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THE DEMONSTRATION OF THE STARLING MECHANISM OF CARDIAC CONTROL IN THE RIGHT VENTRICLE OF THE INTACT, ANESTHETIZED DOG

Dissertation
Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By
ALFRED JOSEPH PRATT, B. S., M. S.

The Ohio State University
1962

Approved by

[Signature]
Adviser
Department of Physiology
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INTRODUCTION

A. A Review of the Problem

A vast amount of literature has been compiled as attempts have been made to demonstrate the Starling mechanism of cardiac control in the intact preparation. According to this mechanism, also referred to as the Frank-Starling mechanism, stroke work is a function of the ventricular diastolic volume or pressure immediately prior to the onset of contraction. These latter parameters are usually designated as the end-diastolic volume or pressure, respectively, and are themselves a function of the venous pressure. This concept of cardiac control stems from the relationship between resting fiber length, tension and the force or energy of contraction originally established for skeletal muscle during the nineteenth century. Its validity for cardiac muscle was demonstrated clearly for the first time by Otto Frank in 1895 (1). Frank measured the ventricular diastolic volume and pressure of isolated frog hearts during isometric and isotonic contractions, in addition to the force of contraction during the following systole. From the data he concluded that frog myocardium is like skeletal muscle in that it develops greater tension as its resting length is increased. Henderson and Prince (2) reported later that the work of each ventricle of an isolated mammalian heart varied with the filling of the same ventricle and independent of the filling of the other.

Prior to Frank, however, Howell and Donaldson (3) had studied the effect of individually varying the venous pressure and arterial resistance in the mammalian heart-lung preparation. An increase in the venous pressure was accompanied by an increase in the combined diastolic volumes, stroke work, and naturally the stroke volume. They concluded that the intraventricular diastolic pressure distending the ventricle was the dominant factor determining the force of contraction. However, varying the arterial pressure by aortic constriction didn't appear to have any clear effect, at least not on stroke volume. Similar studies were performed later by Starling's group (4, 5) in England and Straub (6) in Germany. Using a much
improved heart-lung preparation, these investigators reported that
the work and stroke volume of both ventricles and their combined
diastolic volumes were increased with the raising of the right atrial
reservoir. Similar findings were observed when the arterial pressure
was raised, except only the work of the left ventricle increased.
When plotted, the work increased with the increase in diastolic
volume up to a limit, beyond which there was a marked decline in the
ability to do work. Such a curve with its descending limb became
known as the classical Starling curve. Furthermore, Straub recorded
intraventricular pressures and observed that changes in diastolic
volume are accompanied by corresponding changes in pressure. In
addition, Straub believed that this pressure or tension, produced
largely by atrial systole, was a greater determinant of the force of
contraction than was the diastolic volume. On the other hand,
Starling's group measured only the right atrial pressure and reported
that the increase in diastolic volume was usually, but not always,
associated with a corresponding increase in pressure. They expressed
the opinion that the ventricular diastolic volume immediately prior
to the beginning of the contraction determines the cardiac response
and that changes in the tension are incidental to the changes in
volume. Starling (7) later formulated the law of the heart, eventu­
ally named Starling's Law of the Heart, to be the same as that for
skeletal muscle, namely that the energy of contraction depends on the
length of the muscle fibers prior to their contracting. Except for
the above discrepancy over tension, this is in support of Frank's (1)
conclusions in the isolated frog heart.

Wiggers and Katz (8) later repeated the experiments by Starling's
group, but in the open chest dog rather than the heart-lung prepa­
ration. Saline infusion and markedly improved methods of cardiometry
and pressure measurements were used. Their results concurred with
those of Starling. In addition, the rise in end-diastolic volume and
stroke volume with increased venous return (as measured by right
atrial pressure) occurred whether or not the arterial pressure re­
mained unaltered or increased slightly. The stroke volume during
increased arterial pressure remained unaltered or increased slightly. Foremost and above all, changes in end-diastolic volume were never dissociated from changes in end-diastolic pressure, as determined from atrial pressure measurements. This opinion, in fact, has prevailed since this time.

Evans and Matsuoka (9) demonstrated that pericardiectomy in a heart-lung preparation resulted in an increased work output accomplished by a lower filling pressure and an increased diastolic volume. They concluded that the effective ventricular filling pressure, and thus the fiber length was the determining factor of work, rather than the absolute level of intraventricular diastolic pressure. Katz (10) varied the volume and the absolute ventricular pressure of a turtle heart independent of one another and demonstrated that the force of isometric contraction was a function of the volume and not the absolute pressure. Berglund (11) provided additional evidence more recently in the open chest dog. He reported that during cardiac tamponade there was a decline in the ventricular stroke work as the effective filling pressure was decreased and that there was a close relationship between these parameters in various degrees of tamponade.

Katz (12) discussed the error in using the end-diastolic pressure as an index of the end-diastolic volume; namely because of their curvilinear relationship. According to Katz, the normal exposed heart is small and operates over a range of sizes where a great change in end-diastolic volume is accompanied by only small changes in the end-diastolic pressure. However, in the closed chest the effective filling or end-diastolic pressure distending the ventricles during diastole is greater than the measured end-diastolic pressure by an amount depending upon the amplitude of the surrounding negative intrapleural pressure. In other words, the ventricular volume in the closed chest is greater than that in the open chest for the same end-diastolic pressure. This is evident by the reported decrease in heart size observed upon thoracotomy (13) as compared to its normal maximal size while resting in the reclined position (14). Therefore, such a transmural pressure would place the normal heart
in the closed chest at a point approximately where a change in volume would be associated with a corresponding change in pressure. Furthermore, the use of the effective end-diastolic or filling pressure (end-diastolic pressure minus intrapleural pressure), rather than the absolute pressure within the ventricle, is in better agreement with fiber length as being the determinant of the force of contraction.

The use of mean atrial pressure is, likewise, a poor index of the end-diastolic volume, mainly because it may not accurately reflect changes in the end-diastolic pressure and thus the effective filling pressure (12, 15). Sarnoff and Berglund (16), on the other hand, reported that the use of mean atrial pressures yielded values satisfactorily close to the end-diastolic pressures and that the errors encountered did not appreciably change the shape of their ventricular function curves.

Sarnoff (16, 17) studied the continuous relationship between mean atrial pressure (as an index of end-diastolic pressure and volume) and stroke work of both ventricles simultaneously in the open chest dog. A consistent relationship was found between these parameters, but only for the respective ventricle. Plotting these parameters resulted in ventricular function curves resembling those by Starling, but without a descending limb in the normal heart. In addition, any change in the functional state of myocardium or the circulatory system produced different curves, yet a consistent relationship remained between these parameters. Sarnoff interpreted this finding as suggestive that no single curve can express ventricular performance from one moment to another and that a concept of a family of Starling or ventricular function curves can better explain the ability of a ventricle to do varying amounts of work without the expected directional changes in filling pressure, by simply shifting from one curve to another. The relationship between atrial pressure and stroke volume or cardiac output was not consistent. In fact, the stroke volume relationship resulted in a rather flat curve with only a relatively small initial rise.

Attempts to demonstrate the Starling mechanism in the intact
preparation and human have brought conflicting results. According to Sarnoff (17), the fault lies in using stroke volume or cardiac output instead of stroke work as representative of the force of contraction; using ventricular work per minute rather than per stroke; attempting to relate right atrial pressure with left ventricular stroke work, stroke volume, or cardiac output; and failing to realize that a family of ventricular function or Starling curves exists whereby the heart is able to shift from one curve to another. The more common view is that the Starling mechanism is overshadowed by nervous and humeral influences (12, 14, 18-21). Therefore, its applicability remains questionable, especially in view of the inability of this mechanism to explain the cardiac response to such phenomena as spontaneous activity and exercise. For example, Barger et al. (22) and Dexter et al. (23) observed that the mean right atrial pressure did not change appreciably, but Barger expressed that the effective filling pressure might rise. Likewise, Asmussen and Nielsen (24) reported that an increase in cardiac output can occur without an increase in diastolic volume or heart rate. Rushmer (14), however, failed to observe a characteristic change in cardiac size; the latter increasing one time and decreasing at another, or showing no change. Rushmer et al. (25) also reported that the increased output of the left ventricle was not preceded by an increase in the inferior vena cava flow. In addition, the stroke output of both ventricles were markedly in phase. Furthermore, increased venous return produced by the infusion of blood or dextran, abdominal compression and tilting to the head down position all raised the effective filling pressure, but failed to simulate the cardiac responses seen in exercise (26).

The purpose of this investigation is to demonstrate the Starling mechanism in the right heart of the intact anesthetized dog during dynamic changes in venous return. The results will be compared with those obtained after opening the chest. The applicability of this mechanism will be discussed in addition to determining its applicability during pressure breathing and normal respiration. That aspect
of Starling's Law dealing with the descending limb and oxygen consumption is beyond the scope of this investigation.

Previous investigators have attempted to demonstrate the Starling mechanism in the intact preparation and human by infusion and hemorrhage methods. Such methods and the conflicting results thereof are open to considerable debate because of the concurrent alterations in blood volume and oxygen carrying capacity, as well as vascular tone. In addition, the majority of studies have tried to correlate the cardiac output with the right atrial pressure. Only a relative few have attempted to relate the stroke work with the effective end-diastolic pressure or volume of the same ventricle.

