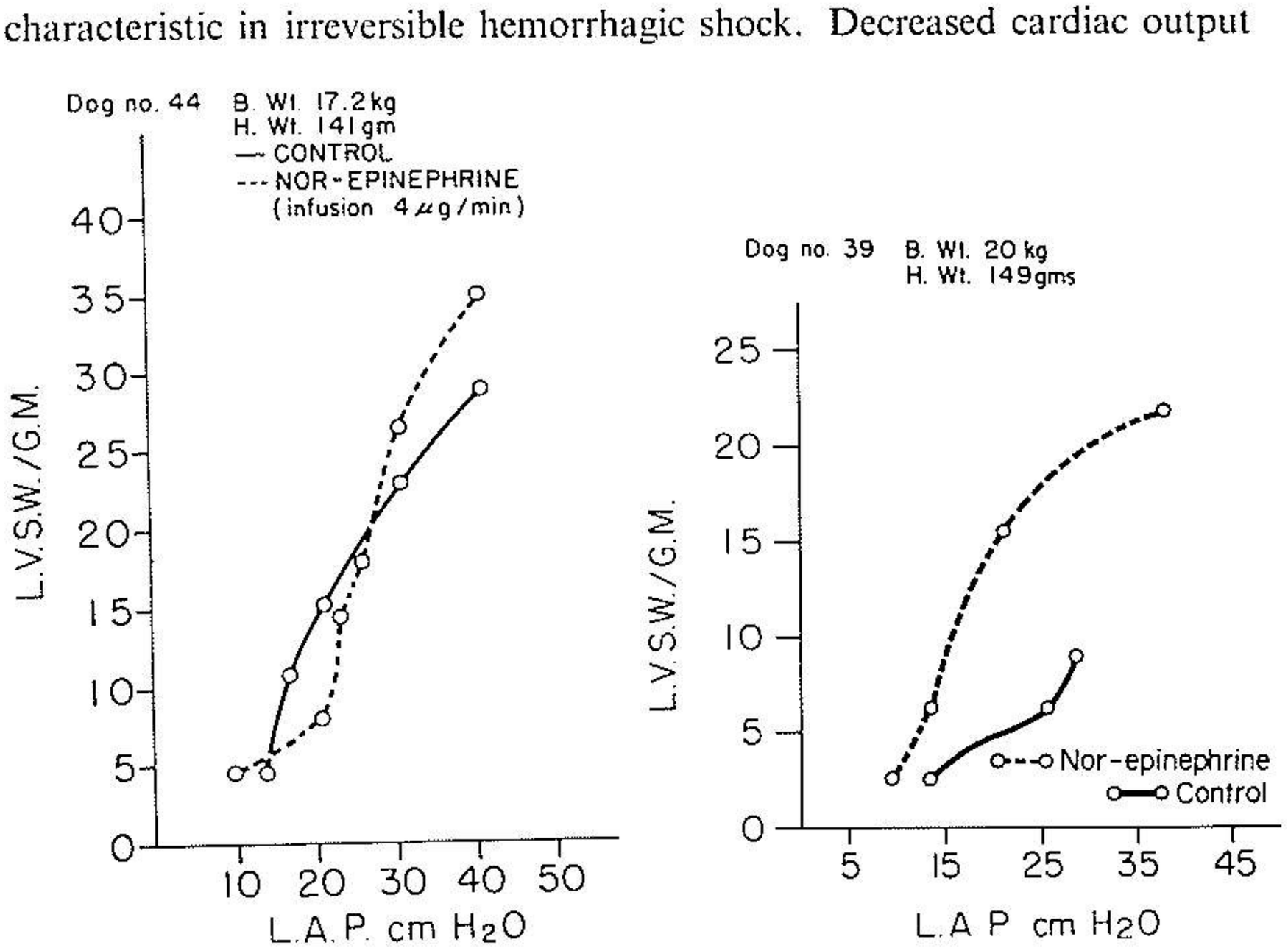
Fig. 8.
Marked restoration of myocardial contractility by norepinephrine infusion, in a control normal preparation after the experiment was continued for three hours and 30 minutes.

Discussion

High performance was characteristic of the isolated heart preparation used in this study. The heart, however, could not sustain its high cardiac outputs for long periods of time. Sarnoff and co-workers (8) have reported similar high performances in their supported isolated heart preparations. In those preparations, the right ventricular output was circulated into a living dog and fresh arterial blood was continuously removed from the animal to enter the circuit. This provided metabolic support for the isolated heart preparation. Deterioration of the myocardial performance in the supported isolated heart preparation was observed by those investigators after a considerable longer period of time than in the present non-supported preparation. Nevertheless, the non-supported preparation lasted up to four hours. Since all the left ventricular function curves in this investigation were obtained within 20 minutes of the isolation, myocardial changes from this procedure were thought to be uniform. Therefore, myocardial deterioration occurring in the hypotension group could only have resulted from the period of hemorrhagic shock to which the animals were subjected before

isolation of the heart was begun. In all the animals in the shock group, the aortic pressure returned to 100 mm Hg. or higher following their re-infusion with the blood remaining in the reservoir. Consequently, changes in myocardial capacity from further hypotension during the isolation procedure in this group was unlikely.

