APPLICATION OF THE LAW OF LAPLACE IN ESTIMATION OF LEFT VENTRICULAR HYPERTROPHY IN RATS WITH EXPERIMENTAL HIGH BLOOD PRESSURE

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By

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ABSTRACT

APPLICATION OF THE LAW OF LAPLACE IN ESTIMATION OF LEFT VENTRICULAR HYPERTROPHY IN RATS WITH EXPERIMENTAL HIGH BLOOD PRESSURE

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It is postulated that a sustained change in pressure within the cardiovascular system results in an alteration of the physical dimensions of the heart. The heart is considered anatomically to be a specialized vessel with modified geometry. It is further assumed that, geometrically, the heart is composed of a cylindrical body and conical apex. This assumption allows us to assign elliptical geometry to the ventricular compartments. The ventricles are, thus, composed of two general curvatures: the major curvature (long axis) as part of an ellipse, and the minor curvature (short axis) as part of a circle. Data were obtained from normal and hypertensive rats. Tail systolic blood pressures were determined by a pulse pressure sensitive transducer. Arcs and chords of major and minor curvatures were measured and thickness of the ventricular wall at the point of intersection of the arcs was determined. Measurements were made on excised hearts (slightly inflated to approximate ventricular volume in isometric contraction). Radii of major and minor curvatures were determined from the ratio arc/chord of each curvature. The values for the radius

of the major curvatures were multiplied by a constant (1.31) to obtain the radius of the major curvature by elliptical approximation. The constant (1.31) was obtained by constructing an ellipse having a major semi-axis twice as great as the minor semi-axis. Using Laplace's equation, $P = T (1/R_1 + 1/R_2)$, tension developed at the point of measurement of wall thickness was calculated. Assuming that tension developed is proportional to wall thickness, the proportionality constant (k) is a measure of the contractile behavior of the ventricular wall. Data obtained for values of tension, (k), mean radii, and radial force (F) showed a definite left ventricular hypertrophy. Wet weight and dry weight determinations on the ventricles confirmed the estimated hypertrophy.

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I. INTRODUCTION

In recent years, much interest has been directed toward a better understanding of cardiac function and its active role in the hemodynamics of circulation. The mechanism of myocardial adaptation to variations of blood pressure has not been explored fully. However, there are indications that a change in pressure within the cardiovascular system would have a definite effect on the physical dimensions of the heart.

The function of smooth muscle within the vessel wall has been referred to as maintenance of "active tension" (Burton, 1951). A change in the pressure of circulating blood from a high value in the aorta to a low value in the capillaries is accompanied by an alteration in anatomical constituents and physical dimensions of blood vessels. Therefore, study of the physics of various constituents of the cardiovascular system is necessary in order to gain a fuller understanding of their physiological significance.

The heart may be considered anatomically as a specialized vessel with a modified geometry. Similarity between the heart and the blood vessels has been the basis for applying to the heart physical laws governing the blood vessels.

The purpose of this study is to apply the Law of Laplace to the heart to determine changes produced in cardiac muscle by experimental high blood pressure.

II. SURVEY OF LITERATURE

A. Heart and the Hemodynamics of Circulation

The function of the heart in the cardiovascular system has been compared to a pump in a hydraulic system. However, there are three unique features possessed by the cardiac pump which distinguish it from reciprocating pumps employed in engineering. They are: (1) the force that must be supported by ventricles during cardiac action does not increase but decreases as systole progresses, (2) the muscle fibers need to exert a force of contraction only one-fourth of that of the distending force of blood pressure, and (3) ventricular filling in diastole indicates a "suction" action by the cardiac pump. The first feature of the cardiac pump was suggested by Gladstone (1929). He explained that cardiac systole involves two types of contractions: an early isometric period, and a later isotonic phase. The length of isometric period, other things being constant, depends upon the size of the force to be supported by the heart. Gladstone pointed out that the isotonic contraction phase begins only when the intraventicular pressure is sufficiently high to open the semi-lunar valves and eject blood. This indicates that the force supported by the heart actually declines as ventricular systole advances. The last two features (2 and 3 above) of

the cardiac pump were proposed by Burch, Ray, and Cronvich (1952). These investigators, assuming the heart to be spherical, and using calculations from theoretical conditions, found that the total radial force, (F_R), upon the internal walls of ventricles is equal to the product of the intraventricular pressure, (P), and the internal surface area, $4\pi R^2$. However, longitudinal force developed within the cardiac muscle is equal to the product of the internal pressure and the cross-sectional area, or $F_L = \pi R^2 \times P$. This is the total force tending to separate the spherical ventricles into two hemispheres. Thus, the tensile force (longitudinal force) developed by cardiac muscle fibers necessary to maintain the radial force is one-fourth of any opposing blood pressure. Burch and co-workers contended that such a relationship between the tensile force and the distending force of blood pressure holds even if the heart is not assumed to be spherical in geometry.

Catton (1957) attributes the peculiarity of the heart as a pump to the elastic nature of cardiac tissue and its contractile ability. Contraction of the heart is dependent on and adjustable to variations in flow and pressure of circulating blood. The energy required to maintain flow of blood in the circulation is provided by contraction of cardiac muscle. This mechanical energy, as expressed in Bernoulli's Theorem

(Stacy, et al., 1955), has three components:

$$E = Z + \frac{P}{\rho g} + \frac{v^2}{2g}.$$

In this equation, the first term, (Z), represents gravitational potential energy or the energy required to raise blood to a height above the initial cardiac level. The second term ($P/\rho g$), where (P) is pressure in mass units per unit area, (ρ) is the mass unit volume, and (g) is the force of gravity, represents the flow work. The last term ($v^2/2g$), where (v) is the velocity of blood, represents kinetic energy. Blood in the left ventricle possesses a form of potential energy during isometric contraction, whereas, blood in any of the arterial branches possesses all three energy components.

When the body is at rest, all energy required for maintenance of circulation is provided by myocardial contraction. Only in the active state is the heart aided by the "thoracic pump" or "muscle pump," and gravity. The contributions of these three mechanisms are small compared to cardiac contraction (Catton, 1957).

Ability of cardiac muscle fibers to adjust to changing conditions in the circulatory system was considered in a series of experiments by Starling and Visscher (1927). They concluded that energy of cardiac muscle fiber contraction increases to an optimum value as the diastolic volume increases.

This process of compensation by the heart was called, by Starling, the law of the heart. Validity of this law with regard to the heart in the unopened chest has been questioned recently (Rushmer, 1959). However, its applicability to the isolated heart is based on a fundamental property of the muscle discovered by Hill (1913). He showed that tension produced by the muscle is greater under isometric contraction than under isotonic contraction, and that a greater amount of energy is liberated when the muscle is stretched to a certain limit prior to contraction.

The question whether a rise in arterial blood pressure will result in a corresponding increase in cardiac output has been investigated by two separate experiments on dogs. Evans and Matsuoka (1915) studied the effects of various mechanical conditions on cardiac efficiency in an isolated heart-lung preparation. They observed that a sustained alteration of blood pressure ranging from 40 to 170 mm. Hg, for a period of 15 minutes, did not significantly change the total cardiac output from a value of about 31 liters per hour. It was shown that a rise in blood pressure with constant cardiac output, or vice versa, results in a proportional increase of both oxygen uptake and mechanical efficiency of the heart followed by a subsequent decline. Maximal mechanical efficiency of about 20% was obtained by moderate increase of

both blood pressure and cardiac output. Gollwitzer-Meier and co-workers (1938) studied oxygen consumption and cardiac output in an intact heart-lung preparation. They found that the intact heart is capable of performing the same amount of work as compared to the isolated heart, but with less oxygen uptake. The interplay of heart rate and arterial blood pressure was found to influence the total cardiac output. It was noted that a rise in arterial blood pressure from 103 to 165 mm. Hg was accompanied by a decrease in heart rate from 95 to 56 per minute. Cardiac output was increased by less than 3%, cardiac work was increased from 1.24 to 1.35 m. kg., and oxygen consumption was decreased from 3.0 to 2.2 ml. per minute. A fall in arterial blood pressure to about 62 mm. Hg resulted in an elevation of heart rate to 114 per minute, and an increase in oxygen uptake to a value of 4.3 ml. per minute. The general conclusion from these two experiments was that only one feature was common to both isolated and intact hearts, namely, that a sustained rise in arterial blood pressure will not result in an elevation of cardiac output.

Efficiency of the heart as a pump has been studied from two aspects: as a mechanical pump, and as a converter of chemical energy into mechanical work (Evans and Matsuoka, 1915). In the first instance, efficiency depends upon physical

structure of the heart and possible defects due to disease. In contrast, efficiency of the heart while converting chemical energy into mechanical work depends upon its ability to consume oxygen and metabolites.

Experiments performed by Starling and Visscher (1927) have shown that over-all cardiac efficiency varies in accordance with conditions confronting the heart, and that cardiac muscle fibers have an unexplained ability to increase their oxygen consumption and energy output when a certain degree of stretching is imposed preliminary to contraction.

B. Cardiac Compensation

A fundamental property of cardiac muscle is the ability to adapt to changing demands of both central and peripheral circulations. In general, cardiac compensation occurs by means of three mechanisms: (1) an increase in the diastolic volume by an increase in the diastolic fiber length, (2) an increase in the force of contraction of the myocardial fibers, and (3) cardiac hypertrophy (Freis, 1960). The first two mechanisms were briefly considered in the previous section.

Cardiac hypertrophy has long been considered as the most important phase of cardiac compensation. However, there is no agreement on the nature of this hypertrophy. Enlargement of the heart in animals with glomerulonephritis was

observed by Richard Bright as early as 1845 (Braun-Menendez, 1946). This observation was pursued by Pässler and Heinecke (1905) who found that when removal of one kidney and one-half of the other in dogs is followed, at certain intervals, by excising portions of the remaining hypertrophied kidney tissue, the animals invariably develop high blood pressure. They noted that only 7 of the 18 operated dogs showed a definite cardiac hypertrophy. The degree of hypertrophy was determined by comparing the weights of right and left ventricles. The ratio of the weight of the right ventricle to that of the left was 1:2.26 in seven experimental dogs and 1:1.76 in the normal dog. The average increase in the blood pressure, determined by femoral cannulation, was about 21.5 mm. Hg. There was no mention of whether hypertrophy was due to hyperplasia of the cardiac muscle fibers or simply a result of enlargement of muscle fibers.

Karsner, Saphir, and Todd (1925) made histological sections of three human hearts. One heart was hypertrophied as a result of chronic glomerulonephritis. The other two hearts, one normal and one atrophied, were from patients with pulmonary tuberculosis. Fibers and nuclei of various sections were counted and their findings confirmed the contention of Edens (1913) that in hypertrophied and normal cardiac muscle ratio of area of nucleus to that of cytoplasm

is nearly the same. However, the hypertrophied heart has larger fibers as compared with that of the normal heart. Cardiac hypertrophy was found to be due to an increase in the dimensions of the muscle fibers as compared with that of the normal heart. Their observations revealed that the degree of variability in size of the muscle fibers is very much less in the hypertrophied and atrophied hearts as compared to that of the normal heart. On this basis, they believed that the phenomenon of variability is characteristic of normal tissues, and that such a condition in the normal tissue allows for greater degree of adaptability in the case of emergency. When cardiac hypertrophy occurs due to excess work by the heart, muscle fibers increase in size, and consequently a greater fiber uniformity prevails. These investigators concluded that the cardiac enlargement is due primarily to hypertrophy of the muscle fibers. Hyperplasia was not considered as the cause of cardiac hypertrophy. They further indicated that the limit of the reserve capacity of the hypertrophied heart is due to the fact that cardiac muscle fibers have reached, then, their maximum growth and functional strength.

Harrison, Ashman, and Larson (1932) found a definite and interesting relationship between heart rate and thickness of cardiac muscle fibers. They noted that the slower the

heart rate, the thicker the cardiac muscle fiber, and vice versa. However, they observed that the hypertrophied heart has a much faster rate than normal. The authors contend that the physiological significance of this relationship is: a slower heart rate allows more time for diffusion of oxygen and metabolites to thicker fibers.

Chanutin and co-workers (1932 and 1933) made an extensive study of the development of cardiac hypertrophy in rats with high blood pressure induced by partial nephrectomy. Results suggested that both cardiac hypertrophy and high blood pressure are the direct result of renal insufficiency, and that elevation of blood pressure in animals with renal insufficiency is necessary to excrete a high volume of less concentrated metabolites. The degree of compensation, in cardiac tissue and in blood pressure, depends upon the amount of renal tissue present. Too much removal of renal tissue was found to cause failure of these compensatory mechanisms. The index for the degree of cardiac hypertrophy was the ratio of heart weight to the body surface area. They found a high positive correlation between the ratio, heart weight/body surface area, and blood pressure.

Hermann, Dechard, and Erhard (1941) attempted to produce cardiac hypertrophy in several ways. They found that wrapping the left kidney with gauze soaked in collodion and removing

the contralateral kidney about 4-7 days after the first operation was the most successful method for producing hypertrophy of the heart. The greatest amount of hypertrophy was found to occur about 50 days after nephrectomy. The average hypertrophy after 50 days was about 92%, whereas the average hypertrophy after 20 days was about 46%. In general, 30 days post-nephrectomy the maximum amount of cardiac hypertrophy occurred.

Other experiments have shown that cardiac hypertrophy will result from any disturbance in the body function that leads to the elevation of blood pressure. Cardiac hypertrophy was found to be directly related to changes in pressure and flow of blood. Benzak (1958) studied cardiac output, reserve force of the heart, total peripheral resistance, and weights of the heart and other organs in normal rats and in rats with aortic coarctation below the diaphragm. She found that cardiac output dropped from a normal value of about 48 $\pm$ 4 ml./min. to a value of about 31 $\pm$ 5 ml./min. after the production of coarctation. Simultaneously, an increase in total peripheral resistance from a normal value of about 210,000 to 320,000 dynes second per $cm.^{-5}$ was observed. Cardiac hypertrophy was confined mostly to the left ventricle which showed an increase of about 45% above the control weight three weeks following coarctation.

C. Myocardial Force in Relation to Blood Pressure

Physical laws governing flow of fluid by a reciprocating pump demand a definite relationship between the capability of the pump to develop a driving force, and the pressure with which the fluid is compelled to flow. In the cardiac pump, which forces blood with a given pressure through vessels, such a fundamental relationship must also exist. Starling's law of the heart, which states that a change in the length of the ventricular muscle fibers influences their force of contraction, contributes little to our understanding of relationship between the force developed by the ventricular muscle during systole and the generated pressure. However, this is the essence of a recent paper by Burton (1957) in which he suggests that the Law of Laplace, previously applied to blood vessels, can provide pertinent information with regard to this vital relationship.

Burton (1951), applying the Law of Laplace, showed that the diameter of a blood vessel is determined by a balance between two forces: a distending force (blood pressure), and a closing force (wall tension). A smaller vessel radius means a lesser tension required to oppose the distending force of blood pressure. Burton (1954) explained that the shape of pressure-flow curves in living vessels is a

reflection of anatomical structure of arteriolar walls. Smooth muscle has a viscoelastic property that is responsible for development of a greater tension when it is subjected to a sudden stretch. Local adjustment to low pressure variations is done by elastic tissue and to high pressure variations through collagen tissue. Smooth muscle is responsible for "active tension" which adjusts the response of both elastic and collagen tissues.