B. Studies Relating Ventricular End-Diastolic Volume to Ventricular Stroke Work of the Same Ventricle

Ferguson et al. (27) measured the left ventricular pressure and cardiac output in anesthetized dogs every 5 to 10 minutes during the continuous intravenous infusion of blood and/or saline. The cardiac output was measured with the photoelectric method by dye dilution. The left ventricular pressure was determined by inserting the manometer through the chest wall by means of removing a segment of the costal cartilage and suturing the apex of the heart to the area several weeks before. The end-diastolic pressure utilized was the average of 10 consecutive pulses, and was corrected for the simultaneously recorded intrapleural pressure. In addition, artificial respiration was administered throughout the experiment. At rates greater than 1.0 cc/Kg/min. the effective end-diastolic pressure increased and was accompanied by a corresponding increase in the stroke work, stroke volume and cardiac output in 75 per cent of the studies. However, with slower infusions the effective end-diastolic pressure was correlated with stroke work in 70 per cent of the studies, and with stroke volume and cardiac output in 50 per cent. Heart rate and total peripheral resistance failed to show any consistent response in all experiments. The lesser correlation between these parameters in the closed chest animal, especially
during moderate rates of infusion, as compared to the nearly perfect correlation in the open chest was believed due to the operation of physiological adjustments and the difficulty of measuring the end-diastolic pressure in the intact preparation. Furthermore, Ferguson et al. attributed the obscurity of these relationships by previous investigators as being due to their using methods which failed to measure the phasic responses of the individual heart beat. Gregg et al. (18) repeated these experiments using the same methods except only whole blood was used for approximately the first 40 minutes of infusion, followed by saline. The results obtained were identical with those of Ferguson. Gregg and coworkers also observed that the end-diastolic pressure always had the same directional trend as the effective end-diastolic pressure. The use of an optical recording rotameter in the aorta to measure cardiac output, including the calculation of coronary flow, in the open chest preparation was the only significant difference from the method used in the intact preparation by these workers. As hinted by these latter workers, the deviations in the correlation between these parameters are more numerous when approaching the normal state due to physiological adjustments. The operation of such adjustments is obvious by the greater number of non-correlations with the slower rate of infusion in either the open or closed chest preparation. The reason was believed due to more time being available for the adjustment of the blood volume toward normal. In other words, the directional changes and thus correlation are higher, the greater the blood volume expansion. The influence of physiological adjustments is further realized by the absence of a characteristic directional correlation between these parameters in studies performed on normal unanesthetized dogs following exercise on a treadmill. Gregg et al. also emphasized the need of a reliable method for determining the ventricular diastolic volume in the intact preparation. Both Ferguson's and Gregg's groups observed that infusion also increased the right ventricular end-diastolic pressure. In addition, beyond a certain or excessive volume of infusion the end-diastolic pressure continued to rise, but the stroke work and stroke
volume decreased along with cardiac output. This occurred occasionally in the open chest, yet earlier than in closed chest dogs; after approximately 15 and 45 minutes of infusion, respectively. These results are in general agreement with those of Wiggers and Katz (8) discussed earlier. There appeared to be no consistent change in peripheral resistance, heart rate or blood pressure. These observations were not discussed for the closed chest animal and therefore cannot be interpreted in the light of cardiovascular adjustments or the descending limb of Starling's curve. However, death resulted 6 minutes after this point in an open chest experiment discussed by Ferguson's group. They also compared open and closed chest animals for hemodynamic differences. In general, the latter was characterized by a higher mean blood pressure, minute cardiac index, stroke work index, stroke volume index, and left ventricular end-diastolic pressure, but a lower total peripheral resistance and heart rate.

Holt (28) devised an electric conductivity method by which the end-diastolic volume and stroke volume of the left ventricle could be estimated. Plethora was performed by infusing a volume of blood or blood-dextran mixture, amounting to 8 per cent of body weight, in approximately 5 minutes. The blood-dextran mixture resulted in an average hematocrit value of 21.5 per cent. This was followed later with successive hemorrhages of 250 ml each, until the death of the animal. As expected, plethora increased and hemorrhage decreased the end-diastolic volume, stroke volume, stroke work and arterial pressure. An equation was given for the linear relationship observed between the end-diastolic volume and the stroke volume. In addition, the effective end-diastolic pressure increased very little as the end-diastolic volume was increased several-fold. Beyond a certain volume, however, a significant rise in the end-diastolic pressure was associated always with little additional increase in the former.

Berglund (11) reported one experiment in a dog in which the chest was closed following the preparation of the method devised by Sarnoff and Berglund (16) for the open chest. Briefly, the mean pressures of both atria, the pulmonary artery and aorta were measured
continuously by electrical capacitance manometers via catheters. The intrapleural pressure in the ventral part of the chest was measured by a similar manometer so that the effective mean atrial pressures could be determined. The left ventricular output (minus coronary flow) was recorded continuously with a Potter Electroturbinometer and apparently assumed to be equaled by that of the right ventricle after equilibrium was established at each of the atrial pressure levels studied. In addition, a reservoir was connected to the right femoral vein. However, Berglund was not clear as to whether this reservoir was filled with blood or a mixture of blood in 6 per cent dextran (in 0.9 per cent NaCl). After the chest was closed and respiration appeared normal, the procedure was first to lower the reservoir until the aortic pressure dropped to 50-90 mm Hg, and then raise it in 2 to 5 cm steps at 30 second intervals until the left atrial pressure reached approximately 35 cm water. The pressure and flow values used were those obtained 30 seconds after each elevation of the reservoir. Thus the mean atrial pressure, stroke volume and stroke work were obtained from both hearts simultaneously. The ventricular function curves for each ventricle, obtained by plotting the stroke work by the effective atrial pressure, closely resembled those obtained by Sarnoff and Berglund (16) in the open chest preparation and discussed earlier. However, the lower part of the curves were steeper in Berglund's work, which he attributes is due to the small errors in measuring the intrapleural pressure and thus the determination of the effective mean atrial pressures.

Schnabel et al. (29) measured the right atrial and pulmonary arterial pressure in normal subjects by means of catheters. An indwelling needle was placed in the brachial artery for sampling and pressure measurements. Dextran was infused as a 6 or 8 per cent solution with either 5 per cent glucose and water or isotonic saline solution for 60 minutes. In addition, infusion of 5 per cent glucose and water, isotonic saline solution and distilled water were administered up to 100 minutes. The rate of infusion was approximately 25 ml/min. for all fluids. The Fick principle was used to measure
cardiac output and was accomplished usually twice before and during the infusion and sometimes 15 to 20 minutes after. Pressure measurements were made at 10 to 15 minute intervals at the beginning of the infusion and more often during the later phases, in addition to the control period. The purpose of this report was to attempt to clarify some of the mechanisms controlling cardiac function during hypervolemia; namely the relation between the filling pressure of the right heart, cardiac output and the right ventricular work in the manner resembling that by Berglund (11). The dextran infusion resulted in a 20 to 35 per cent expansion in blood volume, which was associated with a rise of 2 to 12 mm Hg and 3 to 15 mm Hg of the right atrial and mean pulmonary pressures, respectively. This is in contrast to the absence of significant changes in all parameters when the blood volume was only increased 5 to 8 per cent by infusions of fluids other than dextran. The cardiac output and stroke volume were increased 31 and 20 per cent, respectively, with the greatest expansion of blood volume. However, 7 subjects experienced less than a 15 per cent increase in cardiac output, even though the right atrial pressures increased 4 to 12 mm Hg. Maximum increases in blood volume, as well as right atrial pressure, were always associated with increases in the right ventricular stroke work, except for one subject. In 7 of the 31 subjects this increase in work was relatively small, being less than 40 per cent, while the right atrial pressures rose 2 to 12 mm Hg. However, no significant relationship appeared between the magnitude of the increase in the latter and the per cent change in cardiac output and stroke volume or the change in right ventricular stroke work. Nevertheless, these parameters did demonstrate a linear relationship with the degree of blood volume expansion. The relatively small alterations in cardiac function occurring with the moderate to marked elevations of right atrial pressure were suggestive of the importance of factors other than filling pressure in the control of cardiac function in the intact preparation.

Chapman et al. (30) utilized a rather elaborate procedure for the purpose of studying the relation between left ventricular
end-diastolic volume and the stroke work of the succeeding systoles in intact anesthetized dogs during rest and exercise. Briefly, the left ventricular volume was estimated by biplane cinefluorography and the use of area products and a regression equation. An average error of less than 10 per cent was expected based on elaborate model experiments. Right atrial or main pulmonary arterial pressure and left ventricular or aortic pressure were measured by catheters located in either one of each pair of sites. Sometimes pressures at both members of a site were measured through a double lumen catheter. The natural frequency of the system for measuring pressures of the left side varied from 12 to 20 c.p.s. The dog was anesthetized and suspended horizontally, feet down, in front of two fluoroscopic screens in order to record both of the anterior oblique veins of the heart during the pneumatic injection of 90 per cent Hypaque solution. Exercise was administered by galvanic stimulation via electrodes attached to the upper portions of the hind limbs and to the pelvic region. After suspending the dog for 10 to 15 minutes, resting determinations were performed, followed by mild rhythmic exercise for about 10 minutes which increased the resting oxygen consumption three to four-fold. Recordings were begun within 2 seconds after the cessation of exercise.

The integrated values of pressure and kinetic work per stroke were calculated by rather elaborate means, the sum of which represents the total integrated stroke work. An integrated power curve representing the rate at which work was done during the cardiac cycle was obtained by plotting the total work each one-thirtieth of a second against the time elapsed since the cycle began. The possible sources of error in this overall procedure was discussed. Apparently their magnitude was tolerable. The most serious objection was the frequent bradycardia and arterial hypotension observed due to the very rapid injection of Hypaque into the vena cava or especially the pulmonary artery. Nevertheless, a sufficient number of cardiac cycles were available without arterial hypotension to permit adequate comparisons between resting and exercising conditions in the same dog. However, bradycardia persisted, but was seldom marked. The volume of Hypaque infused was
vascular system and also has some direct vasodilatory action. A catheter-tip balloon was placed in the midesophagus for the purpose of estimating the intrapleural pressure. Arterial pressure was measured from the brachial artery. Cardiac output was measured by the indicator dilution technique and the determinations performed with a densitometer. The intraesophageal pressure was used to obtain the corrected or effective left ventricular end-diastolic pressure. Cardiac output and pressure measurements were performed prior to and at intervals of approximately 10 to 15 minutes during the infusion. The subject's own blood was transfused within 30 to 50 minutes, which in all subjects produced a marked elevation in the end-diastolic pressure accompanied by increases in the cardiac output, stroke volume, stroke work and work per minute. However, mention should be made of the fact that all subjects were mildly anemic prior to infusion, the hematocrits ranging from 34.5 to 38.0 per cent. A similar but more detailed investigation was carried out by Frye and Braunwald (32) earlier, but without measuring the left ventricular end-diastolic pressure. The phlebotomies were performed in an identical manner except the 1500 ml of blood was transfused at the rate of 19.3 ml/min. The procedure was repeated later in a second study, except after partial ganglionic blockade by the continuous infusion of Arfonad. In 2 subjects the procedure was reversed. The Arfonad was infused at an average rate of 4.0 mg/min. as compared to 1.7 mg/min. by Braunwald et al. (31). In addition, the right atrial and not the left ventricular and intraesophageal pressure was measured in these experiments. All parameters were measured before and immediately following the infusion. Duplicate determinations of cardiac output and central blood volume were accomplished in most of the studies in 10 to 15 minute intervals. The results are in agreement with those by Braunwald et al. (31). For example, the cardiac output and left ventricular stroke work were elevated significantly more by blood transfusion during the partial blockage of the autonomic nervous system. However, the central blood volume was increased (348 ml) only during those transfusion studies accompanied by Arfonad infusion. Based on
the data of these two studies, these investigators suggested that the difficulty of previous workers to demonstrate the Starling mechanism during acute hypervolemia was due to the reflex venodilatation and decreased myocardial contractibility by the activity of the autonomic nervous system. This is certainly in support of the view that the Starling mechanism is overshadowed by neurohumeral influences in the intact preparation.

