

THE EFFECT OF PHENOXYBENZAMINE ON MYOCARDIAL CONTRACTILITY IN DOGS

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INTRODUCTION

The adrenergic blocking properties which are inherent in phenoxybenzamine (Dibenzylamine) have made this compound an attractive prospective tool for reversing the peripheral vasoconstriction associated with different types of prolonged hypotension. The beneficial vasodilatory effect of Dibenzylamine has clearly been demonstrated in studies conducted on various types of clinically and experimentally produced shock (4, 11).

The direct myocardial response to this drug, however, in terms of its contractile power, has not been fully investigated. The data available on the cardiac action of Dibenzylamine (1, 3) are mainly concerned with changes in cardiac output which do not necessarily reflect changes in myocardial contractility. Since there is much evidence (2, 5) that impaired myocardial contractility contributes to the production of the irreversible stage of shock,

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it is vital that further understanding of the cardiac action of this drug be gained to justify its extensive therapeutic use. The present experimental model was designed to study only the changes in myocardial ejecting power resulting from the administration of Dibenzylamine.

METHODS

Twelve mongrel dogs ranging in weight from 14 to 20 kg. were anesthetized with intravenous pentobarbital. Tracheal intubation was accomplished, and the animals were respired with a positive pressure room air respirator. A left thoracotomy was performed through the fifth intercostal space. The aortic arch was dissected and umbilical tape tourniquets were passed around the brachiocephalic trunk and around the aorta just distal to the origin of the left subclavian artery. Heparin was administered after hemostasis was attained in a dosage of 2mg./kg. body weight. A cannula was passed into the aortic root through the left subclavian artery and the artery ligated distal to the point of entry. After pericardiotomy, the left ventricle was cannulated through the apex, the cannula being held in place with a purse-string suture.

Rigid cannulae were used to ensure a frequency response adequate for measurement of the first derivative of left ventricular pressure. Pressure measurements were made through these cannulae by means of two Statham AC-Strain gauge transducers, displayed on an oscilloscope screen and recorded photographically together with lead II of the electrocardiogram.

The afterload on the left ventricle was progressively raised by the application of a stepwise progressive tightening of the aortic tourniquet to complete occlusion, followed by progressive constriction of the brachiocephalic trunk by the same means. The entire occlusive sequence was com-

pleted in approximately 60-75 seconds. Total occlusion of the brachiocephalic artery was never allowed to exceed 15 seconds. The left ventricular pressure was recorded at two amplifier gain settings at each level of occlusion. The low gain setting allowed accurate determination of the peak left ventricular pressure, and the higher setting of the left ventricular end diastolic pressure. The paper speed was set at 100 mm/sec throughout the experiment.

The occlusive sequence was carried out in all dogs at the beginning of the experiment to yield a set of control values for the relationships among the pressure parameters. The dogs were then divided into two groups. The myocardial effect of Dibenzylamine was studied in the first group, consisting of seven dogs. After the control values had been obtained in this group, each animal received a single intravenous injection of Dibenzylamine in a dosage of 2 mg/kg body weight, diluted in 10 ml. of a normal saline solution. The myocardial response to pressure load was then restudied at 15 minutes and one hour after the administration of Dibenzylamine. Group two, consisting of five dogs which served as controls, was given no Dibenzylamine. In these animals, identical surgical procedures were carried out in order to study changes in myocardial contractility resulting from the experimental design alone. In all animals the entire experimental procedure was completed within two hours.

The maximum rate of pressure rise during the period of isometric contraction, for each level of occlusion, was determined by drawing a tangent to the left ventricular pressure curve as shown in Figure 1. The slope of this line, which is dp/dt and is expressed in mmHg/sec., was determined by construction of a right-angled triangle, the tangent forming the hypotenuse. The ratio of the sides of the triangle gave the value of dp/dt . It was found convenient and accurate to construct this triangle with the horizontal side equivalent in length to 0.1 sec., since these time intervals were given directly by the recorder. Left ventricular end diastolic pressure and left ventricular peak pressure were also determined graphically. Graphs were made of dp/dt as a function of end diastolic pressure.