As early as 1892 the importance of the role of shape and size of the heart in its pumping function was recognized. In that year, Woods applied the Law of Laplace to post-mortem human hearts. However, the scope of usefulness of this law was not fully described. Recent investigations in connection with the dilated heart and hypertensive cardiac hypertrophy (see Sections A and B) have renewed interest in application of the Law of Laplace to the heart. Burton (1957) suggested that the dilation of the heart, as predicted by this law, results in an increase in the principle radii of the curvature of ventricles. The Law of Laplace applied to ventricles has the formula, $P = T\ (1/R_1 + 1/R_2)$, where (P) is pressure in dynes per square cm., (T) is tension in dynes per cm., and (R_1) and (R_2) are principle radii of ventricular curvatures in cm. Since the amount of tension developed by ventricular walls is proportional to thickness, Burton (1957) pointed out that

the Law of Laplace explained the great variations of the ventricular wall thickness. In the sharply curved region of the ventricle, such as the apex, the wall can be thin and still produce sufficient tension to develop the required pressure. In contrast, the Law explains that, at the region where the wall is nearly "flat," such as midway up the ventricle, the wall must be thicker and the tension developed must be greater in order to produce the necessary pressure. This variation in wall thickness in accordance with developed tension explains the thinner right ventricular wall. It is in the Law of Laplace, Burton believes, that reasons for phenomena of "mechanical advantage" in the normal heart, and "mechanical disadvantage" in the dilated heart should be sought.

There are numerous experiments which demonstrate the significance of tension developed by cardiac muscle and its deviation from normal in cardiac decompensation during myocardial disease. Burch (1955) showed that the dilated heart must work harder and produce greater tension, as compared to normal heart, in order to maintain the same volume of output as systole progresses. The extent of this increase in external work and developed tension is determined by the magnitude of the cardiac enlargement. The amount of cardiac hypertrophy is reflected by the sum of the reciprocal of the principle

radii of curvature $(1/R_1 + 1/R_2)$, the "shape" factor, in the Law of Laplace. Experiments by Hartree and Hill (1921) on isolated skeletal muscle showed that oxygen consumption and heat liberation in the muscle is proportional to the product of tension and the time it is maintained. Therefore, oxygen consumption of cardiac muscle depends upon the sum of two factors: the mechanical work, $(\int P \times \Delta V)$, and the product of tension and time, $(T \times t)$. The expression, $(\int P \times \Delta V)$, for the mechanical or external work of the heart was developed by Katz (1931) who made simultaneous pressure-volume curves recording by optical means on isolated perfused turtle heart preparation.

Starling and Visscher (1927) showed that the total oxygen consumption of both normal and failing hearts depends upon diastolic volume and is relatively independent of the external work $(\int P \times \Delta V)$ that the heart has to do. Burton (1957) pointed out that the Law of Laplace explains why diastolic volume can change the energy turnover of the heart, namely, by increasing the value of the product of tension and time. Therefore, the factor $(T \times t)$ should be given serious consideration when ascertaining cardiac performance. In this respect, both Burton (1957) and Rushmer (1959) believe that cardiac rate can be used as a better index of the total cardiac load. There is also evidence that in the early stages

of hypertension, minute volume output is increased, and that elevation of blood pressure causes an increase in the cardiac work. This increase is due primarily to rise of systolic blood pressure (Freis, 1960). Thus, when high blood pressure is present, the product of tension and time, as well as mechanical work, will be increased. If high blood pressure persists for a long period, ventricular hypertrophy is expected.

III. MATERIALS AND METHODS

Albino rats of Hoppert (M.S.U.) strain, ranging in age from two to three months, and weighing from 138 to 245 grams with a standard deviation of ± 5.65 grams (Table 2) were used in this experiment. All rats, and food jars were weighed weekly so that an assessment of gain or loss in weight and food consumption could be obtained during the course of experiment. All weighings were done on a 500 gram capacity Toledo Balance.

Rats were divided into three groups. Group I was subjected to a surgical procedure introduced by Soskin and Saphir (1932). A flank incision was made on the left side and the kidney was brought to the surface. The adrenal gland was separated from its attachment to the kidney, and all fatty tissues surrounding the kidney were severed. No attempt was made to remove them from the surface of the kidney capsule. Then, all manipulations were stopped for 10 minutes, so that the kidney could resume its normal functional distension. Cotton gauze was cut into small rectangular pieces and placed in a petri dish. Collodion Merck (U.S.P. alcohol 24%) was poured over the gauze, and rectangular pieces were pasted around the kidney so as to form a snug capsule. Care was taken to keep the renal pedicle completely free from the wrapping material. After a lapse of two minutes, to allow

for the wrapping material to dry, the kidney was returned to its original position. The incision was closed by two layers of sutures. Lock stitches were used for peritoneum and muscle, and interrupted sutures for skin to prevent injury from chewing by the rat. After seven days, the rats were nephrectomized. The same process of manipulation of the kidney and a waiting period of 10 minutes was observed during the course of nephrectomy. Group II was subjected to a surgical procedure described by Grollman (1944). A flank incision was made on the left side and the kidney exposed as described above. Then, a small piece of No. 8 cotton thread was wrapped around the poles of the kidney in the form of a figure-eight and knotted tightly. The kidney was returned to its position and after closure of the left incision, the contralateral kidney removed with the same procedure described previously for Group I. The third group was sham-operated at random, with respect to right and left side, and used as controls.

Anesthesia in the above operations was by intra-peritoneal injection of 3% sodium pentobarbital solution. The dose required was 30 mg. per kilogram body weight for females and 40 mg. per kilogram body weight for males. After recovery from anesthesia, the animals were returned to their individual steel wire cages in an air-conditioned room at 70^{o}

Fahrenheit. Feed consisted of a special ration prepared by the Department of Animal Husbandry, Michigan State University, containing 22% protein, 7.5% crude fat, 4% crude fiber, 0.78% calcium, 0.45% chloride, 0.76% potassium, 0.35% sodium, and 0.67% phosphorous, with a T.D.N. of about 86.1%. Tap water was given ad libitum.

Systemic hematocrit on tail blood was determined before operation and prior to sacrificing each animal. Blood samples were drawn, in duplicate, into microhematocrit tubes, sealed, and spun in an International Hemacrit Centrifuge for five minutes.

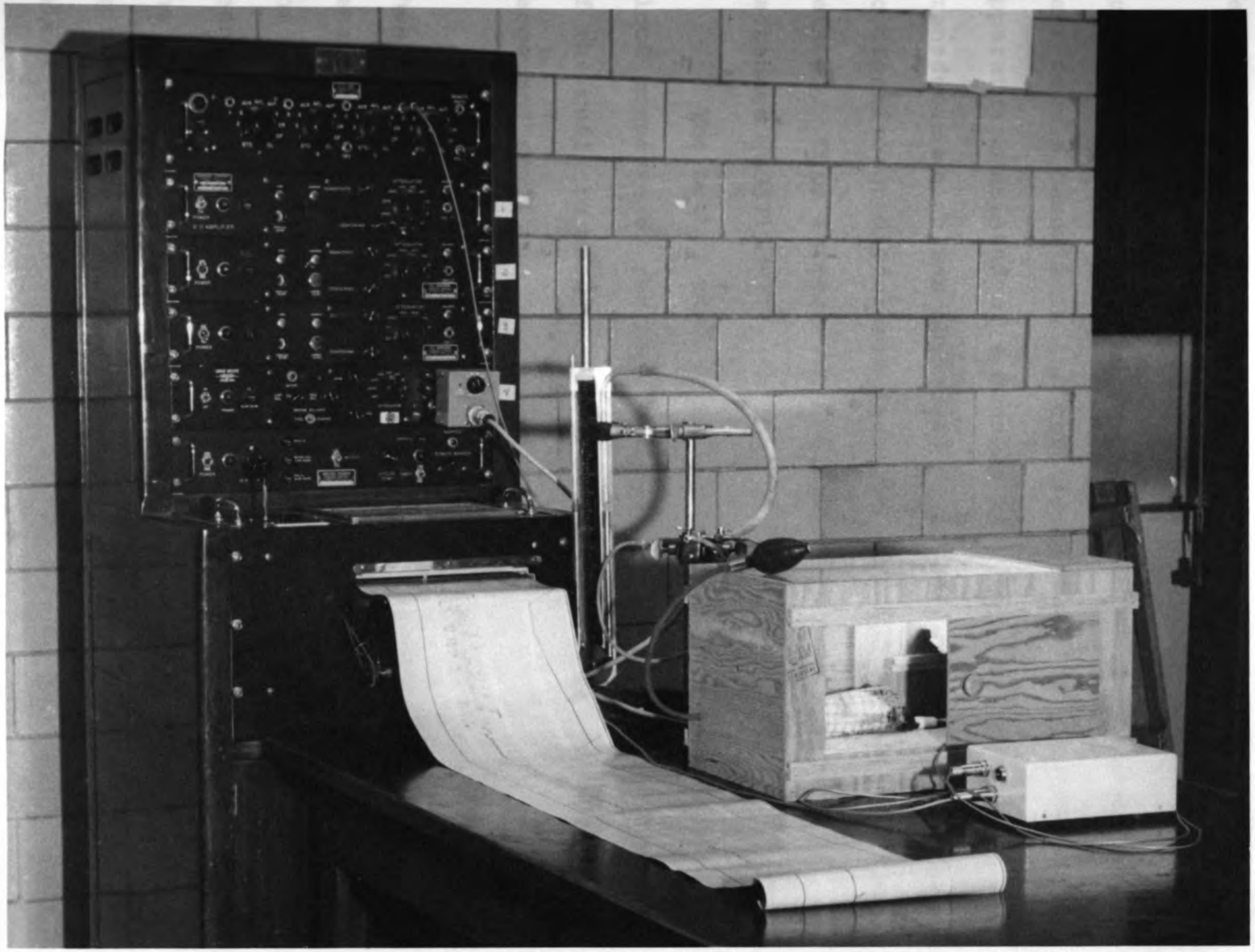
Blood pressure of unanesthetized rats was determined before the experiment, and on the 7th, 10th, and 14th (final) days by a simple method devised especially for this study. The rat was led into a cone-shaped restraining cage made of mesh steel wire. The restrained rat was then placed on a large foam-rubber pad inside a 50 x 25 x 25 cm. wood box with sliding doors and glass top. Temperature of the box was maintained between 37-39^{o} Centigrade with two 25 watt electric bulbs. The rat's tail was passed through a 16 mm. diameter pressure cuff made of surgical rubber, lining a rigid outside metal sleeve. The cuff was connected to a hand bulb from one side, and attached to a pressure transducer from the other side. The transducer was connected from one

end to a mercury manometer, and from the other to a Sanborn carrier amplifier and recorder. The pick-up of a pulse pressure detecting device, called "Infraton" (Beckman, Spinco Division, Palo Alto, California), was attached firmly by means of adhesive tape to the ventral side of the tail immediately distal to the cuff, and the leads of the pick-up were connected to one of the D.C. amplifiers of Sanborn polygraph. The apparatus can be visualized from the accompanying photograph (Figure 1).

Rats were placed in the warmed box for 10 minutes before each blood pressure measurement. The pressure cuff was inflated by means of a hand bulb until pulsations disappeared from the record. As the pressure was released, pulsations reappeared at the point where cuff pressure, read from the recording paper, was slightly less than that of the caudal artery. This pressure was designated as systolic blood pressure. Diastolic blood pressure cannot be determined with this apparatus. Systolic blood pressure was measured in triplicate for each animal at various times during experimental observation. Before and after each series of blood pressure readings the transducer was calibrated with a mercury manometer to ascertain the degree of fluctuation of the recording stylus during each day's run. No significant change in calibration occurred. A calibration record of the kind used

FIGURE 1

Photograph of apparatus used to measure indirect blood pressure.



to read systolic blood pressure, and a typical blood pressure recording are shown (Figures 2 and 3).

The indirect blood pressure recording method was compared with direct, simultaneous arterial pressure measurement from a cannula in the carotid artery. The direct reading apparatus consisted of a cannula attached to a pressure transducer which was connected to a calibrated Brush recorder. No significant difference could be observed between the two methods. This agrees with observations of Dodson and Mackaness (1957).

The method used in this experiment for determining blood pressure of rat can be adapted, with some modification of the cuff, to measure blood pressure of other animals, both large and small.

On the fourteenth day of observation, rats were anesthetized and the abdominal cavity was exposed. Sodium heparin (2 mg. per kilogram body weight) was injected into the inferior vena cava. The chest cavity was opened and the heart, with all its connecting vessels, was removed immediately. The heart was dissected free of adventitious tissues and emptied of blood by flushing with distilled water instead of saline to compensate for dehydration in the next step. Left ventricle, through aorta, was placed under a 20 cm. pressure head of 95% ethyl alcohol for hypertensive rats, and a 10 cm.

FIGURE 2

Typical calibration graph of the kind used to read systolic blood pressure.