C. Studies Relating Right Atrial Pressure to Cardiac Output

McMichael and Sharpey-Schafer (33) catheterized the right atrium of humans and measured the right atrial pressure and cardiac output (Fick principle). Upon infusing 1630 cc saline in 20 minutes, the former rose from -3.0 to +3.0 cm saline and the latter from 4.5 to 9.0 l/min. In contrast, the withdrawal of 420 cc blood twice in succession, or venous occlusion of both thighs resulted in a fall of these parameters. They concluded, in accordance with Starling's Law, that a rise in right atrial pressure increased, while a fall decreased, the cardiac output. In one case Sharpey-Schafer (34) observed a similar rise in these parameters following the infusion of 500 cc concentrated corpuscles. Likewise, Altschule and Gilligan (35) reported a direct correlation between the increases in peripheral venous pressure and cardiac output during and following the infusion of 500 to 1000 cc physiological saline, 5 per cent glucose or 5 per cent glucose in physiological saline. For example, subjects who received the larger volumes and at the higher rates had a greater rise in venous pressure and cardiac output (Ethyl iodide technique). Part of the increase in cardiac output was due sometimes to an increase in the heart rate. They also stated that the cardiac output will exhibit at least a temporary rise, provided that over a liter of saline is infused and at a rate exceeding 20 cc/min. The incline in venous pressure, however, did not persist; even the largest returned to the control value within 10 to 25 minutes after the completion of the infusion. At times the venous pressure failed
also taken into consideration. Apparently its effect was common to both resting and exercising conditions. In addition, this volume was fractionated by entering the left ventricle over several cardiac cycles. The results obtained confirmed the Starling mechanism as evident by the demonstration of a linear or gently curvilinear relationship between left ventricular end-diastolic volume and the stroke work of the following contraction, but only provided conditions remained relatively constant during each of the recordings. Mild exercise in the same preparation usually resulted in a decreased end-diastolic and end-systolic volume, but an increased stroke work and generally an increased stroke volume. These results are in agreement with the concept of shifting between curves proposed by Sarnoff and Berglund (16). However, the results do not define a curve, but rather demonstrate the ventricle is operating at different functional levels between exercise and rest. Chapman et al. proposed that the role played by this mechanism in the intact preparation is to adjust the ventricles to changing demands and that the neural and humeral influences function simply to shift the ventricular function curve. Evidence was also presented that stroke work is usually lower when calculated using mean rather than integrated values. However, this is not as serious a discrepancy during conditions of rest as during exercise. Furthermore, the opinion was expressed that for any condition other than rest the integrated kinetic work should be included.

An attempt was made by Braunwald et al. (31) to demonstrate the Starling mechanism in sedated male subjects when neurohumeral influences were minimized. Three or four phlebotomies totalling 1500 ml were performed on each individual over a period of 7 to 10 days, stored and studies performed 2 to 4 days later. The left atrial pressure was measured by transseptal left heart catheterization. A catheter was placed also in the superior vena cava or right atrium for cardiac output determinations. Arfonad, a ganglionic blocking agent, was infused intravenously at a constant rate throughout the study and lowered the systolic pressure an average of 42 mm Hg. This drug proved to be very effective in reducing the reactivity of the
to increase, in spite of the increase in blood volume. In addition, a diffuse flushing of the skin was sometimes observed. These phenomena were believed due to a progressive peripheral vasodilatation during the course of the infusion. Hackabee et al. (36) observed a steady and progressive rise in right atrial and femoral venous pressures in infusion studies with anesthetized dogs. Large volumes of blood, serum albumin and modified Ringer's solution were used and infused at a rate of 3.3 cc/Kg/min. The cardiac output was determined by the Fick method and revealed only an initial rise parallel to the increase in the preceding parameters, then declined after attaining a peak. The effects of progressive hypervolemia were studied in anesthetized dogs also by Meek and Eyster (37). Acacia saline, physiological saline and blood were infused intravenously in amounts from 25 to 103 per cent of the total blood volume. The right atrial pressure rose immediately and was accompanied by an increase in the diastolic size and stroke volume of the heart, both of which were determined by means of X-ray. The heart discontinued its enlargement when the atrial pressure reached approximately 150 mm water. However, the increases observed during blood volume expansion were not permanent. The major portion of the fluid remained in the circulatory system as determined by hemoglobin measurements. In addition, there was an indication that the capillaries and venules in various regions of the body were dilated and therefore serving as reservoirs possibly to preclude further cardiac dilatation and increased circulating blood volume. Hemorrhage in amounts of 2.1 per cent of body weight or more produced contrasting results (38). Eyster and Middleton (39) later demonstrated that hemorrhage or blood transfusion in amounts within 1.0 per cent of body weight produced only a transient alteration in cardiac size in humans because of the rapid adjustment to the changes in blood volume by the compensatory mechanisms.

Increasing the blood volume of humans was reported by Warren et al. (40) to reveal no consistent change in the cardiac output (Fick method), and only a slight variation of the pulse rate and
arterial pressure. Yet in 5 of the 7 cases, the cardiac output was increased. The remaining 2 had relatively high control outputs which declined to the normal range with infusion. The most important observation was that any changes in the cardiac output compared before and after infusion had no direct relation to the elevation of the right atrial pressure. However, the latter demonstrated a consistent relationship with the increase in blood volume. Hypervolemia was performed in these studies by infusing saline or 5 per cent serum albumin in usually 1000 cc amounts at rates of 32 to 77 cc/min. Saline was found to disappear more rapidly from the vascular system and produced a lesser rise in the plasma volume and right atrial pressure. Veneesection (300 to 900 ml) and the application of venous tourniquets on both thighs caused the right atrial pressure to fall 20 to 65 mm water, but again without a consistent change in cardiac output, pulse rate or arterial pressure (41). Contrariwise, transfusion or releasing the venous tourniquets returned the right atrial pressure to the control level without a change in the cardiac output. Stead and Warren (42) concluded from these and other studies that changes in atrial pressure are not the primary determinants of cardiac output during daily activities.

Hardy and Godfrey (43) demonstrated a prompt and significant rise in the cardiac output; stroke volume and pulse rate of dehydrated subjects upon receiving various fluids intravenously. However, normal subjects did not experience these effects. A liter of isotonic NaCl was infused initially, followed by a second liter of 5 per cent dextrose in isotonic NaCl, which in turn was followed sometimes by 5 per cent dextrose in water until a total of 2500 cc were administered. The infusions were carried out, initially at least, at the rate of 20 cc/min. The cardiac output was determined by means of a ballistocardiograph and was measured with the blood pressure and peripheral resistance after the infusion of each liter of solution. Unfortunately, neither the venous nor the right atrial pressure was measured in these studies.

Witham et al. (44) studied the effect of plasma volume expansion
in mildly sedated non-cardiac patients. The pulmonary arterial pressure was obtained by catheterization. Venous and arterial pressures were also measured and the cardiac output determined by dye dilution technique. 500 cc of a 6 per cent (isotonic and isoncotic) dextran solution were infused at the rate of 25 cc/min. Pressure recordings were made prior to, midway and immediately after infusion and at frequent intervals thereafter. Cardiac output determinations were performed before and at about 10 minutes after infusion. In two cases the second cardiac output determination was accomplished 25 minutes after the infusion, one case of which had a third determination after 90 minutes. The plasma volume appeared to have increased by an amount comparable to the volume infused and not from an osmotic withdrawal of extracellular fluid. This was accomplished by a small, prolonged rise in the pulmonary arterial pressure and an increase in the cardiac output. These results are in agreement with those predicted for saline by Altschule and Gilligan (35) with infusion rates exceeding 20 cc/min. In addition the control values for cardiac outputs were observed to be lower than those reported by Warren et al. (40). The changes in pulse rate and blood pressure were of no consequence. In addition, only a relatively small rise was seen in the peripheral venous pressure. The stroke work of the right ventricle doubled, while that for the left ventricle increased approximately 40 per cent. Above all, the data was interpreted as being suggestive that the increases in cardiac output, mainly due to increase in stroke volume, were due to increases in the total plasma volume. These workers also derived from the dye dilution curve an estimation of the blood volume in the lungs, left heart, aorta and certain large arteries, which served as an index of the pulmonary blood volume. They reported this index, or ("Q"), was increased by an average of about 300 cc with infusion, but expressed the doubt by others in the validity of the technique.

Doyle et al. (45) reported similar results in humans also. The pulmonary arterial and capillary pressures were significantly
increased in proportion to the increase in pulmonary and general blood volume following the rapid infusion (77 to 146 cc/min.) of 950 to 1000 cc physiological saline. The cardiac output was determined by both dye dilution and Fick techniques and showed no consistent change with infusion. This is not in agreement with the rise predicted for saline infusion of over a liter at rates greater than 20 cc/min. (35). In fact, infusion rates of over 100 cc/min. were without effect. Doyle et al. suggested these changes in pulmonary pressures could be explained most adequately on the basis of an abrupt, but not disproportionate, increase in the volume of blood contained in the relatively indistensible pulmonary circuit. Yoemans et al. (46) also demonstrated in dogs the congestion in the peripheral and pulmonary venous systems accompanying rapid infusions. However, the cardiac output, as well as the heart rate and heart size increased. The peripheral venous pressure stabilized during infusion as typical of most of the studies.

Fleming and Bloom (47) more or less repeated the work of Witham et al. (44). They infused 1000 or 1500 ml of 6 per cent dextrose in physiological saline to mildly sedated non-cardiac convalescent patients at a rate of 25 ml/min. Pressure measurements were made during the control period, midway and immediately after the infusion and frequently thereafter. Cardiac output determinations were performed before and usually 10 minutes after infusion, although sometimes 15 minutes to 2 hours after. The atrial, femoral venous and especially the pulmonary arterial pressures became elevated markedly and were usually prolonged following infusion due to the prolonged expansion of the plasma volume. Comparable changes in pulmonary arterial pressure were reported by Doyle et al. (45). This was believed suggestive of an elevation in the left atrial pressure and possibly the left ventricular diastolic pressure. The cardiac output increased 15 to 53 per cent in 13 of the 16 subjects studied, but not consistently with the change in the right atrial pressure. It was concluded that increases in cardiac output cannot be related to those in right atrial pressure because other factors
were operative in altering the cardiac output response to plasma volume expansion. For example, some patients accommodated to the increased plasma volume by a generalized capillary and venous dilatation, thereby permitting the venous and right atrial pressures to return to normal. On the other hand, a few patients did not experience an increased cardiac output in spite of a large increase in the right atrial pressure and plasma volume. Furthermore, the increase in cardiac output was not associated with the degree of plasma volume expansion. They suggested that the inconsistency in demonstrating an increased cardiac output following hypervolemia and hemodilution by previous workers may be due to such factors as differences in the fluids used and their rates of administration, degree of anemia due to hemodilution and to changes in peripheral resistance.

