ABSTRACT

FOURIER ANALYSIS OF THE TIME CURVES OF THE BASIC CARDIAC PARAMETERS OF ACUTELY-PREPARED OPEN-CHEST CATS AND TURTLES UNDER VARIOUS EXPERIMENTAL CONDITIONS

By Esmail Koushanpour

Cardiovascular waveforms are periodic sinusoids. Therefore, to obtain information on the source of distortion of contours from pressure and flow records, the curves must be analyzed into their components. The goal of such analysis is to present as uniquely as possible the intervals which are of most interest so that significant information is not discarded in an averaging process. Fourier analysis of the cardiac time curves involves the representation of an empirical function as it is recorded and not the statistical characteristics of the empirical function.

Using a variable Whitney gauge (mercury-filled latex rubber tubing), intraventricular and aortic catheters, and a force-displacement strain gauge, simultaneous records of cardiac circumference, pressure within the heart, and aortic pressure were obtained in acutely prepared open-chest turtles and cats. To analyze the cardiac time curves by the Fourier method, from a series of control or experimental records, a cardiac cycle was selected at random. Each cycle was then divided into ten equal time intervals. The amplitude values at each of these time

intervals were punched on standard IBM punch-cards and fed into a 160-A Fortran Control Data digital computer programmed to print out the values for area under the curve, sine and cosine coefficients, and amplitude and phase angle values for the first five harmonics.

Spectral and harmonic analyses of cardiac waveforms after adrenalin showed that this drug stimulates turtle heart muscle directly, whereas its action on the cat heart is initially on the conductive system and secondarily on the myocardium. Acetylcholine infusion decreased the force of cardiac contraction and prolonged the systolic phase of the cycle. However, acetylcholine infusion in the cat, in addition to cardiac depression, resulted in peripheral vasodilation. Moreover, it was shown that stimulation of vagus in the cat produces its effect primarily on the heart. These conclusions were based on the changes in the frequency distribution of impedance amplitude and impedance phase angle of the analyzed cardiac function curves. The action of adenylic acid in the cat was primarily on the aorta and not on the heart. The reduction in vascular impedance after adenylic acid was attributed to the vasodilating effect of this drug. Alteration of peripheral resistance by occlusion of the aorta resulted in an increase in vascular impedance and distensibility. Reduction in venous return, by occluding both vena cavae, produced a marked decrease in the inertial characteristics, whereas augmentation of venous inflow resulted in an increase in the distensibility or the elastic components of the vascular system.

It is concluded that the application of Fourier transform is a more realistic approach to the analysis of periodic pressure and flow changes in the circulation. It is suggested that such analysis is capable of deciding the true phasic pattern of the arterial pulse in addition to elucidating the hemodynamic changes of the vascular system.

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INTRODUCTION

Recent studies on the dynamic performance of the heart on open-chest and intact animals have increased markedly our knowledge of cardiac function (Rushmer, 1961). These investigations have become possible through development of highly mechanized and complex electronic recording and data processing instruments. With the rapid advances in physiological technology there is a growing need for continuous monitoring and analysis of physiological data. The impact of this technological progress has opened a new era in physiology in which mathematical and physical analysis of physiological phenomena are replacing the usual statistical methods. This is not to say that statistical treatment of physiological data is not useful. However, since statistical inferences place great emphasis upon the pooled effect of a population and not the individual contributions to the over-all effect, little if any, gain can be obtained from statistical analysis alone. This is particularly true in the case of the cardiovascular system. The signal variations, such as pressure, volume, flow, and tension curves recorded from the various components of the cardiovascular system are multiple-harmonics time curves. In order to determine the over-all changes in these recorded signals under various physiological conditions, we must determine changes in the individual components which are coded in these signals during each cardiac cycle. Since the recorded signal variations

of the cardiovascular system are periodic in occurrence, the tendency has been to consider them as multiple sine and cosine curves with finite frequency. One suitable method for analysis of such multiple-harmonics time curves is the application of a mathematical method known as Fourier analysis. This method has been applied to the analysis of human electrocardiogram (Thompson, 1962), and pressure-flow curves in femoral artery of dogs (McDonald, 1955, and Randall and Stacy, 1956).

In the present study, using a variable resistance gauge (a mercury-filled rubber tube), intraventricular and aortic catheters, and a force-displacement strain gauge, simultaneous records of the circumference, pressure, and weight changes in the heart were obtained in acutely-prepared open-chest cats and turtles. Then, by Fourier analysis of the data an attempt was made to describe quantitatively the changes in the cardiac function curves of these two animals under acute experimental conditions.

This method of analysis is considered to be a powerful tool by means of which we can gain an insight into the mechanisms of changes in cardiac function, for example, after epinephrine, acetylcholine, or adenylic acid injection. Fourier analysis of the cardiac time curves was processed by writing a special program in FORTRAN for 160-A Fortran Control Data computer.

SURVEY OF LITERATURE

Determinants of Cardiac Performance

The cardiovascular system is composed of two functionally and anatomically different components, namely, the heart and the blood vessels. The heart functions basically as a pump in imparting energy to the blood and propelling it through the vascular tree. The blood vessels function as conduits through which blood is transported from one region of the animal body to the other. The interplay of the anatomical constituents of these two components as manifest in their functions should be considered when the function of the cardiovascular system as a whole is evaluated. The circulatory system can be regarded as a black box which generates certain sinusoidal functional curves through the interaction of its components. These generated curves, under a given condition, have coded within them the individual contribution of the components. Therefore, the generated functional curves can be considered as a sum of the fractionate functions of the various components. To gain an understanding of the nature of the action of the components of this black box, attempts have been made to analyze the output curves of the system. Since the nature and usefulness of any analysis depends upon the method by which the functional curves have been obtained, our understanding of the system has been conditioned by the techniques used. Early studies on the functional

activity of the cardiovascular system have been done on cardiac and skeletal muscles of cold-blooded animals. The basic assumptions in these studies have been that the two types of muscle systems are similar in functions. It should be realized that much has been learned about cardiovascular physiology from studies on skeletal muscle.

I. Three Fundamental Discoveries

In 1871 H. P. Bowditch performed the first classical studies in ellucidating the functional activity of the cardiac muscle. Using the apex of the frog's ventricles, Bowditch showed that the amplitude of cardiac contraction remains the same regardless of the strength of the applied stimulus. This phenomenon, some seven years later was phrased into the well-known "all or none" law by the French investigator L. A. Ranvier. Bowditch also demonstrated that the heart muscle exhibits "treppe" or "staircase" phenomenon which indicates that the individual stimulus exerts a beneficial after-effect on the responsiveness pattern of the cardiac muscle.

The second fundamental discovery was the result of the investigations of Howell and Donaldson (1884). Using the Newell Martin heart-lung preparation in the dog, they showed that the heart has some intrinsic mechanisms which allow it to adjust its output to the venous input. When venous inflow to a 76 gm. heart was increased, the cardiac output increased from 480 to 1964 ml. per min. and the stroke volume increased

from 5. 2 to 21. 6 ml. per beat. The increase in venous inflow resulted in the elevation of the right atrial pressure from 10 to 60 cm. of blood. However, when the right atrial pressure was restored to 10 cm. of blood the cardiac output was reduced to 400 ml. per min. and the stroke volume to 2. 38 ml. per beat. The non-linear relation between the venous inflow and the output of blood from the heart was interpreted as a sign of deterioration of cardiac performance as a result of a short period of strain.

In 1895, Otto Frank published his famous treatise on the "dynamics of heart muscle" which contained the results of experiments leading to the third fundamental discovery. In this work, he attempted "to correlate as far as possible the mechanical reactions of cardiac muscle with the well-known responses of skeletal muscle previously established by A. Frick, J. von Kries, and Blix." The latter investigators established the so-called initial length and tension diagrams for the skeletal muscles under various conditions. Otto Frank made isometric and isotonic recordings of the contracting frog's atria and ventricles under various degrees of diastolic filling and pressure. He found that the stepwise increase in the presystolic volume and pressure determined the magnitude of the "all or none" response of the heart.

These three classical discoveries formed the foundation upon which the designs of the future experiments were based.

II. The Law of Uniformity of Behavior

In 1906, Y. Henderson using improved plethysmographic and cardiometric techniques obtained records of the ventricular activity under various filling and emptying conditions. He found that the contour of the volume curve is affected by the coronary blood flow. Henderson (1906) regarded the mammalian auricle as an elastic reservoir and not as a force pump. Based on various experiments, he stated that the ventricular volume curve resembles the form of an isotonic or an after-loaded muscle curve. Henderson (1906) concluded that the cardiac cycle consists of three phases: (1) ventricular systole which represents the contraction and discharge phase of the cycle, (2) ventricular diastole representing the relaxation and filling of the cycle, and (3) diastasis which is the period of the resting phase of the cardiac cycle.

In subsequent studies, Henderson (1909, 1913, 1923) demonstrated that the diastolic volume is the primary determinant of the cardiac function. He concluded that: (1) under normal condition of venous inflow, diastolic volume is determined by a fixed ventricular relaxation pattern, (2) additional increase in venous inflow does not affect the diastolic capacity and subsequent systolic ejection, and (3) greater increase in venous inflow is accommodated only by increasing the heart rate.

III. Starling's Law of Initial Length

In 1914 Patterson, Piper, and Starling carried out a series of experiments on the isolated heart-lung preparation. This artificial circulatory scheme, although it had limitations, was a useful method of controlling the changes in heart rate, mean arterial pressure, and venous inflow. After a series of elaborate experiments, Starling (1918) proposed the well-known law of the heart based on the following conclusions:

1. When peripheral resistance and venous inflow is held constant, changes in heart rate from 60 to 160 per minute did not alter cardiac output per minute significantly. This conclusion was diametrically opposed to that of Y. Henderson (1913).
2. When heart rate and mean arterial pressure were kept constant, changes in venous inflow resulted in a definite change in the diastolic size of the ventricle and cardiac output. A compensatory increase in stroke volume occurs in proportion to the degree of ventricular distension in diastole up to a critical point.
3. During the compensatory state pressure increased in both atria. However, during decompensation pressure increased in the left atrium and dropped in the right atrium.
4. The output of the fatigued and fresh hearts could be the same if the atrial pressure and presystolic volume of the fatigued heart were greater than that of the fresh heart.

IV. Wiggers' Law of Initial Tension

In 1922, C. J. Wiggers and L. N. Katz, using an improved heart-lung preparation as well as optical manometers and cardiometric techniques, made detailed analytical studies of the changes in heart rate, venous inflow, and mean arterial pressure and their relation to presystolic ventricular volume. They concluded that the systolic ejection is determined not by presystolic size, but by the presystolic tension, coronary blood supply, humoral agents, and the nerves which innervate the ventricular muscle. These findings were re-evaluated subsequently by Wiggers (1927, 1928, 1938, 1952) and Katz (1927, 1928, 1955, 1960).

Wiggers (1928) noted that the changes in initial volume and pressure are always in the same direction except in premature beat and after epinephrine. In the latter two conditions, changes in cardiac activity vary in the direction of changes in initial volume and not the initial pressure. These findings were in accord with Starling's concept that the cardiac regulation is in terms of initial volume and the initial pressure. Katz (1928), using an isolated perfused turtle heart demonstrated that despite the constant initial pressure, the changes in amplitude, duration, and tention-time of the pressure curve varied in the same direction as the initial volume. He concluded that in the turtle cardiodynamic regulation depends on the initial volume and not the initial

intraventricular pressure. No influence of the lateral pressure on cardiac activity was found.

V. Modern Views of Cardiac Control

The early experiments which culminated in the establishment of various laws governing the cardiac function were all performed on isolated heart or heart-lung preparations. It was only natural to raise the question as to whether the results of experiments on isolated heart can be applied to intact animals. Katz (1927), reviewing the researches of previous investigators stated that studies on the isolated heart have produced two schools of thought. One school believes that the increase in initial tension causes a prolongation of systole, whereas, increasing peripheral resistance shortens the period of ventricular systole (Wiggers and Katz, 1922). The second school maintains that both these efforts are the results of increase in the length of the myocardial fibers (increase in volume) and not the change in initial tension (Starling, 1918). Katz (1927), on the basis of his own studies, concluded that the heart-lung preparation can be considered as a useful tool in cardiodynamic studies in that it eliminates some of the variables. However, this method introduces other variables of its own and "does not allow the independent variations of two important factors, namely, the initial tension of the left ventricle and the arterial load."

Attempts have been made to analyze the cardiodynamic function under various conditions from the dynamic changes in pressure pulse

contours. Katz and Wiggers (1927) used a method of analysis of pressure pulse contours to evaluate results of the various studies on the heart-lung preparation and their application to intact animals. They concluded that changes in the contour of pressure pulses reflect variation in the systolic pattern of the ventricle and that these changes, as observed in open-chest animals with nervous system intact, do not correspond to those obtained in the heart-lung preparation which lacks innervation. Therefore, results from the heart-lung preparation cannot be extrapolated to those of intact animals nor to open-chest animals.

In 1955 Katz, reviewing literature of the past three decades, stated that the end-diastolic volume has proven to be only one of the determinants of the regulation of cardiac performance. Other factors which are equally, if not more, important are peripheral resistance, humoral and neurogenic factors, cardiac contractility and distensibility, heart rate and systolic residual volume.

Recent studies on the cardiodynamic function of the intact heart by means of modern techniques have questioned the applicability of Starling's law of the heart, based on the heart-lung preparation, to the intact heart in closed chest animals. Recording intraventricular pressure, circumference, and diameter of both right and left ventricles in intact dogs, Rushmer and associates (1951, 1953, 1954, 1956, 1959, 1961) showed that the immediate effects of exercise were an increase in the heart rate with progressive reduction in the systolic and diastolic diameters.

Rushmer (1954) found no evidence of greater diastolic distension during exercise as demanded by Starling's law of the heart. As a result of a series of experiments, Rushmer (1954) concluded that the increase in stroke volume in response to exercise is primarily achieved by a greater systolic ejection which encroached upon the "systolic reserve volume."

Hawthorne (1961) reported his observations on the instantaneous dimensional changes in the left ventricle in unanesthetized intact dogs. He postulated that "during ejections the ventricle tends to become elliptical, and during filling it becomes more circular."

Since the works of Rushmer and his group (1961) many other investigators have recorded the various cardiac parameters in intact animals under various conditions. Remington (1962) reviewing the recent progress made in muscle physiology states that any understanding of the functions of skeletal, smooth, and cardiac muscles must await the analysis of the time course of the contraction process.

Dynamics of Ventricular Function Under Experimental Conditions

Wiggers (1952) classifies the determinants of myocardial response into two categories: (1) the primary coefficients which induce direct myocardial action, such as the effects of drugs, nervous system, and local metabolites, and (2) the secondary coefficients producing a change in the cardiac output by altering the venous inflow. The effect of primary coefficients is characterized by the change in initial tension and amplitude

of ventricular contractions in the same direction. The effects of secondary coefficients are characterized by the changes of initial tension and amplitude of contractions in the opposite direction. In the body these two coefficients operate simultaneously.

I. Effect of Thoracotomy on Cardiac Function

The heart is situated within the pericardium in an environment which is slightly subatmospheric. The existence of negative pressure within the thoracic cavity has been considered necessary to the normal cardiac function. When the chest of the animal is opened the heart is reduced in size and the cardiac performance will be below par (Rushmer, 1961). The marked changes in cardiac function following thoracotomy have been studied by a number of investigators. Ferguson, Shadle, and Gregg (1953) observed that in open chest dogs blood pressure was lower, heart rate was faster, and the peripheral resistance was somewhat greater than the closed chest dogs. They found that the degree of directional correlation between the end-diastolic pressure, stroke work, stroke volume, and cardiac output was a function of whether the chest was closed or open. Ferguson and co-workers (1953), however, found no correlation between the presence of pericardium and cardiac function in open or closed chest dogs. Rushmer, Finlayson, and Nash (1954) made cinefluorographic studies on closed and open chest dogs. After intravenous injection of 50 ml. of thorotrast, films were taken from cardiac silhouette after each of the following procedures: (1) surgical

anesthesia induced by intravenous Nembutal, (2) thoracotomy, and (3) the application of a cardiometer. They found a consistent diminishing of the area of cardiac silhouette and of the left ventricular chambers. The systolic ejection was more complete (greater emptying) in open chest as compared with closed chest dogs. It was concluded that the response of the heart in the open chest animal cannot be extrapolated to the intact heart, since in the open chest condition the heart tends to become larger in response to an increased load. It appears possible that many of these hearts could not have become smaller.

II. Cardiodynamic Actions of Drugs

The regulation and control of ventricular contraction in the intact unanesthetized animals are the results of the interplay of many different factors including the heart rate, coronary blood supply, hormones (such as l-epinephrine and norepinephrine), autonomic nervous system, and perhaps many others. Physiologists have long been interested in the manner by which these factors, in particular hormones and nervous system, regulate and modify myocardial contractility and cardiac performance. Since the discovery of the humoral agents presumably released at the effector endings of cardiac nerves, attempts have been made to stimulate the action of these substances by exogenous preparation and intravenous administration. Among the drugs most widely used are l-epinephrine and l-norepinephrine. The amount of these substances

released at the nerve endings is very small. Cannon and Rapport (1921) found that the amount of epinephrine released as a result of afferent stimulation is about 3.5 to 3.7 μg/kg./min. Wiggers (1927) studying the mechanism of cardiac stimulation by drugs in dogs observed that epinephrine increases the maximum systolic pressure, systolic discharge, and increases pulse pressure. This effect of epinephrine was found to be independent of whether vagus nerves were intact or cut and whether the heart rate is slowed or accelerated. The greater systolic discharge, following epinephrine injection, was thought to be entirely due to the increased velocity of discharge. Wiggers (1927) further observed that the effect of epinephrine on the heart is augmented by the alteration of secondary factors such as peripheral resistance and initial tension. In animals with intact vagus, large doses of epinephrine were found to cause A-V block through the intact vagus stimulation. However, after vagotomy, an A-V block may be removed by epinephrine. Wiggers concluded that epinephrine exerts the following actions on the overall performance of the heart: (1) steeper isometric pressure gradient, (2) higher maximum pressure, (3) increased pulse pressure, and (4) abbreviation of the duration of systole.

Goldberg and co-workers (1948) studied the hemodynamic response of man to norepinephrine and epinephrine. They found that infusion of 0.15 to 0.30 μg/kg./min. of epinephrine for 11 to 14 minutes resulted in an increased systolic pressure and cardiac output and a decrease in

peripheral resistance. They concluded that epinephrine is an overall vasodilator and a cardiac stimulant drug. Goldberg and associates (1948) observed that the bradycardia resulting from infusion of 0.2 μg./kg./min. of nor-epinephrine is of vagus origin, because it is abolished by atropine. They showed that in man nor-epinephrine produces an increase in both systolic and diastolic pressure, an increase in peripheral resistance, but no change in cardiac output. Infusion of both epinephrine and nor-epinephrine combined in equal amounts resulted in a slight fall in the mean blood pressure, increased cardiac output, and decreased peripheral resistance. Ahlquist (1950) reporting on the comparative effects of epinephrine and arterenol-isopropyl arterenol mixture confirmed the results of earlier investigations that epinephrine is a vasoconstrictor and exciting agent but is less active than arterenol. Ahlquist further confirmed the theory that the pressor response to epinephrine is diminished by its simultaneous vasodilating action.

Brown and Boxill (1951) and Brown (1952) determined dose-response curves for l-epinephrine and l-norepinephrine by injecting progressively logarithmically spaced doses of drugs into dogs. They found that the dose-response curves for both drugs were rectangular hyperbolas having the equation,

$$mXY + nY - X = 0,$$

where **X** is μg. of base per kg. of body weight, Y is the rise in blood

pressure in mm. Hg, and m and n are constants so chosen that $\frac{1}{m}$ is the asymptote parallel to the X-axis and $\frac{-n}{m}$ the asymptote parallel to the Y-axis. The values of m and n were determined by locating the center of each hyperbola by the method of least squares, using the Legrange method of undetermined multiplier. They found no evidence of any significant vasodilating action of any of these drugs until a dosage level of about 5 μg./kg. is reached. At this dose level a marked after-depression of blood pressure was observed.

The cardiovascular responses to l-epinephrine and l-norepinephrine in animals with intact and denervated pressoreceptors were studies by Boxill and Brown (1953) and Hilton and Brown (1954). They confirmed the earlier findings that in the presence of amounts of circulating l-epinephrine and l-norepinephrine sufficient to elevate systemic blood pressure, the pressoreceptor reflexes are incapable of limiting either the rise in blood pressure or the peak blood pressure attained. These investigators concluded that if these drugs have any effect upon duration of the blood pressure rises, the pressoreceptor reflexes prolong the rise. Therefore, it appears that pressoreceptor reflexes are important as protecting agents against hypotension, but not against hypertension.