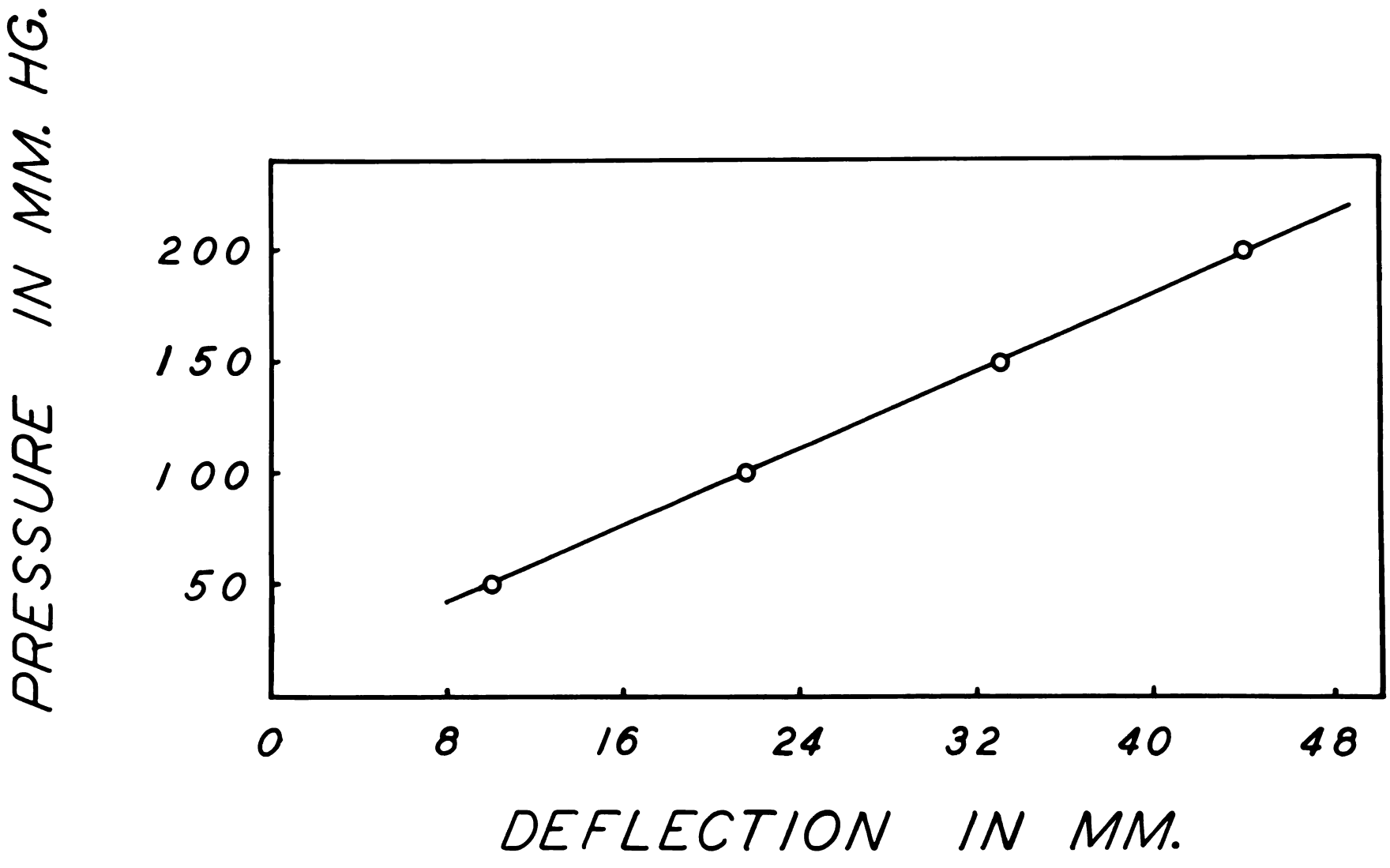
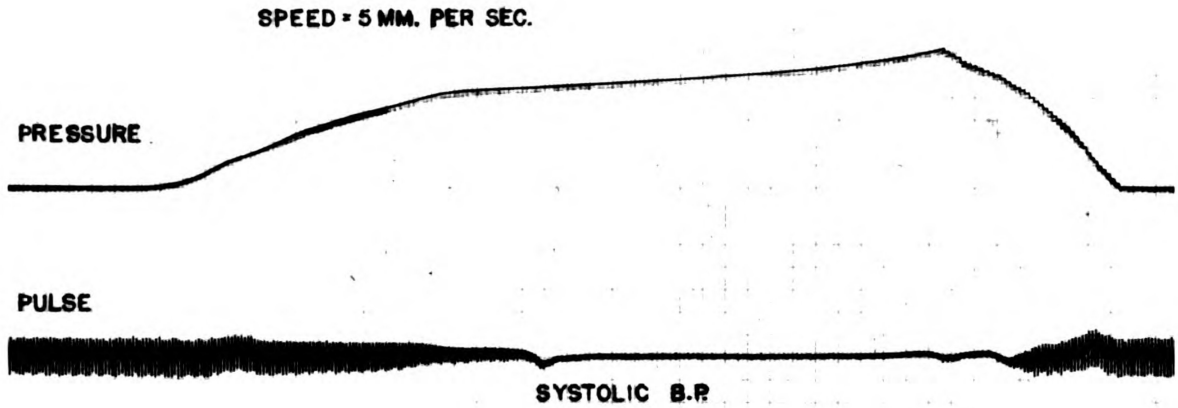

PRESSURE IN MM. HG.
200
150
100
50
0
8
16
24
32
40
48
DEFLECTION IN MM.

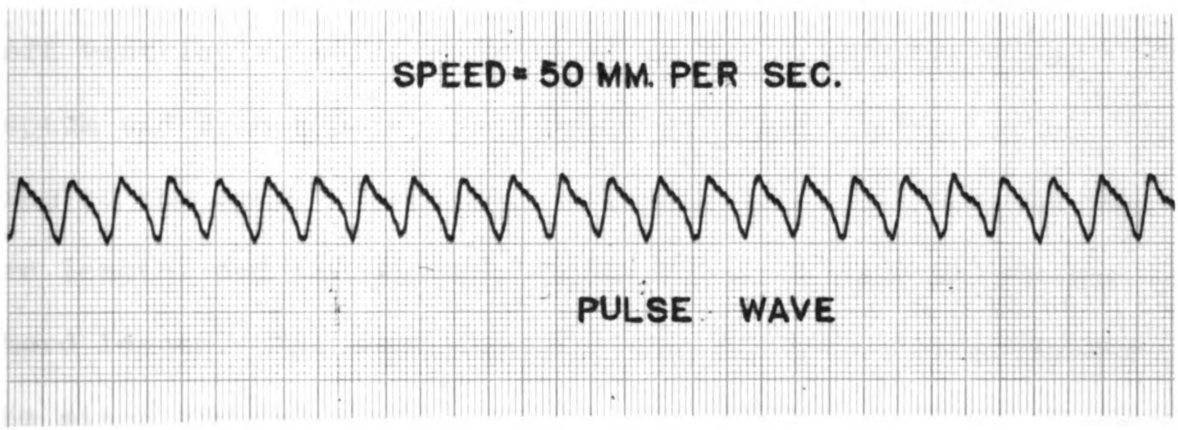
FIGURE 3

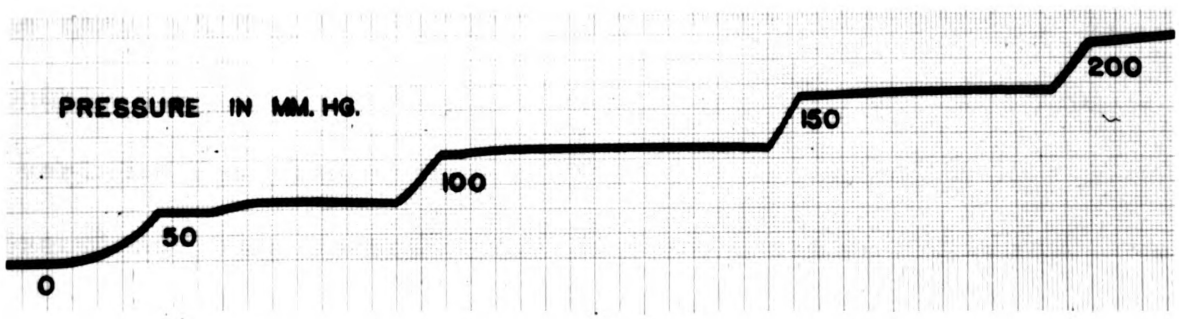
Top- Typical blood pressure recording.

Middle- Normal pulse wave record.

Bottom- Typical calibration record.


SPEED = 5 MM. PER SEC.
PRESSURE
PULSE
SYSTOLIC B.P.


SPEED = 50 MM. PER SEC.
PULSE WAVE


PRESSURE IN MM. HG.
0
50
100
150
200

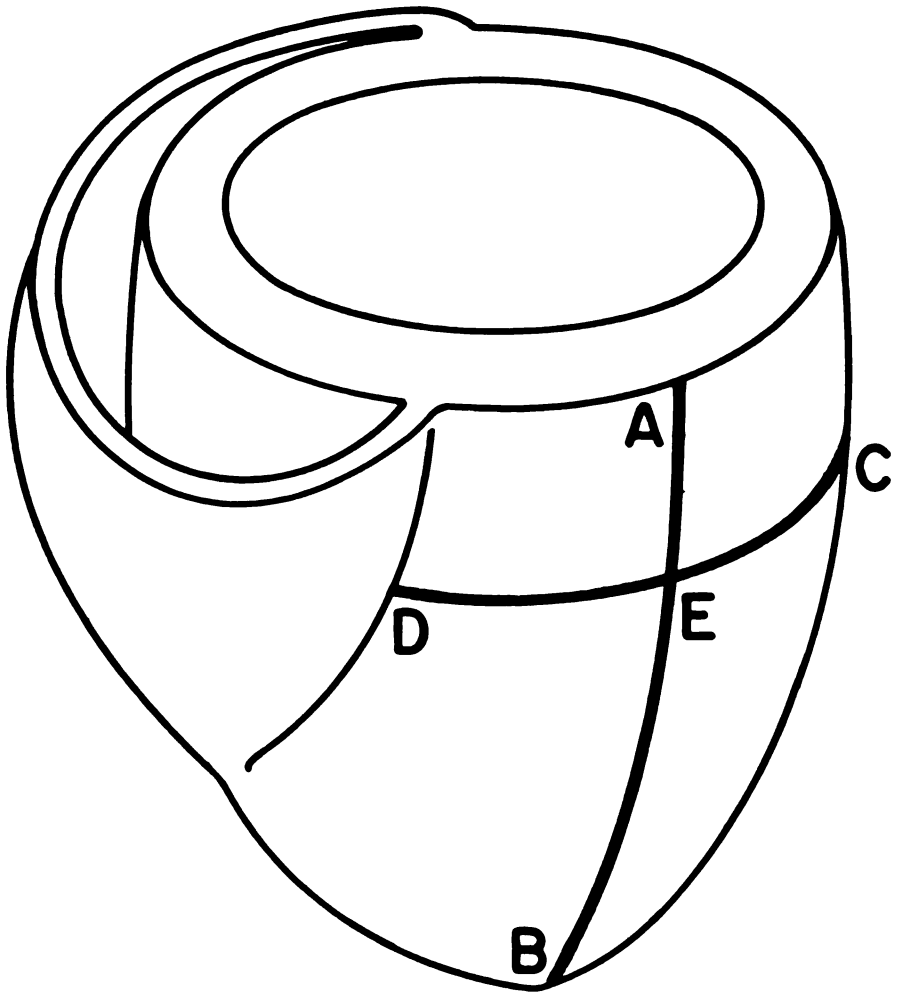
pressure head for normal rats for 20 minutes. This was done to harden the cardiac muscle for subsequent measurements with the heart approximating ventricular volume during isometric (isovolumic) contraction of the systole.

Major (long axis) and minor (short axis) arcs and chords, and heart wall thickness at the intersection of the two arcs, were measured, on the left ventricle in the following manner (Figure 4). A cotton thread was placed on the major left ventricular surface parallel to the interventricular septum and from a point just below atrioventricular valve ring to the apex. The linear distance of the thread was the arc length, and the distance between the two points was the chord length. The same procedure was followed for measuring the minor arc and chord at a site approximately midway between the base and the apex of the left ventricle. The method is roughly similar to that of E. W. Hawthorne (1961) who used a variable resistance strain gauge. Wall thickness was determined at the intersection of the two arcs. Principle radii of the left ventricular curvatures were estimated by methods described in Part IV.

After being measured, ventricles were separated from auricles and other non-ventricular tissues. Isolated ventricles were weighed and dried for 48 hours in an oven at a constant temperature of 97^{o}Centigrade, cooled in a dessicator,

FIGURE 4

Diagram showing sites of major and minor arcs and chords, and wall thickness measurements.



$\overset{\frown}{AB}$ – major (long axis) arc

$\overline{AB}$ – major chord

$\overset{\frown}{CD}$ – minor (short axis) arc

$\overline{CD}$ – minor chord

E – point where wall thickness was measured

and dry weight determined. Previous experiments showed that heart tissues dried to constant weight in 48 hours at the above temperature. All heart weights were determined by a Voland and Sons chain-o-matic balance capable of measuring to the nearest 0.1 mg.

IV. CALCULATIONS AND DATA

In this experiment, two types of calculations were employed for evaluation of raw data. The first type involved the use of the relationship found experimentally by Lee (1929) for determination of rat surface area, which is as follows:

$$\text{Surface Area } (\text{cm.}^2) = 12.54 \times W^{0.60}$$

where (W) is the rat body weight in grams.

In order to obtain more uniform heart-weight data from animals with different body weights, the ratios of both wet and dry weights of the ventricles to the surface area were used in determining the degree of ventricular hypertrophy.

The second type of calculation was used to determine the principle radii of the left ventricular curvatures so that the degree of hypertrophy could be estimated by application of the Law of Laplace. In this operation, two assumptions were made: (1) left ventricle has elliptical geometry; and (2) ventricular wall thickness is negligible as compared to the mean radius. The first assumption is a modification of Rushmer's observation (1951) that the ventricles are composed geometrically of a cylindrical body and conical apex. The second assumption is justified if it is accepted that the tension developed in the ventricular wall is proportional to the thickness. This latter relation is considered reasonable by Burton (1957).

Mathematically, four families of curves could fit the curvatures of the left ventricle. They are: (1) catenary, a curve in which a perfectly flexible chain hangs when suspended between two points, with a general equation of $y = a \cosh x/a$, (2) circle with an equation of $(x-a)^2 + (y-b)^2 = r^2$, (3) ellipse with a general equation of $(x-h)^2/a^2 + (y-k)^2/b^2 = 1$, and (4) parabola with an equation of $(x-a)^2 = \pm 2p(y-b)$. In accordance with Rushmer's observation, any curve that can describe the left ventricular curvature must have a first derivative equal to zero at points of the ventricle with cylindrical geometry. An ellipse is the only one of the above four curves that can fulfill this requirement, and adequately describe the major (long axis) curvature of the left ventricle. Therefore, principle radii of the ventricular curvatures were estimated by assuming that the major (long axis) curvature is part of an ellipse and that the minor (short axis) curvature is part of a circle.

The equation for estimating the radius of the minor curvature was derived from the following considerations. The radius of the circle as a function of the arc and the chord of a particular segment of the circle follows the equations:

$$\theta = \frac{S}{R}, \quad L = 2R \sin(\theta/2)$$

$$\text{Then, } L = 2R \sin(S/2R) \qquad (1)$$

where (S) is the arc length, (L) is the chord length, (θ) is

the central angle describing the arc, and (R) is the radius of the circle.

In order to determine the radius of a circular curvature for any arc and chord, a general graph was constructed from the following manipulation of equation (1).

If the radius is allowed to have a numerical value of (1/2), the equation (1) takes the form,

$$L = 2\ (1/2)\ \text{Sin}\ (S/2\ (1/2)\ ) = \text{Sin}\ S. \qquad (2)$$

A similar equation can be obtained by substituting other numerical values for radius. Numerical value (1/2) was chosen for simplicity.