Fowler and coworkers (48, 49), Gowdey et al. (50-52), and Sunahara et al. (53) demonstrated that the increased cardiac output accompanying hypervolemia is related to the anemia and not to the increase in blood volume. In both hypervolemic (48, 49) and normovolemic (48) dogs the cardiac output increased comparably with similar degrees of anemia, and without any correlation with the mean right atrial pressure. Both the right atrial and pulmonary arterial pressures rose in association with the increase in blood volume. Furthermore, there was a significant decrease in the total peripheral resistance in both groups of dogs (48). Neither group showed a significant change in mean systolic pressure. Hypervolemia resulting from a slow intravenous infusion of gum acacia solution produced an increase in cardiac output, mean right atrial pressure and peripheral blood flows as the hematocrit value became reduced (50, 51). However, there was a closer correlation between the increase in cardiac output and the decrease in hematocrit. Similar results were observed during the intravenous infusion of 6 per cent dextran solution (52). The mean right atrial pressure generally increased early in the infusion concurrently with the increase in cardiac output. This was followed later by an inconsistent relationship between these parameters. The
pulse rate and arterial blood pressure showed no consistent changes, whereas the total peripheral resistance decreased. Experiments with whole blood infusion showed comparable rises in filling pressures without significant increases in cardiac output or peripheral blood flow (50, 53). Sunahara (53), in fact, showed that central venous pressures may be raised to very high levels by infusions of whole blood without an increase in cardiac output. On the other hand, plasma infusions increased the cardiac output, blood flow and intracardiac pressures as the hematocrit decreased. But when the hematocrit was raised to the pre-infusion level by injecting packed cells, the output fell in spite of the continuing rise of filling pressures. The situation could be reversed again by decreasing the hematocrit by plasma or gum acacia infusion (50). The relative oxygen-carrying capacity of the blood was concluded to be more important in the cardiovascular adjustments to hypervolemia. In most human subjects, however, the expansion of blood volume has failed to be associated with a rise in cardiac output, even though accompanied by a decline in the hematocrit (29, 40, 45, 47). Brannon (54), on the other hand, demonstrated under conditions of rest that the hemoglobin concentration had to fall below 7 gms/100 ml blood before the cardiac output began to increase, and yet the right atrial pressure was not changed.
METHODS

A. Preparation and Instrumentation

This study was performed on 12 anesthetized dogs, each of which was investigated in both the intact and open chest condition. Animals of both sexes were used and ranged in weight from 19.0 to 27.2 Kg. Pentobarbital sodium (Nembutal) anesthetic was administered intravenously, usually in dosages of 30 mg/Kg and followed by supplemental doses as required. Several animals, however, received a 10 per cent reduction in dosage for the purpose of determining the effect of the depth of the anesthesia. The position of the relaxed diaphragm prior to inspiration served as an index of such a phenomenon and was observed by means of fluoroscopy several times during the experiment. The animal was confined in a supine position to a dog board and an entotraccheal cannula inserted. The latter was equipped with an inflatable rubber cuff to assure a tight tracheal seal, which in turn was monitored from the outside by a rubber balloon in series with the cuff.

All pressures were measured with catheter-tip manometers of the miniature type described by Wetterer (55), Wetterer and Pieper (56), and Gauer and Gienapp (57). These manometers were mounted to the tip of the lumen of flexible catheters (U. S. Catheter Instrument Company, Glenn Falls, New York) of both the single and double-lumen type. The right ventricular pressure was measured by the insertion of the manometer into the right femoral vein, although the external jugular vein was used in some of the preliminary experiments. The manometer used contained the double-lumen type of catheter for the purpose of injecting heparin sodium and/or pentobarbital sodium during the experiment. The right femoral artery was used for inserting the arterial manometer into the descending aorta, and at a location where the diastolic pressure slope was fairly straight and free of reflected pulse waves. According to Wetterer (58), this nodal point usually lies in the area of the proximal thoracic aorta. This procedure was aided visually with the use of a cathode ray oscilloscope.
and was an essential requirement for an accurate determination of the cardiac output to be described later. The left ventricular pressure was measured only in the preliminary experiments by threading the manometer into the left carotid artery. However, the manometer was adjusted to a high sensitivity and only that pressure range inclusive of the end-diastolic pressures encountered during the experiment was recorded. A similar procedure was applied in measuring the right ventricular pressure in later experiments. A metal tube with a sharp beveled tip, and of an appropriate inside diameter to snugly contain a manometer, was used to penetrate the left 3rd intercostal space following an initial incision of the skin. The proximal end of the tube maintained an air-tight rubber seal around the catheter, yet permitted it to be passed in order to position the manometer in the vicinity immediately anterior to the right ventricle. The tube was then withdrawn from the wound, the latter forming a tight seal around the catheter. To reduce the possibility of outside air leaking into the intrapleural space during and following the penetration, the skin was kept sealed around the metal tube and later the catheter by means of hemostats. The position of the manometer was verified upon autopsy, and sometimes also during fluoroscopy. The intrapleural pressure so obtained was measured only in the more recent experiments and was used for calculating the effective right ventricular end-diastolic pressures. The femoral artery was ligated usually before the femoral vein in order to preclude the engorgement of the limb. The same was applicable during the introduction of catheters into the left femoral vessels as described below.

The right ventricular stroke volume was estimated phasically by means of a differential transformer type flowmeter similar to that described by Pieper (59), except for being mounted to the tip of the lumen of a flexible catheter and without being surrounded by an umbrella-type device. The flowmeter was positioned with the visual aid of a fluoroscope into one of the branches of the pulmonary arterial trunk following its insertion in the caudal section of the right external jugular vein. The latter was kept moist with 1 per cent
xylocaine hydrochloride (10 mg/cc, Astra Pharmaceutical Products, Inc., Worcester, Massachusetts) to preclude vasoconstriction accompanying ligation and catheterization. In preliminary experiments the flowmeter was mounted to the tip of a single-lumen catheter of the type described above for the manometers. In addition, the flowmeter element itself was without a desired means of support required to assure a fixed position and direction within the artery. In later experiments the tip was surrounded by, and centered within, a thin-walled cylindrically shaped envelope having an outside diameter of 8 mm and which could be wedged within the vessel. This improvement centered the flowmeter in the axis of the blood vessel, in addition to maintaining a constant cross-sectional area surrounding the element (ring) sensitive to flow velocity and therefore blood flow. The iron core spring was siliconized and dried prior to the experiment in order to preclude fibrin formation and clotting. Likewise, the flowmeter assembly was filled with heparinized blood but mainly for the purpose of displacing the air and thus avoiding the trapping of air bubbles following catheterization. "Zero" flow calibrations were taken several times during the course of the experiment by the temporary cessation of the heart beat. This was accomplished by the electrical stimulation of the left vagus nerve which had been ligated in the neck region. Furthermore, the flowmeter used in these later experiments was mounted to a double-lumen catheter, the larger lumen of which was filled with blood and connected by means of a "T" to an exterior manometer of the type described earlier. The manometer was detachable, thereby facilitating its calibration at any desired moment during the experiment. A 2-way stopcock containing a syringe was connected to the "T" in order to displace all air bubbles from the system. The frequency response of this system was only 20 c.p.s. and was improved by using a double-lumen polyethylene catheter which had a larger lumen and gave a frequency response of approximately 30 c.p.s. Initially, the full pulse pressure was recorded and from which the mean pressure was estimated. In later experiments a capacitor was installed in the circuit to record the approximate mean
pulmonary systolic pressure. The position of the manometer tip was firmly supported in a horizontal position throughout the experiment. Its hydrostatic level above the opening at the catheter tip was measured at autopsy and used to correct the calibration.

Manometer and flowmeter signals were initially received by separate carrier amplifiers of the type described by Wetterer and Pieper (56) and then fed into Hathaway galvanometers and photographically recorded on a Hathaway oscillograph recorder (Type S-142). Time signals of 1.0 second intervals were recorded also. Usually a paper speed of approximately 50 mm/sec. was used, the exact value being determined for each record. A single channel cathode ray oscilloscope (Model K-11R, Electronic Tube Corporation, Philadelphia, Pennsylvania) with a long persistency tube was used to monitor the different parameters. This was replaced later by a 2-channel oscilloscope (Type RM 561, Tektronix, Inc., Portland, Oregon) which usually monitored the pulmonary arterial pressure and flow simultaneously throughout most of the experiment. Because of the limited number of amplifiers available, the pulmonary arterial manometer was substituted by the arterial pressure manometer during the cardiac output determinations.

A polyethylene catheter (Clay-Adams Company, Inc., New York, New York, Type PE-360) having an outside diameter of 4.82 mm was introduced into the left femoral vein, generally until the tip reached the vicinity of the abdominal vena cava immediately below the diaphragm as confirmed by fluoroscopy. During early studies, however, the tip was placed at different levels of the inferior vena cava and in one experiment a catheter having an outside diameter of 7.2 mm was placed in the superior vena cava via the external jugular vein. A special metal tip was used later for the purpose of preventing occlusion of the opening during the withdrawal of blood by the piston pump described below. A catheter similar to the former above, but with a blunt tip, was placed approximately in the mid-abdominal aorta after its insertion into the left femoral artery.

A piston pump was connected initially to the catheter in the
vena cava in order to dynamically vary the venous return and the right ventricular end-diastolic pressure in a sinusoidal fashion. The pump was driven by a Zero-Max, 1/3 h.p., a-c motor (Zero-Max Company, Minneapolis, Minnesota), the frequency of which could be easily regulated. The piston displacement could be varied up to 82 cc by means of a thumb-screw which regulated the turning radius of the piston's connecting rod on the motor shaft. The piston was constructed of two lobes 10 cm apart and resembling a bar-ball, and each of which contained two O-rings for seals. The space between the lobes was kept filled with a light weight machine oil from an exterior well for the purpose of lubricating the sliding surfaces of the seals and piston. In addition, the seals and oil precluded the entrance of air into the circulatory system as well as the seals minimizing the exchange between the oil and the blood or saline in the cylinder compartment. The cylinder was connected to the catheter by a short piece of plastic tubing and both were initially filled with physiological saline. The latter became thoroughly mixed with blood after the pumping commenced. The piston was always started and stopped approximately midway in the infusion position. The volume displacement used ranged from 33 to 79 cc, depending upon the experiment and the size of the dog. In addition, more than one volume displacement was sometimes used during the course of an experiment. Based upon studies by previous workers conducted on the arterial system for the purpose of establishing the method of determining cardiac output described below, a pump frequency between 0.17 and 0.25 c.p.s. was used to preclude venometer reflexes. The movement of the piston was recorded on the Hathaway oscillograph recorder, a galvanometer of which received signals from an electrical bridge circuit containing a potentiometer whose shaft rotated linearly with respect to the piston. The volume displacement was measured after the termination of the experiment directly by means of a graduated cylinder and in more recent experiments by referring to a calibration curve which converted the piston stroke into volume. During cardiac output determinations, the pump was coupled to the aortic catheter. The volume displacement required
adjustment at times in order to avoid a level or upward diastolic slope of the arterial pulse during infusion.