The action of l-norepinephrine upon pulmonary arteriolar resistance in man was investigated by Fowler and co-workers (1951). They found that infusion of l-norepinephrine resulted in increased pulmonary artery and brachial artery pressure, increased peripheral resistance, diminished

cardiac output and bradycardia. They postulated that increase in pulmonary artery pressure by the action of l-norepinephrine is a protective measure against edema formation and is due to the increased "capillary" or venous pressure in lungs. Increase in pulmonary venous pressure is thought to cause an increase in left atrial pressure which in turn induces pulmonary artery hypertension. Peripheral venous constriction was postulated by Fowler and associates (1951) to be the reason for systemic hypertension following l-norepinephrine injections. This implies that a definite increase in the systemic peripheral resistance is produced during the period of drug administration. If the systemic peripheral resistance (R) is related to mean blood pressure (P) and flow (Q) by the equation, $R = \frac{P}{Q}$, then any change in R should alter the steady state values of P and Q. Jochim (1952) studied the effect of various doses (0.5 to 25.0 μg./kg.) of l-epinephrine and l-norepinephrine on the vascular resistance of intact carotid artery of dogs. He found that both drugs produced a steady decrease in flow and increased vascular resistance. The effect of drugs on flow lasted much longer than the effect on blood pressure.

Akers and Peiss (1963) made a comparative study of the effect of epinephrine and nor-epinephrine on the cardiovascular system of turtle, alligator, chicken, and opossum. They found that both drugs produce an increase in the diastolic pressure in turtle. However, no change in heart rate was observed. They postulated that the increase in diastolic

pressure in turtle could be due to the peripheral vasoconstriction. Since no change in the distensibility of the blood vessels was assumed, increased pulse pressure was attributed to action of the drug on myocardial fibers. Akers and Peiss (1963) concluded that a) epinephrine is more potent than norepinephrine in turtle, b) epinephrine produces an increase in initial velocity of myocardial contraction and, c) epinephrine is destroyed by a process of non-enzymic oxidation.

III. Hemodynamics of Hypervolemia

Cardiovascular response to phasic volume changes of circulating fluid has often been considered as an index of cardiac performance. Henderson (1906), using cardiometric techniques, recognized that the change in the form of ventricular volume curves during cardiac cycle could provide information on the nature of cardiac contraction and relaxation. Wiggers and Katz (1922), using improved cardiometric methods, took cognizance of the fact that a good system of recording volume changes of the heart is one which translates the changes in volume into moderate tension changes. In a series of studies, on open chest dogs, Wiggers and Katz (1922) observed that an increase in the venous inflow produced by infusion of saline solution results in an increased right atrial pressure and greater output of the right ventricle. These two factors will improve the left ventricular emptying and elevate the initial tension. The characteristic effects of hypervolemia were a

steeper gradient of the isometric contraction curve, a quicker rise of pressure to a higher peak during ejection, and a prolongation of systole.

Gregg and Wiggers (1933) studied the circulatory effects of acute experimental polycythemic hypervolemia in dogs. Infusion of concentrated blood produced an increased spleen volume and urine output. These two compartments accounted for more than one-half of the total volume of the injected fluid. Following infusion the pulse pressure was increased by elevation of systolic pressure. They observed further that polycythemic hypervolemia produced an increase in the diastolic pressure and venous pressure accompanied by a prolongation of the isometric contraction phase of systole. It was postulated that polycythemic hypervolemia results in an increase of venous pressure, increased diastolic size of the heart, and augmentation of cardiac output and systemic systolic pressure.

Ventricular response to alteration of venous return, as determined by myographic studies, has offered considerable insight into the mechanisms of myocardial adaptation to increased load. DiPalma and Reiss (1948) made extensive myographical studies in the cat of the effect of changes in venous return and peripheral resistance on ventricular contraction. Increasing venous return with infusion of physiological saline (30 ml. at a rate of 10 ml./min.) resulted in a decreased myographic excursion. Reducing venous return by means of occlusion of the inferior vena cava resulted in decreased arterial pressure and in an increased

myographic excursion of both ventricles. They concluded that a rise in venous return causes a fall in myocardial tension, whereas decreased venous return results in increased myocardial tension. DiPalma and Reiss (1948) maintain that these results are in accord with the assumption that the heart is a hollow elastic sphere. When undergoing change, the volume of the heart increases by $1/3\ R^3$ while the surface area increases by R^2. Therefore, changes of volume cannot be ascertained from changes in surface area. During increased venous return, they postulate, the heart muscle becomes thinner, thus resulting in a decreased force of contraction as determined myographically. It is further postulated that when a drug decreases cardiac contractility, it must do so by increasing the radius of the sphere.

Recent studies of Cotton (1953) on circulatory changes affecting cardiac force provide more insight into mechanisms of cardiac adaptation. Using multiple strain gauge arches, Cotton found that any part of the myocardial syncytium is representative of the rest of myocardium. Furthermore, changes in heart rate had very little effect on the force of myocardial contraction. When Ringer-Locke solution was infused (20 ml./kg.) rapidly no significant increment in the force of cardiac contraction was observed.

IV. Cardiac Performance and Peripheral Resistance

The effect of increased peripheral resistance on patterns of ventricular contractions has been investigated by means of partial or

total occlusion of thoracic aorta. Wiggers (1952) points out that the most obvious effect of increased peripheral resistance produced by this method is prolongation of the isometric contraction phase of the cardiac cycle. In addition, due to a higher aortic pressure, duration of systole is markedly shortened. The peak systolic pressure is also increased. Therefore, immediate response to a sudden increase in peripheral resistance is an increase in initial tension and a shortened systolic contraction. If occlusion persists, there will be an increased diastolic size of the heart, and higher presystolic ventricular tension. Furthermore, Wiggers (1952) believes that contour changes in the pressure pulse reflect changes in the pattern of ventricular function during various segments of the cardiac cycle.

Gupta and Wiggers (1951) studied basic hemodynamic changes produced by aortic coarctation of various degrees. They showed an aortic stenosis must be about 55 to 60 percent of the initial diameter before a significant elevation of aortic and left ventricular pressure could be observed. They postulated that reduction in diastolic pressure and elevation of aortic and left ventricular pressure, observed in aortic coarctation, is due to reduction in distensibility of the aortic compression chamber. Gupta and Wiggers (1951) noted that contour of the central aortic pulse in coarctation depends on the degree of stenosis as well as stroke volume and left ventricular competence. The ascending plateau of the aortic pressure pulse and the displacement of its peak toward the

end of systole was thought to result from increased peripheral resistance. Altered contour of the central aortic pulse during coarctation is postulated by Gupta and Wiggers (1951) to be due to an abnormal pattern of ventricular ejection. They concluded that, in aortic coarctation, the compression chamber is greatly reduced in size and its walls are subjected to a greater stretch. Therefore, the changes in systolic pressure (in part) and those of diastolic pressure (entirely) are attributed to the increase in the volume elasticity coefficient ($\frac{dP}{dV}$) of the aortic compression chamber. With progressive reduction of the pulmonary artery diameter Fineberg and Wiggers (1936) found that both right ventricular and aortic pressures fall. This is opposite to the effect of aortic stenosis. They postulated that decreased right ventricular pressure is associated with an increase in initial ventricular tension. Wiggers and co-workers (1952) concluded that in evaluating clinical stenosis from the results of the experimental aortic stenosis cognizance should be taken of the location of the stenosis and the condition of coronary filling and cardiac anoxia.

Analysis of Cardiac Time Curves

The ventricular pump creates a pulsating pressure flow through non-rigid tubes. The constancy of flow of blood through the non-rigid blood vessels is due to elasticity of the vessels. Therefore, a detailed hemodynamic consideration of the cardiovascular system must include the physical effects of vascular branching, the variable calibre and distensibility of muscular arteries, and the reverberating pressure waves

set up (Wiggers, 1952). Importance of vessel distensibility and its role in maintenance of steady flow and pressure of blood were recognized as early as 1880 by C. S. Roy who studied the elastic characteristic of excised aortae. Roy noted that the thermo-elastic property of animal tissue differs from that of rigid material (metal) in that the animal tissue shows an increase in temperature when stretched. The metal shows a loss of temperature upon stretching. Roy (1880) further noted a marked difference between the tension-length diagram of excised aortae of young and old species. In 1881, Grashey, using the sphygmographic method, made an extensive study of wave propagations in elastic tubes and arterial pulse transmission in man. He concluded that the factors which produce reflection of waves in elastic tubes are identical with those which change resistance and/or velocity of flow such as dilation or constriction of the tube.

I. Qualitative Description of Cardiac Function Curves

The aortic compression chamber accommodates the stroke volume output in a finite period of time by means of two mechanisms: (1) forward movement of blood (kinetic energy of flow), and (2) distension of the elastic aorta due to pressure increment in the ventricle (potential energy of pressure). These phenomena are stated in Bernoulli's equation:

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

where (P) is the pressure difference between two points in the

cardiovascular system, (ρ) is the density of the blood, (v) is the velocity of flow, (Z) is the reference datum (zero pressure with respect to the heart), and (E') is the total mechanical energy. Dynamic interplay of kinetic energy of flow and potential energy of pressure is indicated by the velocity of pulse wave transmission. Physiologists have long been interested in the physical factors responsible for the pulse wave transmission. In 1878, Moens stated that the relationships between the physical factors which determine the velocity of propagation of a pressure pulse through elastic tubes filled with fluid are governed by elasticity, thickness of the wall, bore of the tube and density of the fluid. Assuming that the modulus of elasticity of the tube wall is constant, wall thickness is negligible as compared to tube diameter, and the generated pressure wave is small, Moens derived the following useful equation:

$$v_p = K\sqrt{\frac{gEa}{wd}}$$

where (v_p) is the pulse wave velocity in m./sec., (E) is Young's modulus of elasticity in gm./cm.^{2} ($E = V\frac{dP}{dV}$), (a) is wall thickness in cm., (w) is fluid density in gm./cm.^{3}, (d) is the internal diameter in cm., (g) gravitational constant, and (K) is a constant. On the basis of various experiments Moens assigned K = 0.9.

In 1878, Korteweg, independent of Moens, derived an equation of propagation of a wave whose speed is controlled by the lateral displacement of the walls of the elastic tubes similar to the arterial system.

Korteweg's equation has the form,

$$v_p = \sqrt{\frac{gE\,a}{wd}} .$$

In 1922 Bramwell and Hill, assuming the blood density to be constant at 1.055 and wall thickness negligible, applied Korteweg's equation to the propagation of pulse wave in arterial system. They derived an equation relating the pulse wave velocity to the physical characteristics of the arterial system,

$$v_p = \sqrt{\frac{Ed}{2R\rho}}$$

where (v_p) is the velocity of the front of the pulse wave, (E) is the modulus of elasticity, (d) is the wall thickness of the artery, (R) is the radius of the artery at the end of diastole, and (ρ) is the density of the blood. Substituting $\rho = 1.055$ and $E = V\frac{dP}{dV}$ and neglecting (d), in the above equation, an expression is obtained which relates the pulse wave velocity to the elastic modulus or the volume and pressure changes within the arterial system,

$$v_p = 0.357\sqrt{V\,\frac{dP}{dV}} .$$

Bramwell and Hill (1922) attributed the discrepancy between calculated and observed values to the effect of viscous drag of the arterial wall when it was subjected to a rapid stretch. On the basis of several experiments, they concluded that the efficiency of circulation can be characterized by: (1) the greatest possible amount of blood flow for a given

pressure (small velocity) and (2) the existence of high, constant flow through capillaries. Bramwell and Hill (1922) maintained that low velocity of the pulse wave is a sign of both an efficient and a continuous circulation. They concluded that pulse wave transmission is purely a mechanical phenomenon and that pulse wave velocity depends on diastolic pressure and elasticity of the arterial system.

In 1937 Woodbury and Hamilton, using the Hamilton optical manometer connected to a 26 gauge hypodermic needle, made a comparative study of the systolic and diastolic pressures and pressure pulse contours in rat, pigeon, starling, robin, canary, sparrow, frog, turtle, and carp. In order to make inferences about the hemodynamics in these species, they calculated the rate of descent of the arterial pressure. This calculation was based on the assumption that a short portion of the pressure pulse curve is linear. Since blood pressure is the result of cardiac output and peripheral resistance, these investigators believed that such a calculation will provide an insight into the mechanisms of cardiac function. Plotting the logarithm of the rate of descent against pressure, they obtained a straight line with equation,

$$\log \frac{dP}{dt} = KP + C,$$

where $(\frac{dP}{dt})$ is the rate of descent of pressure, (P) is pressure in mm. Hg, (K) is the slope of the linear relationship, and (C) is a constant. Woodbury and Hamilton (1937) suggested that this equation is similar to that proposed by Otto Frank in 1899,

$$-\frac{dP}{dt} = \frac{EP}{W},$$

where $(-\frac{dP}{dt})$ is the decrement in the rate of descent, (P) is pressure in mm. Hg, (E) is volume elasticity coefficient, and (W) is the resistance of the system. Upon integration of Frank's equation,

$$\log \frac{dP}{dt} = \log E + \log P - \log W.$$

If W is assumed to be constant, the above equation becomes,

$$\log \frac{dP}{dt} = \log E + \log P$$

Combining this last equation with $\log \frac{dP}{dt} = KP + C$, gives an expression which relates volume elasticity coefficient to some function of pressure,

$$\log E = KP - \log P + C.$$

Woodbury and Hamilton (1937) showed that K remains constant for any pressure and does not change after epinephrine injection. This implies that volume elasticity (E) varies directly with some function of pressure under various physiological conditions. They observed further that the rate of descent of arterial pressure in diastole is more rapid in smaller animals than in larger ones. Duration of diastole was shorter in smaller animals as compared with larger ones, and the short diastolic period is associated with thin muscle fibers. Woodbury and Hamilton (1937) concluded that any assessment of the ratio of percentage of cycle time devoted to systole and diastole must be coupled with the consideration of the stasis of coronary blood flow. Furthermore, blood pressure level is a characteristic of the species and is not related to the size of the animal.

Physiologists have long been interested in the interpretation of the recorded pressure pulses as a means of understanding cardiac function. In 1922 Koch theoretically considered the force of contraction of frog's cardiac muscle as a summation of fractionate contraction. Wiggers (1927) considered intraventricular pressure curves as a graphic record of the tension developed by the myocardial fibers. The contour, amplitude, and duration of various segments of the pressure pulse curve were regarded by Wiggers as an index of the dynamics of contraction processes of the myocardium. Since not all the parts of the heart are excited at the same time, then intraventricular pressure cannot be considered as an addition of contractions in phase but rather as a summation of many rapidly succeeding fractionate contractions. Wiggers (1952) believes that, "The dynamics of ventricular contractions, which concerns itself with the mechanisms through which cardiac output is altered, can be evaluated to a considerable extent by a rigid analysis of pressure pulses recorded from the ventricular cavities." In order to make physiological inferences from the recorded pressure pulses a certain measure of assurance of the reliability and faithful registration of the recording and detecting instruments is a minimum requirement. As Wiggers (1952) states, "Theoretic physical formulations and practical tests have demonstrated that reliable curves can be recorded by a manometer system which has an adequate frequency and proper damping characteristics expressed by the logarithmic decrement of its free vibration." In order to distinguish the true contour

of the ventricular pressure pulses from that of artifacts and distortions of the recording and sensing instruments a number of factors should be investigated carefully. The change in position of catheter within the heart cavity during systole and diastole will affect the contour of the recorded pulses. The sensitivity of the manometer and the speed at which the pressure pulses are recorded will affect the contour of the pulse. Therefore a judicious balance between ordinate and abscissal values is obviously important in the registration of pressure pulses.

Review of recent literature on circulatory disorders reflects the growing interest in using the velocity of pulse wave transmission as a key to better understanding of the physiology of circulation, in general, and circulation pathology in senility and hypertension, in particular. Dow and Hamilton (1939) made an experimental study of the velocity of the pulse wave transmission through the aorta. They reported that when pulse wave velocity is plotted against the distance from the heart, the curve obtained has a general shape which is concave toward axes. The slope of the curve gives the velocity of the foot of the wave at any point in the circulatory system. Occlusion of the thoracic aorta resulted in an increase in pulse cycle due to depressor reflex of the vagus nerve. Pulse wave velocity increased with occlusion, but fell off when depressor activity set in. Dow and Hamilton (1939) concluded that the pulse wave velocity corresponds to different functions of the diastolic pressure in the thoracic and abdominal portion of the aorta. They postulated that

the slowing of pulse wave velocity, after vagus stimulation, could be due to the fact that, "vagus stimulation either nervous or hormonal brings about a change in the elasticity of the arterial wall by varying the tone of the smooth muscle fibers." Hamilton and Dow (1939) further studied the standing waves in the pulse propagated through the aorta. Using optical manometers, they recorded pressure pulses from carotid, aorta, iliac, and femoral arteries in dog and found a progressive increase in the systolic pressure toward periphery. Hamilton and Dow (1939) suggested that since wave reflection and resistance to flow go hand in hand, then, "any increase in pressure within an artery is bound up with an increase in its content of blood." Furthermore, standing waves "show that the proximal and distal ends of the aorta-femoral system accommodate alternatively, each at the expense of the other, an excess of blood." Hamilton and Dow (1939) concluded that, "In a system without a continuous flow this would mean the oscillation of a certain amount of blood back and forth from one-half of the system to the other. Actually, in a flowing stream, it may represent an alternate acceleration and retardation of the flow from the proximal to the distal end."

Hamilton (1944) suggested that the fundamental difference in hemodynamics of turtle, dog, and man can be understood from the patterns of the recorded pressure pulses. The smooth pressure curve observed in turtle, Hamilton believes, is due to the filling and emptying of the arterial tree (the compression chamber). In higher animals, such as dog and man,

the complex pattern of the pressure curve is due to filling, emptying, and pulse waves of arterial origin. The observed contour of the carotid pulse is due to the superimposition of the carotid filling and emptying curve on the aortic and fundamental filling and emptying curves. If there is any vasoconstriction or occlusion in some point downstream, there will be an increase in the amplitude and frequency of the carotid standing wave. Using this method of analysis, Hamilton (1944) attributes the rise of pressure central to occlusion of an artery to three factors: (1) increased peripheral resistance, (2) increased velocity energy, and (3) creation of a new standing wave. The marked alteration of the contour of pressure pulse following the administration of large doses of acetylcholine is attributed to the instantaneous elimination of the standing wave. Hamilton believes that the presence or absence of the reflected wave can be used to determine the cause of disturbance. As blood pressure falls the velocity of pulse wave transmission increases and the frequency of the standing waves decreases. Therefore, study of the pressure pulse contour offers an insight into the changes in the reflected wave produced by vasoconstriction or vasodialation.

The work of Hamilton (1945, 1947, and 1948) and Remington (1945 and 1945) on the measurement of cardiac output from a central aortic pressure pulse is of great interest in understanding the pressure-flow patterns in large arteries. In a series of experiments, these investigators and their colleagues have established an essentially empirical

formula that relates various subdivisions of the pulse contour with the volume ejected. Remington (1952) showed that the prediction of the empirical formula under normal conditions is fairly good but when conditions are altered the correlation becomes poor. Alexander and Webb (1947), taking cognizance of the effect of the distensibility of the arterial system on the contour of pressure pulse, suggested that analysis and synthesis of arterial pulses recorded from periphery, should be based on the summation of transmitted and reflected waves. This, they believed, is a sound and logical method of quantitatively describing phasic changes of these pulses under normal and experimental conditions. Based on this type of analysis, Alexander and Webb (1947) studied the changes in the contour of the femoral arterial pulse of dog during hemorrhagic shock. They concluded that the shock pulses differ significantly from the hemorrhage pulses in the prolonged slow fall of the descending limb. This difference in the form of the recorded shock and hemorrhagic pulses was attributed to a definite qualitative change in the contour of the reflected wave. While such a theoretical synthesis of pulse does not in itself prove the mechanism of changes in pulse contour observed in the animal, they believed that this method offers a rational approach to the interpretation of pulse form. On this basis, Alexander (1953) studied the genesis of the aortic standing wave and concluded that the analysis of the standing wave is difficult since arterial pulse waves are distorted in transmission by the hysteresis properties of the vessels. Alexander

(1953) pointed out further that vascular impedance is determined by two properties of the vascular bed, namely, the diameter and the modulus of elasticity of the blood vessels. These two factors determine the propagation and transmission of pressure wave in the vascular system. A distortion in the contour of the advancing pressure pulse can be interpreted as a change of the vascular impedance. Hardung (1962), using mathematical and physical models, discussed the nature of propagation of pulse wave in viscoelastic tubings. He concluded that in the strict physical sense, the standing wave is possible only in the absence of damping. Since anatomical and physical characteristics of the blood vessels have been considered as sources of damping and vascular impedance (Alexander, 1953), then the existence of the standing wave in the vascular system can be regarded as an experimental artifact. The limitations and shortcomings of the qualitative methods of analyzing pressure pulses and relating the distortion of the contour to definite anatomical pathology led investigators to seek quantitative methods of pulse analysis.

II. Mathematical Analysis of Cardiac Time Curves

In the past, cardiovascular physiologists used the method of transient analysis in explaining the functional significance of the pressure pulse contour. In applying transient analysis to individual pulse forms, some model of circulatory systems must be postulated in advance. For

example it may be applied as in the case of the "windkessel" model (Taylor, 1957). The disadvantage of this method is twofold. First, no rigorous circulation model accounting for all the observed facts is available. Second, this method is based on single pulse analysis and considers the pulse as an isolated event, so that the analysis has been, in effect, aimed at determining the transient response of the arterial system to a single excitation. The explanation of the genesis of pressure pulse contour, on the basis of "aortic standing wave," by Hamilton (1947) and Alexander (1949) serves as an illustration of the application of the transient analysis. Since the cardiovascular system is a dynamic system, a more profitable approach to the pulse analysis is the "steady-state" method.