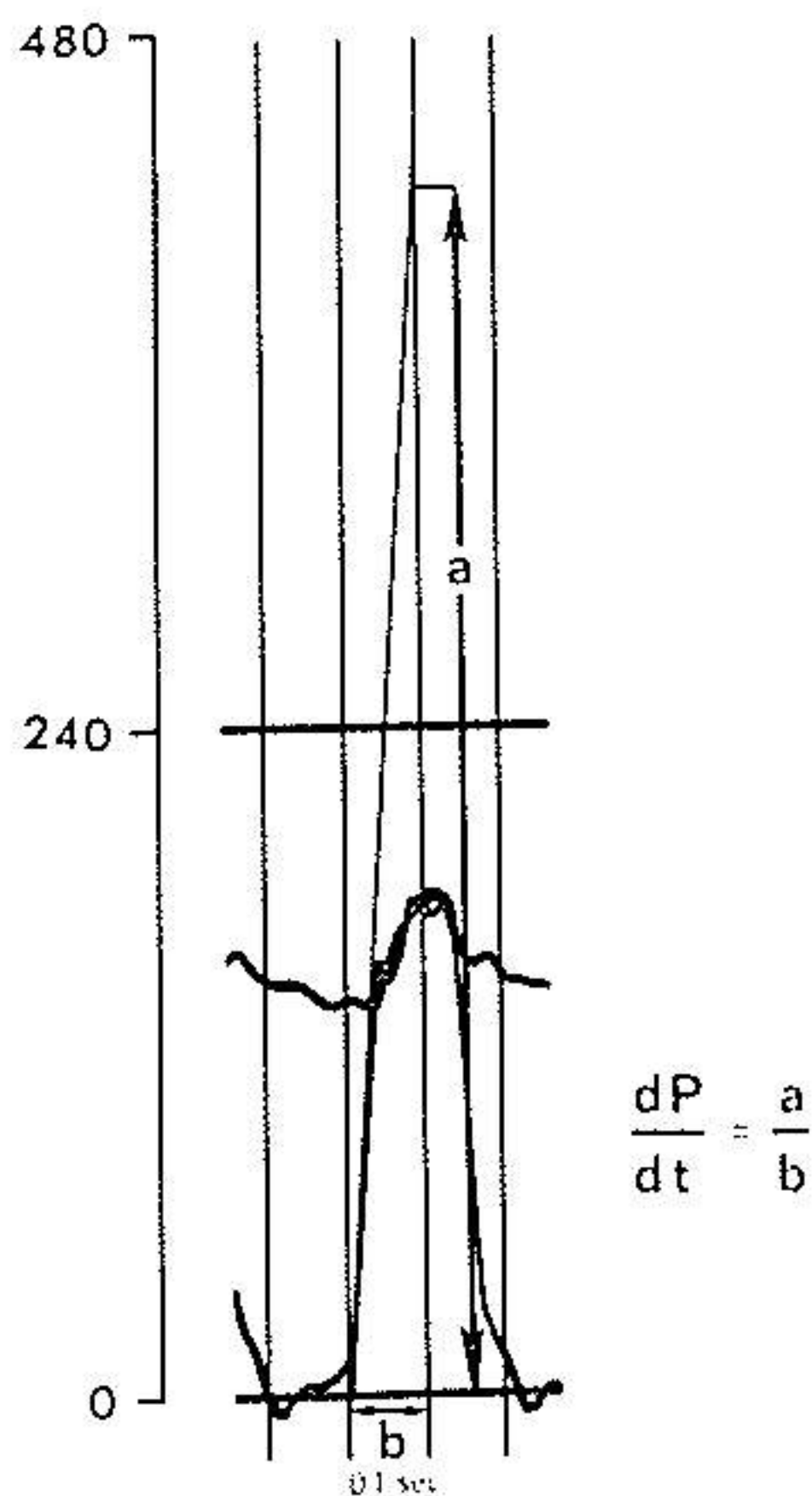


Figure I: Diagram showing the exact method by which dp/dt determinations were made in these experiments.