Pressure breathing and artificial respiration in the intact and open chest, respectively, were performed by connecting a respiration pump (Model No. 607, Harvard Apparatus Company, Inc., Dover, Massachusetts) to the endotracheal catheter. The pump was adjusted to provide usually 350 cc air at a rate of 24 r.p.m. of whatever was required to maintain normal lung expansion and preclude spontaneous respiratory movements and excessive hyperventilation.

The opening of the chest was performed by a rapid penetration through the right 4th intercostal space following an initial removal of all but the inner muscle layer. Artificial respiration was begun simultaneously and regulated as described above. An approximate 10 cm$^2$ opening was maintained by the use of a surgical spreader. The mediastinal septum was traversed also in order to assure a total pneumothorax.

Heparin sodium (10 mg/cc, Upjohn Company, Kalamazoo, Michigan) was administered into the right ventricular double-lumen catheter or vena cava catheter in dosages of 5 mg/Kg at least prior to the insertion of the pulmonary flowmeter and the operation of the piston pump.

B. Analytical Procedure

The above-mentioned parameters were measured over a series of consecutive cardiac cycles for each record analyzed in an attempt to demonstrate their relationship during different physiological conditions. The effect of varying the venous return was studied by selecting a portion of record inclusive of at least one pump cycle free of respiratory influence and preferably after the first or second pump cycle. The effects due to respiration were determined in control records and found to last the duration of 10 to 14 cardiac cycles, the first 5 of which occurred during inspiration. These effects were apparent, for example, by a decrease in the right ventricular end-diastolic pressure during inspiration, in addition to
an increase in the stroke output per beat. Expiration was characterized by a sudden initial fall in the stroke volume followed by a steady return to normal. Control recordings exclusive of respiration were analyzed also. An analysis during pressure breathing and artificial respiration was performed over a period of at least 2 respective cycles. Generally, a short recording was taken of control conditions prior to the operation of the piston pump, pressure breathing and artificial respiration, and sometimes following these procedures. The heart rate, frequency of respiration and arterial pressure (when measured) were evaluated before, during and sometimes after the above physiological conditions to detect the possible effect of the latter on the homeostasis of the animal. Furthermore, recordings during and closely following the occurrence of pulsus alternans and/or extra-systoles were not analyzed.

As an index of the effect of the depth of anesthesia, the position of the relaxed diaphragm prior to inspiration was observed for progressive changes by means of a fluoroscope. An initial observation was made as soon after anesthetizing the animal as possible and was repeated several times throughout the experiment. The validity of the observations was assured by the fluoroscope screen always being positioned with reference to a lead rod fastened to the dog's chest.

All manometers, except the pulmonary arterial manometer, were calibrated generally for "warm" zero values immediately upon their removal from the vascular system or after opening the chest, as applicable, and while the tip was maintained in the same spatial orientation observed in the animal upon autopsy or otherwise. In the case of the right ventricular manometer the right ventricle was opened at the most anterior region. It was assumed that blood continued to escape until all tension, except the hydrostatic pressure, was removed from the walls of the ventricle. The "warm" zero was recorded at this moment. All manometers were calibrated with reference to the "warm" zero, where applicable, and in 10^3 dynes/cm^2. The intrapleural pressure was used mainly for calculating the
effective right ventricular end-diastolic pressure. The pulmonary arterial pressure was corrected for the hydrostatic level of the manometer tip above the opening of the catheter in the pulmonary artery.

Right ventricular stroke work \(10^3\) dyne-cm was calculated as the product of the stroke volume \(\text{cm}^3\) times the approximate mean pulmonary systolic pressure \(10^3\) dynes/cm\(^2\). The intrapleural pressure (intact preparation) was algebraically subtracted from the mean pulmonary systolic pressure in an attempt to define the parameter of stroke work more clearly, especially when comparing the intact and open chest preparations.

The flowmeter was calibrated to represent the total stroke output of the right ventricle, rather than a portion of it. This was based on the assumption that the fraction of the stroke output distributed to each main branch (one of which contained the flowmeter) of the pulmonary arterial trunk remained constant, at least throughout the duration of one pump cycle, if not longer. This assumption was based primarily upon the observations and discussion by Von Euler and Liljestrand (60). According to these investigators the pulmonary blood flow is regulated mainly by the blood and alveolar gases exerting a local action on the pulmonary vessels, thereby resulting in a redistribution of the flow. This is as expected from the standpoint that the pulmonary vascular bed, unlike the systemic, consists basically of the same type of functional unit throughout and serves primarily to aerate the blood. There was no reason to believe in the present investigation that the operation of the pump would produce a need for a redistribution of the blood by this mechanism. Von Euler and Liljestrand concluded also that neural and humeral mechanisms were of doubtful significance in the control of pulmonary blood flow. This is quite evident by the fact that the mechanisms regulating the systemic arterial pressure seem relatively independent of those for the pulmonary bed. For example, stimulation of the vaso sympathetic nerves in the neck and the stellate ganglion generally produced quite small and inconsistent changes in the
pulmonary arterial pressure as compared with the systemic pressure. Arterenol and acetycholine simulated these effects, respectively. In addition, large variations in the systemic pressure due to pressoreceptor responses were not accompanied by significant changes in the pulmonary pressure. Likewise, clamping the pulmonary artery to one lung produced a moderate increase (20 per cent) in the latter, while not affecting the systemic pressure. This fact, in addition to the slight fall in the pulmonary arterial pressure upon injecting Ringer's solution directly into the pulmonary artery are illustrative of the ability of the pulmonary vascular bed to adjust easily to increased flow. Daly (61), however, recently reported evidence establishing separate pulmonary vasoconstrictor and vasodilator fibers. Nevertheless, their significance in reflexly controlling the pulmonary blood vessels requires further investigation. Finally, the flow velocity was observed to be the same in the main branches of the pulmonary artery as in the pulmonary trunk (62). This is understandable since rapid changes in flow velocity occurring at each branching, otherwise, would stress the arterial wall. The calibration factor (cubic centimeters per square centimeter) for converting area into volume was obtained from the cardiac output determination described below, the latter being performed prior to opening the chest. "Zero" flow calibrations were taken several times during the course of the experiment in both the intact and open chest preparation. The diastolic portion of the flow tracing was included in the area measured since the pulmonary arterial reservoir was assumed to be still distributing each stroke volume through the flowmeter during diastole. The characteristics of the flowmeter were determined by the method outlined by Pieper (59). Briefly, the flowmeter was placed tip-down in an upright Plexiglass tube, the inside diameter of which accommodated the flowmeter envelope perfectly. The tube was an extension of the cylinder of a true sinusoidal piston pump mounted to and operated by a lathe drive. The cylinder was filled with heparinized blood to a level approximately 2.0 cm above the flowmeter tip. The linearity of the response of the flowmeter
at different flow velocities was tested by altering the volume displacement of the pump, \( v \), or the frequency of the lathe, \( f \), according to the equation

\[ U = \frac{v f}{Q}, \]

where \( U \) is the flow velocity and \( Q \), the cross-sectional area within the flowmeter envelope. However, the procedure was simplified by comparing the Hathaway galvanometer deflections of the flowmeter with those by a linear velocity meter connected to the pump for recording frequency and displacement. Regardless of the method of altering the flow velocity, the flowmeter showed the same characteristic which was slightly parabolic (Figure 1). However, the characteristic is nearly straight in the range of the experimental observations. The flowmeter was calibrated in situ in relation to stroke output (see page 33) and is therefore considered to be adequate for the estimation of changes thereof in the analysis of consecutive pulses of any one recording. The natural frequency of the flowmeter in air was determined to be 280 c.p.s.

The method used for determining the cardiac output has been described elsewhere (63) and its validity established by means of simultaneous dye dilution determinations (63, 64). The principle is basically simple. Under conditions of constant vasomotor tone, the fall in pressure in the arteries during diastole is an exponential function of the rate of outflow into the periphery. Therefore, in order to maintain the diastolic pressure at any mean level the inflow into the system, or cardiac output, would have to equal the outflow. Unfortunately, the latter cannot be measured. Nevertheless, if we observe the changes in the slope of the diastolic pressure produced during measured simulated changes in the outflow, this parameter can be calculated. By attaining mean diastolic values equal to the mean arterial pressure the outflow and thus cardiac output are obtained. The method is to attach the piston pump described above to the catheter in the aorta. The operation of the pump simulates changes in peripheral outflow in a sinusoidal pattern by altering the volume of
Figure 1. Relationship of changes in flowmeter deflection to changes in velocity meter deflection at different velocities of flow.
Figure 1

FLOWMETER DEFLECTION

VELOCITY METER DEFLECTION

mm
the arterial system. This is accompanied by rhythmical oscillations of the mean arterial and diastolic pressures as well as the arterial pulses (Figure 2). In addition, the diastolic slopes are steeper during the infusion than the withdrawal phase. Nevertheless, the peripheral outflows are assumed to be equal provided the mean diastolic pressures are equal. Such a matching pair of pulses, having equal mean diastolic pressures (± 2 per cent) and each recorded during opposite phases of the pump, are selected for analysis (Figures 2 and 3, Pulse A and B). The justification for this procedure is verified in the derivation of the formula given below; namely the elimination of a second unknown, $E'$, or elastic coefficient of the total arterial reservoir ($E_j$). The diastolic slope \( \left( \frac{P_1 - P_2}{\Delta t} \right) \) of each pulse, $\xi_A$ and $\xi_B$, is calculated in addition to the respective volume displacement of the pump ($N \times cc/mm$) in the same period of time, $\Delta t$. The latter is converted next into flow (cc/sec.), $i_A$ and $i_B$. The average flow rate from the total arterial reservoir during diastole, $i_R$, respective of the mean diastolic pressure of this matching pair of pulses, is calculated by substituting the above values in the following formula:

\[
i_R = \frac{\xi_A i_B - \xi_B i_A}{\xi_A - \xi_B} = cc/sec,
\]

which is converted into cc/min. By selecting other matched pairs of pulses at different mean diastolic pressures, a curve may be obtained which demonstrates a segment of the pressure/flow relationship or peripheral resistance of the circulatory system under conditions of constant vasomotor tone. The construction of such curves or points thereof can be used to detect alterations of vasomotor tone as evidenced by the relative change in the slope and position of the curves. However, the calibration factor (cubic centimeters per square centimeter) for converting the stroke area of the flowmeter tracing into stroke volume was obtained as follows. The portion of the pressure-flow curve which included the geometric mean arterial pressure was
Figure 2. Photographic reproduction of an experimental record indicating the pump cycle ($V_p$), arterial pressure ($AP$), stroke output ($F$), and intrapleural pressure ($IPP$). EDP = right ventricular end-diastolic pressure. Time lines are at 1.0 second intervals.
Figure 3. Tracings of Pulse A and B from Figure 2 illustrating the analytical procedure for determining diastolic outflow.
Figure 3

AVPUMP

PULSE A

PUMP

PULSE B
constructed, and the corresponding flow per minute (cardiac output) determined. The former was measured by planimetering 3 or 4 arterial pressure pulses recorded preceding the operation of the piston pump. Likewise, the area of the corresponding flow tracings was measured and the average area per stroke was obtained thusly. The stroke volume was calculated from the heart rate and flow per minute and the consequent division by the average area per stroke lead to the correlation factor.