In applying this method the only assumption made is that the system is linear to a first approximation. However, a more realistic approach is to express the periodic-flow and pressure changes in the circulations in terms of Fourier series.

McDonald (1955), reviewing the recent literature on pulse wave analysis, stated that the hemodynamic investigations in the past have tended to treat the arterial system as a whole and from this arose theories, such as the "windkessel" of Frank, and the system of standing waves of Hamilton. Although these concepts have been fruitful in their application, McDonald (1955) pointed out that these general theories involve too many assumptions in their approximations of the arterial

tree to a simple system of elastic tubes. Therefore, it is difficult to apply rigorous physical analysis to these theories. McDonald (1955) maintained that the function of physical analysis may be regarded at the outset as being a means of deciding the true phasic pattern of the arterial pulse in addition to elucidating the hemodynamic changes. In a series of experiments, he studied the pressure-flow patterns in the femoral artery of dogs. He suggested that the relation of pressure to flow resembles that of voltage to current. On the basis of this analogy, Poiseuille's equation of flow would be analogus to D.C. theory of flow and description of pulsatile flow would be similar to the A. C. theory of flow. By applying Fourier analysis to the recorded pressure and flow curves, he concluded that flow pattern is related to the pressure gradient and not to the pressure level. This conclusion was based on the dissimilar contour of pressure and flow curves. The calculations of flow from the pressure gradient agreed very well with the phase relations of the flow pattern. Such calculations predicted the systolic flow well. There were variations in the back flow and diastolic forward flow. McDonald's studies influenced his colleague Womersley to publish a series of papers (1955, 1957, 1958, and 1958) on the nature of oscillation of flow in arteries. Womersley derived a series of equations which describe the dynamics of pulsatile pressure and flow in the arterial system as it is in the living system.

McDonald and Taylor (1957) studied the pulse velocities of harmonic

components of the pulse wave in the dog and concluded that distortions in the contour of the pulse wave with distance are due to changes in the phase relations of the wave components. Applying Fourier analysis to pulse waves recorded simultaneously at two points in the aorta, they calculated the phase-shift over a given distance and phase velocity for a given frequency. McDonald and Taylor (1957) found that oscillations of the lower frequency travelled faster than those of higher frequency. The increase in velocity of lower frequencies was attributed to the effect of reflections within the arterial system. This conclusion was based on the finding that when additional reflection is produced by occluding a major vessel, there was a further increase in the phase velocity. They suggested that "the foot-to-foot velocity bears a reasonable relation to the elastic properties of the arteries in spite of the existence of reflections." Although theoretical considerations of Taylor (1957) and experiments of Taylor (1957), McDonald (1955) and McDonald and Taylor (1957) have demonstrated the usefulness of Womersley's mathematical model and equations, any generalizations of the theory and model must await additional refined and controlled experiments.

MATERIALS AND METHODS

Experimental Animals

Mature false map female turtles (Graptemys pseudogeographica), ranging in size from 7 x 7 to 11 x 11 inches, and in weight from 785 to 1512 grams (Table 1) and young female domestic cats (Felis catus), about one year old, ranging from 1.70 to 4.00 kilograms (Table 5) were used in this investigation.

Turtle Experiments

Turtles were anesthetized by pithing the brain. Then a 3-inch diameter hole was drilled in the middle of the upper half of the plastron. This window exposed the heart and its attached vessels. Minimum bleeding and dehydration occurred during the experiment. The pericardium was exposed and partially removed so as to make the heart and the vessels accessible to the monitoring instruments. Exposed tissues were kept moist at all times with cold-blooded Ringer's solution. After 15 minutes, allowing for the animal to recover from surgical shock, two No. 100 polyethylene tubings 20 cm. in length were connected each to a 22 gauge needle which was inserted into the left ventricle and the left aortic arch. Pressures were recorded by Statham model P23AC pressure transducer. The left ventricular circumference was monitored by placing a specially constructed variable resistance gauge (a

mercury-filled latex rubber tubing) around the ventricle (see figure 1 for the site). In some cases records of volume changes of the heart during the cardiac cycle were obtained by both gravimetric and myographic methods. The sensing and recording instruments used and their physical characteristics will be discussed later.

Each turtle, serving as its own control, was given an intracardiac injection of approximately 20 micrograms of adrenaline chloride and acetylcholine chloride. The immediate and subsequent cardiovascular changes were monitored continuously until the cardiac time curves returned to their control contours. In order to ascertain the accuracy of the recorded changes in cardiac signals, injections were repeated two or three times in some animals. In most cases, the same changes in the contours and amplitudes of the time curves were observed. One source of difficulty in these experiments was the frequent coagulation of the blood at the tip of pressure catheters, even though catheters contained a 2 per cent heparinized Ringer's solution. Another difficulty was the occasional slipping of the variable resistance gauge used to record the changes in the cardiac circumference. However, this slipping could easily be monitored on the recording polygraph and was easily adjusted prior to the start of an observation. Upon the termination of each experiment, the heart was removed and ventricle was separated from auricles and other non-ventricular tissues. The ventricular thickness was measured at approximately midway between the base and the apex.

FIGURE 1

Top--Position of circumference (volume) transducer around the turtle ventricle.

Bottom--Position of circumference (volume) transducer around the cat ventricles.

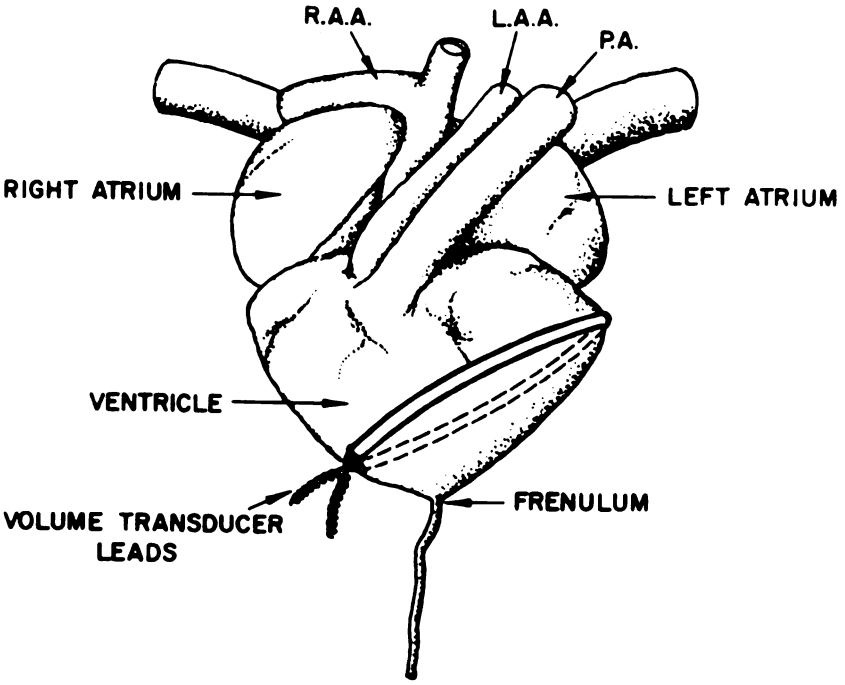


DIAGRAM OF TURTLE HEART

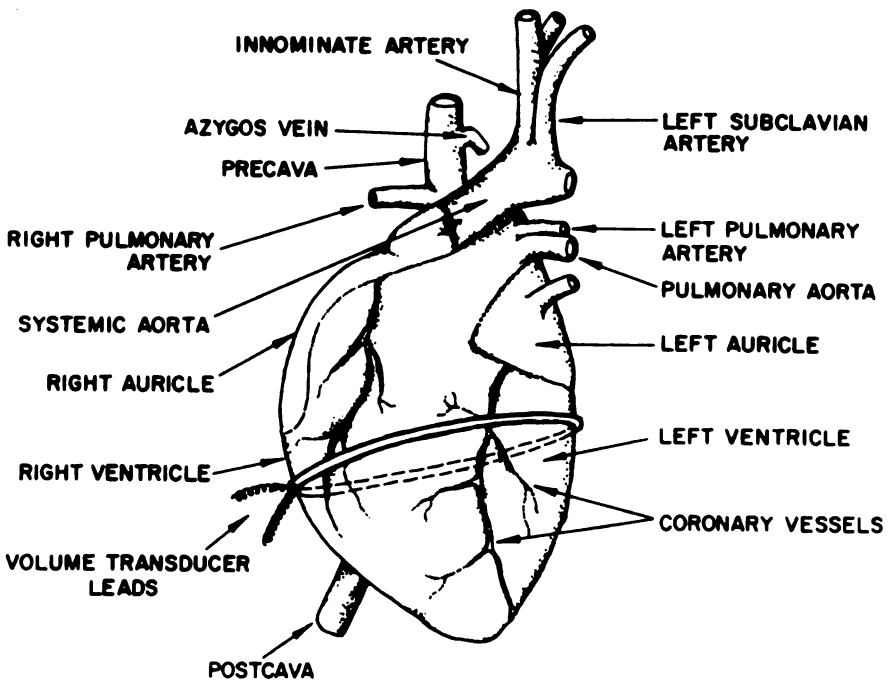


DIAGRAM OF CAT HEART

The wet weight of the ventricle was determined by a Voland and Sons chain-o-matic balance capable of measuring to the nearest 0.1 mg. The circumference of the variable resistance gauge was measured for subsequent determination of the stroke volume using formulae derived in the calculations section of this thesis.

In order to determine the time relation of electrical and mechanical activities of the heart, in some turtles, lead II of electrocardiogram was recorded simultaneously with ventricular and aortic pressures and ventricular circumference. A typical record of these recordings is shown in figure 2.

Cat Experiments

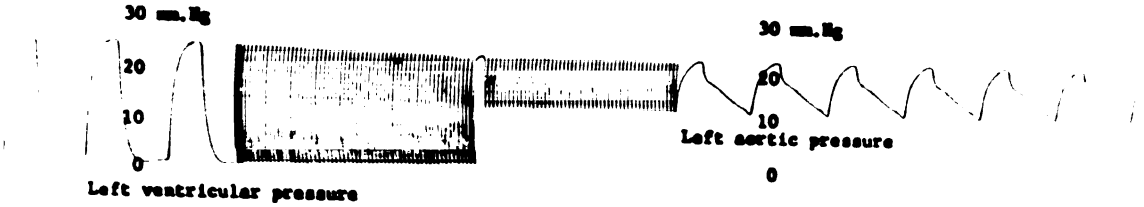
Cats were anesthetized by intraperitoneal injection of sodium pentobarbital (30 mg. per kilogram body weight), placed on a constant temperature heating pad, and fastened in position on the animal board. A midline incision was made on the neck, both common carotid arteries and vago-sympathetic trunks were exposed, and a tracheal cannula was introduced into the sectioned trachea. Blood pressure from the right common carotid was recorded by means of a No. 100 polyethylene tubing 25 cm. in length connected to a Statham model P23A pressure transducer. Blood pressure and the lead II of electrocardiogram were recorded while the animal was recovering from the initial surgery and prior to the exposure of the thorax. After 15 minutes, a midline incision was made

FIGURE 2

Typical records of cardiac function curves in turtle.

Top--From above downwards, left ventricle and left aortic pressure pulses, left ventricular circumference, and lead II electrocardiogram.

Bottom--From above downwards, left aortic pressure pulse, left ventricular pressure pulse, left ventricular circumference, and lead II electrocardiogram recorded at speed of 50 mm./sec.

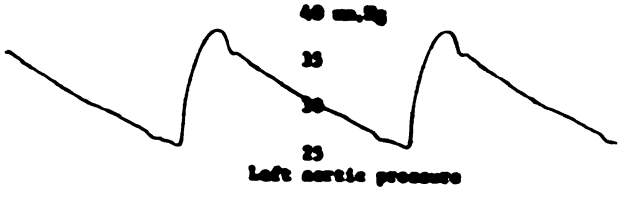


Left ventricular pressure

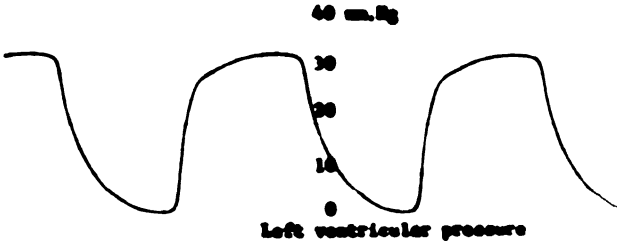
Left aortic pressure

Left ventricular circumference

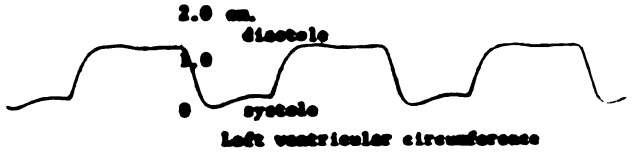
Lead II Electrocardiogram
Speed .5 and 10 mm/sec.



Left aortic pressure



Left ventricular pressure



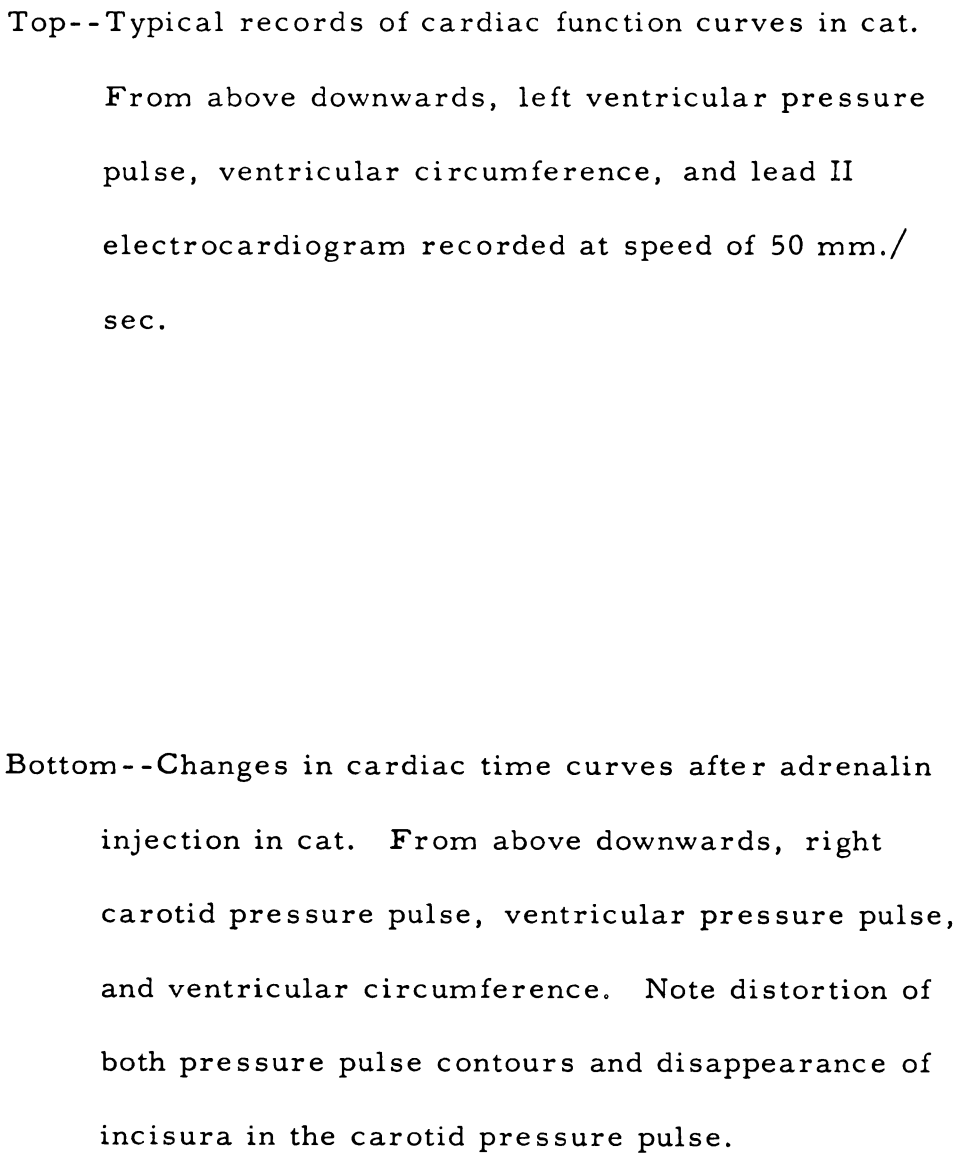
Left ventricular circumference

Lead II Electrocardiogram

Speed 50mm/sec.

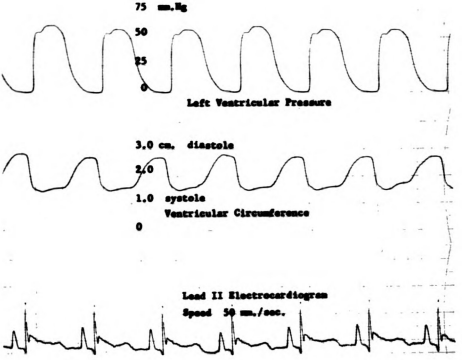
over the body of the sternum and superficial vessels were tied off to prevent skin bleeding. Then, the thorax was exposed by cutting the sternum from the tip of the xyphoid-sternal junction to the suprasternal notch. Mammary arteries and veins of both sides were carefully separated and the rib-cage was spread open by means of a spreader so that the heart and the attached vessels were accessible to the sensing instruments. From this point on the cat was given artificial respiration using a standard laboratory pump with its rate adjusted to the respiratory rate of the closed-chest animal. The cat was left undisturbed for 30 minutes to recover from the surgical shock of thoracotomy. During this period changes in the contour and amplitude of the right common carotid artery pressure, lead II of electrocardiogram, and in some animals, femoral venous pressure and the arterial hematocrit were monitored. When the animal maintained a relatively stable hemodynamic status, as judged by the constancy of the carotid pressure curves, additional sensors for recording cardiac function curves were introduced. Ventricular circumference changes were monitored (see figure 1 for the site). The intraventricular, aortic, and pulmonary artery pressures were recorded by means of No. 190 polyethylene tubings, each 25 cm. in length, connected to an 18 gauge needle. A typical record of the cardiac function curves is shown in figure 3. In some cats simultaneous records of volume changes were obtained by means of both the variable resistance gauge and the gravimetric methods.

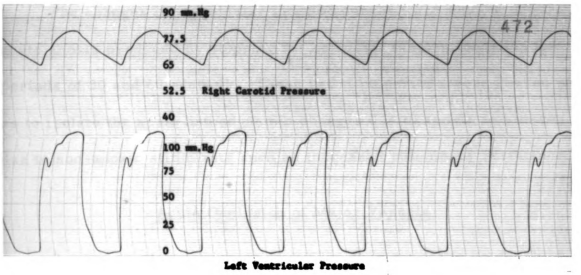
FIGURE 3

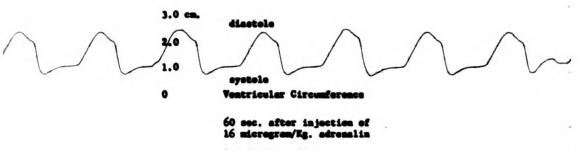


Top--Typical records of cardiac function curves in cat. From above downwards, left ventricular pressure pulse, ventricular circumference, and lead II electrocardiogram recorded at speed of 50 mm./sec.

Bottom--Changes in cardiac time curves after adrenalin injection in cat. From above downwards, right carotid pressure pulse, ventricular pressure pulse, and ventricular circumference. Note distortion of both pressure pulse contours and disappearance of incisura in the carotid pressure pulse.







60 sec. after injection of
16 microgram/Kg. adrenalin

Speed 50 mm./sec.

Each cat, serving as its own control, was subjected to several different experimental treatments in the following order.

Cardiac Response to Nervous Stimulation

In order to simulate sudden cardiac inhibition and study the resultant changes in the contours of the recorded cardiac parameters, faradic stimulation of 30 volts strength and a frequency of 30 cps. was applied to either right or left vago-sympathetic trunk for periods ranging from 10 to 30 seconds.

Effect of Anoxia

The changes in ventricular function curves were studied under acute anoxia produced by stopping the artificial respiration pump for periods of 30 and 60 seconds. These two time periods were chosen so as to isolate the acute hemodynamic changes due to anoxia and those due to non-anoxic stimulants such as increased pulmonary resistance.

Acute Occlusion of Major Vessels

Cardiovascular responses to sudden changes of the diameter of the major vessels leading to and away from the heart have been of great interest. Acute reduction in venous return to the heart was produced by occluding the superior vena cava, or inferior vena cava, or both vena cavae simultaneously for a period of 30 seconds.

Changes in the inflow to and outflow from the left ventricle were induced by means of acute occlusion of pulmonary artery and thoracic aorta respectively for a period of 30 seconds. Since complete occlusion of the thoracic aorta may actually enhance coronary blood flow, then pulmonary artery occlusion can be used to analyze the effect of coronary insufficiency upon the mechanisms of ventricular functions.