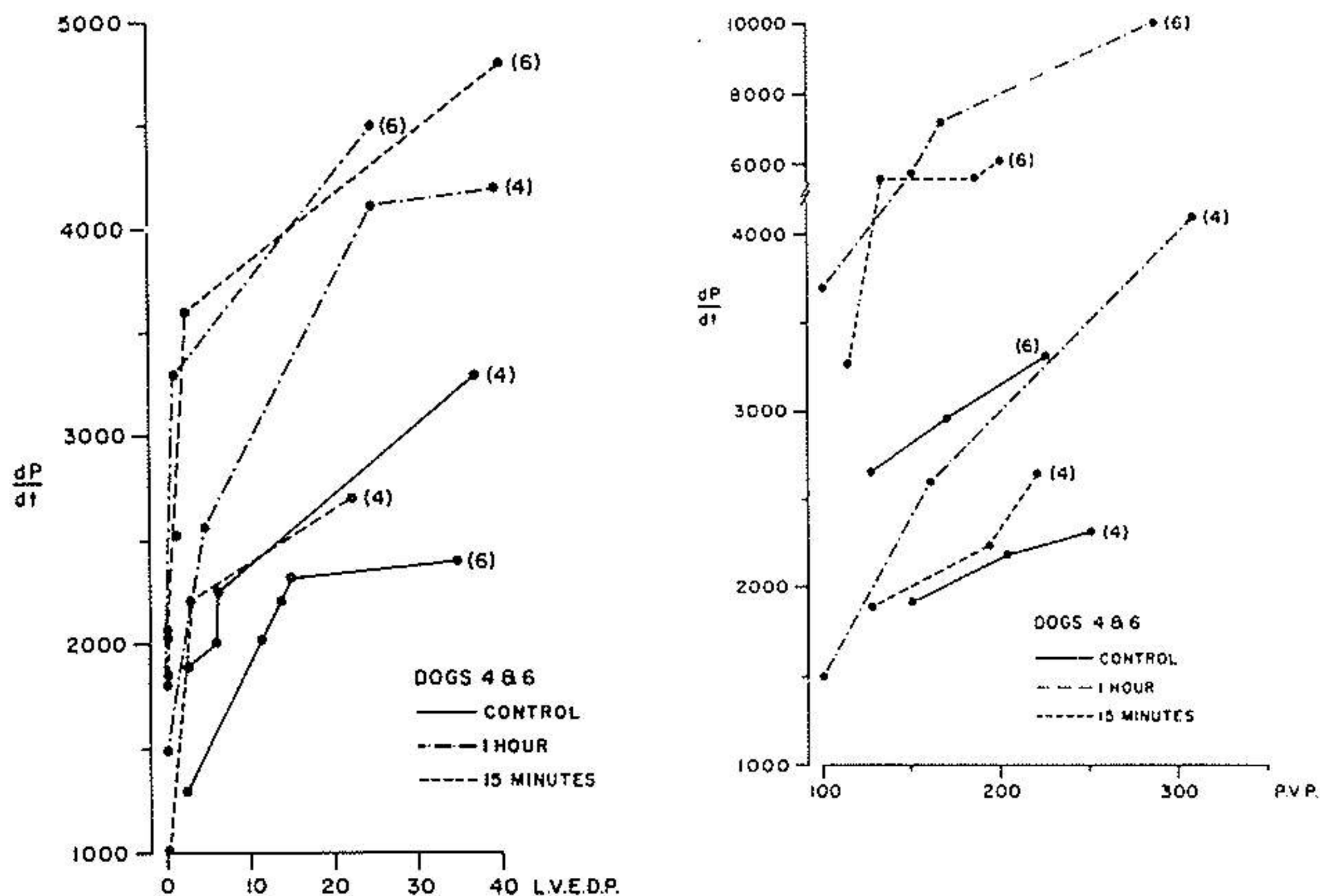


Figure II: Curves showing the dependence of dp/dt on left ventricular end diastolic pressure (L.V.E.D.P.) and left ventricular peak pressure (P.V.P.) for dogs 4 and 6 of the first group. Dibenzyline was administered to these animals after the data for the control curve had been obtained. The curves taken at 15 and 60 minutes after Dibenzyline administration are seen to be shifted to the left.