C. **Experimental Procedure**

Although variations were common as shown in the RESULTS, the general procedure was as follows:

1. The flowmeter and all manometers were tested and balanced, then positioned into their respective regions and tested for proper operation along with the catheters. A short control record was taken to adjust, if applicable, the quality, position and sensitivity of the recordings, as well as the paper speed.

2. The piston pump was connected to the catheter in the abdominal vena cava. A short control record was taken, followed by a recording during the operation of the pump. Generally 2 or 3 complete cycles were performed in which to test the operation and recording of the pump, in addition to determining any need for adjusting its frequency and/or volume displacement. This procedure was repeated at least once, but with 3 to 6 pump cycles, in an attempt to obtain a full pump cycle free of respiratory effect. Long control records were obtained generally at this time also.

3. The preceding procedure was repeated following several pressure breathing cycles, the latter being used to preclude respiration during the operation of the piston pump. Records were taken also during the pressure breathing phase.

4. The piston pump was connected to the catheter in the aorta and a cardiac output determination was made.

5. The chest was opened and the animal maintained by artificial respiration (pressure breathing).

6. Artificial respiration was stopped while the lungs were
maintained in a fully inflated condition. This was followed immediately by usually a short control record, which in turn was followed by recordings of several complete cycles of the piston pump. Recordings during artificial respiration generally were obtained also.
RESULTS

The relationship observed between the effective ventricular end-diastolic pressure or filling pressure and the stroke work of the succeeding beat in the right heart is illustrated in Figure 4. The values for this illustration were obtained from the recording shown in Figure 5. The venous return and right ventricular end-diastolic pressure were made to oscillate rhythmically by the operation of the piston pump as described previously and were associated with similar fluctuations in the stroke volume and mean pulmonary systolic pressure (Figure 5). However, the relationship between effective filling pressure and stroke work was extremely difficult to demonstrate using this method because respiration generally accompanied each infusion. Recordings taken with the piston pump following pressure breathing were free of respiratory influence as planned and further established the Starling mechanism (Figure 6). In addition, the slopes were observed to be similar in magnitude for both methods, thereby indicating the absence of an effect by prior pressure breathing. The results obtained in the open chest preparation following artificial respiration (Figure 7) resembled those shown in Figures 4 and 6 for the intact animal, except steeper slopes were observed. Figure 7 represents the analysis of the recording shown in Figure 8.

A nearly perfect pulse-by-pulse correlation was observed between the effective filling pressure, end-diastolic pressure, stroke volume, mean pulmonary systolic pressure, and stroke work in all studies performed on the intact preparation (Figures 9 and 10). Even the intrapleural pressure demonstrated a very slight oscillation, supposedly due to accompanying changes in the central blood volume. However, this alternation of the intrapleural pressure was relatively insignificant. Therefore, the change observed in the effective filling pressure was attributed mainly to the change in the end-diastolic pressure. The former was calculated to be negative occasionally during the early part of an experiment (Figure 4), being
associated with negative intrapleural pressures of reasonably low
magnitude (Figure 9). This occurrence was attributed to the sucking
of blood from the venous and right atrial system by the piston pump.
Nevertheless, these values did not result in deviations of the re-
lationships studied as illustrated in the previously mentioned
figures. On the other hand, the effective filling pressure increased
as an experiment progressed, since the intrapleural pressure became
increasingly negative as discussed later. (The behavior of the
intrapleural manometer is not questioned since the recording of
phasic responses was uniform throughout the experiment.) This phe-
nomenon is well illustrated by comparing Figures 4 and 6 and explains
the higher effective filling pressures observed following pressure
breathing. In fact, pressure breathing was not observed to produce
an increase in the negativity of the intrapleural pressure, in spite
of being reported to lower the central blood volume (65). The end-
diastolic pressure remained rather uniform in its degree of oscil-
lation throughout an experiment. The peak of the mean pulmonary
systolic pressure was shown to be phasically behind the stroke volume
by usually 2 pulses. In addition, the stroke work values obtained
were due primarily to the changes in the magnitude of the stroke
volume, the mean pulmonary systolic pressure oscillating by only
approximately 4.0 to 5.0 x 10^3 dynes/cm^2 even after opening the chest.
Furthermore, the control levels of the latter parameter were observed
to be little affected by time or opening of the chest. Except for
the inapplicability of the intrapleural pressure and effective
filling pressure, studies performed after opening the chest revealed
correlations identical to those mentioned above for the intact pre-
paration (Figure 11). However, the stroke volume exhibited a greater
degree of oscillation and was sometimes seemingly larger in magni-
tude (Figures 8 and 11). The end-diastolic pressure, to the contrary,
was influenced usually to only approximately half the degree of that
observed in the closed chest preparation. The latter observation is
believed indicative of a greater distensibility of the thoracic
venous system and right atrium owing to the partial collapse of these
chambers upon thoracotomy (13). The heart rate was unaffected in all of the above studies. Figures 4 to 11 were obtained from the same experiment and were presented together for the purpose of a clearer demonstration. Such illustrations were representative of observations made in identical studies. However, some variation in slopes relating the effective filling pressure with the stroke work were obtained on occasion in the same experiment and were attributed to an alteration in the contractility of the myocardium. This reasoning was applicable, likewise, in explaining the variation in slopes between experiments. Nevertheless, open chest preparations characteristically displayed steeper slopes.

The rhythmically induced alterations of the venous return appeared to be accompanied by equivalent, if not equal, alterations in the right ventricular stroke output. To illustrate, in the experiment discussed above 54 cc of blood were infused and then withdrawn in a sinusoidal manner, each during a 2.5 second period. This may be expressed also as a 650 cc/min. increase or decrease of the mean venous return level, respectively, since the piston pump was begun always at the mid-infusion position. The concurrent cardiac output and thus venous return was approximately 2170 cc/min., based upon an average control value of 15.5 cc/stroke and a heart rate of 140 beats/min. The magnitude of change in venous return, therefore, was one-third of the average level. However, an estimation of the cumulative changes in the stroke output revealed equivalent and sometimes equal changes accompanying the corresponding values for the venous return (Figure 12). Similar results were obtained after opening the chest (Figure 13).

In spite of the relatively large and rapid changes produced in the venous return of the above studies, the right ventricular end-diastolic pressure was observed to vary up to only $3.2 \times 10^3$ dynes/cm$^2$ and $1.6 \times 10^3$ dynes/cm$^2$ in intact and open chest preparations, respectively. Although this may represent the relative difference in the distensibility of the venous system, these values cannot be used as an index of the distensibility for each system in
view of the above-mentioned cumulative change in stroke output accompanying the change in venous return. Earlier studies demonstrated that the magnitude of change in the end-diastolic pressure, in addition to that in the right ventricular peak pressure, was greater the closer the venous catheter tip was to the heart (Figure 14). This was demonstrated more clearly in the open chest preparation, besides revealing changes of greater magnitude. More important, however, was the observation that the left ventricular end-diastolic pressure and peak pressure also demonstrated a rhythmic response, except for a slight phase lag of generally 1 to 2 pulses (Figures 14 and 15). A similar response was demonstrated in the aortic pressure in other experiments, although a slightly greater phase lag was observed (Figure 16). Nevertheless, such fluctuations in the aortic pressure are reflective of the left ventricular peak pressure.

The validity of the Starling mechanism was investigated also during pressure breathing and normal respiration. The results obtained during the former are illustrated in Figure 17 and resemble that produced with the piston pump (Figures 4 and 6). These observations could not be demonstrated after opening the chest. In addition, the degree of pressure breathing used produced a relatively small change in the mean pulmonary systolic pressure similar to, but even less than, that by the operation of the piston pump. These latter facts imply that this method of respiration depends upon the changes induced in the intrapleural pressure and thus venous return for its effect. Normal respiration, likewise, revealed a similar correlation between stroke work and effective filling pressure when analyzed separately (Figure 18) and in combination with the operation of the piston pump (Figure 19). Furthermore, the stroke work in all these studies was found to have a high pulse-by-pulse correlation with the effective filling pressure and not necessarily with the end-diastolic pressure when all parameters concerned were plotted separately in the order of consecutive pulses (Figures 20-22, respectively). In fact, the end-diastolic pressure, together with the intrapleural pressure, varied inversely with the effective filling pressure.
pressure and stroke work during pressure breathing (Figure 20). The findings, otherwise, were similar to those resulting from the operation of the piston pump (Figures 9 and 10). The simultaneous operation of the piston pump during pressure breathing failed to reveal the reliable relationships described for each separately, perhaps because of the incompatibility of their individual effects.