Effect of Drugs on Cardiac Function

Cardiotonic, cardiodepressor, and vasodilator drugs were used to simulate the responses of cardiac function to different emergency conditions such as exercise and shock. For this purpose 20 micrograms each of adrenaline chloride, nor-adrenaline, acetylcholine chloride, and adenylic acid were injected either through the femoral vein or the central aorta. In addition to above drugs, 20 pressor units of pitressin and 0. 275 mg. of histamine base were injected intravenously and their effects upon the dynamic changes of the ventricular time curves were monitored.

Cardiac Function and Hypervolemia

In order to study the effect on the heart of sudden changes in the total circulating fluid within the vascular system, 50 ml. saline, warmed to 37^{o} Centigrade and equal to approximately 50 per cent of the total blood volume (calculated on the basis of 7 per cent body weight (Hamlin and Gregersen, 1939 and Conley, 1941), were infused into the superior vena cava at a rate of approximately 10 ml. per minute. Care was taken

not to occlude the superior vena cava during infusion. Cardiac response to hypervolemia during and after infusion was monitored continuously.

Upon termination of the experiment, the heart was removed and right and left ventricular wall thickness was measured approximately midway between the base and apex. Then, the wet weight of the ventricle was determined by Voland and Sons chain-o-matic balance. The circumference of the variable resistance gauge was also measured for the subsequent calculation of ventricular residual and stroke volumes.

Physical Characteristics of the Monitoring Instruments Used

In physiological investigations two types of recording instruments are used. One type is a mechanical system which is composed of inertial elements (mass), elastic components, and frictional resistance. The other type is the electrical system which has analogous units, namely, inductance, capacitance, and resistance. It is the combination of these three elements which allows the system to behave similar to a damped-harmonic oscillator.

An oscillator responds to changes of a function with respect to time. An ideal oscillator is one which shows no time shift between the input and output signals. In a mechanical system the inertia and the elastic components are associated with this time shift, while in an electrical system it is the inductance and the capacitance which cause the

phase lag between the input and the output signals. It is the presence and magnitude of such a phase lag that are the cause of the distortion of the input signals. In order to study the time dependence of an instrument two types of input signals have been introduced generally into the system. One type is the transient signal such as the square wave which has a signal occurrence in a finite time. The other is the steady state signal which is periodic in occurrence such as sinusoidal signals.

When an input signal is introduced into a mechanical instrument, the output signal is affected by the three elements of the system, namely, inertia, elasticity, and friction. The physical quantities associated with these three elements are acceleration, velocity, and displacement, respectively.

The relation between the input signal (F) and the output signal is best described by the following mathematical equation (Stacy, 1960)

$$F = M \frac{d^2x}{dt^2} + R \frac{dx}{dt} + Sx \qquad (1)$$

where, x = displacement,

t = time,

M = inertial constant,

R = frictional or viscous constant,

and S = stiffness constant.

For an electrical system the terms M, R, and S are replaced by L (inductance), R (resistance), and 1/C (capacitance) respectively.

Thus, the fundamental equation (1) takes the form,

$$F = L\frac{d^2x}{dt^2} + R\frac{dx}{dt} + \frac{x}{C}. \qquad (2)$$

Since in the electrical system the quantity (x) represents the electrical charge (q), then its variation with time is the current (I). When the corresponding values for x, $\frac{dx}{dt}$, and $\frac{d^2x}{dt^2}$ are substituted in equation (2), an expression is obtained which describes the relation between the input and output signals in an electrical system.

$$F = L\frac{d^2I}{dt^2} + R\frac{dI}{dt} + \frac{q}{C}. \qquad (3)$$

Equations (1) and (3) are second-order differentials. They can describe the behavior of three types of instruments, namely, zero-order, first-order, and second-order.

A <u>zero-order</u> instrument is one in which the inertia (M) and damping friction (R) have negligible effects on the output signals. Thus, by setting M and R equal to zero, equation (1) becomes,

$$F = Sx. \qquad (4)$$

This equation states that the output signal is proportional to the input signal. The proportionality constant being (S) which is the elastic (calibration) constant. Furthermore, equation (4) indicates that the input signal is not in any way distorted by the recording instrument.

A <u>first-order</u> instrument contains, in addition to the elastic element (S), some viscous friction (R), or in addition to capacitance ($\frac{1}{C}$)

some electrical resistance (R). The mathematical equations describing the behavior of a first-order mechanical and electrical instrument are, respectively,

$$F = R\frac{dx}{dt} + Sx \tag{5}$$

and

$$F = R\frac{dI}{dt} + \frac{q}{C}. \tag{6}$$

Equations (5) and (6) indicate the factors which distort the output signals of the recording instrument. The source of distortion is the time required to move the elastic membrane by the motion of the fluid in the mechanical system or to charge the condenser by passing current through a resistor in an electrical system. Solving equation (5) for x under the condition of a step function input signal, we obtain,

$$x = \frac{F}{S}(1 - e^{-\frac{t}{T}}) \tag{7}$$

where $T = \frac{R}{S}$. The quantity T is called the time constant or the characteristic time of the instrument. The reciprocal of the time constant, that is $\frac{1}{T} = \frac{S}{R}$, is called the damping coefficient (Stacy, 1960). Equation (7) states that the rate of change of displacement (x) decreases as the time (t) increases.

If the input signal is sinusoidal, that is $F = F_o \sin \omega t$, such as the generated cardiac signals, then equation (5) becomes,

$$F_o \sin \omega t = R\frac{dx}{dt} + Sx \tag{8}$$

where (ω) is the angular frequency in radians, and is related to frequency (f) by the following equation,

$$\omega = 2\pi f. \tag{9}$$

Solving equation (8) for (x) under the condition of large values of time (t), we obtain

$$x = \frac{F_o \sin(\omega t - \alpha)}{S\sqrt{1 + T^2\omega^2}} \tag{10}$$

Equation (10) indicates that the shape of the waveform of the output signal is the same as that of the input signal. Therefore, there is no distortion of the output signals. However, the term (α) in equation (10) indicates that there is a time lag between the input and the output signals. The magnitude of this time lag is determined by the following equation,

$$\alpha = \arctan(T\omega). \tag{11}$$

Sinusoidal signals encountered in nature have different frequencies and vary in both phase and magnitude with respect to their lowest frequency (Stacy, 1960). To understand the functional behavior of these types of sinusoidal signals frequent use is made of Fourier transform. That is, a sinusoidal function f(t) can be written in terms of its harmonic components as follows,

$$f(t) = A_o + \sum_{n=o}^{\infty} A_n \sin(n\omega t - \beta). \tag{12}$$

This simple analysis of a sinusoidal function offers an insight into the usefulness of Fourier transform in decoding time-variable biological

waveforms into their harmonic components. The phase lag of each harmonic is given by the equation,

$$\beta n = \arctan T(n\omega) \tag{13}$$

and the amplitude of each harmonic is expressed by the ratio

$$\frac{1}{\sqrt{1 + T^2(n\omega)^2}} \tag{14}$$

Equations (13) and (14) indicate the range of frequencies at which an instrument will best reproduce a time-variable biological input function. Therefore, the frequency-response of an instrument must be determined prior to its use in physiological experiments. The frequency response curve of an instrument is the plot of response against all frequencies for a constant input signal. The relation between maximum frequency response (f_m) and the time constant of the instrument (T) for a response which is 95 per cent of the low frequency value is (Stacy, 1960)

$$0.95 = \frac{1}{\sqrt{1 + T^2(2\pi f_m)^2}} \tag{15}$$

This equation can be written in the following useful form,

$$f_m = \frac{0.34}{2\pi T} = \frac{0.054}{T} \tag{16}$$

A second-order instrument is one which has inertia in the case of a mechanical system or inductance in the case of an electrical system. Equations (1) and (3) are the differential equations for these two systems. The presence of inertia results in the response leading the input at low frequencies, whereas the presence of the elastic component or capacitance

causes the response to lag behind the input signals at high frequencies. These two factors allow an input signal with intermediate frequency to be reproduced faithfully and without any distortion or phase lag. The frequency at which such an output can be obtained is called the natural frequency (f_n) of the instrument and is determined from the equation

$$f_n = \frac{1}{2\pi}\sqrt{\frac{S}{M}}. \qquad (17)$$

Another important facet of instrumentation for physiological research deals with the range and sensitivity of the monitoring devices. Therefore, the relationship between the range of an instrument and its sensitivity must be considered prior to its use for physiological investigations.

Sensitivity of an instrument can be described in two ways. One is the deflection sensitivity, which is the amount of deflection per unit input signal (Trimmer, 1950). The second type is, as Trimmer (1950) calls it, the scale sensitivity of the instrument. This latter terminology refers to the amount of input signal required to produce a given output deflection.

Range of an instrument is also described in terms of the scale range and frequency range. The significance of these two terms will become clear later.

The instruments used in this investigation fall into two categories: (1) the detecting and sensing elements, and (2) the recording and read-out devices.

I. Detecting and Sensing Elements

Three types of detecting devices were used in this study. The first type was the Statham model P23AC pressure transducer for recording changes in the arterial pressure. This transducer consists of an unbounded strain gauge mounted in such a way that the movement of the sensitive diaphragm results in the shortening of two elements and the lengthening of the remaining two elements. The four elements of the strain gauge form the four arms of a Wheatstone bridge. Since the transducer elements are housed as a unit they are not subject to changes in the ambient temperature.

Statham model P23AC has inertia, elastic, and frictional elements. Therefore, this transducer is a second-order instrument and its frequency response, sensitivity, and range of operation must be considered with respect to equations (3) and (17). The manufacturer of Statham model P23AC pressure transducer lists the following specifications:

Usable range: 0 to +750 mm. Hg

Sensitivity--maximum: 0.05 mm. Hg/cm. paper deflection
minimum: 100 mm. Hg/cm. paper deflection
(minimum = 2000 x maximum)

Recommended minimum reliable measurement: 0.025 mm. Hg

Gauge factor: 0.8 cu. mm./100 mm. Hg

When transducer connected to No. 5 catheter (PE 190) 100 cm. in length, the transducer will have a natural frequency of 9 cps. and damping approximately 50 per cent of critical.

In 1913, Otto Frank derived an equation for determination of natural frequency (f_n) of a manometer system. This equation has the same form as equation (17). Frank's equation states that the natural frequency (f_n) varies directly with volume elasticity coefficient (E) and indirectly with effective mass (M). Volume elasticity is defined by the equation,

$$E = \frac{dP}{dV} \tag{18}$$

or the change in volume per unit change in pressure. Effective mass is defined by equation,

$$M = \frac{sL}{\pi R^2} \tag{19}$$

where, s = specific gravity of manometer fluid,

L = length of connecting tubing and catheter,

and R = radius of connecting tubing and catheter.

Substituting corresponding values for (E) and (M) from equations (18) and (19) into equation (17), we get,

$$f_n = \frac{1}{2\pi} \sqrt{\frac{E\pi R^2}{sL}} \tag{20}$$

Equation (20) can be rearranged in such a way that an expression relating natural frequency to characteristics of catheters is obtained,

$$f_n = \frac{1}{2}\sqrt{\frac{E}{\pi s}}\ R \sqrt{L} \tag{21}$$

Eauation (21) assumes that the catheter is sufficiently thick so that it has negligible resonant frequency. The term $\frac{1}{2}\sqrt{\frac{E}{\pi s}}$ is constant for the

same manometer system and, using the manufacturer's specifications for the Statham model P23AC transducer, the constant has a value of 1500. Thus, equation (21) becomes,

$$f_n = 1500 \frac{R}{\sqrt{L}} \qquad (22)$$

In turtle experiments, PE 100 tubing was used. This tubing was 20 cm. in length with an inner diameter of 0.086 cm. and wall thickness of 0.041 cm. Substituting these values in equation (22) we obtain a value of 31 cps for the manometer used to record pressure pulse in turtle. The frequency of occurrence of cardiac function curves as determined by the heart rate has an upper limit less than 2 cps. Therefore, the manometer system used had adequate frequency response to record dynamic changes of the various harmonics of the cardiac time curves.

In cat experiments, PE 100 tubing, of above specifications, was used to record right common carotid artery pressure. However, the length of the catheter was 25 cm. Thus, using equation (22), the natural frequency of the manometer system in this case was approximately 26 cps. Ventricular, aortic, and pulmonary artery pressures were recorded using PE 190 catheters. This tubing was 25 cm. in length with an inner diameter of 0.12 cm. and wall thickness of 0.05 cm. Substituting these values in equation (22), the natural frequency was found to be 18 cps. The frequency of occurrence of cardiac time curves, as determined from heart rate, had an upper limit of approximately 5 cps.

Therefore, the manometer system had adequate frequency response to record faithfully and without distortion various cardiac time curves.

One of the serious problems which reduces the frequency response of a manometer system is the presence of air bubbles in the system (Hamilton, Brewer, and Brotman, 1934). To avoid this problem, heparinized Ringer's solution was boiled and allowed to cool to room temperature prior to its use in filling the transducer and connecting tubings.

Myographic and gravimetric changes of ventricular functions in both turtle and cat were recorded using Statham model G1-32-450 force displacement transducer. This strain gauge was calibrated at the sensitivity which was sufficiently adequate to record changes in ventricular time curves. Figure 4 shows the calibration curve used for thie purpose. Model G1-32-450 force displacement transducer consists of a bounded strain gauge in a Wheatstone bridge connection and measures the strain produced on a cantilever beam by the force applied.

Ventricular circumference changes were recorded by a variable resistance gauge (a mercury-filled rubber tube). The gauge operates on the principle that when it is stretched the resistance is changed (Eagan, 1960, 1961). The sensing element of the gauge used in this study consisted of a thin latex rubber tubing (obtained from Huntington Rubber Mills, Box 570, Portland, Oregon), having an inside diameter (I. D.) of 0. 35 mm. and an outside diameter (O. D.) of 1. 25 mm. The rubber tubing was

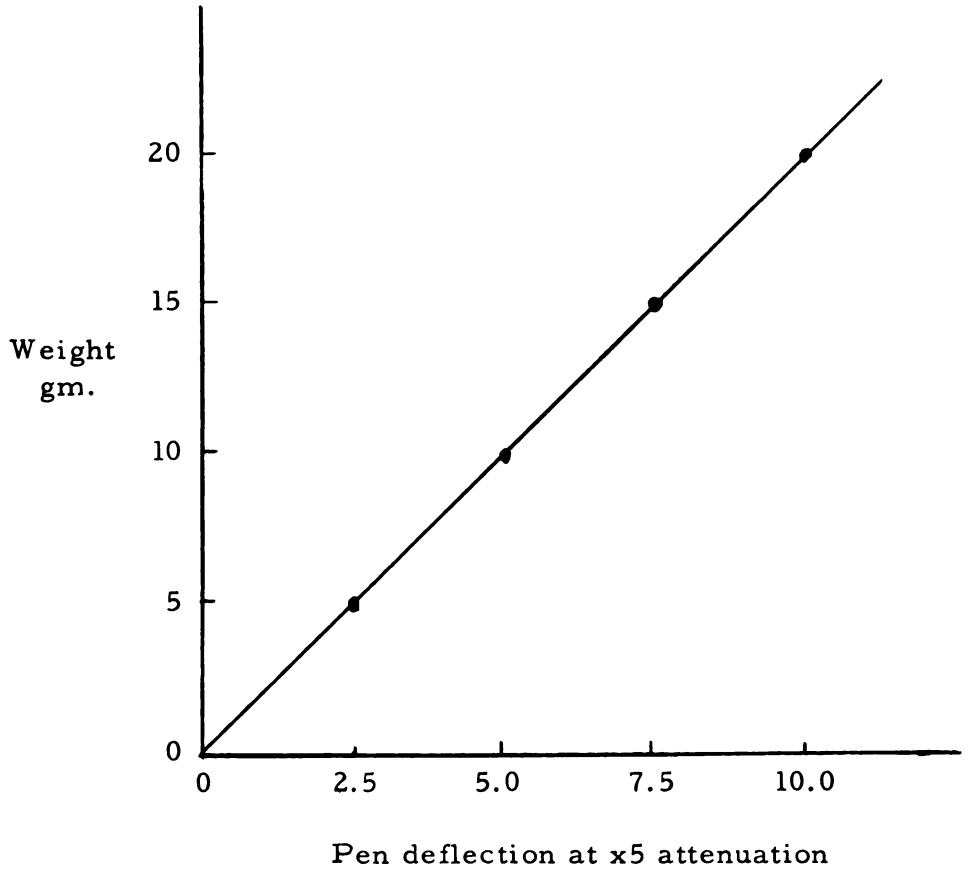


FIGURE 4

Standard calibration curve for Statham model G1-32-450 force-displacement transducer.

filled with clean mercury under slight pressure. Each end of the tubing was sealed off by inserting a small piece of silver wire. The electrical continuity between the two silver pieces was established by a suitable galvanometer. Then, lead wires (multi-strand copper wire) were soldered, at each end, to the short silver wires. A layer of insulation was placed over the lead-gauge connections by applying liberally latex rubber cement. The entire assembly was left undisturbed overnight until the insulating layers were dried and hardened (Eagan, 1960).

To calibrate the gauge used, the strain gauge resistance which was part of one arm of Wheatstone bridge circuit was shunted by an open-circuited resistor of considerably higher value (Perry and Lissner, 1962). When this resistor circuit is closed a definite bridge unbalance will result. This bridge unbalance can be considered as a controlled strain and as such it will appear on the polygraph record. The size of the calibration resistor R_c is selected so that the resistance change obtained by shunting the gauge is equal to that produced by a particular strain.

The change in resistance of a strain gauge (with known initial resistance R_g and gauge factor F) for any assumed strain $\epsilon \left(= \frac{\Delta L}{L}\right)$ is

$$\Delta R = F \epsilon R_g . \tag{23}$$

Similarly, the change in resistance of the parallel combination of the strain gauge and the calibration resistor is

$$\Delta R = R_g - \frac{R_g R_c}{R_g + R_c} . \tag{24}$$

Equating equations (23) and (24) and solving for R_c, we obtain

$$\Delta R_c = \frac{R_g(1 - F\epsilon)}{F\epsilon} . \qquad (25)$$

Figure 5 shows (top) the Wheatstone bridge diagram in which the strain gauge forms part of an arm, and (bottom) the plot of experimental determination of the gauge factor. In practice, resistances $R_2 = R_3 = R_4 = 150$ ohms and $R_1 = 149$ + gauge resistance = 150 ohms. The variable resistance gauge used in this study was reliable over a range from 1 mm. to more than 100% of the resting length. The response time of the gauge was approximately 0.01 seconds. Therefore, no change in the frequency response of the recording instrument was produced.

II. Recording and Read-Out Devices

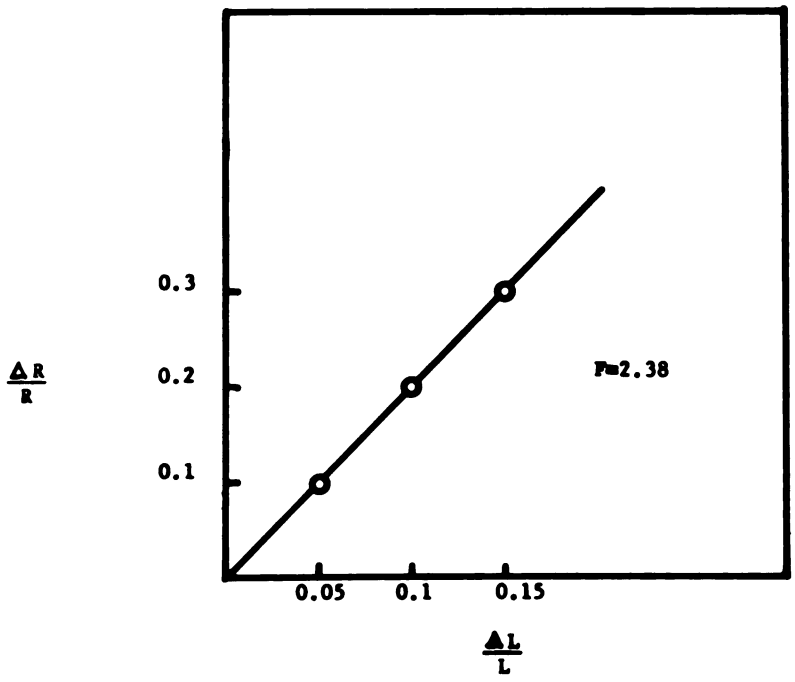
Pulsating d-c signals from the sensing transducers were fed into a Grass model 5 polygraph (manufactured by Grass Instrument Company) which uses a chopper-type d-c amplifier. The sequence of operation of the amplifiers is (1) conversion of d-c signals into an a-c signal by means of a chopper, (2) amplification of the a-c signal to the desired level using an a-c amplifier, and (3) conversion of the a-c signal back to a d-c signal. The d-c amplifiers had a frequency range from d-c to 45 cps. Amplitude linearity of direct-writing oscillographs was 2 per cent for the central 40 mm. and 4 per cent for the central 50 mm. of paper. Writing points had curvilinear motion and the recording paper used had curvilinear lines.

FIGURE 5

Top--Diagram of the Wheatstone bridge in which the variable resistance gauge (R_g is included in R_1) forms part of an arm.

Bottom--The plot showing the experimental determination of the gauge factor (F) for the variable resistance gauge.