Dividing both sides of the equation (2) into (S) and (R) respectively, the following two equations will be obtained:

$$S/L = S/\ \text{Sin}\ S \qquad (3)$$

and

$$R/L = 1/2/\ \text{Sin}\ S. \qquad (4)$$

From the table of Natural Functions for Angles in Radians, the values of (Sin S) for any value of (S) from S = .00 to S = 2.00 radians were compiled (Table 1). Then, the ratios S/Sin S and 1/2/Sin S were calculated and the values of the ratio (1/2/Sin S = R/L) were plotted against the values of the ratio (S/Sin S = S/L) on an ordinary graph paper. A glance at this graph (Figure 5) indicates that, from the ratio (S/L), the ratio (R/L) can be determined. When the latter ratio is multiplied by the value for chord length, (L), the

Table 1

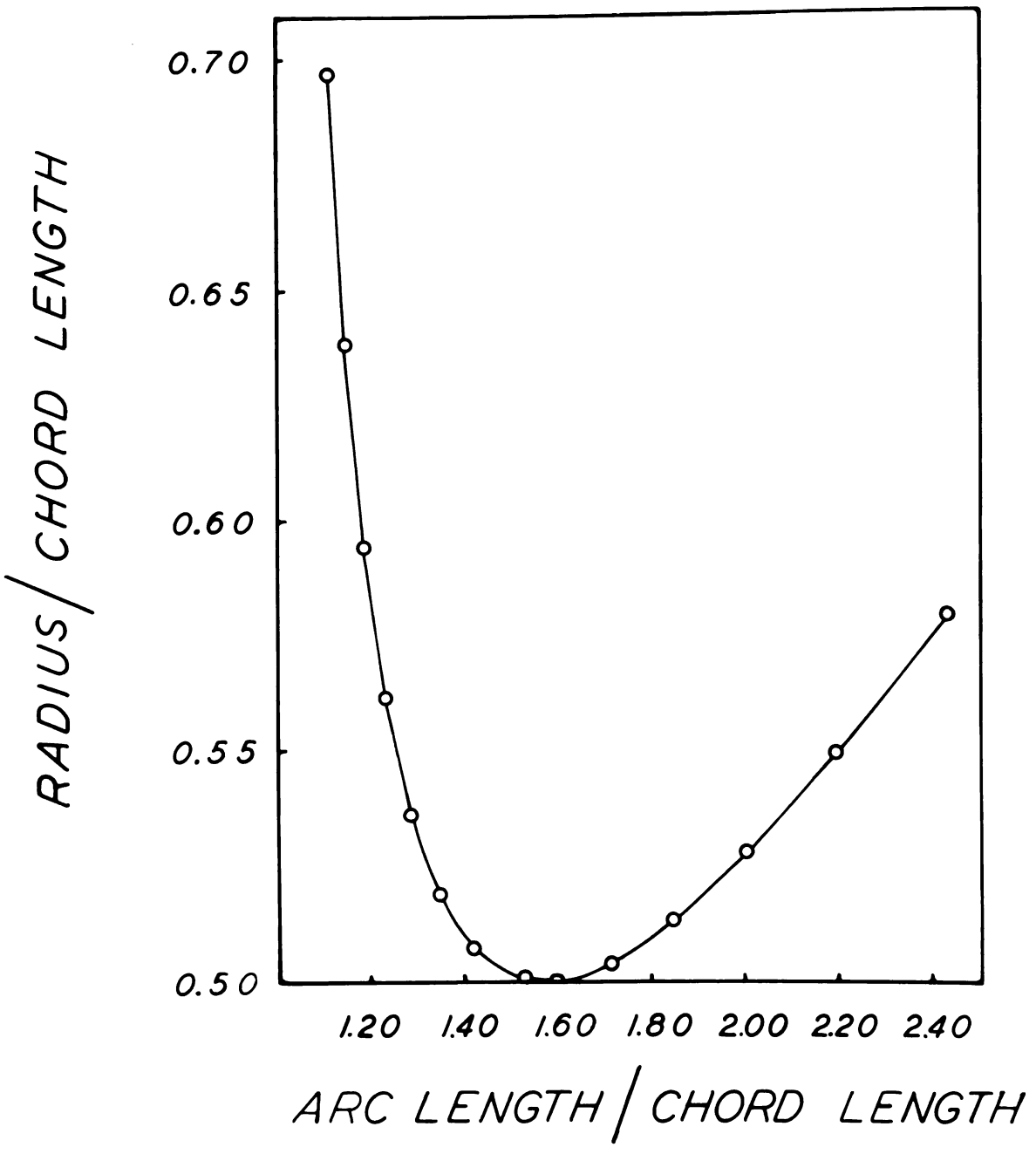
Numerical Values of Parameters S, Sin S, S/Sin S, and 1/2/Sin S

S (radian)	Sin S	S/Sin S = S/L	1/2/Sin S = R/L
0.10	0.09983	1.002	5.009
0.20	0.19867	1.007	2.517
0.30	0.29552	1.015	1.692
0.40	0.38942	1.027	1.284
0.50	0.47943	1.043	1.043
0.60	0.56464	1.063	0.866
0.70	0.64422	1.087	0.776
0.80	0.71736	1.115*	0,697*
0.90	0.78333	1.116*	0.638*
1.00	0.84147	1.188*	0.594*
1.10	0.89121	1.234*	0.561*
1.20	0.93204	1.287*	0.537*
1.30	0.96356	1.349*	0.519*
1.40	0.98545	1.420*	0.507*
1.50	0.99745	1.503*	0.501*
1.60	0.99957	1.600*	0.500*
1.70	0.99166	1.714*	0.504*
1.80	0.97385	1.848*	0.513*
1.90	0.94630	2.008*	0.528*
2.00	0.90930	2.200*	0.550*

*The sign (*) indicates the points plotted in Figure 5.

FIGURE 5

Standard curve for determination of radius of the curvature.


RADIUS / CHORD LENGTH
0.70
0.65
0.60
0.55
0.50
1.20
1.40
1.60
1.80
2.00
2.20
2.40
ARC LENGTH / CHORD LENGTH

result is the value of the radius for the particular arc and chord values.

Major curvature of the left ventricle is considered to approximate elliptical geometry. By definition, the absolute value of the reciprocal of the curvature (K) is called the radius of curvature, R. In mathematical expression,

$$R = \frac{1}{|K|} \tag{5}$$

In rectangular coordinates, the radius of curvature is given by the equation,

$$R = \frac{(\,1 + (dy/dx)^2\,)^{3/2}}{(d^2y/dx^2)} . \tag{6}$$

In order to find the radius of an ellipse with an equation of $(\, x^2/a^2 + y^2/b^2 = 1\,)$, one must determine the first and second derivatives of the equation describing the ellipse. The equation of an ellipse can be rearranged and written as follows:

$$y^2 = b^2\ (\,1 - x^2/a^2)$$

or $$y^2 = b^2/a^2\ (a^2 - x^2)$$

or $$y = b/a\ (a^2 - x^2)^{1/2}. \tag{7}$$

The first derivative of the equation (7) is,

$$dy/dx = b/a\ (1/2)\ (a^2 - x^2)^{-1/2}(-2x) = -bx/a$$

$$(a^2 - x^2)^{-1/2}. \tag{8}$$

The second derivative of the equation (7) is,

$$d^2y/dx^2 = - ab\ (a^2 - x^2)^{-3/2}. \qquad (9)$$

Substituting in equation (6) for the first and second derivatives, equations (8) and (9), rearranging and simplifying, we obtain an equation for the radius of an elliptical curvature:

$$R = - \frac{(a^4 - (a^2 - b^2)\ x^2\ )^{3/2}}{a^4\ b}. \qquad (10)$$

Since we are dealing with the absolute value of equation (10), the negative sign before the expression can be ignored in calculating the numerical value of the radius.

In order to evaluate the radius of the major curvature of the left ventricle by elliptical approximation and compare it with the value for radius by circular approximation, the following procedure was adopted.

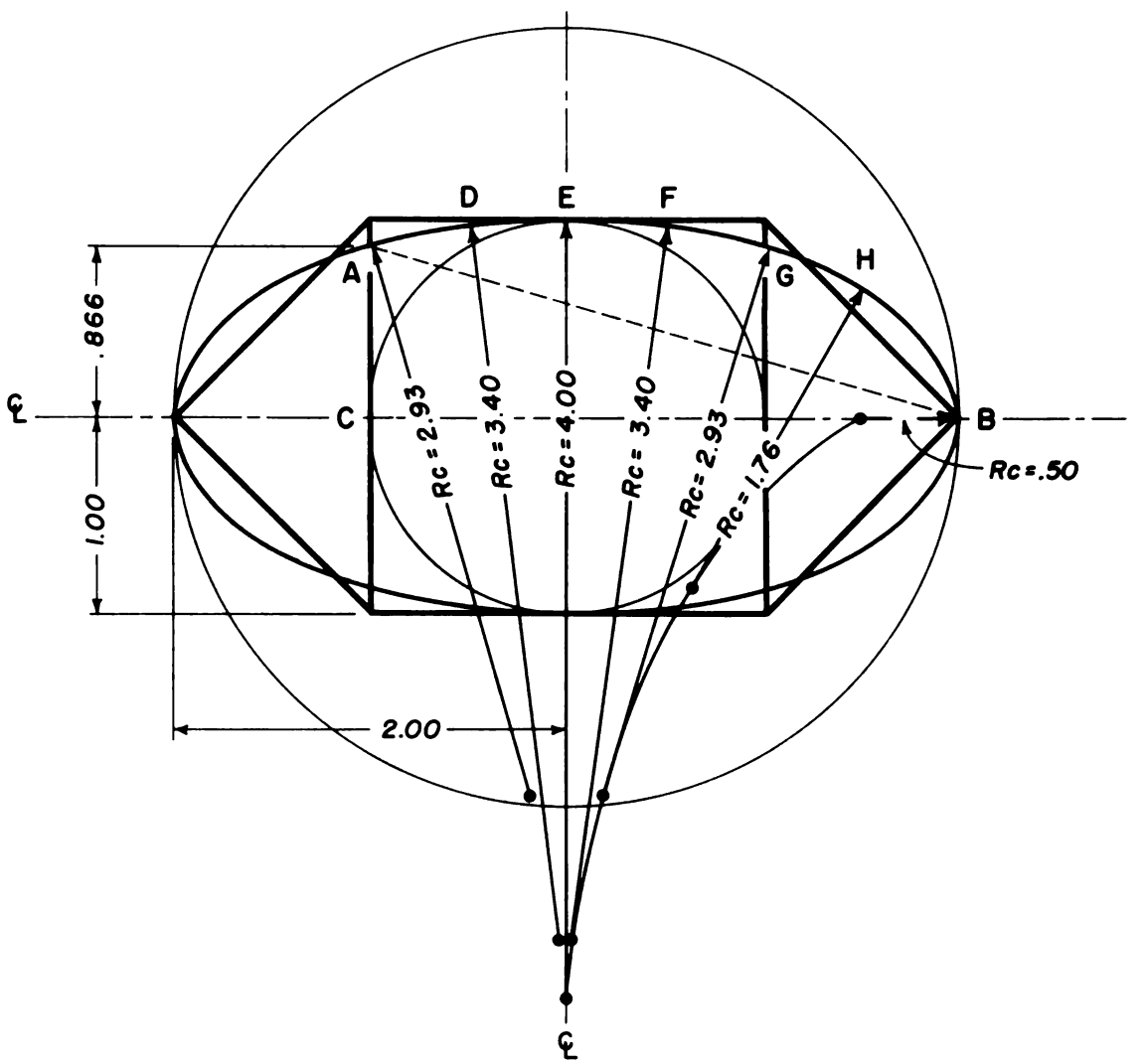
An ellipse was constructed with the major semi-axis (a) twice as great as the minor semi-axis (b). Specifically, when (b = 1), by substituting numerical values for (a) and (b) in equation (10), a more simplified expression for the radius of the elliptical curvature was obtained:

$$R = \frac{(\ 16 - 3\ x^2\ )^{3/2}}{16}\ . \qquad (11)$$

The radii of the elliptical curvature at points A, D, E, F, G, H, and B (Figure 6), by substituting for (x) in the equation (11) values zero, $\pm$ 1/2, $\pm$ 1, $\pm$ 3/2, and $\pm$ 2, were found to

FIGURE 6

Diagram of elliptical model used in estimating the radius of the major curvature of left ventricle.


D
E
F
A
G
H
C
B
.866
1.00
2.00
Rc = 2.93
Rc = 3.40
Rc = 4.00
Rc = 3.40
Rc = 2.93
Rc = 1.76
Rc = .50

be 2.929, 3.394, 4.000, 3.394, 2.929, 1.758, and 0.500 respectively. The mean radius of the curvature having the above radii at the corresponding points can be calculated from the relationship,

$$\text{Mean Radius} = \frac{(a/2 + b + c + \ldots + n/2)}{(n - 1)} . \qquad (12)$$

Using the above values for the various radii, the value of the mean radius from the equation (12) will be:

$$\text{Mean Radius} = (0.500/2 + 1.758 + 2.929 + 3.394 + 4.000 + 3.394 + 2.929/2) / 6.$$

$$\text{Mean Radius} = 2.865.$$

The value for the mean radius by circular approximation can be found if the values for arc AB and chord AB were known. The value for arc length can be calculated from the perimeter of the ellipse. The equation for perimeter of an ellipse is:

$$P = 2 (4 + 1.1m + 1.2m^2) \qquad (13)$$

where ($m = b/a$). Substituting for (m) in the equation (13), the perimeter will be equal to,

$$P = 2 (4 + 1.1 (1/2) + 1.2 (1/2)^2) = 9.70$$

The value of P/4 will be,

$$P/4 = 2.425.$$

This value is equal to the distance BE of the arc. The distance AE of the arc was found by direct measurement to be 1.012. Thus, from these two values, the total length of the arc AB will be,

$$\text{Length of Arc AB} = 2.425 + 1.012 = 3.437.$$

The length of the chord AB can be determined by using the Pythagoras Theorem on the triangle ABC.

$$\text{Length of Chord AB} = (3^2 + 0.866^2)^{1/2} = 3.122.$$

The ratio S/L (arch length to chord length) is about 1.101. From the graph (Figure 5), the mean radius by circular approximation was found to be about 2.22. Thus, the ratio of mean radius of curvature by elliptical evaluation to the mean radius by circular approximation is about 1.31. This indicates that the mean radius of the major curvature of the left ventricle is 1.31 times that of the mean radius calculated by circular approximation. Consequently, to obtain the true value for the mean radius of the major curvature of the left ventricle, the calculated mean radius for the major curvature by circular approximation was multiplied by the constant 1.31. This procedure is considered justified, since the average ratio S/L, in the hypertensive animals was about 1.345, and in the normal animals about 1.300. These values do not seem to be very different from the value 1.101 obtained in the ideal condition. Secondly, the procedure used results in a greater numerical difference between the mean radius and the wall thickness, as indicated by their ratio. The ratio (mean radius/ wall thickness) was increased by about 19.2% in the hypertensive animals, and by about 19.9% in normal animals, when elliptical approximation was used instead of

spherical approximation. The significance of this difference will be discussed in Part V.

In calculating the volume and surface area of the left ventricle, a spherical geometry was assumed. The radius for this sphere was the mean radius of the major and minor curvature's radii. The formulae employed were, $(4/3\pi R^3)$, for the volume, and $(4\pi R^2)$, for the surface area. No attempt was made to calculate the volume and the surface area of the left ventricle by assuming an elliptical geometry. This would have involved the process of integration of a series of measurements. The experimental procedure for making such an evaluation is under consideration.

The values for radial force(F_R) were calculated from the formula ($F_R = P.A$), where (P) is pressure and (A) is area.

The calculated values for volume and surface area refer to the total volume and outer surface area of the left ventricle. Since the thickness of the left ventricular wall varies from one point to another, calculated values do not indicate the internal change. It would be interesting to find a mathematical relationship between the inner and outer volumes and surface areas. This might indicate the manner in which the various ventricular parts respond to the changes in the blood pressure. It would further show the over-all

dimensional changes of the heart, and relative changes in the ventricular dimensions and their relation to each other in response to alteration of blood pressure.