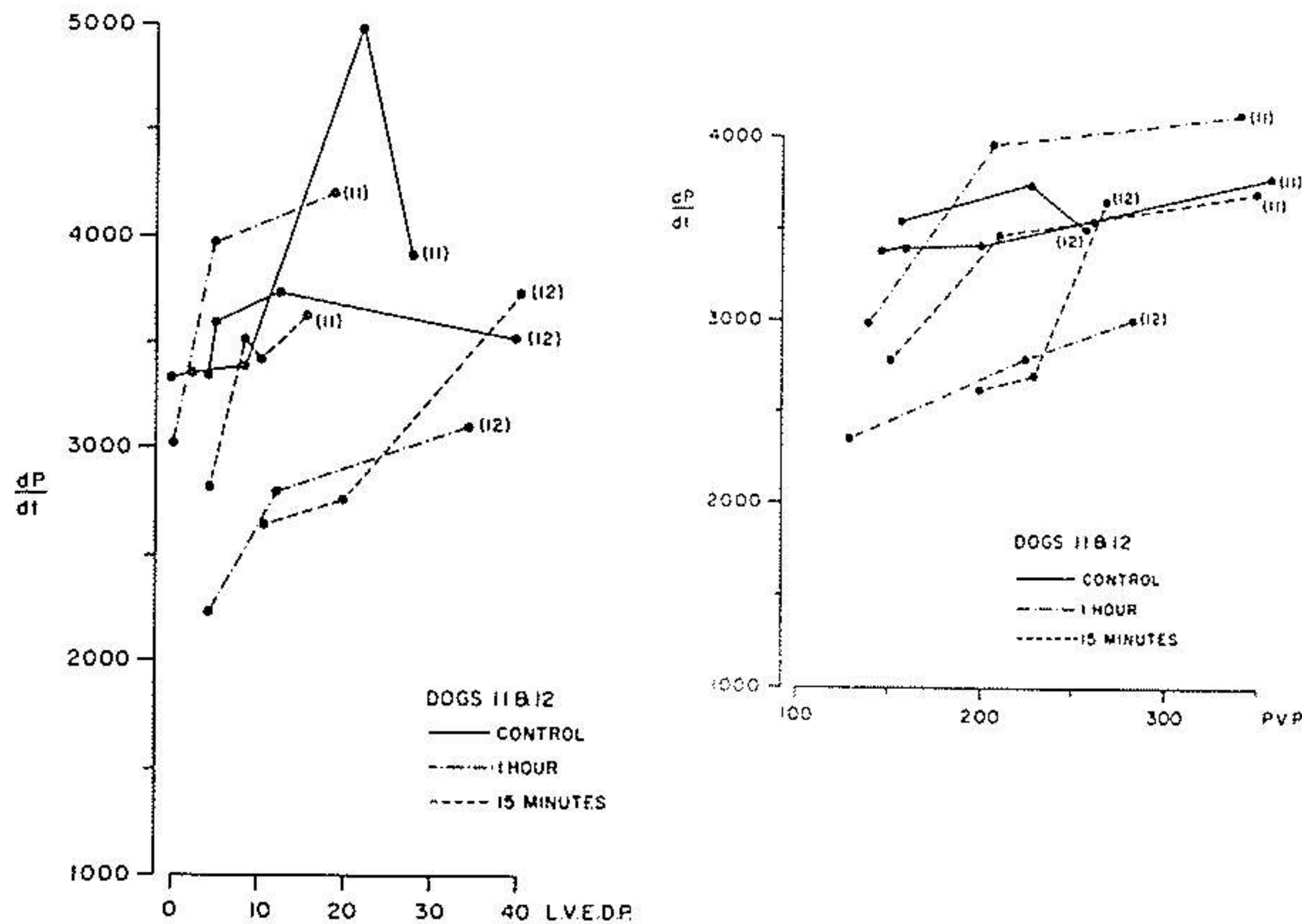


Figure III: Curves showing the dependence of dp/dt on L.V.E.D.P. and P.V.P. for dogs 11 and 12 of the second group. These animals received no Dibenzylamine after the control data had been obtained. The shift to the left seen in the first group did not occur in these animals.