DETERMINATION OF GAUGE FACTOR (F) FOR MERCURY-FILLED-RUBBER STRAIN GAUGE



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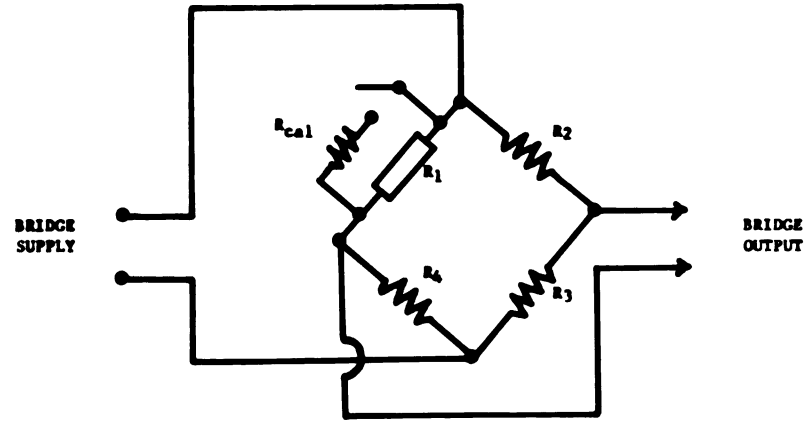
CALIBRATION TECHNIQUE FOR USE IN MEASURING DYNAMIC STRAIN



R_1 = 150 ohms R_3 = 150 ohms

R_2 = 150 ohms R_4 = 150 ohms

R_{cal} = 4 ohms

R_g (gauge resistance) = 1 ohm which is included in R_1.

This latter feature partially compensated for the disadvantages of curvilinear recording.

Fourier Analysis of Cardiac Time Curves

The goal of analysis is to represent as uniquely as possible the intervals of interest so that the significant information is not discarded in an averaging process. In the following paragraphs, a mathematical method of analysis is considered which is better suited for analyzing cardiac function curves than the averaging process of the statistical method. This analysis is applicable to any time-variable signal which is periodic in occurrence, such as the recorded signal variations of the cardiovascular system. Furthermore, since these signals are usually recorded at fixed points, they are functions of time only. Because these signals are used as a basis for clinical interpretation, it is desirable to use more exact mathematical analysis (Fourier transform) to differentiate quantitatively between signals which are "normal" and those which are not.

Most of the analyses performed on the various cardiac parameters in the past have been more or less of a statistical nature. It should be recognized that the statistical inference, by its nature, does not provide all the information on the chosen sample. The statistical analysis provides information only on the pooled-effect and not on the individual variations. For instance, a given dose of epinephrine raises blood

pressure by a certain amount. Establishing its relative statistical significance does not necessarily explain why administration of epinephrine caused a given rise in blood pressure. It is this latter phenomenon that we are interested in, and statistics cannot provide the desired information. Unless there is prior knowledge of how information is coded into a given signal, a unique representation should be the goal of the analysis.

One particular method of representation involves the use of Fourier transform. Using this method, the recorded signal variations in analog form are converted into a frequency spectrum as a function of time in digital form. Since Fourier analysis involves the use of harmonic functions, a brief introduction to harmonics appears to be in order before describing the method of Fourier analysis.

A function $f(x)$ is considered to be a periodic function if it can be written as

$$f(x) = f(x+T) \tag{26}$$

where T is the period of occurrence of function $f(x)$. The simplest periodic function which describes an harmonic function can be defined as (Webster, 1955),

$$y(x) = A \sin(\omega x + \phi) \tag{27}$$

where A = amplitude of the function,

ω = angular frequency,

and ϕ = phase angle.

The graph of the harmonic function given by equation (27) is obtained from the graph of familiar sine curve by uniform compression (or expansion) along the ordinate axes plus a shift along the x-axis. Using the trigonometric formula for sum of two angles, equation (27) can be decomposed into its components,

$$y(x) = A(\cos \omega x \sin \phi + \sin \omega x \cos \phi). \tag{28}$$

Setting $A \sin \phi = a$, and $A \cos \phi = b$, in the above equation, then every harmonic function such as given by equation (27) can be written as,

$$y(x) = a \cos \omega x + b \sin wx. \tag{29}$$

Since the period of occurrence (T) is twice the cycle length ($T = 2L$) and the angular frequency (ω) varies inversely with the period ($\omega = \frac{2\pi}{T}$), then any harmonic function with period of 2L can be written as,

$$y(x) = a \cos (\frac{\pi x}{T}) + b \sin (\frac{\pi x}{T}). \tag{30}$$

Equation (30), which is the basis of Fourier analysis, states that any periodic time-waveform function such as f(t) defined in the interval $0 \leqslant t \leqslant L$, where L is the cycle length ($L = \frac{1}{2} T$) can be expanded by Fourier transform. However, it should be understood that this expansion is possible if the function f(t) has a finite number of points of ordinary discontinuity and a finite number of maxima and minima in the above interval (Hildebrand, 1962 and Webster, 1955). In practice, there is no discontinuity in empirical functions which have passed through amplifiers, because the amplifiers have finite bandwidth. Thus, the

problem of convergence of a series at points of discontinuity need not be considered.

Using Fourier transform the function f(t) can be represented in a chosen interval as follows,

$$f(t) = \frac{A_o}{2} + \sum_{n=1}^{\infty} \left(A_n \cos\left(\frac{n\pi t}{L}\right) + B_n \sin\left(\frac{n\pi t}{L}\right) \right). \tag{31}$$

Using Fourier integrals, coefficients A_o, A_n, and B_n are determined for that interval as follows,

$$A_o = \frac{1}{L} \int_o^L f(t)\, dt \tag{32}$$

$$A_n = \frac{2}{L} \int_o^L f(t) \cos\left(\frac{n\pi t}{L}\right) dt, \quad \text{for } n = 0.1, 2, \ldots \tag{33}$$

$$B_n = \frac{2}{L} \int_o^L f(t) \sin\left(\frac{n\pi t}{L}\right) dt, \quad \text{for } n = 1, 2, 3, \ldots \tag{34}$$

If an empirical function has its highest frequency (N) equal to the highest harmonic representation (n) by Fourier series, then we can say that the function f(t) has 2N +1 terms or 2N +1 degrees of freedom. If the highest frequency representation in the function f(t) is W, then

$$N = W\, T. \tag{35}$$

Therefore, there are 2WT + 1 possible degrees of freedom involved in a signal representation with a highest frequency (W) and duration (T).

When the signal is fed into an a-c amplifier, the average value of the output signal will approach zero. This implies that the first term in equation (31) will become zero and the empirical function f(t) will have 2WT terms or 2WT possible degrees of freedom. The remaining terms of the series in equation (31) will converge to the function f(t) in the interval 0 to T if the coefficients A_n and B_n in equations (33) and (34) are known to a sufficient order of accuracy (Lowenberg, 1961).

Using Fourier analysis an attempt is made to represent an empirical function as it is recorded and not the statistical characteristics of the empirical function. Fourier representation of an empirical function f(t) involves determination of the amplitude and phase spectra. The amplitude spectrum, C_n, of the chosen interval is obtained from evaluation of the following equation,

$$C_n = \sqrt{A_n^2 + B_n^2}. \tag{36}$$

It should be noted that for a single frequency (n =1) all the points on a circle of the radius C_n are equivalent and therefore the value of the phase angle is ignored. The amplitude spectrum is constructed by plotting C_n against frequency (n).

The phase spectrum, D_n, of the function f(t) for the chosen interval is determined from evaluation of the following equation,

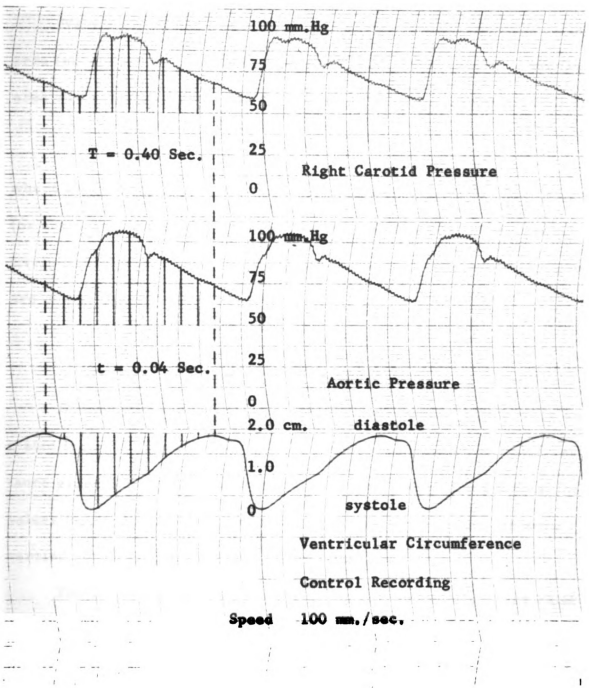
$$D_n = \arctan\left(\frac{A_n}{B_n}\right). \tag{37}$$

The phase spectrum is constructed by plotting D_n against frequency.

In order to apply the above theoretical analysis to actual recordings of cardiac time-waveforms the recorded empirical functions were treated as follows. From a series of records, either control or experimental, one cardiac cycle was selected at random. Each cycle was then divided into 10 equal time intervals and the values of various cardiac parameters were computed at each of these time intervals (see figure 6). These values were punched on standard IBM punch-cards and fed into a 160-A FORTRAN computer programmed to print out values for A_o, A_n, B_n, C_n, and D_n for $n = 1$ to $n = 10$. The actual program used and the detailed instruction for preparation of data are described in Appendix B.

FIGURE 6

Typical illustration of the procedure used to divide various cardiac function curves into equal time intervals. From above downwards, right carotid pressure, aortic pressure pulse, and ventricular circumference recorded at speed of 100 mm./sec.


100 mm.Hg
75
50
25
0
T = 0.40 Sec.
Right Carotid Pressure
100 mm.Hg
75
50
25
0
t = 0.04 Sec.
Aortic Pressure
2.0 cm.
1.0
0
diastole
systole
Ventricular Circumference
Control Recording
Speed 100 mm./sec.

CALCULATIONS

Ventricular weight as percentages of body weight and body surface area (except in turtle) were calculated (Table 1) and (Table 5). Surface area was calculated using Rubner's surface area law (Kleiber, 1961),

$$\text{Surface Area} = 0.107 \times W^{2/3}$$

where (W) is body weight in kilograms. Expressing ventricular weight (or any organ weight) as a function of body surface area gives a relatively linear and uniform relation when animals of different weight groups are compared.

Estimation of Residual and Stroke Volumes from Circumference

End systolic volume (residual) and stroke volume output were estimated from the measurement of the circumference of the variable resistance gauge (a mercury-filled rubber tubing). Tables 1 and 6 show these values for turtle and cat ventricles respectively. Calculations were carried out using the following sets of equations.

The circumference (C) is expressed mathematically by the relation,

$$C = 2\pi R \qquad (1)$$

where (R) is the radius. Koushanpour and Collings (1961), Rushmer (1961) and others have suggested a physical model of the heart in which the ventricles were considered as ellipsoid in geometry. The volume of an ellipsoid is given by equation,

$$V = \frac{4}{3}\pi a b c \qquad (2)$$

where (a) is the major semi-axis along the x-axis, and (b=c) are the minor semi-axes along the y- and z-axes, respectively. The maximum lengths of the minor semi-axes (b=c) are equal to the diameter measured at the center of the ellipse. From equation (1) we have,

$$b = c = 2R = \frac{C}{\pi}. \qquad (3)$$

Measurements on the surface of the ventricles of cats and turtles used have shown that the outer volume of the combined ventricles is approximately equal to one-half of the ellipsoid. This information allows one to estimate the value of (a), major semi-axis, which is taken to be (a = 2b). Thus, we can write,

$$a = 2b = \frac{2C}{\pi}. \qquad (4)$$

Assuming that both ventricles have equal outputs and equal volumes, then the end-systolic volume of the left ventricle (V_{EL}) is given by,

$$V_{EL} = \frac{1}{2} \times \frac{1}{2} \times \frac{4}{3}\pi \left(\frac{2C}{\pi}\right) \times \left(\frac{C}{\pi}\right)^2. \qquad (5)$$

The first ($\frac{1}{2}$) indicates that the total volume of both ventricles is one-half the ellipsoid generated by the ventricular curvatures. The second ($\frac{1}{2}$) stands for the fact that volume of the left ventricle is one-half of the total volume of both ventricles. Equation (5), when rearranged, can be written as,

$$V_{EL} = \frac{2}{3}\frac{C^3}{\pi^2}. \qquad (6)$$

Substituting for (π) the value of 3.14, and carrying out the arithmetical calculations, equation (6) becomes,

$$V_{EL} = 0.0675\ C^3. \qquad (7)$$

Equation (7) gives the value for outer end-systolic volume of the left ventricle. To estimate the inner-end-systolic volume the equation (7) is corrected for ventricular mass by the following relation,

$$V_{EL}\ 0.0675\ C^3 - \frac{2}{3}m \qquad (8)$$

where (m) is the ventricular mass and the coefficient ($\frac{2}{3}$) stands for the fact that on the average (see ventricular thickness values in Table 6) the left ventricle has roughly 2/3 greater mass than the right ventricle. In the case of turtle, equation (8) was modified as follows,

$$V_{EL} = 0.0675\ C^3 - \frac{1}{2}m. \qquad (9)$$

The coefficient ($\frac{1}{2}$) in equation (9) stands for the fact that the left chamber of turtle heart has one-half as much mass as both chambers of turtle heart.

In order to estimate the stroke volume output of the left side of the heart, it was assumed that approximately 10 per cent of the blood volume is contained within the heart chambers (Kjellberg et al., 1949). Using the value of 7 per cent for blood volume as a percentage of body weight (Hamlin and Gregersen, 1939 and Conley, 1941) the total amount of blood in diastole in the left ventricle is given by,

$$V_{DL} = \frac{1}{2} \times 0.1 \times 0.07 \times W \qquad (10)$$

where (W) is the body weight in kilograms. The above equation can

be written in a compact form, after calculation of coefficients,

$$V_{DL} = 0.0035\ W. \tag{11}$$

The stroke volume output of the left ventricle can be estimated by subtracting equation (8) from (11),

$$SV_L = 0.0035\ W - (0.0675\ C^3 - \frac{2}{3}\ m). \tag{12}$$

The stroke volume output of the left chamber of turtle heart was estimated from the assumption that the total blood volume is approximately 9 per cent of body weight (Semple, 1960). Therefore, equation (10) was modified as follows,

$$V_{DL} = \frac{1}{2} \times 0.1 \times 0.09 \times W \tag{13}$$

where (W) is the body weight in gram. After calculation of coefficients, equation (13) can be written as,

$$V_{DL} = 0.0045\ W. \tag{14}$$

The stroke volume output of the left chamber of turtle heart can be estimated by subtracting equation (9) from (14),

$$SV_L = 0.0045\ W - (0.0675\ C^3 - \frac{1}{2}\ m). \tag{15}$$

Equations (12) and (15) can equally be applied to hearts under control and experimental conditions. In order to account for changes in the left ventricular stroke volume under experimental conditions the values of V_{EL} in equations (8) and (9) should be corrected by a constant. This constant is calculated from the ratio of the first Fourier coefficient (A_o) of control over the experimental conditions. This correction factor

for end-systolic volume is in accord with recent findings of Rushmer (1959) that under certain experimental conditions the immediate changes in minute volume output are brought about by alteration of end-systolic volume.

Mathematical Derivation of Tension Time Curves

One of the important determinants of cardiac function is the tension developed during the cardiac cycle (Burton, 1957). Many attempts have been made to determine the course of tension developed during cardiac cycle using gravimetric and myographic methods (Wiggers, 1952). Using Laplace's surface tension law ($P = \frac{T}{R}$) (Landau and Lifshitz, 1959) and making use of simultaneous recordings of the intraventricular pressure, aortic pressure, and combined ventricular circumference, an expression is derived which relates tension time curves to those of pressure and circumference time curves.

If it is assumed that ventricles are spherical in geometry, then Laplace's surface tension law can be applied in its simple form, $P = \frac{T}{R}$. The ventricular circumference (C) as recorded by the variable resistance gauge is related to radius by equation (1). The volume of a sphere is given by equation,

$$V = \frac{4}{3}\pi R^3. \tag{16}$$

Assuming that the volumes of the right and left ventricles are equal, then the volume of the left ventricle is given by,

$$V_L = \frac{1}{2} \times \frac{4}{3}\pi R^3. \tag{17}$$

Substituting for (R) in equation (17) its corresponding value from equation (1), an equation relating the volume to circumference is obtained,

$$V_L = \frac{2}{3}\pi \left(\frac{C}{2\pi}\right)^3. \tag{18}$$

Equation (16) gives the volume of any spherical object. Therefore, when equations (16) and (18) are set equal, an expression is obtained in which the radius of the left ventricle is related to the circumference of both ventricles,

$$R^3 = \frac{1}{2}\left(\frac{C}{2\pi}\right)^3. \tag{19}$$

Taking the cube root of above equation gives the following relation,

$$R = 1.26 \left(\frac{C}{2\pi}\right). \tag{20}$$

Since (π) is a constant, equation (20) can be written as,

$$R = 0.194\ C. \tag{21}$$

It should be noted that equation (21) applies equally to hearts with geometry other than sphere. In the case of non-spherical heart the coefficient (0.194) should be modified so as to obtain an exact mathematical relationship between radius and circumference.

Substituting the value of (R) from equation (21) into Laplace's surface tension law for sphere, an expression is obtained which relates tension to the products of pressure, circumference, and a constant,

$$T = 0.194\ P \times C. \tag{22}$$

Since tension (T) is given in units of dynes per cm.^{2}, by using a proper

conversion factor (1 mm. Hg = 1330 dynes per cm.^{2}) equation (22) can be written in the following form,

$$T = 258\ P \times C. \qquad (23)$$

This is an extremely useful equation. It states a fundamental relationship between tension, pressure, and circumference changes of the ventricle which is independent of the shape and size of the heart. Although equation (23) was derived by assuming that ventricles are spherical in geometry, it should be noted such an assumption is not contained in equation (23). Therefore, equation (23) can be used to calculate the tension developed by the myocardium at any time during the cardiac cycle from simultaneous records of the pressure and circumference time curves.

RESULTS AND DISCUSSION

The object of this study was to analyze mathematically the recorded cardiac waveforms. The manner by which information is coded in the recorded signal variations from the heart and attached vessels is not known. Fourier analysis was applied to the time curves so that a time spectrum of the individual coded signals could be determined. In applying this mathematical method two assumptions were made. First, that the heart, during its cycle, generates a periodic signal which can be represented as a sum of sinusoids. Second, that we know nothing of the sequence of the physical forces which generate such a signal. Analysis was performed on a graphical record of the generated signal. The characteristics of the sensing and recording instruments were discussed in the previous section. However, before presenting the results, it is necessary to point out that the recording polygraph utilized a curvilinear moving stylus and a curvilinear chart paper. The question arises as to whether such a recording system lends itself to a mathematical analysis which bases its information on the rectilinearly determined values. The author justifies the procedure used on the basis of the following reasons. First, to eliminate partially the disadvantages of curvilinear recording, the chart paper used was also curvilinear (Stacy, 1961). Second, since Fourier analysis involves the determination of a series of points on the recorded pulse, it is immaterial whether these points are connected to

a given base-line by a curvilinear or rectilinear line. Moreover, the same recording system and procedure for obtaining the points were used throughout the study.

The next point which requires consideration is whether certain instrumental undulations in the record will in any way reduce the usefulness of the method and the results obtained. In this study more than 5,000 records were analyzed. Special care was taken, both during the recording and in the course of analysis, to discard those records which in the judgment of the author contained obvious artifacts. Because of lack of instruments, no attempt was made to compare the signals recorded by the system used with another system, such as optical manometry. However, casual comparison of the records obtained by the system used with those published in the literature, using optical manometry, showed satisfactory agreement. Therefore, results obtained in this study using the recording system described are believed to be reliable and relatively free of experimental artifacts.

Turtle Experiments

The turtle heart has long been used as experimental material to determine cardiac function. The assumption has been that since the turtle heart is free from a specialized conductive system, it could be used to study the mechanical aspect of cardiac function. Table 1 presents data on comparison of some cardiac parameters in the turtle. The last

Table 1

COMPARISON OF SOME CARDIAC PARAMETERS IN TURTLES

Turtle No.	Body Weight gm.	Heart Weight gm.	$\frac{\text{Heart Wt.}}{\text{Body Wt.}} \times 100$	Wall Thickness mm.	Loop Circumference of Vol. Transducer cm.	Stroke Vol. cc.
1	1150*	-	-	-	-	-
2	1320*	-	-	-	-	-
3	1145	2.118	0.204	4	42	1.15
4	1562	2.634	0.169	3	42	3.20
5	1058	1.708	0.171	3	38	1.89
6	1055	1.859	0.176	3	40	1.36
7	1212	2.390	0.197	4	42	1.65
8	1478	3.168	0.214	4	44	2.47
9	1500*	-	-	-	-	-
10	785	1.330	0.170	3	30	2.37
Mean	1185.0	2.172	0.186	3.4	39.7	2.013
± S.D.	265	0.615	0.046	0.5	4.7	0.710

* They were not included in calculation of Mean and S.D.

column of this table shows the values for stroke volume of one side of the heart for 7 turtles as calculated from the loop circumference of the volume transducer (see equation 15 in Calculations section). The stroke volume ranges from 1. 15 to 3. 20 cc. with an average of 2. 0 cc. Expressed as fraction of body weight, the stroke volume was about 2. 0 cc. per kilogram body weight. These values compared well with those obtained by measuring weight changes of the heart and by collecting the amount of blood ejected during systole after removing aortic clamps from the excised heart.