In those experiments in which the intrapleural pressure was measured it was observed that the initial values were of low negative magnitude (-2.0 to $-2.3 \times 10^3$ dynes/cm$^2$). However, this parameter gradually became more negative as the experiment progressed, attaining values of -6.0 to $-7.0 \times 10^3$ dynes/cm$^2$ within 30 to 50 minutes and at which time the chest was opened. Earlier studies demonstrated a progressive cranial movement of the diaphragm during the course of the experiment, amounting to 1.0-2.5 cm within 45 minutes to 2 hours. These observations are suggestive of a progressive decline in the central blood volume, the initial values of which may be higher than normal for some unexplained reason. The latter observation, however, may be indicative of a decrease in the muscle tone of the diaphragm associated with the depth of anesthesia.
Figure 4. The relationship between stroke work (SW) and effective filling pressure (EFP) in the right ventricle during dynamic changes in the venous return. Intact preparation. Values obtained from recording shown in Figure 5.
Figure 5. Photographic reproduction of the experimental record from which the values in Figures 4 and 9 were obtained. Time markings are at 1.0 second intervals. Pump displacement ($V_p$) = $54$ cc; frequency = 0.21 c.p.s. Intact preparation.
Figure 6. The relationship between stroke work (SW) and effective filling pressure (EFP) in the right ventricle during dynamic changes in the venous return following pressure breathing. Intact preparation.
Figure 7. The relationship between stroke work (SW) and end-diastolic pressure (EDP) in the right ventricle during dynamic changes in the venous return. Open chest preparation. Values obtained from recording shown in Figure 8.
Figure 7
Figure 8. Photographic reproduction of the experimental record from which Figures 7 and 11 were obtained. Time markings are at 1.0 second intervals. Venous return dynamically varied (pump displacement = 54 cc; frequency = 0.194 c.p.s.) following artificial respiration. Open chest preparation.
Figure 9. The consecutive pulse-by-pulse correlation between the ventricular end-diastolic pressure (EDP), effective filling pressure (EFP), stroke volume (SV), stroke work (SW) of the right ventricle, respectively, intrapleural pressure (IPP), and mean pulmonary systolic pressure (PAP) during dynamic variations in venous return. Values obtained from recording shown in Figure 5. Intact preparation.
Figure 9

![Graph showing consecutive pulses with various measurements including SW, SV, PAP, EFP, EDP, and IPP](image-url)

**Variables:**
- **SW**: Stroke Work
- **SV**: Stroke Volume
- **PAP**: Pulmonary Artery Pressure
- **EFP**: End-diastolic Pressure
- **EDP**: End-systolic Pressure
- **IPP**: Intraventricular Pressure

**Axes:**
- **Y-axis**: 10^3 dynes-cm (for SW and PAP)
- **Y-axis**: cc (for SV)
- **X-axis**: Consecutive Pulses
Figure 10. The consecutive pulse-by-pulse correlation between the ventricular end-diastolic pressure (EDP), effective filling pressure (EFP), stroke volume (SV), stroke work (SW) of the right ventricle, respectively, intrapleural pressure (IPP), and mean pulmonary systolic pressure (PAP) during the same pulses from which the values in Figure 6 were obtained. Venous return dynamically varied (pump displacement = 54 cc; frequency = 0.20 c.p.s.) following pressure breathing. Intact preparation.
Figure 10
Figure II. The consecutive pulse-by-pulse correlation between the ventricular end-diastolic pressure (EDP), stroke volume (SV), stroke work (SW) of the right ventricle, respectively, and mean pulmonary systolic pressure (PAP) during dynamic variations in venous return following artificial respiration. Open chest preparation. Values obtained from recording shown in Figure 8.
Figure 11

The graph shows the changes in various parameters over consecutive pulses.

- **SW** (640 dyne-cm) shows a peak around pulse 6, decreasing towards pulse 9, and then increasing again towards pulse 12.
- **SV** (cc) shows a peak around pulse 6, decreasing towards pulse 9, and then increasing again towards pulse 12.
- **PAP** and **EDP** (10^3 dynes cm^-2) remain relatively stable throughout the pulses.

The x-axis represents consecutive pulses, and the y-axis represents the values of each parameter.
Figure 12. The simultaneous cumulative volumes of the venous return (VR) and right ventricular stroke output (SO) during consecutive pulses. Intact preparation.
Figure 12

Cumulative volume over consecutive pulses.

- ○ VR
- × SO

Volume in cc versus consecutive pulses.
Figure 13. The simultaneous cumulative volumes of the venous return (VR) and right ventricular stroke output (SO) during consecutive pulses. Open chest preparation.
Figure 14. The consecutive pulse-by-pulse correlation between the right ventricular end-diastolic pressure (EDP) and peak pressure (RVP), the left ventricular end-diastolic pressure (LEDP) and peak pressure (LVP), and the variation in venous return (Vp). A, B, and C represent the different levels of the inferior vena cava in which the venous return was varied, being at the lower abdominal vena cava, diaphragm and right atrial orifice, respectively. Pump displacement = 64 cc; frequency = 0.19 c.p.s. Values obtained from recording shown in Figure 15. Intact preparation.
CONSECUTIVE PULSES

Figure 1A

<table>
<thead>
<tr>
<th>cc</th>
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<table>
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10³
Figure 15. Photographic reproduction of the experimental record from which Part C of Figure 14 was obtained.
Figure 15

10^3 dynes/cm²

LVP
LEDP
RVP

Vp = 64 cc

7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

1 sec
Figure 16. Photographic reproduction of the experimental record illustrating the effect of dynamic variations in venous return on the aortic pressure (AP). Pump displacement = 39 cc; frequency = 0.18 c.p.s. Intact preparation.
Figure 16
Figure 17. The relationship between stroke work (SW) and effective filling pressure (EFP) in the right ventricle during pressure breathing. Intact preparation.
Figure 18. The relationship between stroke work (SW) and effective filling pressure (EFP) in the right ventricle during normal respiration.
Figure 19. The relationship between stroke work (SW) and effective filling pressure (EFP) in the right ventricle during normal respiration simultaneously with dynamic changes in venous return.
Figure 20. The consecutive pulse-by-pulse correlation between the end-diastolic pressure (EDP), effective filling pressure (EFP), stroke volume (SV), stroke work (SW) of the right ventricle, respectively, intrapleural pressure (IPP), and mean pulmonary systolic pressure (PAP) during the same pulses from which the values in Figure 17 were obtained. Pressure breathing. Intact preparation.
Figure 20

CONSECUTIVE PULSES
Figure 21. The consecutive pulse-by-pulse correlation between the end-diastolic pressure (EDP), effective filling pressure (EFP), stroke volume (SV), stroke work (SW) of the right ventricle, respectively, intrapleural pressure (IPP), and mean pulmonary systolic pressure (PAP) during the same pulses from which the values in Figure 18 were obtained. Normal respiration.
Figure 21

CONSECUTIVE PULSES

1000 dyne cm

SW

cc

SV

PAP

1000 dynes/cm$^2$

EFP

EDP

1000 dynes/cm$^2$

EDP

IPP

1000 dyne cm

CONSECUTIVE PULSES
Figure 22. The consecutive pulse-by-pulse correlation between the end-diastolic pressure (EDP), effective filling pressure (EFP), stroke volume (SV), stroke work (SW) of the right ventricle, respectively, intrapleural pressure (IPP) and mean pulmonary systolic pressure (PAP) during the same pulses from which the values in Figure 19 were obtained. Pump displacement = 54 cc; frequency = 0.22 c.p.s.
Figure 22

- SW
- SV
- PAP
- EFP
- EDP
- IPP

10^3 dyne-cm

Consecutive Pulses
DISCUSSION

The data presented show that a relationship between the effective filling pressure and the stroke work can be clearly demonstrated in the intact preparation provided that neural adjustments do not occur during the period this relationship is being studied. This was accomplished in principle by altering the venous return and thus the parameters it affected in a sinusoidal manner in order not to disturb their respective average or control levels. Furthermore, this procedure was performed dynamically and at a sufficient rate to prevent neural receptors from making adjustments to any level but the average. To illustrate, the piston pump was adjusted to a frequency which precluded an arterial pressoreceptor response to the accompanied oscillation of the arterial pressure (63). This was evident mainly by the aortic pressure returning to the previous control level following the operation of the pump. In addition, the heart rate was observed to remain unchanged. According to Bainbridge (66) a 2 to 5 mm Hg (2.7 to 6.7 x 10^3 dynes/cm^2) change in the central venous pressure is adequate for producing a change in the heart rate, the response occurring at variable periods depending on the change in the pressure. For example, 50 cc saline infused in 10 seconds produced a noticeable increase in heart rate approximately 5 seconds after the infusion began. At least the magnitude of change observed in the right ventricular end-diastolic pressure (up to 4.3 mm Hg) was usually sufficient, therefore, to elicit a Bainbridge reflex in the present study. Coleridge and Linden (67) and Jones (68), to the contrary, claim that the directional alteration of the heart rate is related inversely with the initial rate prior to the infusion. Coleridge and Linden reported also that the changes in heart rate were related to the venous return and not always to the central venous pressure. In addition, Jones expressed the view that the heart rate is regulated under conditions of infusion to its optimal value (130/min.) for increasing the cardiac output and returning the venous pressure to its original value. The heart rates observed in the present
investigation ranged from 105 to 170/min. However, respiration usually was induced during infusion, but was believed to be the result of the sudden inflow of venous blood into the lungs since this effect was precluded by mild hyperventilation (pressure breathing) prior to the operation of the piston pump.

The relationship between stroke work and effective filling pressure was found to be straight in all experiments and resembled that between stroke work and end-diastolic volume reported in a similar study by Chapman et al. (30) for the left ventricle. At first, this appears to be contradictory to the curvilinear relationship demonstrated in the right ventricle by Sarnoff and Berglund (16) in the open chest preparation and Berglund (11) in the closed chest preparation. However, the range of effective filling pressures produced in the present investigation is assumed to represent only a small (but the physiological) segment of the total curve of which resembles that described by Starling's group (5). Therefore, the relationship appears straight and is in agreement with the work of the previously mentioned investigators. For example, Berglund reported a curvilinear relationship while varying the filling pressure (mean right atrial pressure) between 6 and 23 cm water (6.1 to 23.4 x 10^3 dynes/cm^2). Nevertheless, the curve was straight and extremely steep between 6 and 7 cm water, being relatively flat thereafter. Identical studies performed by Sarnoff and Berglund in the open chest preparation revealed both straight and curvilinear relationships accompanying alterations of 1 to 9 cm water in the filling pressure in the range between 4 and 18 cm water. However, a significant curvilinear relationship was observed when the filling pressure was varied between 9 and 10 cm water. For purposes of comparison the end-diastolic pressure in the present study was varied up to 5.7 x 10^3 dynes/cm^2 in the range between -3.6 to 4.7 x 10^3 dynes/cm^2, while comparable values in the effective filling pressure were 3.2, and -0.1 to 6.3 x 10^3 dynes/cm^2, respectively. The total curve in the intact animal might be relatively straight over a much greater range of filling pressures, since the normal physiological
condition of the myocardium was not sacrificed by exposure to the deteriorating conditions typical of the open chest and especially the heart-lung preparation (including changes occurring in the blood due to glassware). Furthermore, special care was taken in the present investigation to avoid myocardial trauma by the volume displacement of the piston pump and during catheterization. Variations in the slope during an experiment have not been evaluated since the alinearity of the flowmeter may contribute partially to the differences observed.