RESULTS

The dependence of dp/dt on left ventricular end diastolic pressure is depicted in Figure 2a in two typical experiments during the control period, at 15 minutes and at 60 minutes after Dibenzylamine administration. Figure 2b depicts the relationship of dp/dt to the left ventricular peak pressure in the same two animals. Similar data obtained from two animals in group two are shown in Figures 3a and 3b. An upward and leftward displacement of the curves is noticeable at 15 minutes and marked at one hour after Dibenzylamine administration. No such displacement was seen in any of the animals which were not given Dibenzylamine. In other words, at any given end diastolic pressure, or peak ventricular pressure, pressure rise in the ventricle is gene-

rated more rapidly after Dibenzylamine administration. Since the relationships among the parameters have been shown to be practically linear, in both groups the least squares regression line was calculated for the dependence of dp/dt on left ventricular end diastolic pressure, and for the dependence of dp/dt on peak left ventricular pressure. These three regression lines were determined for the value obtained during the periods of control; and at 15 minutes and one hour after Dibenzylamine administration. The regression lines for the data from all seven dogs in group one representing the statistically best, or "average line", are shown in Figures 4a and b. Average lines for five dogs in group two are shown in Figures 5a and b. The lines are seen to shift toward larger values for dp/dt at any given left ventricular end diastolic pressure and at any given peak left ventricular pressure in animals given Dibenzylamine. The aggregated data from the seven dogs of the first group show the same tendency as is seen in individual dogs: the rate of pressure development for a given peak left ventricular pressure and left ventricular end diastolic pressure in the left ventricle was found to increase only after the administration of Dibenzylamine.