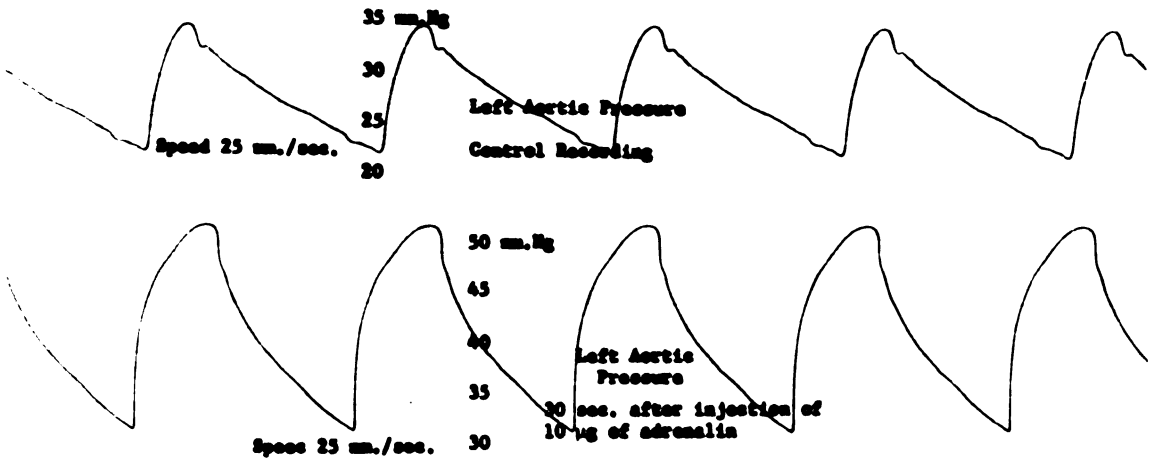
The effects of intracardiac injection of adrenaline and acetylcholine were studied in 4 turtles. Figure 7 shows the typical changes observed in the contours of the left aortic pressure, left ventricular pressure, and left ventricular circumference. The smooth and rapid rise of blood pressure in the aorta during systole and sharp decline of pressure in diastole (as shown in top photograph) is altered after adrenaline infusion. Note that both systolic and diastolic segments of the aortic pressure curve show a characteristic curvilinear rise and fall after adrenaline. The dichrotic notch which signals the closure of the aortic valves is peculiarly absent from the adrenaline curve. Visual inspection of the left ventricular pressure and circumference recordings after adrenaline and acetylcholine infusion discloses some changes in the contours of these waveforms (see figure 7).

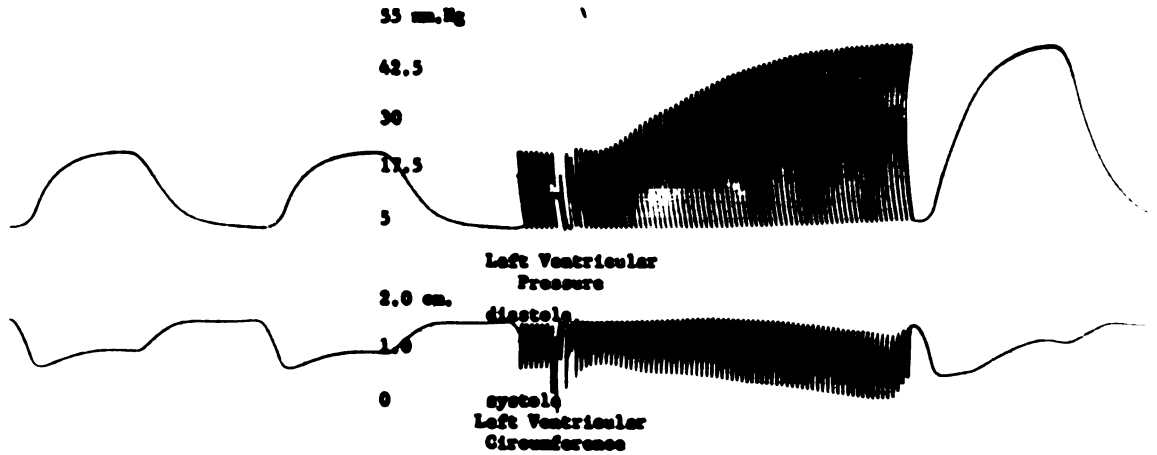
FIGURE 7

Top--Changes in the left aortic pressure curve after adrenaline injection in turtle. From above downwards, control left aortic pressure and left aortic pressure after adrenaline injection recorded at a speed of 25 mm./sec.

Middle--Changes in ventricular function curves after adrenaline injection in turtle. From above downwards, left ventricular pressure and left ventricular circumference. The point at which adrenaline was injected is the middle of the record.

Bottom--Changes in ventricular function curves after acetylcholine injection in turtle. From above downwards, left ventricular pressure and left ventricular circumference. The point at which acetylcholine was injected is the middle of the record.





Effect of injection of 5 µg of adrenalin

Speed .5 and 25 mm./sec.

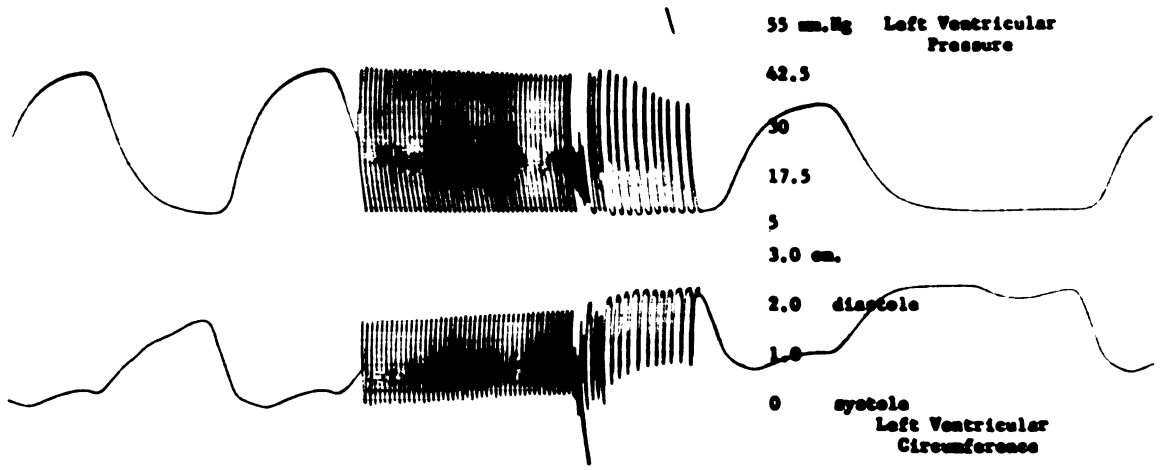


Table 2 presents a comparison of cardiac function curves under control conditions and after intracardiac infusion of adrenaline and acetylcholine. If it is assumed that any change in left ventricular circumference indicates a change in ventricular volume flow (cardiac output) then it can be concluded that in the turtle adrenaline in the doses injected increases cardiac output. Indeed, the last column of Table 2 shows that adrenaline increased cardiac output by about 35%. These results are in accord with those obtained by Akers and Peiss (1963).

Table 3 presents the values for the first Fourier coefficient (area under the cardiac time curves). To appreciate the significance of the values for area, it is helpful to think of the recorded waveforms as the sum of the contributions of myocardial contractile force during the cardiac cycle. When analyzed properly, the time distribution of the area under the curve affords more useful information about the nature of systole and diastole than the usual method of recording peak pressure developed during the cardiac cycle. Methods of analysis of cardiac function curves vary with different investigators. For instance, Woodbury and Hamilton (1937) used the rate of decline of the pressure curve as a useful index of cardiac function, and Alexander and Webb (1947) considered the pressure pulse as a summation of the transmitted and reflected waves. A more satisfactory representation of time distribution of the cardiac activity is by Fourier transform. The Fourier analysis of cardiac time curves of the turtle is presented in Table 4. The values

Table 2

COMPARISON OF BASIC CARDIAC PARAMETERS UNDER VARIOUS CONDITIONS IN TURTLES

Treatment	Turtle No.	Left Aortic Systolic Pressure mm. Hg	Left Ventricular Systolic Pressure mm. Hg	Ventricular Circumference (ΔC) cm.
Control	1	-	40	1.8
30 sec. after 10 μg. Adrenalin injection	1	-	90	2.7
Effect of 5 ml. saline infusion	1	-	102	-
Control	2	-	35	-
Control	2	34.5	34.5	1.8
Effect of 10 μg. Adrenalin injection	2	55.5	-	-
Control	3	-	16	1.2
Control	3	-	30	1.9
Control	3	26	-	1.1
30 sec. after 10 g. Adrenalin injection	3	56	-	2.85
Control	6	-	14	1.25
Control	7	-	26.5	1.30
Control	9	-	30	1.20
Control	9	-	27	2.50*
Control	9	-	37	2.75**
Control	8	49	49	1.5
Control	10	21	24	-

Table 2 (Continued)

Treatment	Turtle No.	Left Aortic Systolic Pressure mm. Hg	Left Ventricular Systolic Pressure mm. Hg	Ventricular Circumference (ΔC) cm.
Effect of 5 μg. Adrenalin injection	10	51.25	48.75	-
Control	10	29.75	47.5	1.8
30 sec. after 25 μg. Acetylcholine injection	10	17.0	32.0	1.75

* Ventricular weight

** Ventricular myogram

Table 3

COMPARISON OF FIRST FOURIER COEFFICIENTS OF BASIC CARDIAC PARAMETERS UNDER VARIOUS CONDITIONS IN TURTLES

Treatment	Turtle No.	Left Aortic Systolic Pressure A_o - mm. Hg	Left Ventricular Systolic Pressure A_o - mm. Hg	Ventricular Circumference (ΔC) A_o - cm.
Control	1	-	38.500	1.625
30 sec. after 10 μg. Adrenalin injection	1	-	89.450	3.415
5 ml. saline injection	1	-	51.000	-
Control	2		23.500	-
Control	2	-	36.450	-
Control	2	48.00	-	-
Effect of 10 μg. Adrenalin injection	2	72.950	-	1.430
Control	3	-	8.010	.700 1.040*
Control	3	-	15.500	.900 1.260*
Control	3	38.700	-	.553 1.278*
30 sec. after 10 μg. Adrenalin injection	3	73.200	-	2.593 3.526*

Table 3 (Continued)

Treatment	Turtle No.	Left Aortic Systolic Pressure A_o - mm. Hg	Left Ventricular Systolic Pressure A_o - mm. Hg	Ventricular Circumference (ΔC) A_o - cm.
Control	6	-	12.050	.868
Control	7	-	23.500	1.170
Control	9	-	31.600	.980
Control	9	-	25.950	1.775 (weight)
Control	9	-	38.950	2.750 (myogram)
Control	8	77.725	41.850	1.205
Control	10	26.200	26.400	-
Effect of 5 μg. Adrenalin injection	10	83.600	54.625	-
Control	10	48.475	51.375	2.020
Effect of 50 μg. Acetylcholine injection	10	27.138	29.650	1.230

* Total ventricular circumference

Table 4

FOURIER COMPONENTS FOR LEFT VENTRICULAR PRESSURE, LEFT AORTIC PRESSURE, AND LEFT VENTRICULAR CIRCUMFERENCE UNDER VARIOUS CONDITIONS IN TURTLES

Treatment	No. of Animals	A_o Mean ± S. D.	First Harmonic	Second Harmonic	Third Harmonic
Left Ventricular Pressure					
Control	5	38 ± 4	+60 sin 1.5t	+29 sin 3t	-
After Adrenalin injection	4	90 ± 7	+152 sin 1.55t	-33 sin 3.1t	-
After Acetyl-choline injection	4	30 ± 2	+48 sin 1.2t	+48 sin 2.4t	-2 sin 3.6t
Left Aortic Pressure					
Control	4	45 ± 5	+64 sin 1.4t	+1.3 sin 2.8t	-
After Adrenalin injection	4	73 ± 8	+ 108 sin 1.8t	+9.5 sin 3.6t	+14.5 sin 5.4t
After acetyl-choline injection	4	27 ± 4	+41 sin 1.2t	-2 sin 2.4t	+4 sin 3.6t
Left Ventricular Circumference					
Control	4	1.3 ± .5	+1.9 sin 1.2t	+1.4 sin 2.4t	-
After Adrenalin injection	4	3.5 ± .6	+5.5 sin 1.65t	+1.8 sin 3.3t	+0.3 sin 4.95t
After Acetyl-choline injection	3	1.2 ± .2	+1.4 sin 1.2t	+1.9 sin 2.4t	+1.5 sin 3.6t

for A_o for the Fourier components of left ventricular pressure show a definite increase for adrenalin and a slight decrease for acetylcholine as compared with controls. However, harmonic analysis discloses a distinct difference in the time course of action of these two drugs. The modulus of the first harmonic (column 4) for adrenalin shows a 2.5 fold increase (152 for adrenalin and 60 for control). However, no change in the argument of the sine function is observed (1.55 for adrenalin and 1.5 for control). The modulus of the second harmonic (column 5) shows a change in sign for adrenalin as compared with the control. This shift of modulus (-33 for adrenalin and +29 for control) might be related to the manner of action of adrenalin upon turtle heart. The significance of this interpretation will be discussed shortly. The harmonic analysis of acetylcholine experiments shows the expected decrease in the modulus as compared with the control. This is because the value of the modulus of various harmonics, as calculated by Fourier integrals (see section on Fourier analysis in Materials and Methods part of the thesis) refers to the amplitude of the component frequencies of the pulse. Since the value of the amplitude (the numerical value of the modulus) indicates the pressure developed by the heart, then any change in amplitude reflects the force of myocardial contraction. Examination of the acetylcholine data (Table 4, line 3) shows that the moduli of the first and second harmonics remain unchanged. This is interpreted to mean that acetylcholine prolongs the systolic phase of the cardiac cycle and decreases the force of

contraction of the myocardial fibers. Further graphical support for these conclusions will be presented below.

Harmonic analysis of the left aortic pressure is presented in Table 4. The moduli of first and second harmonics show a marked increase after adrenalin injection. The argument of the sine function also shows a definite increase. Note that the third harmonic of the aortic pressure curve appears when adrenalin is infused. This is in contrast to ventricular pressure. Moreover, there is no change in sign of modulus of the second harmonic as compared with that of the left ventricular pressure. One is tempted to attribute the change in sign of modulus for ventricular pressure, as compared with aortic pressure, to the difference in the action of adrenalin on the heart and aorta. However, validity of such a conclusion requires further experimentation.

Fourier components of ventricular circumference time curves (Table 4) reveal the dynamic difference in the action of adrenalin and acetylcholine upon turtle heart. Adrenalin infusion resulted in an increase in cardiac output as shown by increase in A_o values and the value of moduli of first and second harmonics. Whereas, acetylcholine infusion resulted in prolongation of systole as shown by the rise and fall of values of the moduli of first, second, and third harmonics (compare columns 4, 5, and 6 last line).

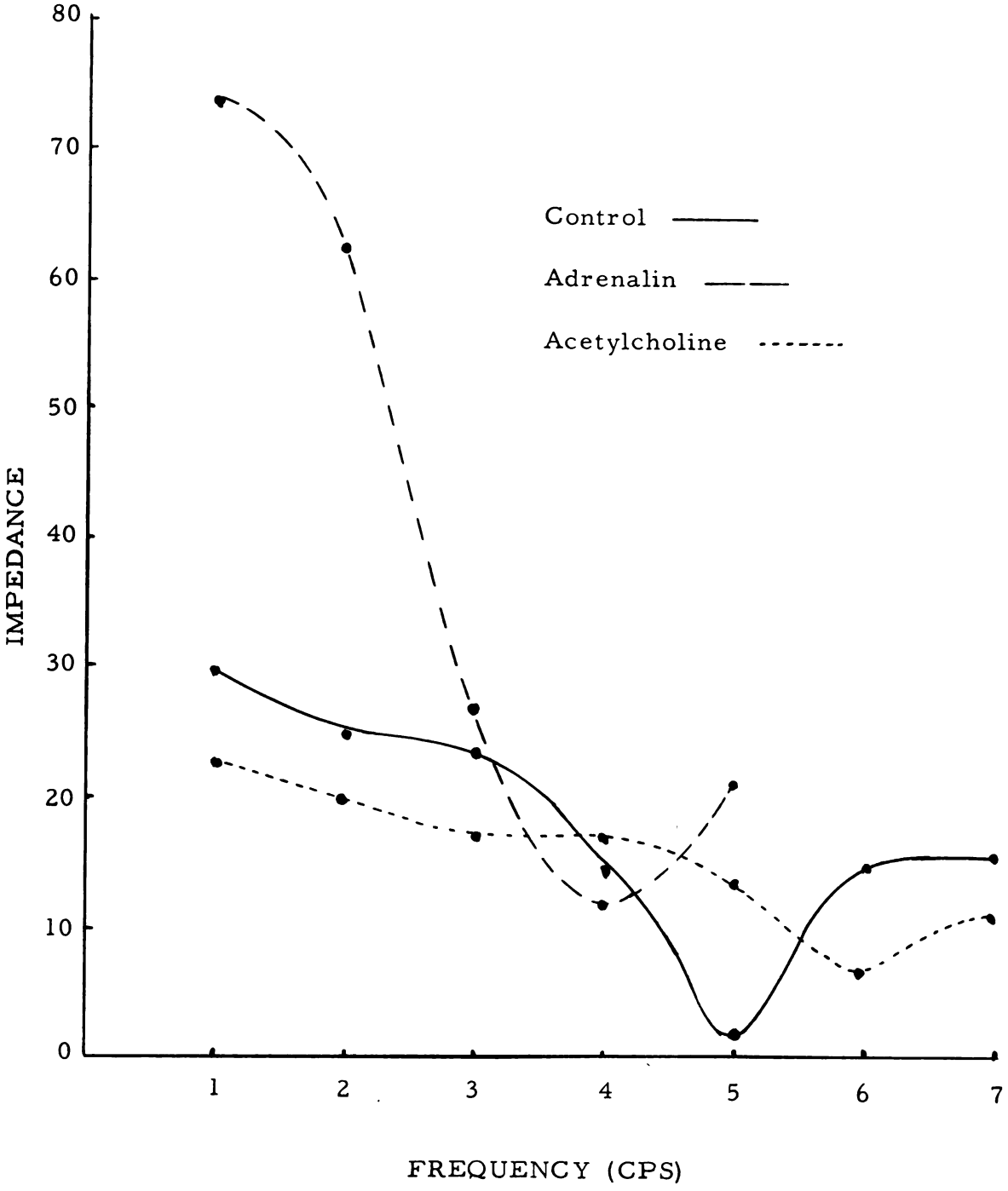
In a pulsatile system impedance is defined as the ratio of pulsatile pressure to pulsatile flow (McDonald, 1960). An estimate of the arterial

input impedances, at the various component frequencies of the pulse, will give information about the presence or absence of reflected waves. Since flow is directly related to the pressure gradient, then any increase in impedance and pressure is accompanied by a decrease in pulsatile flow. This explains the observation that peripheral vasoconstriction produces an increase in pulse pressure and a reduction in blood flow. Moreover, since impedance can be regarded as a measure of the degree of "obstruction" to flow where pulsatile flow occurs, then it is imperative to determine this impedance under various experimental conditions. To analyze further the action of drugs on the heart, ventricular impedance at each sinusoidal frequency was computed from the ratio of the pressure component to the circumference component. The phase angles (their significance is discussed below) associated with impedance were computed also. Then, amplitude impedance and impedance phase angle spectra were constructed. Figure 8 shows the variation of impedance for the turtle ventricle. Each curve represents five different experiments. In essence, all curves had the same contour distribution over the frequency analyzed. In this figure, note that the adrenalin curve (broken line) shows an initial increase in impedance which is indicative of increased force of ventricular contraction and wave reflection. The impedance amplitude falls off rapidly as ventricular systole progresses (at higher frequencies). On the other hand, the acetylcholine curve (dotted line) indicates that the drug appears to act as a relaxing and

FIGURE 8

Variations of impedance with pulsating frequency of the turtle ventricle under control conditions (solid line), after adrenalin injection (broken line), and after acetylcholine injection (dotted line).

(Impedance units = mm. Hg/cm.^{3}/sec.)


80
70
60
50
40
30
20
10
0
IMPEDANCE
Control
Adrenalin
Acetylcholine
1
2
3
4
5
6
7
FREQUENCY (CPS)

vasodilating agent, resulting in decreased force of contraction and prolonging the ejection phase of ventricular systole. These conclusions are based on a decrease in impedance (at low frequencies) and a shift of the minimum impedance by one frequency upward, from 5 to 6 cps. In addition the observed alteration, by drugs, in the impedance distribution might be attributed to the vasomotor activity of the blood vessels in the turtle (figure 8). This is in agreement with deductions made by McDonald (1960) on similar observations in the dog. Other than this, the physiological significance of such curves (figure 8) is not known at present.