Wiggers and co-workers (9, 10) were first to make a detailed analysis of the hemodynamic alterations resulting from hemorrhagic shock. Those investigators noted that the rise of right atrial pressure preceded the terminal phase of the irreversible hemorrhagic shock. On the basis of their findings, it was postulated that reduction of the myocardial capacity is a significant factor in the deaths of animals undergoing periods of severe hypotension. The general and hemodynamic changes observed in more recent studies are typical of those previously reported (5, 12). Thus pyrexia, metabolic acidosis, decreasing cardiac output and systemic blood pressure are all characteristic in irreversible hemorrhagic shock. Decreased cardiac output



Figs. 9 & 10. Limited effect of norepinephrine infusion on myocardial contractility in two failing isolated heart preparations from animals subjected to two hours period of hemorrhagic shock.

Table 1 — Data obtained from 16 isolated canine heart preparations showing characteristics of myocardial performance for eight preparations in each group.

Dog #	Heart Wt. gr.	Maximum Cardiac Output ml.	Mean Aortic Pressure Hg.	L. V. S. W. gr.	L. V. M. W. Kg.	L. V. M. W./100 Heart Gram; Kg.
Control normal group:						
42	182.5	3,100	210	49.8	7.9	4.3
45	150.0	2,750	140	31.4	4.3	2.9
46	215.0	3,480	160	50.8	6.6	3.0
47	198.0	4,680	130	42.4	6.3	3.1
50	158.0	3,400	140	30.0	5.1	3.2
52	133.5	3,700	190	43.2	7.7	5.8
53	140.0	2,960	190	30.9	6.1	4.4
55	161.5	3,100	160	27.2	5.1	3.1
Hemorrhagic Shock Group:						
37	130	640	110	8.1	0.7	0.5
38	260	2,700	140	28.9	4.0	1.5
39	149	2,220	130	22.1	3.0	2.0
40	195	1,800	130	15.1	2.1	1.5
41	209	2,100	90	15.3	2.1	1.0
43	182	2,400	170	25.8	4.5	2.5
44	141	2,000	150	29.1	3.3	2.3
48	198	2,750	120	18.7	3.3	1.6

in irreversible hemorrhagic shock has been related to an expansion of the

vascular space and pooling of the blood in some areas of the body, resulting in the reduction of venous return. Guyton and Crowel (1, 2) have carefully examined this problem in intact dogs with irreversible hemorrhagic shock. In their animals, the cardiac output could be maintained at normal level only by transfusion with large amounts of blood. Continuous rise of pressures in both atriae was noted as the animals were treated in this manner: and as the shock was allowed to progress further, the heart was found unable to sustain its normal output even at the very high atrial pressures.

The displacement of the left ventricular function curves to the right in animals subjected to hemorrhagic shock in this study suggests the reduction of myocardial capacity. Normal cardiac output could not be obtained in any of these preparations because the left atrial pressure began to rise at lower atrial return rates than were required to raise left atrial pressure in control group preparations. By eliminating the extrinsic factors in this experiment it is clearly demonstrated that the deficiency of the left ventricular pumping mechanism is related to a myocardial factor resulting from the period of hypotension in which the animals were held prior to the isolation of the heart. The altered inotropic response of the myocardium to norepinephrine infusion in preparations subjected to hypotension is further evidence that myocardial injury is an important factor in leading hemorrhagic shock toward the irreversible stage. This response was, however, not completely lacking, and the pumping mechanism of the left ventricle in this group was still assisted somewhat by addition of norepinephrine to the circuit.

The mechanism by which the myocardium is injured in shock remains an enigma. The role of ischemia has been supported by the gross and microscopic examination of the heart in animals who had recovered from long periods of hemorrhagic shock. In that study, Melcher and Walcott (6) were able to demonstrate local degenerative changes similar to those found in myocardial ischemia. Nevertheless, in that investigation, all the animals had recovered from shock after they were re-infused with blood and, there-

fore, the myocardial functional deterioration was still at its reversible stage. More data supporting the role of ischemia were presented in the experiment conducted by Sarnoff and co-workers (7). In their study, increased left atrial pressure resulting from the irreversible hemorrhagic shock could be returned to normal by augmenting myocardial blood flows with perfusion of the left main coronary artery by a pump.

More recent experiments conducted by Gomez and Hamilton (3, 4) tend to minimize the role of ischemia as an important factor in producing irreversible myocardial damage in hemorrhagic shock. In their study, normal myocardial performance was shown in dogs immediately after 90 minutes of hemorrhagic shock. However, a lapse of 60 minutes from the moment that the shock was treated with re-infusion of blood, resulted in some deterioration in the cardiac pumping mechanism. From these findings, these authors were led to support the possibility that some cardiotoxic agent resulting from the period of hypotension can be present in the circulating blood. This factor, perhaps a metabolic by-product, is thought to effect the deterioration of myocardial performance. Our current interest is directed toward clarifying some of these conflicting results. Normal isolated hearts are being infused with blood circulating in an animal kept in irreversible hemorrhagic shock, and their performance studied.

Summary

Myocardial performance, utilizing the isolated canine heart preparation, was studied in two groups: normal control dogs and those subjected to hemorrhagic shock. A marked deterioration in myocardial functional capacity was observed in the shock group. From this study, myocardial incapacity resulting from the period of acute hypotension is felt to be a contributing factor in the death of animals with irreversible hemorrhagic shock.

Résumé

Utilisant le coeur isolé, le fonctionnement du myocarde a été étudié

dans deux lots de chiens: un lot témoin et un deuxième lot soumis au choc hémorragique. Dans ce dernier groupe, on a noté une importante altération de la capacité fonctionnelle du myocarde.

Il semble résulter de cette étude que l'atteinte du myocarde que provoque l'hypotension aiguë est un facteur qui favorise la mort des animaux atteints de choc hémorragique irreversible.

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