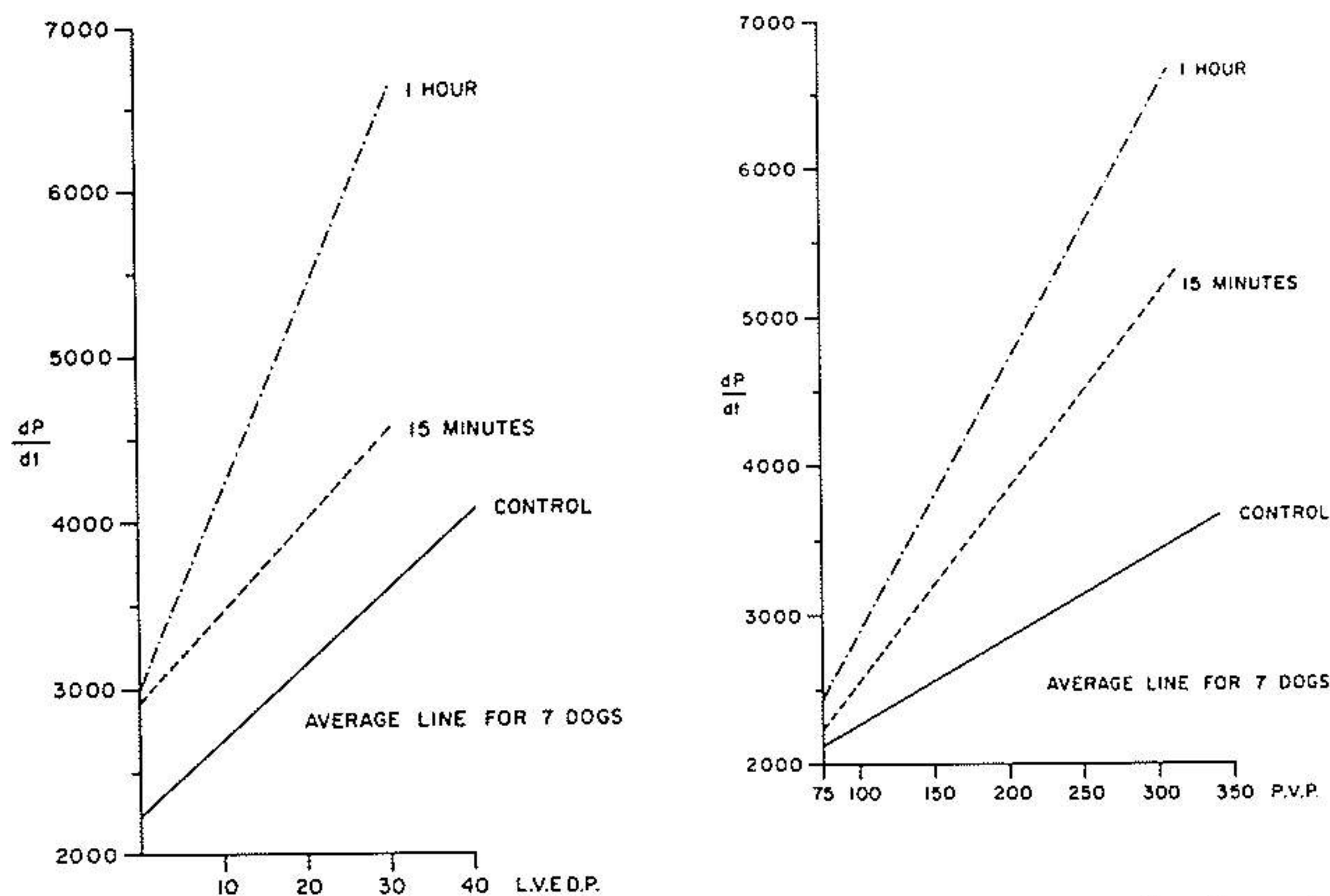


Figure IV: The average lines for the dependence of dp/dt on L.V.E.D.P. and P.V.P. for the first group (7 dogs). The lines for 15 and 60 minutes following Dibenzylamine administration are seen displaced to the left.