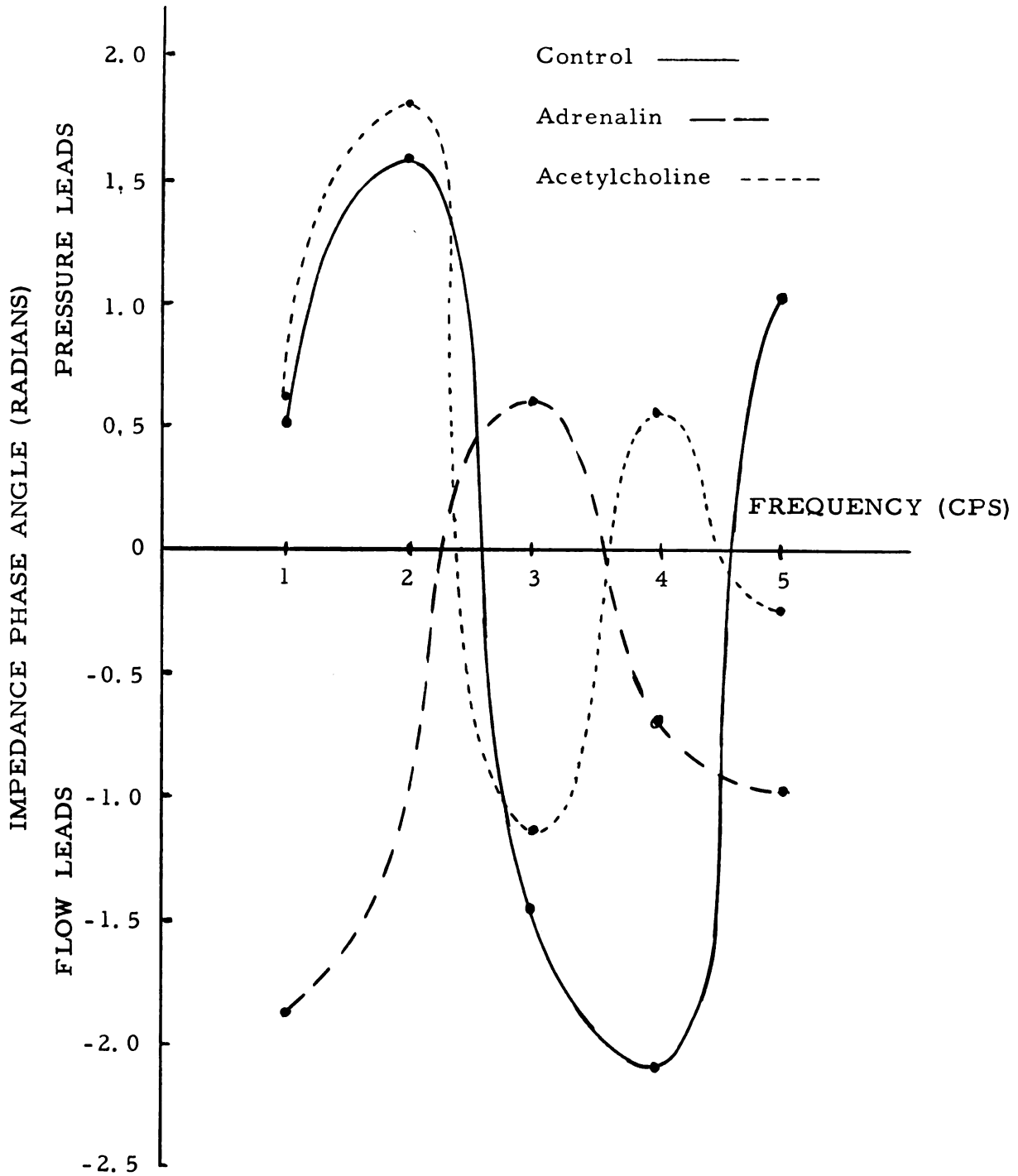
Randall and Stacy (1956) computed the magnitudes and phase relationships of Fourier components of the pulsatile blood pressure and blood flow in the femoral artery. The relationship between these sinusoidal components was studied as a function of their frequency. Based on such analysis, they concluded that in a system in which flow is determined by friction only, the magnitude of the impedance is independent of the frequency of the sinusoidal pulsations. Moreover, the pressure and flow fluctuations are in phase. If the predominant factor determining the flow is compliance of the system, then the flow fluctuations precede pressure fluctuations. However, when the system is predominantly inertial, then pressure fluctuations precede flow fluctuations. The points at which phase angle fluctuation crosses the abscissa is called "resonant" frequency and indicates that the impedance is entirely a viscous resistance or pressure and flow fluctuations are in phase. Therefore, a system which

contains all three components, namely, friction, inertia, and compliance will exhibit a complex behavior characterized by combinations of the individual characteristics. Peterson (1954) observed that the relationship of flow and pressure in a pulsatile system is variable and that such variability can be attributed to three parameters, namely, mass, friction, and distensibility. He concluded that, a) these three parameters vary in a nonlinear fashion and affect each other, b) that the vascular pressure pulse is the sum of these three factors, and c) that despite constant stroke volume, the pulse pressure amplitude varies considerably.

Variation in impedance phase angle of the turtle ventricle is shown in figure 9. The control curve (solid line) indicates that pressure precedes flow fluctuations at frequencies below 2. 5 cps and above 4. 5 cps. These two segments of the curve (solid line) demonstrate the effects of the inertial components of cardiac function. On the other hand, the compliance (distensibility) of the system (that is, when flow precedes pressure) is indicated at frequencies above 2. 5 and below 4. 5 cps. The adrenalin curve (broken line) shows a definite reversal of the above pattern, whereas the acetylcholine curve (dotted line) shows a shift of the curve toward the lower frequencies. This is the first time that the actions of adrenalin and acetylcholine on the sequence of the physical forces which generate cardiac time curves in the turtle have been thus demonstrated. This insight into the mechanism of action of these drugs

FIGURE 9

Variations of impedance phase angle with pulsating frequency of the turtle ventricle under control conditions (solid line), after adrenalin injection (broken line), and after acetylcholine infusion (dotted line).


IMPEDANCE PHASE ANGLE (RADIANS)
PRESSURE LEADS
FLOW LEADS
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2.0
-2.5
1
2
3
4
5
FREQUENCY (CPS)
Control
Adrenalin
Acetylcholine

became possible only after application of Fourier analysis to the ventricular function curves. Fourier analysis can be used with success to work out a most complete dose-response spectrum of any cardiovascular drug and to provide an insight into the nature of their actions.

Cardiac activity, under control and experimental conditions, can be depicted by a plot of the time course of tension developed by the ventricle. This is based on equation (23) described in the Calculations section. Figure 10 shows the comparison of the time course of tension of turtle ventricle under control conditions and 30 sec. after 10 μg. of adrenalin. These curves represent five different experiments. All curves showed similar contour over the time intervals analyzed. In turtle hearts the peak systolic pressure occurred about 0. 8 sec. after onset of systole. The control curve (dotted line, figure 10) exhibits the time course of pressure and tension developed in the ventricle during the cardiac cycle. The adrenalin curve (broken line) shows an initial delay followed by a rapid increase in the developed tension. Peak tension in the adrenalin curve is maintained approximately 1. 0 sec. as compared to only 0. 5 sec. in the control. The area under the tension-time curve, as calculated by trapezoidal method of integration, was increased approximately 4 times as compared to control. Figure 11 shows the effect of 50 μg. of acetylcholine on the tension-time course of turtle ventricle. Note the prolongation of the plateau of the peak tension shown by the acetylcholine curve (broken line) as compared

FIGURE 10

Comparison of the time course of tension of the turtle ventricle under control conditions (dotted line) and 30 sec. after 10 μg. of adrenalin injection (broken line).

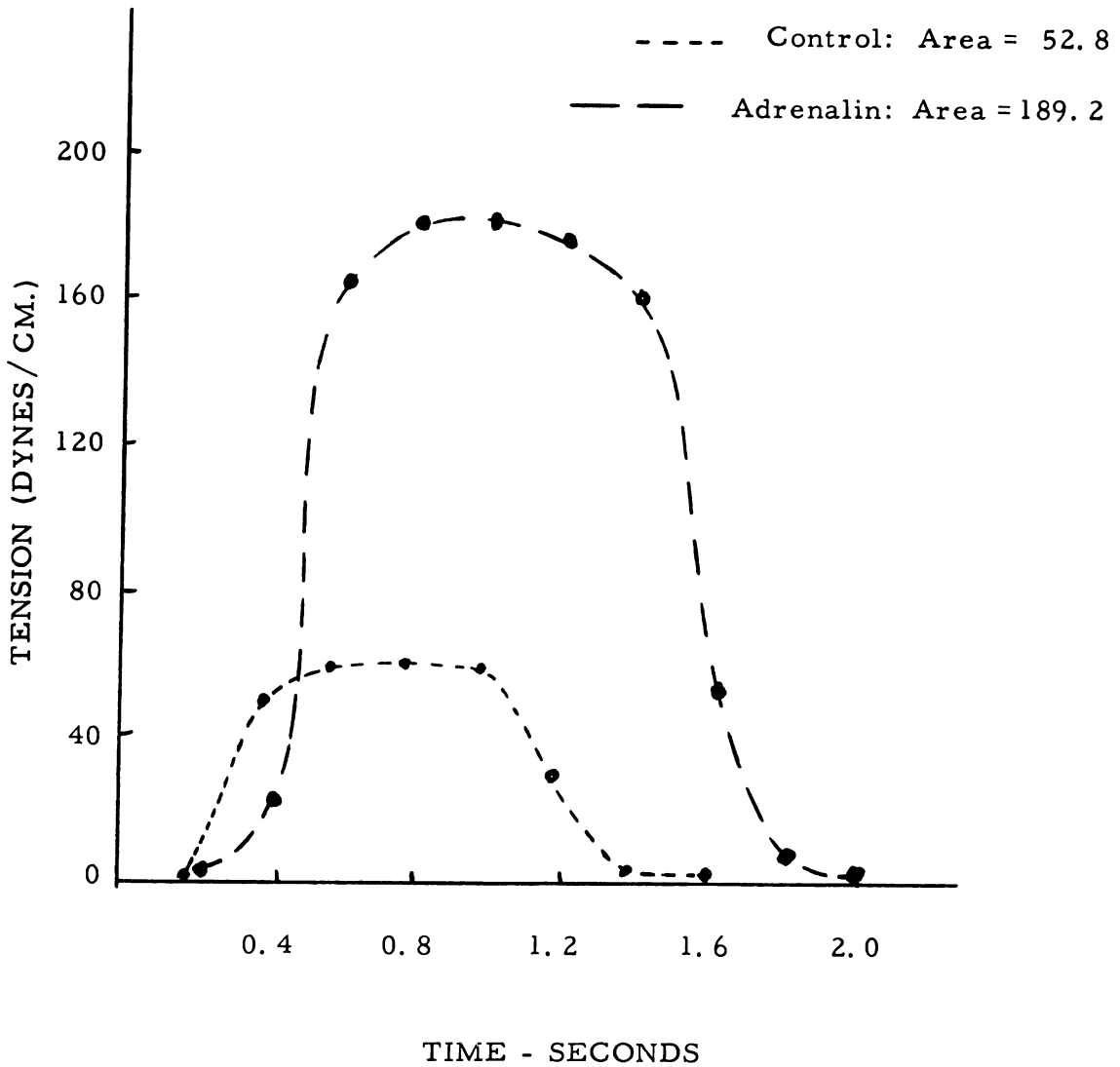
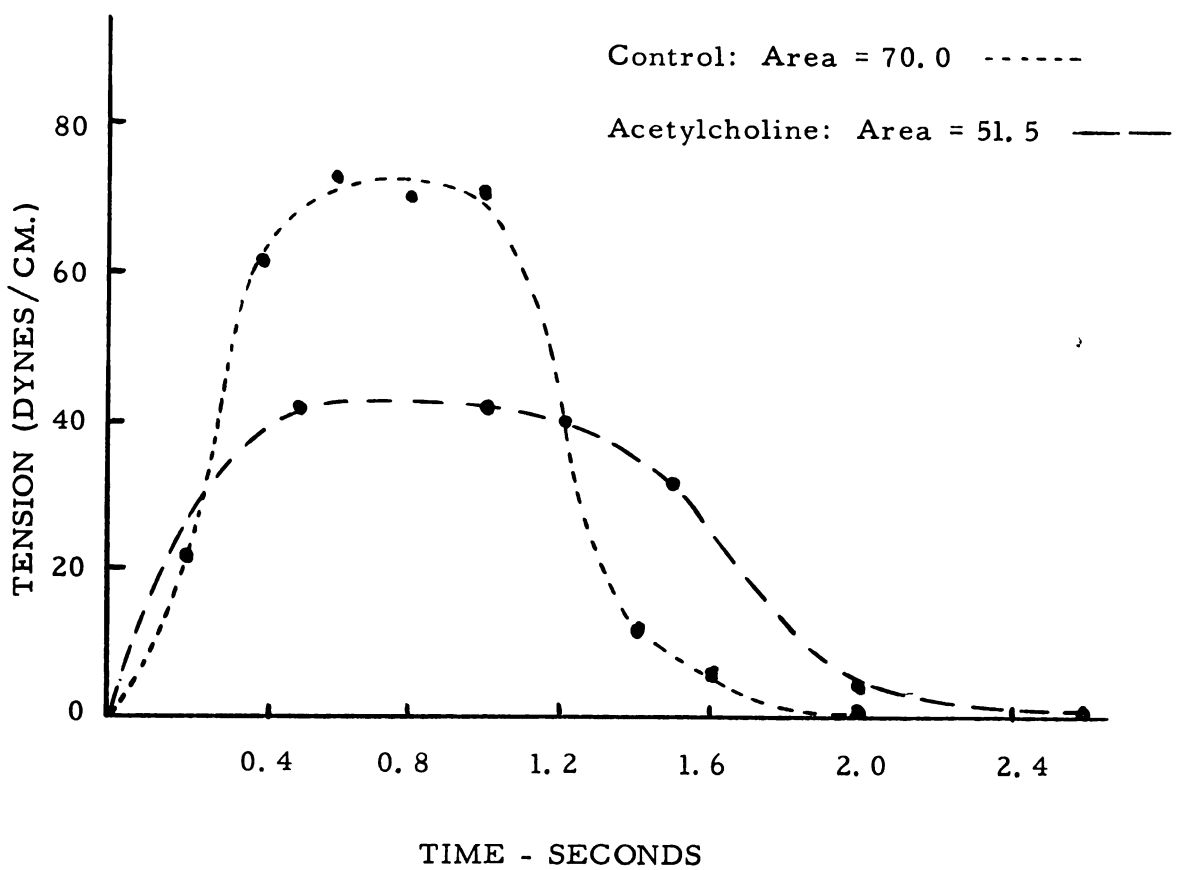

Control: Area = 52.8
Adrenalin: Area = 189.2
TENSION (DYNES/CM.)
200
160
120
80
40
0
0.4
0.8
1.2
1.6
2.0
TIME - SECONDS

FIGURE 11

Comparison of the time course of tension of the turtle ventricle under control conditions (dotted line) and 10 sec. after 50 μg. of acetylcholine injection (broken line).


Control: Area = 70.0
Acetylcholine: Area = 51.5
TENSION (DYNES/CM.)
80
60
40
20
0
0.4
0.8
1.2
1.6
2.0
2.4
TIME - SECONDS

with the control. The prolonged plateau seen in the acetylcholine curve is attributed to the delay of the cardiac systole and inefficient emptying of the heart. There was an average of 20-25% decrease in the total tension developed during systole after acetylcholine infusion.

Cat Experiments

A total of 17 female cats ranging in weight from 1. 7 to 4. 0 kg. were used in this study. Table 5 presents values for body weight, heart weight, the percent ratio of heart weight to body weight, and the percent ratio of heart weight to surface area. In contrast to the turtle, it appears that the cat has some 50% more heart mass than turtle. It might be implied that this excess heart mass is related to the greater mean blood pressure of cat as compared to turtle. Although it is customary to express organ weight with respect to surface area in order to achieve uniformity, the data from present study do not support such a concept. In fact, when heart weights were expressed as a percentage of body surface area the standard deviation of the mean increased some 10 fold when compared with the usual method of expressing organ weight as a percent of the body weight.

Table 6 presents the comparison of some cardiac parameters in cats. It can be seen that the left ventricular wall is more than twice as thick as the right ventricular wall. This is in accord with the expected values predicted by Laplace's surface tension law (Burton, 1957). The

Table 5

COMPARISON OF WET WEIGHT OF VENTRICLES AS PERCENTAGES OF BODY WEIGHT AND BODY SURFACE AREA IN CATS

Cat No.	Body Weight Kg.	Heart Weight gm.	$\frac{\text{Wet Weight}}{\text{Body Weight}} \times 100$	$\frac{\text{Wet Weight}}{\text{Surface Area}} \times 100$ gm./m.^{2}
1	2.5	10.445	0.418	5.437
2	2.0	6.866	0.343	4.189
3	3.0	11.103	0.370	5.193
4	1.75	6.807	0.545	5.808
5	2.75	-	-	-
6	1.70	5.515	0.315	3.701
7	2.0	6.259	0.313	3.819
8	1.85	8.713	0.471	5.621
9	2.0	6.113	0.306	3.730
10	2.25	8.529	0.379	4.786
11	2.5	8.797	0.352	4.579
12	1.7	-	-	-
13	3.0	12.373	0.412	5.787
14	3.0	9.492	0.316	4.440
15	3.1	14.723	0.475	6.573
16	1.7	4.909	0.289	3.362
17	4.0	16.350	0.409	6.089
Mean:	2.39	9.133	0.381	4.874
± S.D.	0.71	3.37	0.073	0.995

Table 6

COMPARISON OF SOME CARDIAC PARAMETERS IN CATS

Cat No.	Wall Thickness mm.		Loop Circumference of Vol. Transducer cm.	Residual Vol. cc.	Stroke Vol. cc.
	Left	Right			
1	8	2	5.8	6.10	2.65
2	6	2	5.0	3.85	3.15
3	8	2	6.0	7.15	3.35
4	6	2	4.8	2.89	1.48
5	-	-	-	-	-
6	4	2	4.6	2.80	3.35
7	6	3	4.9	3.70	3.30
8	6	2	-	-	-
9	6	3	4.8	3.40	3.60
10	6	3	5.5	5.30	2.58
11	7.5	3	5.6	5.80	2.95
12	-	-	-	-	-
13	7	3	6.2	7.60	2.90
14	7	3	5.7	6.25	4.25
15	8.5	3.5	6.4	7.82	3.03
16	6	2	4.6	3.22	2.73
17	8	4	6.6	8.50	5.50
Mean	6.7	2.6	5.46	5.31	3.20
+ S.D.	1.18	0.66	0.69	1.89	0.90

fourth and fifth columns of Table 6 show the range and the mean value for the loop circumference of the volume transducer at the end of systole and the end systolic volume of the left ventricle respectively. The last column of this table indicates the range and mean values for the stroke volume of the left ventricle. The values for residual and stroke volumes were calculated from the equation (12) described in the Calculations section. On the average, under control conditions, stroke volume constituted approximately 37% and residual volume comprised approximately 62% of the total end-diastolic volume. On the other hand, using this method and visual observations, no detection of the end-systolic blood in the turtle heart could be made. Turtle ventricles appeared to empty completely and in this respect had a much higher efficiency. The values reported here for cardiac efficiency, based on emptying, are somewhat higher than those obtained by Holt (1944) in the dog using the dye dilution technique. However, it should be noted that the efficiency of cardiac emptying varied with the size and stasis of the heart during diastole.

Thoracotomy has been considered as one of the factors which causes cardiac embarrassment and reduced cardiac efficiency. Holt (1944) reported that when dogs were allowed to breathe air under a positive pressure of 16 cm. of water, there was a 33% reduction in the cardiac output. However, no change in cardiac output occurred when air under a negative pressure of 16 cm. of water was breathed. Furthermore, Rushmer and co-workers (1954) demonstrated that there is a definite

shrinkage of the heart upon thoracotomy. Table 7 summarizes the data obtained for systemic blood pressure after thoracotomy. The carotid pressure showed a drop of approximately 60% when chest was exposed. There was approximately a 65% reduction in the pulse pressure after thoracotomy. The reduction of the systemic blood pressure indicates a definite decrease in cardiac efficiency. In order to delineate the possible extracardiac factors from the cardiac factors responsible for this drop in systolic blood pressure in some animals, femoral vein pressure and arterial hematocrit were determined before and after thoracotomy. Contrary to the expectation that thoracotomy might produce a venous pooling, no change in venous pressure and arterial hematocrit was observed.

In order to ascertain the degree of decrease in cardiac emptying efficiency, the last two columns of Table 7 were prepared. It was assumed that the total cardiac mass did not change during the course of the experiment, namely, before and after thoracotomy. The data presented in these two columns indicate a trend towards cardiac inefficiency after thoracotomy. On the basis of cardiac mass, there was a noticeable decrease in the pressure developed per unit mass of the heart in the open-chest as compared with the closed chest animals. In view of the works of Ferguson and co-workers (1953), Rushmer and associates (1954) and the work reported here, a hypothesis is suggested which attempts to explain the source of reduction in cardiac performance.