The changes observed in stroke work in all studies, including the open chest preparation, were due primarily to corresponding changes in the stroke volume. The pulmonary arterial resistance adapted readily to changes in blood flow since the mean pulmonary systolic pressure varied only by a relatively small degree, and then after a slight phase lag. Seemingly higher stroke volumes were observed sometimes after opening the chest and were responsible for the greater stroke work values obtained in such cases as compared to the intact animal. It was believed that the major factor was the redistribution of blood flow within the pulmonary vascular bed, thereby resulting in an increase in the flow through the flowmeter (positioned in one of the branches of the main pulmonary artery), rather than an increase in the cardiac output. In fact, the shrinking of the heart and the reduction in the central blood volume associated with opening the chest (13) and pressure breathing (65), respectively, would lead one to predict a decrease in cardiac output unless neural factors were operating to shift the physiological condition of the myocardium to a more efficient ventricular function curve as proposed by Sarnoff and Berglund (16). Alternatively, an increased distribution of blood flow through the flowmeter as contrasted with the other main branches of the pulmonary artery could have produced the higher slopes and the greater degrees of oscillation in apparent stroke volume in open chest preparations during the operation of the piston pump.

The nearly perfect pulse-by-pulse correlation demonstrated
between stroke work and effective filling pressure during consecutive pulses illustrates more emphatically the potential ability of this mechanism when not influenced by neural control and other factors. However, the controversial results obtained in attempts to demonstrate this mechanism in the intact preparation by infusion and hemorrhage studies, together with its failure to explain the cardiac adjustments to exercise and spontaneous activity have served to create doubt as to the validity and therefore applicability of the Starling mechanism in the intact and especially the unanesthetized animal and human. In addition, the effects of the nervous system and adrenal medullary secretions on cardiac dynamics are well established. In the present investigation the right ventricle was observed to be quite responsive to the rhythmically induced alterations of the venous return by demonstrating equivalent, cumulative changes in the stroke output. This observation is more or less in agreement with the view expressed by Wiggers (71) and Katz (12) that the heart puts out only as much blood as it receives. However, this axiom originated by comparing the input into the right heart with the output from the left heart and, therefore, was applicable only over an extended period of time. Nevertheless, these observations contribute to the validity of the output balance concept expressed by Hamilton (21) and Berglund (69). According to these investigators, the Starling mechanism serves as a simple servo-mechanism for maintaining a balance between the left and right ventricular outputs. In other words, if the load of either or both ventricles is changed with respect to the other, their respective filling pressure and thus fiber length will be altered to the proper degree and bring about the necessary change in the stroke output. In this manner a proper balance is maintained also between the blood volume of the pulmonary and systemic systems. This concept is supported by the results reported by Franklin et al. (70) based upon similar studies. These workers observed that a rapid intravenous injection of saline into unanesthetized dogs produced a progressive increase in the right ventricular stroke volume for a few beats and then diminished. After a phase lag of at least 3 pulses,
the left ventricular output increased similarly. Likewise, the oscillation of the right ventricular output in the present study was accompanied by a corresponding response in the end-diastolic and peak pressure of the left ventricle, as well as in the aortic pressure. In addition, the mean pulmonary systolic pressure was observed to behave similarly; being phasically behind the right ventricular stroke volume by 1 to 2 pulses, the latter generally being almost in perfect phase with the respective effective end-diastolic pressure. In view of this data, it would appear that the pulmonary vascular bed does not absorb or "buffer" the changes produced in the right ventricular stroke output to any degree, but rather serves more or less as a simple connection between both hearts. In addition, the pulmonary arterial pressure was indicative of the resulting change in the filling pressure of the left ventricle and therefore is representative of the imbalance in the outputs of the two ventricles. The effectiveness of this mechanism is indicated by the rapid adjustment in the stroke output, in addition to the relatively small change in the pulmonary arterial pressure that is produced as well as the fairly rapid onset of the change in the left ventricular and aortic pressures.

The Starling mechanism appears to be applicable during such dynamic phenomenon as pressure breathing and normal respiration. This was supported by the straight line relationship demonstrated between stroke work and effective filling pressure (Figures 17 and 18) resembling that observed during the operation of the piston pump (Figures 4 and 6). Likewise, a high pulse-by-pulse correlation was always observed between stroke work and the effective filling pressure (Figures 20 and 21). However, it was noted in these studies that the end-diastolic pressure and intrapleural pressure behaved similarly, yet sometimes opposite to the effective filling pressure. This observation is in agreement with the opinion expressed by others (9-11) that the effective filling pressure and thus the ventricular fiber length determines the work of the heart rather than the absolute intraventricular pressure. Furthermore, the
end-diastolic pressure and thus the mean right atrial pressure would not be always indicative of the end-diastolic volume. This supports the work of previous investigators (12, 15).

It appears, therefore, that the Starling mechanism can be demonstrated most clearly if studied under dynamic conditions as opposed to a more or less steady state. Nevertheless, this does not deny that the change in cardiac output reportedly associated with corresponding changes in the filling pressure of the right heart during infusion or hemorrhage are demonstrative of this mechanism. In fact, if the output balance concept is correct, the right atrial pressure would be representative of the output of the left ventricle. This is contrary to the view expressed by Sarnoff (16, 17). However, the question arises as to whether the increase in the cardiac output observed can be attributed to the Starling mechanism or, at least in part, to neural adjustments in response to the induced changes in blood volume. For example, the temporary rise in the venous pressure (35, 37, 39) and the more significant correlation between the above parameters following ganglionic blockage of the autonomic nervous system (31, 32) are indicative of the intervention by the nervous system during infusion. In addition, the increase in cardiac output in experimental plethora has been attributed by some workers (48-53) to be the result of anemia induced by the infusion of fluids other than whole blood. Sunahara (53), in fact, has shown that the cardiac output failed to change regardless of how much the right atrial pressure was raised with the infusion of blood. Furthermore, the results obtained during these infusion and hemorrhage studies were based upon a comparison of measurements conducted after a considerable span of time, thereby allowing more time for neural adjustments to take place. This is certainly supported by the construction of Starling curves (11) and a pulse-by-pulse correlation between the parameters (18, 27) when measurements were conducted after successive short intervals during the infusion of blood. In other words, when infusion or hemorrhage is performed at a rapid rate and frequent measurements were made, the results obtained would be assumed to
represent more clearly the Starling mechanism before compensated, at least in part, by neural adjustments. This view is supported by the results obtained in the present investigation. As discussed earlier, neural adjustments were averted by not disturbing the average or control values of the venous return and other parameters concerned, even though they were cyclically altered. In addition, comparisons and measurements were made over relatively short time intervals by studying the phasic responses of consecutive pulses. Furthermore, the venous return was varied dynamically without concomitant anemia and blood volume changes. Precautions were taken also to prevent such phenomena from attaining any significant importance as an experiment progressed.

In conclusion, the Starling mechanism relating stroke work to the effective filling pressure was demonstrated in the right ventricle of intact anesthetized dogs during dynamic changes in the venous return. The preclusion of neural adjustments cannot be overemphasized as a strict requirement in order for its establishment. The applicability of this mechanism was discussed from the standpoint of maintaining a balance between the outputs of both ventricles. In addition, the Starling mechanism appears to be applicable during pressure breathing and normal respiration.
SUMMARY

A successful attempt has been made to demonstrate the existence of the Starling mechanism in the right ventricle of intact anesthetized dogs. The data presented clearly show that a straight relationship can be demonstrated between the effective filling pressure and stroke work in the same ventricle provided that neural adjustments do not occur during the period that this relationship is being studied. This was accomplished by dynamically alternating the venous return and effective filling pressure of the right ventricle in a sinusoidal manner and at a frequency precluding neural reflexes due to arterial and venous (Bainbridge) baroreceptor stimulation. The values obtained from the analysis of consecutive pulses revealed a straight relationship between the effective filling pressure and the stroke work of the succeeding contraction. The change observed in the effective filling pressure was attributed mainly to the corresponding alteration in the end-diastolic pressure, the intrapleural pressure demonstrating only a slight oscillation. The end-diastolic pressure remained relatively uniform in its degree of oscillation throughout an experiment. However, the intrapleural pressure was observed initially to be of reasonably low negative magnitude and to become increasingly more negative as an experiment progressed. This was related possibly to the progressive cranial movement of the diaphragm. Both of the latter observations may have been due to alterations in the central blood volume. The magnitude of the changes observed in stroke work were attributed mainly to the changes in the stroke volume, the pulmonary arterial pressure oscillating by a relatively small amount (4.0 to 5.0 x 10^3 dynes/cm²) even after opening the chest. The mean values of the latter parameter were affected little with time or opening the chest. Furthermore, a nearly perfect pulse-by-pulse correlation was observed between the effective filling pressure, end-diastolic pressure, stroke volume, and stroke work. The mean pulmonary systolic pressure behaved similarly with respect to the effective filling pressure, but revealed a phase lag of 1 to
2 pulses. This phase lag was more or less associated with a corresponding oscillation of the left ventricular end-diastolic pressure and peak pressure, as well as the aortic pressure. The variations induced in the venous return appeared to be accompanied by equivalent, if not equal, cumulative changes in the right ventricular stroke output. Both of these latter results, in addition to the relatively small oscillation in the pulmonary arterial pressure, were interpreted as evidence in support of the concept that the Starling mechanism serves to maintain a balance between the outputs of both ventricles. Similar results to all of the above (excluding the intrapleural and effective filling pressures) were obtained after opening the chest.

Pressure breathing and normal respiratory activity revealed results similar to those obtained during the operation of the piston pump described above, and therefore, were concluded to be representative of the applicability of the Starling mechanism in the intact preparation. In addition, the stroke work was found to have a high pulse-by-pulse correlation with the effective filling pressure, regardless of the directional change occurring in the end-diastolic pressure and intrapleural pressures. This obviously indicates that the effective filling pressure and thus the ventricular end-diastolic fiber length determines how much work the ventricle can perform, rather than the absolute intraventricular pressure. By the same reasoning, the mean right atrial pressure is not always representative of the ventricular end-diastolic fiber length either.

The failure and conflicting results by previous investigators in attempts to establish the Starling mechanism in the intact preparation and human was attributed to the concurrent operation of neural adjustments in response to slow and progressive blood volume changes and anemia. In addition, most of the parameters were measured after considerable lengths of time. The preclusion of neural adjustments cannot be overemphasized as a strict requirement in order to demonstrate the Starling mechanism most clearly.
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AUTobiography

I, Alfred Joseph Pratt, was born in Newark, New Jersey, November 13, 1927. I received my secondary-school education in the public schools of Springfield, New Jersey, and my undergraduate training at the University of Maryland, which granted me the Bachelor of Science degree in 1949. In 1954 I received my Master of Science degree in physiology from the same university and held a research position with the National Heart Institute until commissioned in the United States Air Force in 1955. I applied to the Air Force Institute of Technology for additional graduate education in physiology for the purpose of obtaining a Doctor of Philosophy degree. I was accepted and matriculated in The Ohio State University in 1959 in order to complete the requirements for the Doctor of Philosophy degree.