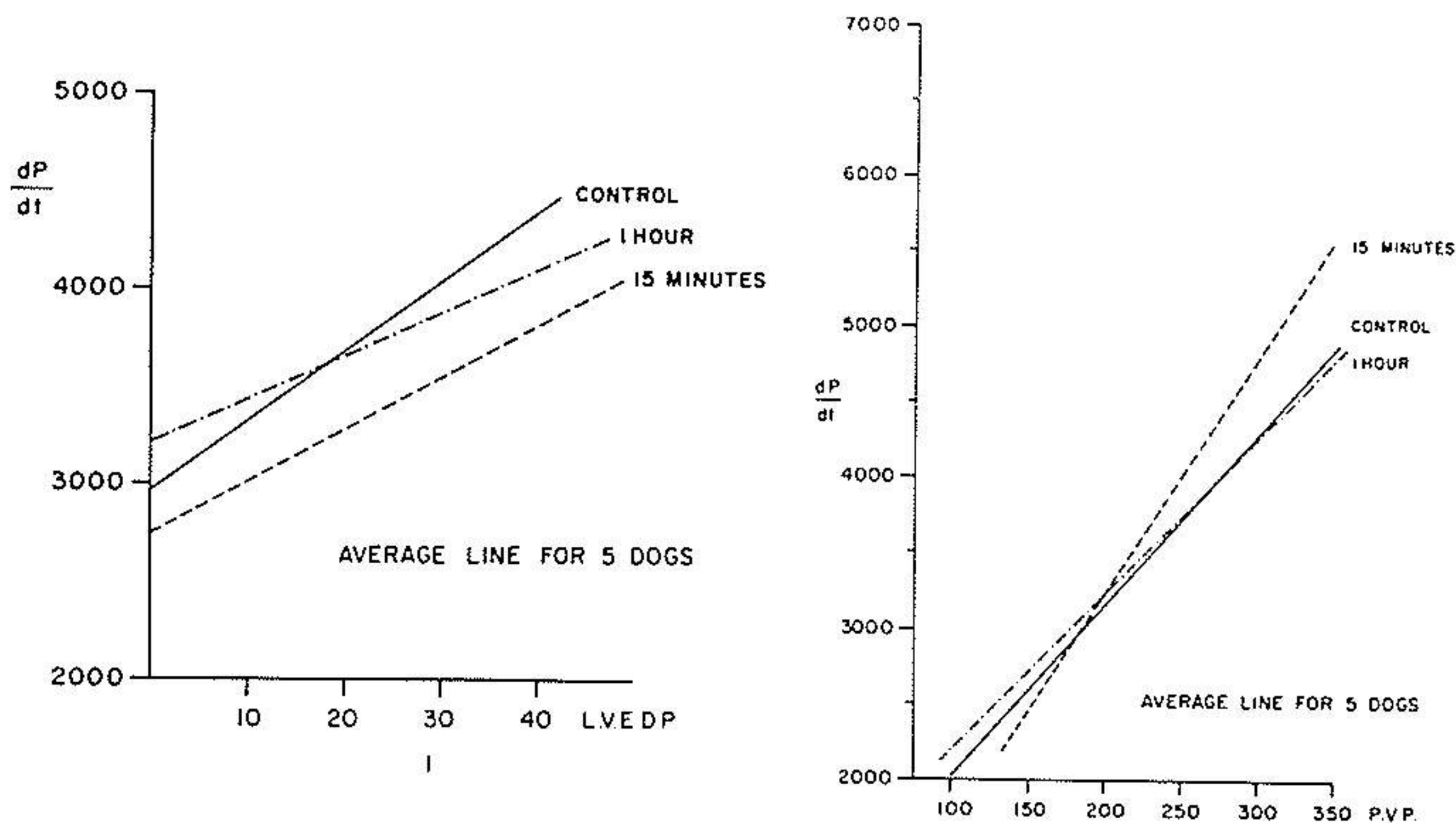


Figure V: The average lines for the dependence of dp/dt on L.V.E.D.P. and P.V.P. in the second group (5 dogs). The lines for 15 and 60 minutes after the control line are seen to present no displacement to the left shown in the first group which were treated with Dibenzylamine.

The results obtained from animals given Dibenzylamine were statistically analyzed by testing the hypothesis that there was no difference among the slopes of the regression lines of dp/dt on left ventricular end diastolic pressure calculated from values obtained before, 15 minutes after, and one hour after the administration of Dibenzylamine. The statistic "t" for the 15 minute and one hour values was calculated while treating the regression line from the control period as the "correct" slope. The slopes of the regression lines of dp/dt on peak left ventricular pressure for the control period, at 15 minutes and one hour were treated similarly. The difference between the slopes of the regression lines relating dp/dt and left ventricular end diastolic pressure obtained during the control period and at 15 minutes after Dibenzylamine administration was not statistically significant. However, at one hour the difference in slope from the line of the control period was highly significant

($T = 2.55, p > .05$). At 15 . minutes and at one hour, the slopes of the regression lines relating dp/dt to left ventricular peak pressure were significantly different from the regression line obtained during the control period.

(15 min: $t = 10.5, p > .05$; 1 hr: $t = 3.66, p > .05$).

The experimental results may be summarized by the statement that Dibenzylamine alters cardiac response to pressure load, which is in the direction of a more rapid rate of pressure development, at any given level of end diastolic pressure or peak ventricular pressure.

DISCUSSION

Much evidence has accumulated that alpha-adrenergic blocking agents such as phenoxybenzamine do not inhibit the chronotropic and inotropic responses of myocardium to circulating catecholamines (12). It is to be noted that these studies were designed to show that alpha-blockade does not change the inotropic response of the myocardium, but were not designed to reveal a possible stimulatory effect on the myocardium.