Table 2

Comparison of Body Weight and Food Consumption

Rat No.	Sex	Initial Weight gm.	7th-day Weight gm.	Final Weight gm.	Weight Change gm.	Food Consump. gm.
Group I - Hypertensive						
1	F	138	138	105	-33	92
2	F	163	166	142	-21	94
3	F	140	145	132	-8	126
4	M	157	174	131	-26	129
5	M	166	162	106	-60	102
6	M	180	178	150	-30	87
Group II - Hypertensive						
1	M	213	195	195	-18	137
2	F	160	170	175	15	167
3	M	200	220	245	45	221
4	M	195	205	233	38	208
5	M	245	260	292	47	246
6	M	220	224	170	-50	134
7	M	205	195	225	20	178
8	M	225	215	230	5	165
9	M	225	230	252	27	214
10	M	220	250	280	60	242
Mean:		190.8	195.4	191.4	0.69	158.9
Standard Deviation:		± 8.35	± 9.01	±15.23	± 9.18	± 13.61
Group III - Normotensive						
1	F	190	195	208	18	258
2	F	195	195	200	5	217
3	F	185	185	185	0	148
4	F	215	208	215	0	165
5	F	220	218	220	0	146
6	F	192	190	192	0	144
7	F	195	195	196	1	176
8	F	212	212	215	3	150
9	F	242	243	245	3	214
10	F	203	208	212	9	166
Mean:		204.9	204.9	208.8	6.5	178.4
Standard Deviation:		± 12.01	± 3.60	± 3.61	± 1.25	± 8.40

Table 3

Comparison of Blood Pressures and Hematocrits

Rat No.	Initial B.P. mm. Hg	7th-day B.P. mm. Hg	10th-day B.P. mm. Hg	Final B.P. mm. Hg	Initial Hct. %	Final Hct. %
Group I - Hypertensive						
1	108	153	192	195	44	41
2	148	140	195	176	43	22
3	135	149	170	198	37	33
4	135	140	170	214	36	32
5	130	165	190	135	35	26
6	104	178	210	210	40	44
Group II- Hypertensive						
1	110	158	195	175	43	37
2	90	150	165	205	45	44
3	110	145	160	165	41	41
4	130	145	140	170	43	43
5	112	120	135	160	42	41
6	122	128	158	170	39	40
7	124	154	172	208	43	43
8	120	120	120	140	42	40
9	120	130	155	190	43	41
10	114	134	145	208	43	39
Mean:	119.5	144.3	167.0	182.4	41.2	37.9
Standard Deviation:	±3.57	± 3.97	± 6.24	± 6.23	± 0.74	± 1.62
Group III - Normotensive						
1	125	115	130	130	42	41
2	135	145	130	120	40	41
3	130	110	130	125	44	43
4	110	110	120	125	40	41
5	110	115	120	120	40	41
6	115	125	130	135	40	40
7	125	125	120	125	41	42
8	130	125	128	125	42	43
9	120	120	122	120	42	44
10	135	130	128	130	42	41
Mean:	123.5	122.0	125.8	125.5	41.3	41.7
Standard Deviation:	± 2.05	± 2.31	± 1.01	± 1.09	± 0.29	± 0.27

Table 4

Comparison of Wet and Dry Weights of Ventricles

Rat No.	Wet Weight mg.	Dry Weight mg.	Wet Wt. x 100 / Surface Area gm./cm.^{2}	Dry Wt. x 100 / Surface Area gm./cm.^{2}
Group I - Hypertensive				
1	460.0	116.2	0.2248	0.0568
2	603.2	132.2	0.2457	0.0538
3	548.6	111.6	0.2336	0.0475
4	591.7	167.1	0.2532	0.0715
5	383.5	99.5	0.1864	0.0484
6	667.6	141.3	0.2634	0.0557
Group II - Hypertensive				
1	646.4	144.5	0.2179	0.0487
2	508.9	135.0	0.1830	0.0486
3	597.5	160.6	0.1756	0.0472
4	554.7	133.2	0.1680	0.0404
5	861.0	204.2	0.2278	0.0540
6	698.7	138.7	0.2557	0.0508
7	609.0	143.3	0.1884	0.0443
8	610.4	143.1	0.1864	0.0437
9	756.5	168.6	0.2186	0.0458
10	823.0	182.3	0.2233	0.0495
Mean:	620.0	145.09	0.2157	0.0504
Standard Deviation:	±31.13	± 6.68	± 0.0077	± 0.0057
Group III - Normotensive				
1	450.1	133.4	0.1460	0.0433
2	458.0	139.1	0.1520	0.0462
3	399.0	125.1	0.1388	0.0435
4	429.5	133.5	0.1365	0.0424
5	452.6	136.0	0.1419	0.0426
6	416.3	124.2	0.1418	0.0423
7	445.9	125.6	0.1498	0.0422
8	356.6	113.4	0.1134	0.0361
9	483.0	142.8	0.1420	0.0420
10	515.6	143.6	0.1653	0.0460
Mean:	440.7	131.67	0.1428	0.0427
Standard Deviation:	± 9.59	± 1.94	± 0.0029	± 0.0019

Table 5

Comparison of Water Content and Dry Matter of Ventricles

Rat No.	Water Content %	Dry Matter %
Group I - Hypertensive		
1	74.73	25.27
2	78.10	21.90
3	79.67	20.33
4	71.76	28.24
5	74.03	25.97
6	78.85	21.15
Group II - Hypertensive		
1	77.65	22.35
2	73.44	26.56
3	73.12	26.88
4	75.95	24.05
5	76.29	23.71
6	80.13	19.87
7	76.49	23.51
8	76.56	23.44
9	79.04	20.96
10	77.83	22.17
Mean:	76.48	23.52
Standard Deviation:	± 0.63	± 0.63
Group III - Normotensive		
1	70.37	29.63
2	69.62	30.38
3	68.65	31.35
4	68.92	31.08
5	69.96	30.04
6	70.08	29.92
7	71.83	28.17
8	68.21	31.79
9	70.45	29.55
10	72.15	27.85
Mean:	70.02	29.98
Standard Deviation:	± 0.28	± 0.28

Table 6

Comparison of Left Ventricular Measurements

Rat No.	Major Arc mm.	Major Chord mm.	Minor Arc mm.	Minor Chord mm.	Wall Thickness mm.
Group I - Hypertensive					
1	16.0	11.7	10.5	7.5	2.4
2	16.4	12.7	11.5	7.4	2.4
3	16.1	11.7	10.4	7.2	2.5
4	16.3	12.1	10.2	6.9	2.4
5	14.5	11.0	10.2	7.2	2.6
6	15.4	10.7	11.2	8.0	1.8
Group II - Hypertensive					
1	17.2	11.6	10.7	7.1	2.5
2	13.9	10.9	10.4	6.9	2.7
3	15.4	12.4	10.2	7.2	2.4
4	14.0	11.2	10.4	6.7	2.6
5	18.5	14.3	12.8	8.8	2.7
6	14.4	11.2	11.3	7.7	2.8
7	13.2	10.0	9.3	6.7	2.6
8	15.7	10.6	10.5	7.1	2.5
9	15.1	11.6	10.5	7.4	2.6
10	18.2	13.0	12.5	8.2	2.8
Mean:	15.64	11.67	10.79	7.4	2.52
Standard Deviation:	± 0.36	± 0.27	± 0.22	± 0.14	± 0.06
Group III - Normotensive					
1	15.5	10.4	11.5	6.7	2.1
2	15.2	12.1	11.2	7.3	1.8
3	15.9	13.2	11.7	7.4	2.0
4	19.1	15.2	13.3	9.2	1.8
5	16.0	12.0	12.3	7.8	1.9
6	15.5	11.8	10.9	7.4	2.1
7	14.3	11.3	10.7	7.4	2.0
8	14.6	12.7	11.1	7.8	1.8
9	19.5	14.8	10.2	7.9	2.0
10	15.6	10.9	11.7	8.1	2.2
Mean:	16.12	12.44	11.46	7.7	1.97
Standard Deviation:	± 0.38	± 0.33	± 0.19	± 0.14	± 0.03

Table 7

Comparison of Ratios of Major Arc to Major Chord and Minor Arc to Minor Chord

Rat No.	Major Arc / Major Chord	Minor Arc / Minor Chord
Group I - Hypertensive		
1	1.37	1.40
2	1.29	1.55
3	1.38	1.44
4	1.35	1.48
5	1.32	1.42
6	1.44	1.40
Group II - Hypertensive		
1	1.48	1.51
2	1.28	1.51
3	1.24	1.42
4	1.25	1.55
5	1.29	1.46
6	1.29	1.47
7	1.32	1.39
8	1.48	1.48
9	1.30	1.42
10	1.40	1.52
Mean:	1.34	1.46
Standard Deviation:	± 0.019	± 0.013
Group III - Normotensive		
1	1.49	1.72
2	1.26	1.53
3	1.21	1.58
4	1.26	1.45
5	1.33	1.58
6	1.31	1.47
7	1.27	1.45
8	1.15	1.42
9	1.32	1.30
10	1.43	1.44
Mean:	1.30	1.50
Standard Deviation	± 0.022	± 0.025

Table 8

Comparison of Values for Product of Wall Thickness, t, and Sum of the Reciprocal of Principle Radii of Curvature

Rat No.	Elliptical Approximation $t\ (1/R_1 + 1/R_2)$	Spherical Approximation $t\ (1/R_1 + 1/R_2)$
Group I - Hypertensive		
1	0.9314	1.0255
2	0.9192	1.0030
3	1.0055	1.1043
4	0.9838	1.0742
5	1.0561	1.1625
6	0.6955	0.7742
Group II - Hypertensive		
1	1.0300	1.1315
2	1.1310	1.2396
3	0.9223	1.0046
4	1.0967	1.1960
5	0.8778	0.9612
6	1.0744	1.1894
7	1.1365	1.2537
8	1.0583	1.1690
9	1.0145	1.1144
10	1.0041	1.1038
Mean:	0.9961	1.0944
Standard Deviation:	$\pm$ 0.0276	$\pm$ 0.0303
Group III - Normotensive		
1	0.9288	1.0242
2	0.7839	0.7636
3	0.7406	0.8028
4	0.5526	0.6035
5	0.7182	0.7898
6	0.8209	0.9097
7	0.7440	0.8612
8	0.6260	0.6790
9	0.6720	0.7328
10	0.8406	0.9350
Mean:	0.7428	0.8102
Standard Deviation:	+ 0.0238	$\pm$ 0.0274

Table 9

Comparison of Left Ventricular Radii and Calculated Tension and (k), Assuming Spherical Geometry

Rat No.	Major Radius cm.	Minor Radius cm.	Tension x 10^4 dynes/cm.	(k) x 10^4 dynes/cm.^{2}
Group I - Hypertensive				
1	0.6025	0.3825	6.084	25.352
2	0.6776	0.3700	5.615	23.395
3	0.6002	0.3636	5.977	23.905
4	0.6268	0.3471	6.374	26.560
5	0.5775	0.3650	4.026	15.483
6	0.5404	0.4080	6.510	36.164
Group II - Hypertensive				
1	0.5834	0.3557	5.155	20.620
2	0.5886	0.3457	5.953	22.048
3	0.6919	0.3650	5.255	21.897
4	0.6194	0.3350	4.927	18.951
5	0.7665	0.4435	5.992	22.193
6	0.6003	0.3873	5.336	19.056
7	0.5260	0.3424	5.751	22.119
8	0.5332	0.3571	3.992	15.967
9	0.6171	0.3752	5.910	22.731
10	0.6630	0.4108	7.035	25.123
Mean:	0.6127	0.3723	5.618	22.598
Standard Deviation:	± 0.0157	± 0.0072	± 0.205	± 1.191
Group III - Normotensive				
1	0.5221	0.3377	3.554	16.923
2	0.6631	0.3657	3.772	20.952
3	0.7630	0.3700	4.152	20.759
4	0.8330	0.4646	4.970	27.614
5	0.6276	0.3900	3.849	20.257
6	0.6242	0.3722	4.155	19.785
7	0.6136	0.3737	3.870	19.351
8	0.8040	0.3955	4.418	24.544
9	0.7785	0.4203	4.367	21.833
10	0.5526	0.4099	4.078	18.537
Mean:	0.6782	0.3900	4.119	21.056
Standard Deviation:	± 0.0237	± 0.0077	± 0.087	± 0.667

Table 10

Comparison of Left Ventricular Radii and Calculated Tension and (k), Assuming Elliptical Geometry

Rat No.	Major Radius cm.	Minor Radius cm.	Tension x 10^4 dynes/cm.	(k) x 10^4 dynes/cm.^{2}
Group I - Hypertensive				
1	0.7894	0.3825	6.699	27.913
2	0.8876	0.3700	6.127	25.528
3	0.7863	0.3636	6.563	26.254
4	0.8211	0.3471	6.961	29.001
5	0.7565	0.3650	4.431	17.043
6	0.7079	0.4080	7.246	40.256
Group II - Hypertensive				
1	0.7644	0.3557	5.663	22.652
2	0.7711	0.3457	6.525	24.165
3	0.9064	0.3650	5.724	23.851
4	0.8114	0.3350	5.373	20.667
5	1.0041	0.4435	6.562	24.302
6	0.7964	0.3873	5.907	21.096
7	0.6891	0.3424	6.344	24.400
8	0.6985	0.3571	4.410	17.637
9	0.8084	0.3752	6.492	24.969
10	0.8685	0.4108	7.733	27.618
Mean:	0.8011	0.3723	6.173	24.835
Standard Deviation:	± 0.0205	± 0.0072	± 0.227	± 1.330
Group III - Normotensive				
1	0.6840	0.3377	3.919	18.661
2	0.8687	0.3657	3.674	20.410
3	0.9995	0.3700	4.500	22.502
4	1.0912	0.4646	5.428	30.157
5	0.8222	0.3900	4.233	22.277
6	0.8177	0.3722	4.604	21.925
7	0.8038	0.3737	4.480	22.399
8	1.0532	0.3955	4.792	26.621
9	1.0198	0.4203	4.762	23.808
10	0.7239	0.4099	4.536	20.619
Mean:	0.8884	0.3900	4.493	22.938
Standard Deviation:	± 0.0311	± 0.0077	± 0.105	± 0.600

Table 11

Comparison of Values for Mean Radius, Surface Area, and Volume, Assuming Spherical Geometry

Rat No.	Mean Radius cm.	Surface Area $cm.^2$	Volume $cm.^3$
Group I - Hypertensive			
1	0.4925	3.0485	0.5005
2	0.5238	3.4481	0.6019
3	0.4819	2.9178	0.4687
4	0.4869	2.9794	0.4834
5	0.4712	2.7897	0.4381
6	0.4742	2.8261	0.4465
Group II - Hypertensive			
1	0.4695	2.7695	0.4335
2	0.4671	2.7420	0.4268
3	0.5284	3.5084	0.6178
4	0.4772	2.8613	0.4553
5	0.6050	2.5992	0.8515
6	0.4938	3.0636	0.5043
7	0.4342	2.3687	0.3426
8	0.4451	2.4893	0.3694
9	0.4961	3.0925	0.5114
10	0.5369	3.6228	0.6484
Mean:	0.4927	3.0567	0.5030
Standard Deviation:	± 0.0102	± 0.1325	± 0.0310
Group III - Normotensive			
1	0.4299	2.3222	0.3330
2	0.5144	3.3250	0.5701
3	0.5665	4.0324	0.7615
4	0.6488	5.2890	1.1439
5	0.5088	3.2533	0.5516
6	0.4982	3.1189	0.5181
7	0.4937	3.0623	0.5039
8	0.5998	4.5212	0.9039
9	0.5994	4.5150	0.9022
10	0.4813	2.9115	0.4670
Mean:	0.5341	3.6351	0.6655
Standard Deviation:	± 0.0146	± 0.1990	± 0.0548

Table 12

Comparison of Values for Mean Radius, Surface Area, and Volume, Assuming Elliptical Geometry

Rat No.	Mean Radius cm.	Surface Area $cm.^2$	Volume $cm.^3$
Group I - Hypertensive			
1	0.5859	4.3140	0.8423
2	0.6288	4.9686	1.0413
3	0.5749	7.4581	0.7958
4	0.5841	4.2875	0.8348
5	0.5608	3.9520	0.7389
6	0.5579	3.9118	0.7276
Group II - Hypertensive			
1	0.5600	3.9407	0.7355
2	0.5584	3.9181	0.7292
3	0.6357	5.0779	1.0761
4	0.5732	4.1292	0.7891
5	0.7238	6.5833	1.5883
6	0.5918	4.4006	0.8681
7	0.5158	3.3438	0.5751
8	0.5278	3.5009	0.6161
9	0.5918	4.4006	0.8681
10	0.6396	5.1408	1.0962
Mean:	0.5881	4.5830	0.8702
Standard Deviation:	$\pm$ 0.0125	$\pm$ 0.2723	$\pm$ 0.0605
Group III - Normotensive			
1	0.5109	3.2797	0.5588
2	0.6172	4.7864	0.9847
3	0.6848	5.8935	1.3454
4	0.7779	7.6037	1.9716
5	0.6061	4.6168	0.9328
6	0.5950	4.4484	0.8821
7	0.5888	4.3566	0.8549
8	0.7244	6.5946	1.5925
9	0.7201	6.5155	1.5640
10	0.5669	4.0387	0.7632
Mean:	0.6392	5.2134	1.1450
Standard Deviation	$\pm$ 0.0182	$\pm$ 0.2969	$\pm$ 0.0977

Table 13

Comparison of Radial Force Calculated from both Spherical and Elliptical Approximations of the Principle Radii

Rat No.	Spherical Approximation dynes x 10^4	Elliptical Approximation dynes x 10^4
Group I - Hypertensive		
1	79.2549	112.1554
2	80.9097	116.5882
3	77.0241	196.8789
4	85.0053	122.3267
5	50.2118	71.1321
6	79.1252	109.5226
Group II - Hypertensive		
1	64.6152	91.9405
2	74.9416	107.0856
3	77.1778	111.7036
4	64.8514	93.5883
5	98.1101	140.4350
6	69.4365	99.7396
7	65.6843	92.7269
8	46.4628	65.3443
9	78.3361	111.4716
10	100.4639	142.5595
Mean:	74.4757	111.5750
Standard Deviation:	$\pm$ 0.7234	$\pm$ 7.6950
Group III - Normotensive		
1	40.2484	56.8438
2	53.1967	76.5776
3	67.2000	98.2152
4	88.1412	126.7157
5	52.0496	73.8642
6	56.1340	80.0623
7	51.0332	72.6027
8	75.3458	109.8990
9	72.2355	104.2415
10	50.4621	69.9988
Mean:	61.5046	86.9021
Standard Deviation:	$\pm$ 2.7800	$\pm$ 3.3700

Table 14

Comparison of Results

Final Values Mean ± S.D.	Normal	Hypertensive	Diff. %	t
Blood Pressure (mm. Hg)	125.5 ± 1.09	182.4 ± 6.23	+45.3	7.084*
Hematocrit (Percent)	41.4 ± 0.27	37.9 ± 1.62	-8.5	1.998**
Wet Weight (mg.)	440.7 ± 9.59	620.0 ± 31.13	+40.7	4.360*
Dry Weight (mg.)	131.67 ± 1.94	145.09 ± 6.68	+10.2	0.488
$\frac{\text{Wet Weight x 100}}{\text{Surface Area (gm./cm.}^2\text{)}}$	0.1428 ± 0.0029	0.2157 ± 0.0077	+51.1	7.050*
$\frac{\text{Dry Weight x 100}}{\text{Surface Area (gm./cm.}^2\text{)}}$	0.0427 ± 0.0019	0.0504 ± 0.0057	+18.0	2.450*
Wall thickness (mm.)	1.97 ± 0.03	2.52 ± 0.06	+27.9	6.651*
$t(1/R_1 + 1/R_2)$ Spher. Approx.	0.8102 ± 0.0274	1.0944 ± 0.0303	+35.1	5.738*
$t(1/R_1 + 1/R_2)$ Ellip. Approx.	0.7428 ± 0.0238	0.9961 ± 0.0276	+34.1	5.646*
Tension (dynes/cm.) x 10^4 Spher. Approx.	4.119 ± 0.087	5.618 ± 0.205	+36.4	5.347*
Tension (dynes/cm.) x 10^4 Ellip. Approx.	4.493 ± 0.105	6.173 ± 0.227	+37.4	5.365*

Table 14 (Continued)

Final Values Mean ± S.D.	Normal	Hypertensive	Diff. %	t
Constant k (dynes/cm.^{2}) x 10^4 Spher. Approx.	21.056 ± 0.667	22.598 ± 1.191	+ 7.3	0.908
Constant k (dynes/cm.^{2}) x 10^4 Ellip. Approx.	22.938 ± 0.600	24.835 ± 1.330	+ 8.3	1.037
Mean Radius (cm.) Spher. Approx.	0.5341 ± 0.0146	0.4927 ± 0.0102	- 7.8	1.969**
Mean Radius (cm.) Ellip. Approx.	0.6392 ± 0.0182	0.5881 ± 0.0125	- 8.0	1.959**
Radial Force (dynes) x 10^4 Spher. Approx.	61.5046 ± 2.7800	74.4757 ± 0.7234	+21.1	3.949*
Radial Force (dynes) x 10^4 Ellip. Approx.	86.9021 ± 3.3700	111.5750 ± 7.5750	+28.4	2.343*

* Significant at < 0.01 level. ** Significant at < 0.1 level.

V. RESULTS AND DISCUSSION

Data are presented in two parts. The first part is composed of determinations of body weight, food intake, blood pressure, hematocrit, and wet weight and dry weight of ventricles. The second part of the data, measurements of left ventricular arcs and chords, and calculation of mean radius, tension, proportionality constant (k), and radial force, was obtained after making several assumptions as mentioned above in discussion of calculations. In order to facilitate discussion, data in Tables 2-13 are summarized in Table 14 where mean values are tabulated.

Comparison of mean final blood pressures of control and experimental animals indicates an increase of about 45.3% in the blood pressure of rats in Groups I and II (Table 3) at the termination of the experiment. Graphic comparison of blood pressure measurements at the four designated intervals is presented in Figure 7. Results are in full agreement with those obtained by Chanutin and co-workers (1932 and 1933) and Hermann and associates (1941). However, it should be noted that these investigators measured blood pressures only at the termination of experiment by means of direct carotid cannulation. There can be little doubt that the hypertension-inducing methods employed here, especially the one proposed by Grollman (1944), successfully produced high blood pressure.

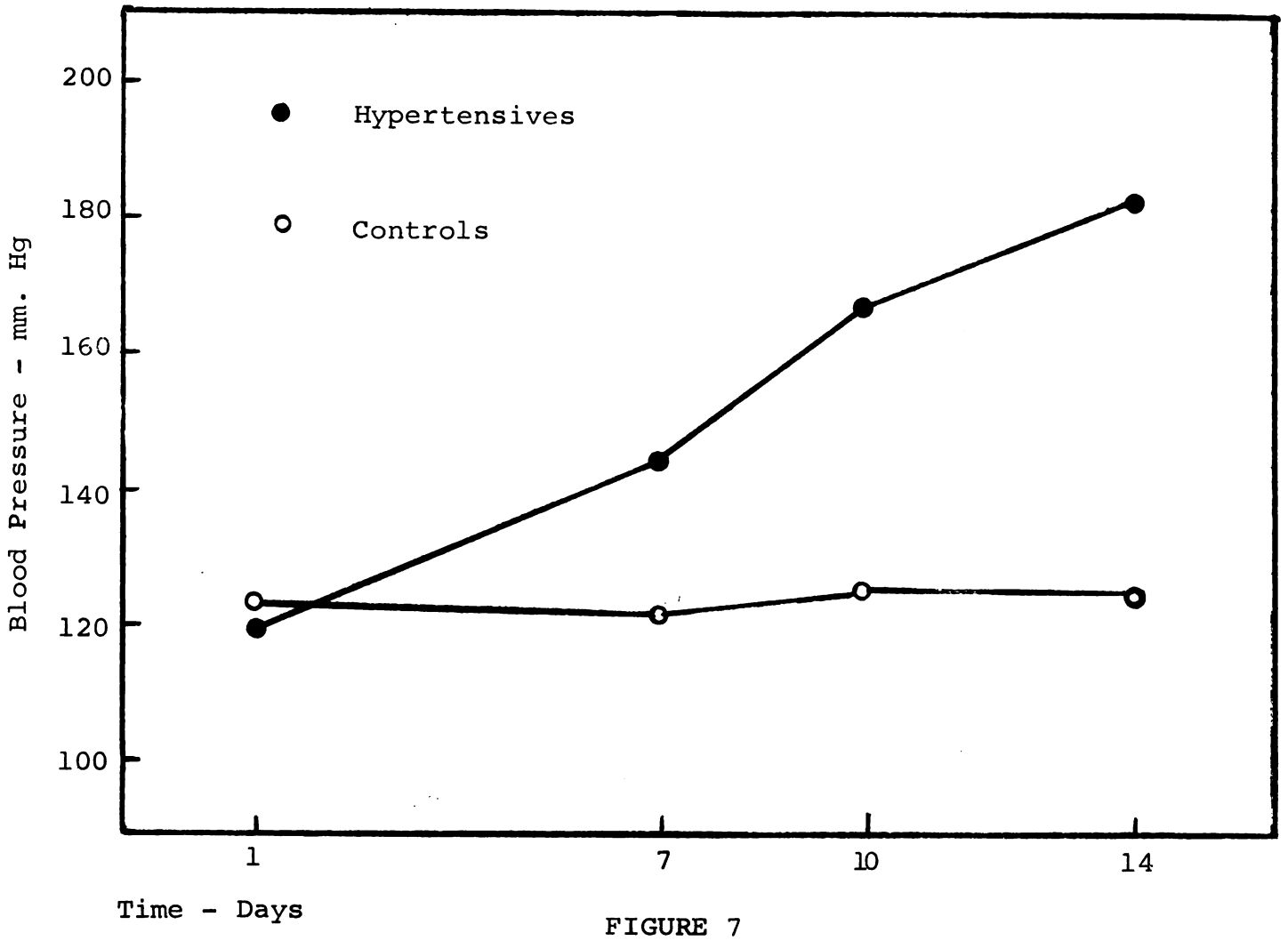


FIGURE 7

Comparison of blood pressures of normal and hypertensive rats.

A further indication that animals in Groups I and II developed high blood pressure was the decrease of about 8.5% in the mean value of final hematocrit of experimental animals as compared to controls. This accords with observations made on rats by Beckwith and Chanutin (1941). They found an increase in plasma volume and a subsequent decrease in red cell volume in hypertensive rats which were attributed to development of anemia. Since no blood or urine analyses were made in this study, the presence or absence of anemia in rats of Groups I and II cannot be confirmed.

Wet weight of ventricles showed a 40.7% increase in hypertensive rats as compared to normotensive animals, suggesting a definite ventricular hypertrophy. Reliability of the wet weight determinations and their significance can be debated on the basis that ventricles were weighed after removal from alcohol following the ventricular measurements step. Data listed in Table 4 indicate that such an argument is not well-founded and can be discarded on the basis of the uniformity of wet weight determinations for both hypertensive and control animals, and the fact that the standard deviation in both groups was low. Furthermore, since the same procedure was employed in wet weight determinations of all three groups, any objection will be applicable to both normotensive and hypertensive rats. It should be noted also that the results

show, in a comparative sense, relative hypertrophy of ventricles of animals in Groups I and II as compared to those in Group III. There is no doubt that the degree of ventricular hypertrophy as demonstrated by wet weight determinations is highly significant (Table 14).

It is equally important to note that dry weight determinations indicate about 10.2% increase in mass of ventricles of hypertensive rats as compared to controls (Table 14). This difference suggests possible cardiac hyperplasia.

In order to ascertain the degree of correlation of both wet and dry weights of ventricles with blood pressures, Figures 8 and 9 were prepared. Figure 8 shows that there exists a definite relationship between blood pressure and the ratio of wet weight to surface area. This correlation is in agreement with that suggested by Chanutin and co-workers (1932 and 1933). However, no conclusion as to the significance of the degree of correlation between ratio of dry weight to surface area and blood pressure (Figure 9) can be made from this graphic presentation.

Left ventricular wall thickness measurements indicated that there was an increase of about 27.9% in hypertensive rats as compared to normotensives (Table 14). This is highly significant ($p < .01$) and agrees with the ventricular wet weight data.