Experimental data reported to date are inconclusive concerning the direct myocardial response to Dibenzylamine administration. Abrams and co-workers (1) have reported a fall in blood pressure and cardiac output in normovolumic dogs with endotoxin shock treated with Dibenzylamine. Conversely, others have reported a noticeable increase in cardiac output with some elevation of blood pressure in patients with shock receiving phenoxybenzamine (3). Since the cardiac output is intimately dependent on peripheral resistance and venous return, and both of these factors can be affected concomitantly by alpha-adrenergic blocking agents, the actual changes in myocardial contractile state cannot be properly assessed from these studies.

Goodyer and co-workers (8) have suggested that left ventricular response to graded proximal aortic obstruction can be taken as a measure of myocardial contractility. Changes in the rate of development of pressure in the left ventricle are closely related to changes in myocardial contractility.

This rate (dp/dt) reflects the velocity of shortening of the myocardial fibers. Much evidence has been compiled to support the validity of dp/dt as measure of myocardial contractility (7,15,16,17). These authors have shown that dp/dt increased in all situations where increased myocardial contractility was recognized. The results of the study reported here indicate an enhanced myocardial contractility consequent upon the administration of Dibenzylamine.

Lowered peripheral blood pressure occurring during the experiment could have a stimulatory effect upon the baroreceptors and could, therefore, be responsible for the mechanism of the results obtained in our experiment. Such a mechanism is unlikely, since it has been stated that the baroreceptors are inhibited by alpha-adrenergic blocking agents (13). Since the exact mechanism by which increased myocardial contractility is obtained from the administration of Dibenzylamine is not known, three factors may be responsible for the findings reported in our study: 1) As the peripheral alpha-receptors are blocked by Dibenzylamine and are thus unable to take up the circulating catecholamines, it is reasonable to assume a consequent rise in the circulatory level of endogenous catecholamines, and this may secondarily cause increased myocardial contractility (2). Phenoxybenzamine has been shown to facilitate the entry of potassium ions into the cells and block the hyperkalemia which follows epinephrine or glucagon administration (6,10). These changes in potassium pool may affect the myocardium, accounting for the results obtained in this experiment. 3) Finally, phenoxybenzamine may have a direct positive inotropic effect on the myocardium.

The present study does not offer evidence which would distinguish between these possible mechanisms. It does, however, show that Dibenzylamine has no depressive action on the myocardium but may have, in fact, a salutary effect.

SUMMARY

The cardiac action of phenoxybenzamine (Dibenzylamine) was studied

using the maximum rate of pressure rise in the left ventricle as a measure of myocardial contractility. Cardiac function was assessed by increasing the pressure load on the heart and measuring contractility as reflected by dp/dt . Dibenzylamine was found to change the cardiac response to pressure load. The rate of pressure increase in the left ventricle at any specified left ventricular end diastolic pressure was found to be greater after the administration of Dibenzylamine. Similarly, the rate of pressure development was found to be greater at any specified peak ventricular pressure after Dibenzylamine administration. These changes were analyzed statistically and were found to be significant. The mechanism producing these changes is not known.

RÉSUMÉ

L'action cardiaque de phénoxybenzamine (Dibenzylamine) a été étudiée pour voir s'il y a une alteration de la contractibilité du myocarde par l'usage de médicament pour les indications qui peuvent se présenter. Le maximum degré d'élévation de la pression ventriculaire gauche a été pris pour arriver à une estimation de la contractibilité du myocarde par moyen de mesurer dp/dt . Etudiant par ce moyen, on a constaté que la Dibenzylamine peut augmenter la contractibilité du myocarde; c'est à dire qu'on trouve à chaque fois après l'administration de Dibenzylamine, il y a une augmentation de degré de la pression ventriculaire par rapport de la pression de la fin diastolique mesuré en même temps. La même chose, le développement de la pression ventriculaire a été trouvé d'être plus grande à chaque pression maximale du ventricule gauche, obtenu en même temps après l'administration de Dibenzylamine. Tous ces changements statiquement analysés, ont été trouvés significative. Le mécanisme de ces changements du myocarde n'est pas connu.

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