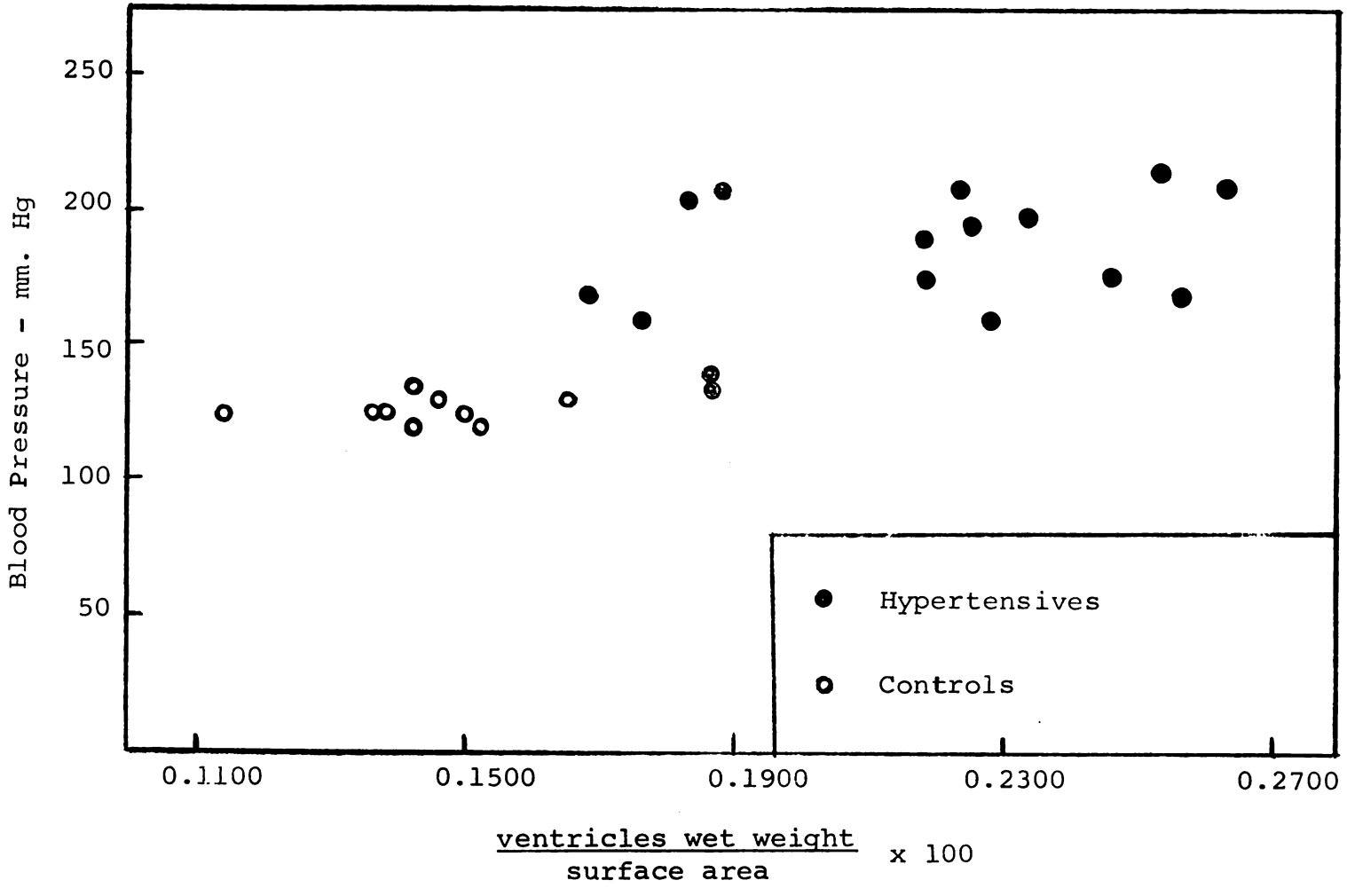


FIGURE 8

Relationship between blood pressure and ratio of ventricular wet weight to surface area of both normal and hypertensive rats.

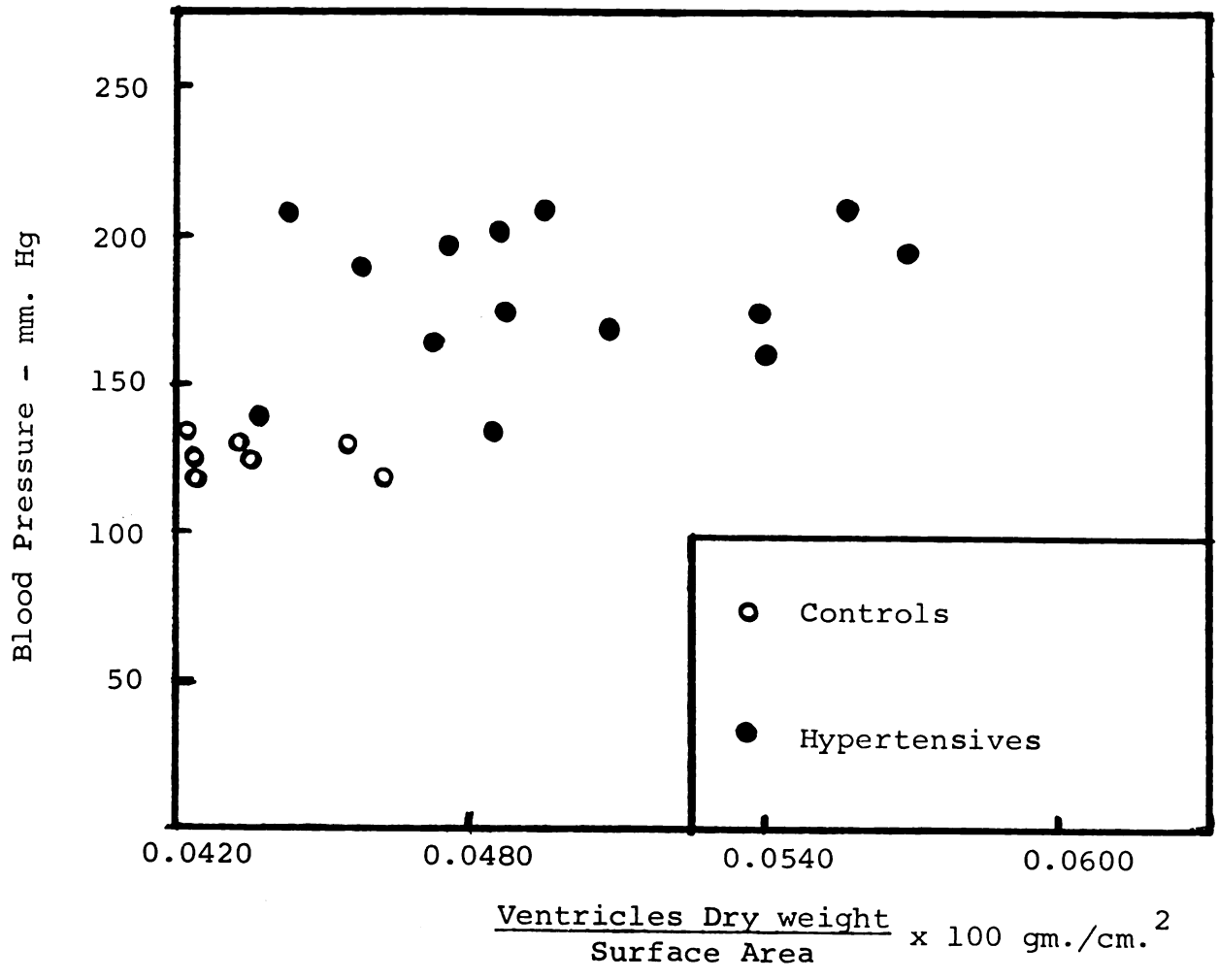


FIGURE 9

Relationship between blood pressure and ratio of ventricular dry weight to surface area of both normal and hypertensive rats.

The second portion of the data was obtained from application of the Law of Laplace, $P = T (1/R_1 + 1/R_2)$, to the left ventricle. Tail systolic pressure of rats was determined in mm. Hg and converted to dynes per square cm., using the equality 1 mm. Hg = 1.3333×10^3 dynes per square cm. Values for radii were obtained on excised and slightly inflated hearts whose volumes approximated the isometric (isovolumic) contraction phase of systole. This procedure was used for convenience in obtaining a fixed heart size. However, it should be admitted that tail systolic blood pressure is greater than the pressure generated by the left ventricle during the isometric (isovolumic) contraction phase to which the volume of excised hearts was presumably adjusted. This discrepancy could be avoided in future experiments by direct and simultaneous recording of cardiac pressure and dimensions. Refined techniques for this procedure have recently been described (Hawthorne, 1961).

In the course of inflation, normotensive hearts were subjected to a pressure head approximately one-half of that of hypertensive hearts. The reason for this difference in pressure head was that intact, normotensive hearts were under a lower pressure load than the hypertensive hearts. The quantity, one-half, was selected by comparing the lowest blood pressure with the highest. It was found that the latter was

twice as great as the former.

Calculated results of the Laplace data were obtained from initial measurements of four parameters, namely, blood pressure, wall thickness, arcs, and chords of both major and minor curvatures. Coupled with these four parameters were four major assumptions: (1) that the left ventricle has an elliptical geometry; (2) that major curvature is part of an ellipse, and minor curvature is part of a circle, (3) that the ellipse, in general, has a major semi-axis twice as great as the minor, and (4) that the tension developed is proportional to the ventricular wall thickness. Accuracy of initial measurements can be questioned only in the case of determinations of wall thickness, arcs, and chords of both major and minor curvatures. Blood pressure measurements have been carried out with an apparatus which is considered relatively free from error. However, values of the other three parameters cannot be so considered. On the other hand, it is more pertinent here to look for the relative difference between normotensive and hypertensive animals.

With respect to the application of the Law of Laplace to the heart, Freis (1960) suggests that, "if there is cardiac dilatation the principle radii of curvature of the ventricle will increase. Because of the Laplace equation, $P = T (1/R_1 + 1/R_2)$, greater myocardial tension will be required

to produce a given intraventricular pressure." He points out further that, "this interpretation of Laplace's law must be accepted with some reservations, however, as the law applies primarily to situations in which the thickness of the wall is negligible in comparison to the radius of curvature." In the present study, calculation of the principle radii of curvatures show that there is a definite decrease in the mean radius of ventricular curvature at the point of intersection of major and minor arcs. This decrease is about 8.0% in the case of elliptical approximation and 7.8% by spherical approximation (Table 14). It should be noted that a decrease in mean radius of curvature indicates that there should have been a definite increase in the surface area at this point. However, as calculated here, both surface area and volume decreased (Table 14). These results are not in contradiction with expected findings because values for the mean radius of curvature refer only to one point and not the entire surface area or volume of the ventricle. Furthermore, values for surface area and volume, as mentioned above in discussion of calculations, were obtained by assigning a spherical geometry to the left ventricle with the value of the calculated mean radius as its radius. Therefore, obviously, the reduction in the ventricular surface area and volume is due to the calculated decrease in mean radius. However, it should be

pointed out that this decrease in mean radius indicates that there has been a change in the ventricular curvature and suggests a possible geometrical interpretation of the nature of cardiac hypertrophy in response to pressure load. The interpretation suggested here is, if we assume the normal left ventricle has elliptical geometry, it will tend to assume spherical geometry in the hypertrophied state. The advantage of the spherical shape is obvious, as seen from the Law of Laplace. The pressure load is uniformly distributed throughout the ventricle and the required developed tension is produced equally by all parts. Since the tension developed is proportional to the wall thickness, this geometrical interpretation also accounts for the increase in ventricular wall thickness in hypertension and, hence, cardiac hypertrophy.

Tables 9 and 10 list the principle radii of left ventricular curvatures by spherical and elliptical approximations, respectively. Both methods show a reduction of less than 10% in the major, and less than 5% in the minor, radii of the left ventricular curvatures. These results are not in accord with the predicted increase from the Laplace equation. The discrepancy lies in the fact that in accordance with the Law of Laplace, the principle radii of ventricular curvature should increase if there is cardiac dilatation. No application of Laplace's equation has been made to cardiac hypertrophy. It

is further suggested here that a distinction should be made between cardiac dilatation and hypertrophy. This distinction, as Rushmer (1961) suggests, is based on the response of the heart to two entirely different changes within the cardiovascular system. Myocardial hypertrophy occurs in response to a chronic pressure load, as in arterial hypertension; whereas, cardiac dilatation results in response to an increased volume load. However, both conditions can be present at the same time. Rushmer (1961) remarks that, "the usual response to a chronic pressure load is myocardial hypertrophy with various degrees of ventricular dilatation unless heart failure should supervene. The thickened ventricular walls probably have diminished distensibility, requiring a greater effective filling pressure to attain a particular diastolic volume. In other words, the myocardial hypertrophy tends to permit utilization of the systolic reserve capacity with some sacrifice of distensibility. On the other hand, ventricular dilatation involves an encroachment on the diastolic reserve capacity, apparently with some sacrifice of the contractility, since these distended ventricles fail to empty as completely during systole as the normal." Therefore, it is suggested that ventricles in the present study have merely hypertrophied without any accompanying dilatation.

Comparison of tension developed (Table 14) shows an

increase of 37.4% by elliptical and 36.4% by spherical approximations in hypertension. Also, elliptical approximation of radial force shows about 28.4% increase in hypertension as compared to controls; whereas, spherical approximation shows an increase of 21.1% (Table 14). These results substantiate theoretical considerations of Burch and co-workers (1952), Burch (1955), and Burton (1957). Values of proportionality constant (k) which are indicative of contractile behavior of ventricular wall at the point of measurements show an increase of about 10.7% in hypertensive as compared to normotensive animals as calculated by assuming elliptical geometry and about 9.7% increase when the spherical method was used (Table 14).

Figure 10 shows the relationship between blood pressure and calculated values for tension in hypertensive and control rats. Figure 11 shows the relationship between calculated tension and radial force in hypertensive and normal animals. These graphs indicate that elliptical approximation provides a better picture of changes undergone by the ventricle in hypertension than spherical approximation.

Another parameter which showed a slight difference between spherical and elliptical assumptions was the quantity $t(1/R_1 + 1/R_2)$ or the "shape" factor (Table 14). This parameter refers to the over-all shape and size of the ventricle subjected to a given intraventricular pressure. It should be

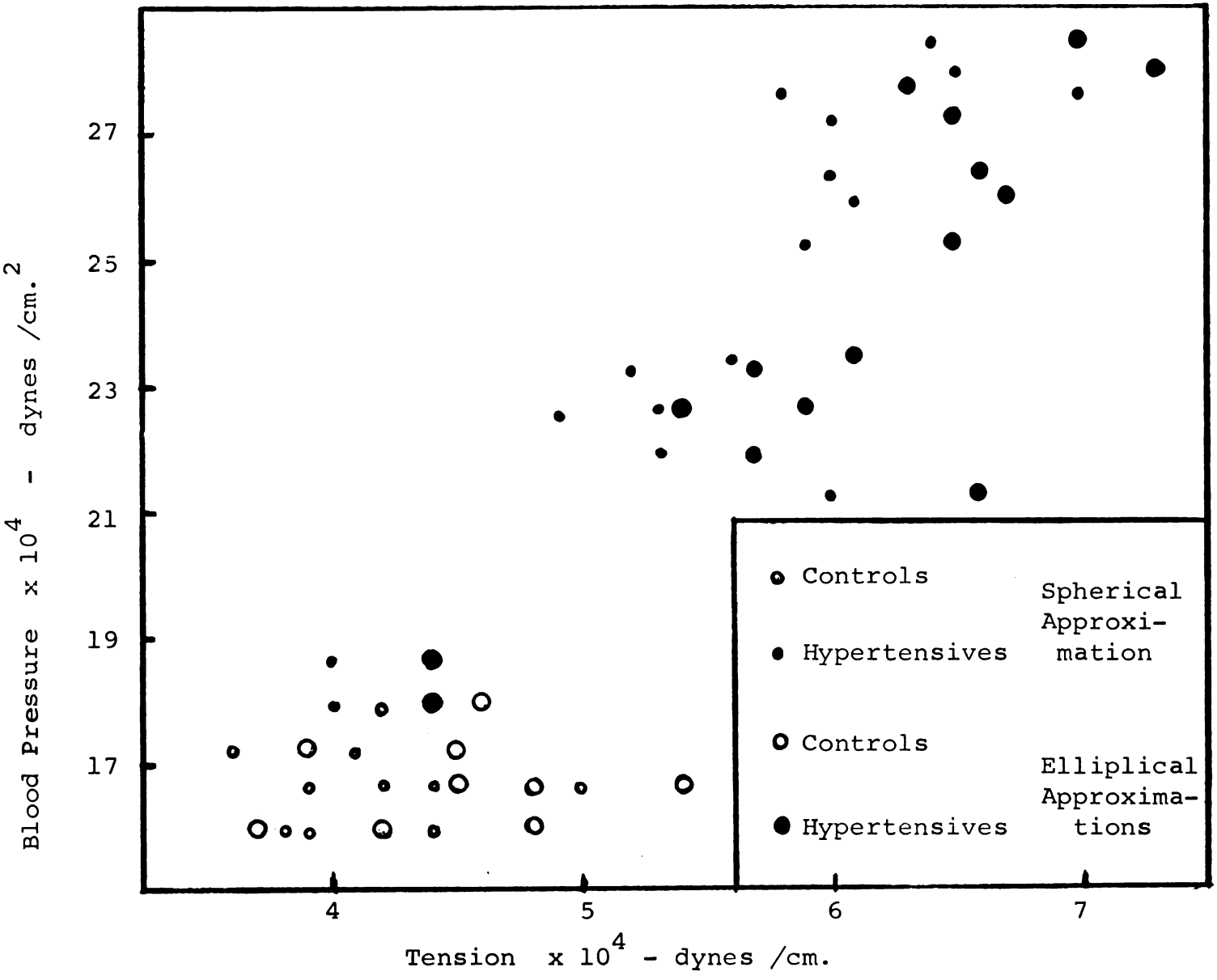


FIGURE 10

Relationship between blood pressure and tension of normal and hypertensive rats, showing both spherical and elliptical approximations.

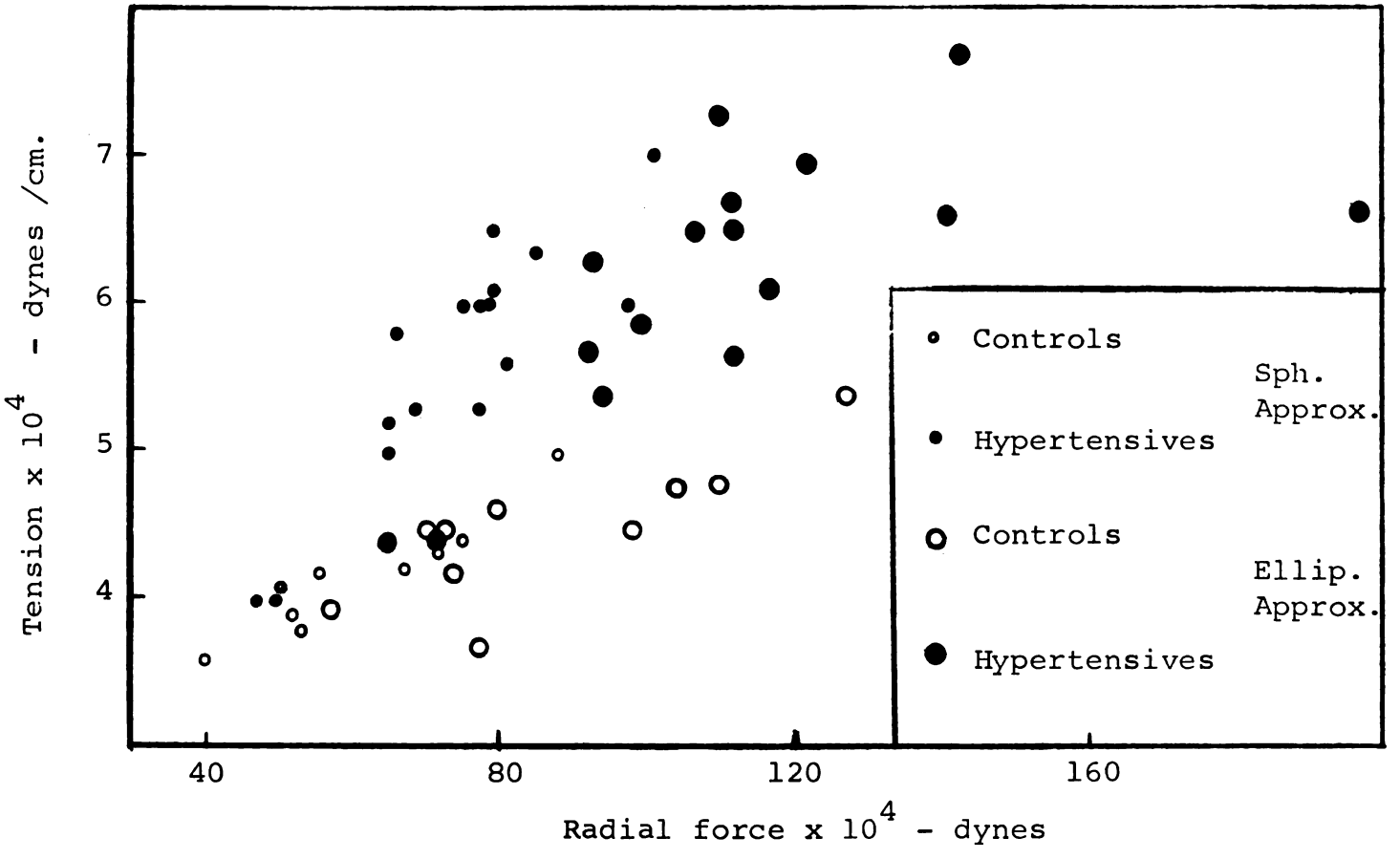


FIGURE 11

Relationship between tension and radial force of normal and hypertensive rats, showing both spherical and elliptical approximations.

recalled that the justification for the application of the Law of Laplace, as mentioned above in discussion of calculations, was based upon an assumption that the ventricular wall thickness is negligible as compared to the radius of curvature. It was then mentioned that the ratio of the mean radius to wall thickness was increased by 19.2% for hypertensive and 19.9% for normotensive rats when elliptical approximation was used. These considerations, and data obtained, suggest that probably assigning elliptical geometry to the left ventricle is a better and closer approximation of its normal shape than the spherical geometry.

This writer realizes that results presented are incomplete. Further methods should be devised to improve the quality and accuracy of initial ventricular measurements. It is believed that progress in such direction will result in much improvement of final data capable of shedding some light upon the nature of cardiac compensation in response to sustained high blood pressure.

VI. SUMMARY AND CONCLUSIONS

This study was designed to compare estimation of cardiac hypertrophy in hypertension by means of two methods: application of the Law of Laplace, and wet weight dry weight determinations. In using the first method, data were obtained by assuming both spherical and elliptical geometry for the left ventricle. Results are encouraging and indicative of the applicability with some limitations, of the Law of Laplace in determining changes in physical dimensions of the left ventricle in response to variation in blood pressure. For an average increase of 45.3% in blood pressure, there were a 40.7% increase in wet weight and a 37.4% increase in tension. The usefulness of the Law of Laplace in estimating cardiac hypertrophy is affirmed. Precision and accuracy of the application of the Law of Laplace will naturally increase as new methods are devised to obtain more refined initial ventricular measurements.

Estimation of cardiac hypertrophy by application of the Law of Laplace provides more clues to the nature of hypertrophy and effects of high blood pressure than the simple method of wet weight dry weight determinations. There was a definite change in curvatures of ventricular surface. Both wall tension and radial force increased in proportion to the

rise in blood pressure. Ventricular wet weight determination also showed a fairly good correlation with rise in blood pressure. Application of the Law of Laplace showed further that there was a definite change in contractile behavior of cardiac muscle wall, as indicated by the value of constant (k), in the equation, $T = k.t$, where (T) is wall tension, and (t) is wall thickness, and (k) is proportionality constant. Quantity (k) is the force that must be exerted per square cm. of cross-section of ventricular wall in order to generate required systolic pressure. Increase in value of constant (k) was paralleled by an increase of 10.2% in ventricular mass as shown by dry weight determinations. Data indicated that a better understanding of changes undergone by the heart during a sustained high blood pressure may result if the heart is assumed to be elliptical in geometry.

It is concluded that when the heart is subjected to a sustained elevation of blood pressure, as in the case of renal hypertension, there will be a definite change in both physical dimensions and contractile behavior of the heart. The change in physical dimension is reflected by an alteration of curvatures of cardiac surface. Contractile ability of the heart is impaired due to hypertrophy accompanied by hyperplasia of cardiac muscle fibers. However, it is hypertrophy of muscle fibers that is primarily responsible for alteration in the contractile ability of cardiac muscle fibers.

VII. LITERATURE CITED

Beckwith, J. R., and A. Chanutin. 1941. Blood Volumes in Hypertensive Partially Nephrectomized Rats. Proc. Soc. Exp. Biol. and Med., 46:66-69.

Benzak, M. 1958. Cardiac Output in Rats during the Development of Cardiac Hypertrophy. Circulation Research 6:207-12.

Braun-Menendez, E., J. C. Fasciolo, L. F. Leloir, J. M. Munoz, and A. C. Taquini. 1946. Renal Hypertension. Springfield, Illinois, C. C. Thomas, pp. 249-300.

Burch, G. E., C. T. Ray, and J. A. Cronvich. 1952. Certain Mechanical Peculiarities of the Human Cardiac Pump in Normal and Diseased State. Circulation, 5:504-13.

Burch, G. E. 1955. Theoretic Considerations of the Time Course of Pressure Developed and Volume Ejected by the Normal and Dilated Left Ventricle during Systole. Am. Heart J., 50:352-55.

Burton, A. C. 1951. On the Physical Equilibrium of Small Blood Vessels. Am. J. Physiol., 164:319-29.

Burton, A. C. 1954. Relations of Structure to Functions of the Tissues of the Wall of Blood Vessels. Physiol. Rev., 34(4):619-42.

Burton, A. C. 1957. The Importance of the Shape and Size of the Heart. Am. Heart J., 54(6):801-10.

Catton, W. T. 1957. Physical Methods in Physiology. New York: Philosophical Library, Inc., pp. 59-73.

Chanutin, A., and E. B. Ferris, Jr. 1932. Experimental Renal Insufficiency Produced by Partial Nephrectomy. I. Control Diet. Arch. Int. Med., 49:767-87.

Chanutin, A., and E. E. Barksdale. 1933. Experimental Renal Insufficiency Produced by Partial Nephrectomy. II. Relationship of Left Ventricular Hypertrophy, the Width of the Cardiac Muscle Fiber, and Hypertension in the Rat. Arch. Int. Med., 52:739-51.

Dodson, L F., and G. B. Mackaness. 1957. The Estimation of Basal Blood Pressure in the Rat by Tail Oscilloscope. Brit. J. Exp. Path., 38(6):618-27.

Edens, E. 1913. Über Herzhypertrophie. Deutsches Arch. f. Klin. Med., 111:288-309.

Evans, C. L., and Y. Matsuoka. 1915. The Effect of Various Mechanical Conditions on the Gaseous Metabolism and Efficiency of the Mammalian Heart. J. Physiol., 49:378-401.

Freis, E. D. 1960. Hemodynamics of Hypertension. Physiol. Rev., 40(1):27-54.

Gladstone, S. A. 1929. A Few Observations on the Hemodynamics of the Normal Circulations; and the Changes which Occur in Aortic Insufficiency. Bull. Johns Hopkins Hospital, 44:83-121.

Gollwitzer-Meier, K., C. Kroetz, and E. Krüger. 1938. Sauerstoffverbrauch und Kranzgefässdurchblutung des innervierten Herzens in ihrer Beziehung zu Arbeit und Arbeitsform des Herzens. Arch. ges. Physiol., 240:263-81.

Grollman, A. 1944. A Simplified Procedure for Inducing Chronic Renal Hypertension in the Mammals. Proc. Soc. Exp. Biol. and Med., 57:102-4.

Harrison, T. R., R. Ashman, and R. M. Larson. 1932. Congestive Heart Failure. XII. The Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart. Arch. Int. Med., 49:151-64.

Hartree, W., and A. V. Hill. 1921. The Regulation of the Supply of Energy in Muscular Contraction. J. Physiol., 55:133-58.

Hawthrone, E. W. 1961. Instantaneous Dimensional Change of the Left Ventricle in Dogs. Circulation Research 9(1):110-19.

Hermann, G., G. Dechard, and P. Erhard. 1941. Production of Cardiac Hypertrophy in Rats. Proc. Soc. Exp. Biol. and Med., 47:464-5.

Hill, A. V. 1913. The Heat-Production in Prolonged Contractions of an Isolated Frog's Muscle. J. Physiol. 47:305-24.

Karsner, H. T., C. Saphir, and T. W. Todd. 1925. The State of the Cardiac Muscle in Hypertrophy and Atrophy. Am. J. Path., 1:351-72.

Katz, L. N. 1931. Observations on the External Work of the Isolated Turtle Heart. Am. J. Physiol., 99:579-97.

Lee, M. O. 1929. Determination of the Surface Area of the White Rat with Its Application to the Expression of Metabolic Results. Am. J. Physiol., 89:24-33.

Pässler, H., and D. Heinecke. 1905. Versuche zur Pathologie des Morbus brightii. Verhandl. d. Deutsch. Path. Gesellsch., 9:99.

Rushmer, R. F. 1961. Cardiovascular Dynamics. Philadelphia: W. B. Saunders Company, pp. 435-53.

Rushmer, R. F., and D. K. Crystal. 1951. Changes in Configuration of the Ventricular Chambers during the Cardiac Cycle. Circulation, 4:211-18.

Rushmer, R. F., and O. A. Smith, Jr. 1959. Cardiac Control. Physiol. Rev., 39(1):41-68.

Rushmer, R. F., and N. Thal. 1951. The Mechanics of Ventricular Contraction - A Cinefluorographic Study. Circulation, 4:219-28.

Soskin, S., and O. Saphir. 1932. The Prevention of Hypertrophy and the Limitation of Normal Pulsation and Expansion of the Kidney by Means of Casts. Am. J. Physiol., 101:573-82.

Stacy, R. W., D. T. Williams, R. E. Worden, and R. O. McMorris. 1955. Essentials of Biological and Medical Physics. New York: McGraw-Hill Book Company, Inc., pp. 380-1.

Starling, E. H., and M. B. Visscher. 1927. The Regulation of the Energy Output of the Heart. J. Physiol., 62:243-61.

VIII. APPENDIX

Statistical analyses were carried out as follows:

$$\text{Standard Deviation} = \sqrt{\frac{\Sigma_i (X_i - \bar{X})^2}{n - 1}}$$

Where X_i = Individual of sample population

$\bar{X}$ = Mean of sample population

n = Size of sample population

The Unpaired Rank Analysis of "t" test of significance between two samples population means was performed using the following formula:

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{\Sigma_i (X_i - \bar{X}_1)^2 + \Sigma_i (X_{2i} - \bar{X}_2)^2}{n_1 + n_2 - 2} \left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

Where X_i = Individual of sample population 1

X_{2i} = Individual of sample population 2

$\bar{X}_1$ = Mean of sample population 1

$\bar{X}_2$ = Mean of sample population 2

n_1 = Size of sample population 1

n_2 = Size of sample population 2

With $(n_1 + n_2 - 2)$ degrees of freedom.