Table 7

RIGHT COMMON CAROTID AND PULSE PRESSURE OF CATS BEFORE AND AFTER THORACOTOMY AND THE RATIO OF CAROTID PRESSURE TO WET VENTRICULAR WEIGHT

Cat No.	Carotid Pressure mm. Hg		Pulse Pressure mm. Hg		Carotid Pressure / Heart Weight mm. Hg/gm.	
	Before Thoracotomy	After Thoracotomy	Before Thoracotomy	After Thoracotomy	Before Thoracotomy	After Thoracotomy
2	-	65	-	14	-	-
3	-	-	25	13.75	-	-
4	100	62.5	11.25	8.75	14.691	9.182
5	-	-	15.00	10.00	-	-
6	-	90	-	37.5	-	16.319
7	125	67.5	50	25	19.971	10.785
8	145	110	50	30	16.642	12.625
9	-	110	-	40	-	17.994
10	-	80	-	30	-	9.380
11	-	95	-	30	-	10.799
12	110	70	25	20	-	-
13	170	100	60	40	13.740	8.082
14	180	-	50	-	18.963	-
15	200	95	55	35	13.584	6.452
16	135	85	45	35	27.500	17.315
17	120	70	50	30	7.339	4.281
Mean	142.78	84.62	39.64	25.99	16.554	11.201
+ S.D.	33.8	16.75	17.2	12.2	5.88	4.46

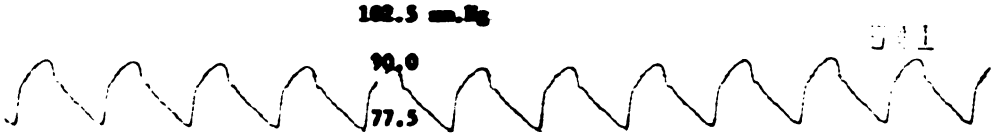
It is postulated that the drop in the systolic pressure and the shrinkage of the heart in the open-chest animals are due to the absence of the stretching of the myocardium produced by the negative thoracic pressure. Since no reduction in the length of the myocardial fibers is assumed, then the difference between systemic pressure before and after thoracotomy must have resulted from the absence of the negative thoracic pressure. The presence of the negative pressure is theorized to act as a suction force which stretches the myocardium and is partly responsible for the systemic pressure prior to thoracotomy.

The contour of the pressure pulse changed markedly after thoracotomy. Figure 12 shows (top photograph) the alterations in the pressure pulse contour after pneumothorax and complete thoracotomy. Note the drop in systolic pressure, pulse pressure and the change of pressure summit to one of sustained plateau. When such a record was subjected to Fourier analysis (Table 9) a decrease in A_o (area under the curve) and the moduli of the first and second harmonics was observed. The modulus of the third harmonic and the argument of the sine function remained the same when compared with pulse pressure before thoracotomy. The decrease in the moduli of the first and second harmonics is an indication of cardiac inability (due to shrinkage) to develop the expected pressure. This interpretation is based on the assumption that vascular tone and distensibility remained unchanged after thoracotomy.

FIGURE 12

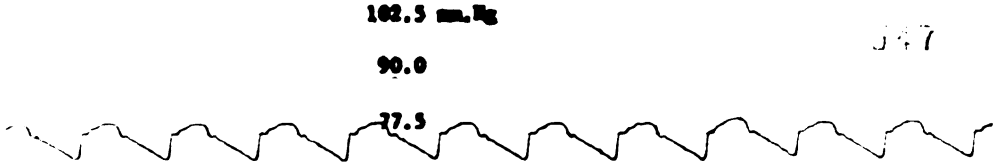
Top--Changes in the right common carotid pressure pulse after pneumothorax and thoracotomy in the cat. From above downwards, right common carotid pressure before thoracotomy, after pneumothorax, and after thoracotomy recorded at speed of 50 mm./sec.

Bottom--Changes in the right common carotid pressure pulse as a result of pulsus alternans in the cat. From above downwards, right common carotid pressure before and during the occurrence of pulsus alternans recorded at speed of 100 mm./sec.



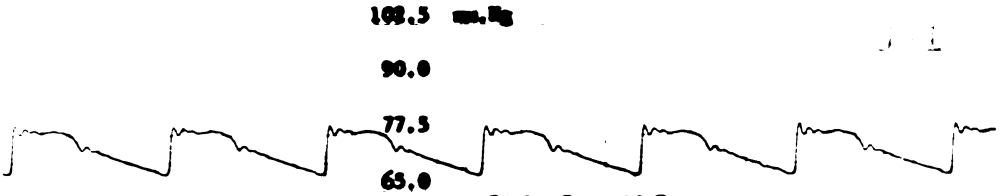
Right Carotid Pressure
Before Thoractomy

Speed 50 mm./sec.



Right Carotid Pressure
After Pneumothorax

Speed 50 mm./sec.

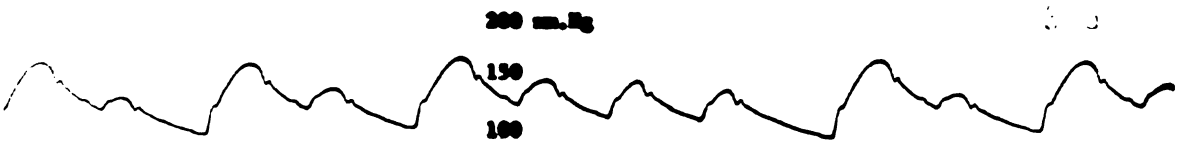


Right Carotid Pressure
After Thoracotomy

Speed 50 mm./sec.

Right Carotid Pressure

Control Recording
Speed 100 mm./sec.



Right Carotid Pressure

Pulsus Alternans

Speed 100 mm./sec.

Table 8 presents further data on the changes of blood pressure and pulse rate under various conditions. It should be noted that cats used in this study showed a reduction in the blood pressure and increase in the heart rate after thoracotomy. The increase in heart rate could be due to the reflex action of pressoreceptors and the vasomotor center. In addition, Table 8 shows values for greater and smaller pulses of the pulsus alternans couple observed in two cats. Figure 12 (bottom photograph) shows the contour changes of pulse pressure of a pulsus alternans couple. Note that except for the displacement of the pressure summit to a higher value, there is no apparent difference in the contour of the greater and smaller pulses of the couple. There have been three theories which attempt to explain ventricular alternation (Green, 1936). The first theory suggests that all muscle fibers contract during both larger and smaller beat. The second theory claims that all muscle fibers contract equally but the phasic entry of contraction is slower in the smaller beat. Finally, the third theory advances the concept that fractions of muscle fibers fail to contract in every alternate beat. The last theory is the generally accepted one, although without conclusive proof. When pulsus alternans couple records, such as those shown in figure 12, were subjected to Fourier analysis (see Table 9) the following results were noted. In the case of the greater pulse, there was a definite increase in the values of A_o and the modulus of the first harmonic. However, both moduli of the second and third harmonics and the argument of the

Table 8

CHANGES IN SYSTOLIC BLOOD PRESSURE AND PULSE RATE UNDER VARIOUS CONDITIONS IN CATS

Treatment	Cat No.	Systolic Blood Pressure mm. Hg		Pulse Rate per min.	
		Before	After	Before	After
Inspiration					
	3	25**	25**	-	-
	5	14**	14**	-	-
	12	100	100	168	168
Expiration					
	3	26**	26**	-	-
	5	15**	15**	-	-
	12	113	113	168	168
Thoracotomy					
	3	25**	14**	-	-
	4	11**	9**	-	-
	5	14**	9**	-	-
	7	125	68	120	120
	8	150	110	156	210
	12	100	70	168	192
	13	170	95	-	-
	15	200	150***	168	175
	15	200	120	168	175

Table 8 (Continued)

Treatment	Cat No.	Systolic Blood Pressure mm. Hg		Pulse Rate per min.	
		Before	After	Before	After
Pulsus Alternans					
Greater Pulse	8	170	170	156	156
Smaller Pulse	8	150	150	156	156
Greater Pulse	14	200	200	200	200
Smaller Pulse	14	173	173	200	200
Fibrillation					
	8	55	50	165	115

** Pulse pressure
***Pneumothorax

Table 9

FOURIER COMPONENTS FOR RIGHT COMMON CAROTID PRESSURE UNDER VARIOUS CONDITIONS IN CATS

Treatment	No. of Animals	A_o Mean ± S. D.	First Harmonic	Second Harmonic	Third Harmonic
Pressure Pulse*					
During inspiration	4	13. 5 ± 2	+21. 3 sin 10. 8t	+8. 5 sin 21. 6t	+1. 3 sin 32. 4t
During expiration	4	17 ± 4	+26. 6 sin 10. 8t	+5. 5 sin 21. 6t	+0. 3 sin 32. 4t
After thoracotomy	5	11. 8 ± 3	+18 sin 10. 8t	+3. 3 sin 21. 6t	+1. 4 sin 32. 4t
Pressure Pulse					
Control	6	84 ± 12	+107 sin 11. 6t	+10. 2 sin 23. 2t	+27. 4 sin 34. 8t
After adrenalin injection	6	174 ± 38	+250 sin 5. 2t	+12. 3 sin 10. 4t	+50 sin 15. 6t
Pulsus Alternans					
Greater pulse	2	275 ± 20	+397 sin 8. 7t	+2. 8 sin 17. 4t	+70 sin 26. 1t
Smaller pulse	2	235 ± 13	+322 sin 9. 8t	+16. 3 sin 19. 6t	+76 sin 29. 4t

* Pressure pulse records were obtained without reference to base-line (zero mm. Hg pressure).

sinusoidal functions of the smaller pulse showed a definite increase over that of the greater pulse. These changes in moduli of various harmonics, based on previous interpretation given to numerical value of modulus, reflect alterations in cardiac contraction. Since the numerical values of the moduli reflect the sum of the contributions of the contractile force of myocardial fibers, then any change in values of moduli can be interpreted as a change in force of contraction of the heart. In the case of the greater pulse, the modulus of the first harmonic shows a marked increase indicating a more vigorous cardiac contraction. However the somewhat reduced value of the modulus of the first harmonic of the smaller pulse indicates a much weaker myocardial contraction which is sustained longer. This latter point is shown by the substantial increase in the moduli of the second and third harmonics. Therefore, the Fourier analysis of pulsus alternans curves provides additional support to the currently accepted theory of the genesis of pulsus alternans.

Table 10 presents the data on blood pressure during inspiration, expiration and pulsus alternans, and after thoracotomy in cat. The area under the pressure pulse curves, as calculated by the first Fourier coefficient, for the above conditions are shown in Table 11. Note that the values of systolic pressure, as indicated in Table 10, do not reflect the dynamic and time distribution changes of the blood pressure under the above conditions. For instance, changes in blood pressure due to

Table 10

CHANGES IN SYSTOLIC BLOOD PRESSURE UNDER VARIOUS CONDITIONS IN CATS

Cat No.	Inspiration mm. Hg	Expiration mm. Hg	Thoracotomy mm. Hg	Pulsus Alternans mm. Hg	
				Greater	Smaller
3	25**	26**	14**	-	-
4	11**	-	9**	-	-
5	14**	15**	9**	-	-
7	125	-	68	-	-
8	150	-	110	170	150
12	100	113	70	-	-
13	170	-	95	-	-
14	173	-	-	200	173
15	200	-	120	-	-
15	200	-	150***	-	-

** Pulse pressure

*** Pneumothorax

Table 11

COMPARISON OF FIRST FOURIER COEFFICIENTS OF RIGHT CAROTID PRESSURE UNDER VARIOUS CONDITIONS IN CATS

Cat No.	Inspiration A_o - mm. Hg	Expiration A_o - mm. Hg	Thoracotomy A_o - mm. Hg	Pulsus Alternans A_o - mm. Hg	
				Greater Pulse	Smaller Pulse
3	16.95*	23.20*	11.00*	-	-
4	10.00*	-	8.70*	-	-
5	10.00*	10.30*	9.50*	-	-
8	215.00	-	135.50	253.50	220.00
12	159.50	171.50	61.00	-	-
			105.00**		
13	233.50	-	128.00	-	-
			140.00**		
14	269.25	-	-	297.00	251.38
15	293.50	-	128.00	-	-
			142.50**		
16	160.00	-	142.38	-	-
17	131.63	-	35.25	-	-

* Pressure pulse records were obtained without reference to base-line (zero mm. Hg pressure).

** 30 min. after thoracotomy

respiration and after thoracotomy in cat 12 are not as great when data of Table 10 instead of Table 11 are used. Therefore, whenever cardiodynamic changes are considered from the data on blood pressure, cognizance should be taken, not merely of changes in the diastolic and systolic pressures, but of the area under the curve and time distribution of the pressure pulse. It could be misleading to place undue emphasis on values of pressures alone. Much additional significant information, which is coded in the pressure pulse, can be recognized when the time distribution of the pressure pulse, and not its statistical mean, are properly analyzed. Further comparison of Tables 10 and 11 and the succeeding tables of this kind will reinforce the significance of the above statements.

Changes in the left ventricular pressure were recorded by means of two methods, namely, via a catheter through the aorta and via a needle catheter through the apex. Many investigators (see Rushmer, 1961) have used the latter method in recording the intraventricular pressure. When intraventricular pressure is recorded via a catheter through the aorta the tracings depict the true course of pressure in the same direction as the blood flow. Whereas, the intraventricular pressure recorded via a needle catheter through the apex represents the pressure fluctuations in the opposite direction of blood flow. From the standpoint of rigorous mathematical and physical analysis of the system, the pressure tracings obtained via a catheter through the aorta yield

much more information about the physical nature of the system than the other method. Indeed, the validity of the second method of obtaining pressure and its usefulness as a physiological parameter can be argued on a very strong physical and mathematical basis. In accordance with Bernoulli's theorem, the best index of pressure fluctuation of a system is one which is in the same direction as the flow change. Since in the cardiovascular system we are interested in the time course of pressure energy which causes flow, then the pressure recording in the direction of flow should be used as the criterion of true pressure fluctuation of the system. In this study, intraventricular pressure was recorded, whenever instrumentation allowed, by both methods. When records were subjected to Fourier analysis the information obtained from both tracing were nearly identical. However, such negative results do not necessarily reduce the soundness of the explanation advanced above. It can only be concluded that the number of points chosen on the pressure pulse curves for Fourier analysis were not sufficient to indicate the expected differences.

Changes in Cardiac Function with Drugs

The dynamic response of the heart to various cardiotonic and cardiodepressor drugs was studied. The dose-duration of the drugs used are presented in Table 12. Note that except for nor-adrenaline a nonlinear dose-duration relation was obtained for all other drugs used. Brown (1952) and Hilton and Brown (1954, 1955) reported that cardiovascular

Table 12

COMPARISON OF DOSE-DURATION OF VARIOUS DRUGS

Cat No.	Dose - μg./kg.		Duration sec.
17	Adrenalin	5	180
17		5	90
10		8.9	320
10		8.9	120
7		10	200
16		12	135
4		16	560
11		20	225
8		54	350
17	Nor-adrenalin	2.5	150
13		13	320
10		17.8	750
4	Acetylcholine	16	35
11		20	210
10		22.2	85
13		170	760
11		200	140
10		222	750
13	Adenylic Acid	7	300
11		8	145
10		8.9	290
7		10	100
6		11.4	200
16		12	110
6	Pitressin	5.7 (units)	80
10	Histamine	122	80

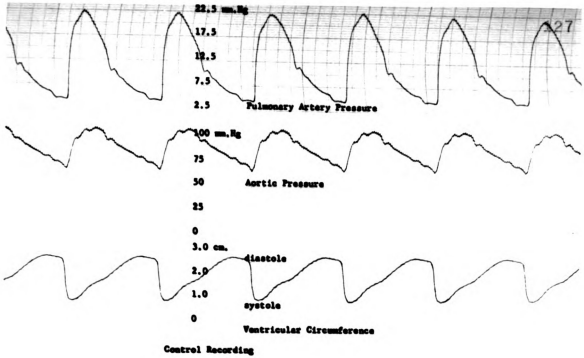
responses to graded doses of adrenalin and histamine, as determined by changes of peak blood pressure, follow a rectangular hyperbolic curve. No attempt was made in this study to correlate the changes in blood pressure with graded doses of the drugs used.

Changes in the pressure pulse contours of pulmonary artery pressure, aortic pressure, and ventricular circumference after adrenalin infusion are shown in the bottom photograph of figure 13. Note a definite distortion of both systolic and diastolic segments of all these tracings. Figure 14 illustrates the effect of small dose (top photograph) and large dose (bottom photograph) of acetylcholine on the contours of ventricular function curves. The marked changes in systolic and diastolic segments of the various cardiac time curves as compared with controls (top photograph of figure 13) can clearly be seen. The data on changes in the peak values of blood pressure and pulse rate after various doses of adrenalin and acetylcholine are presented in Table 13. The values for area under the curve, as calculated by the first coefficient of Fourier transform, for various cardiac function curves are shown in Table 14. It should be noted that injection of various doses of adrenalin did not produce a consistent change in the stroke volume output, as shown by the values of A_o in the last two columns of Table 14. However, the values of A_o in the same two columns indicate that infusion of acetylcholine resulted in a reduction of stroke volume output, except at a dose of 200 μg/Kg. When graphical records such as those shown in figures 13 and 14 were analyzed, and

FIGURE 13

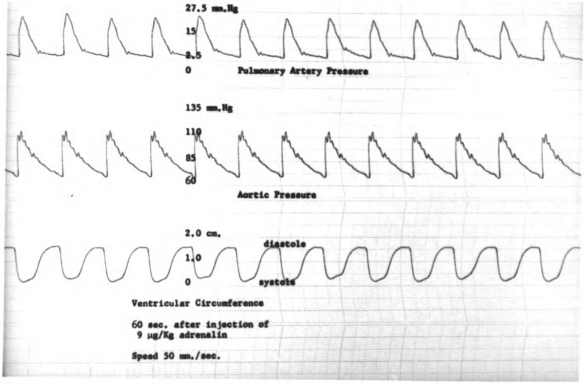
Top--Cardiac time curves under control conditions in the cat. From above downwards, pulmonary artery pressure, aortic pressure, and ventricular circumference recorded at a speed of 100 mm./sec.

Bottom--Changes in contours of ventricular function curves 60 sec. after 9 μg./kg. of adrenalin injection in the cat. From above downwards, pulmonary artery pressure, aortic pressure, and ventricular circumference recorded at a speed of 50 mm./sec.



Control Recording

Speed 100 mm./sec.



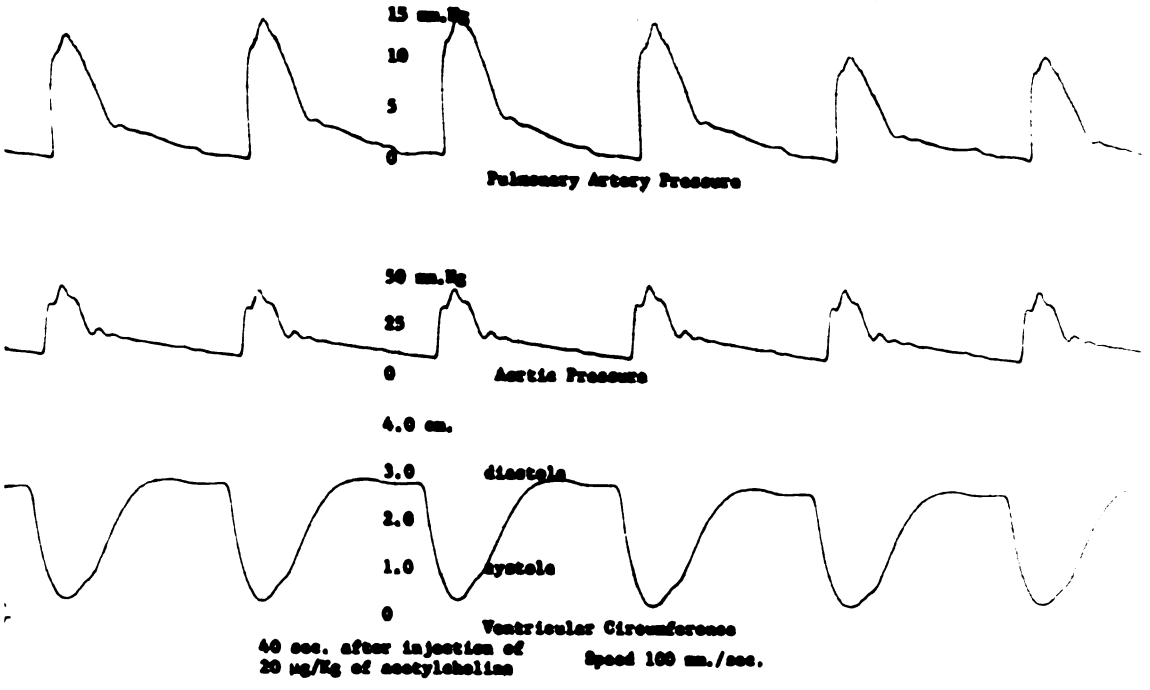
60 sec. after injection of
9 µg/Kg adrenalin

Speed 50 mm./sec.

FIGURE 14

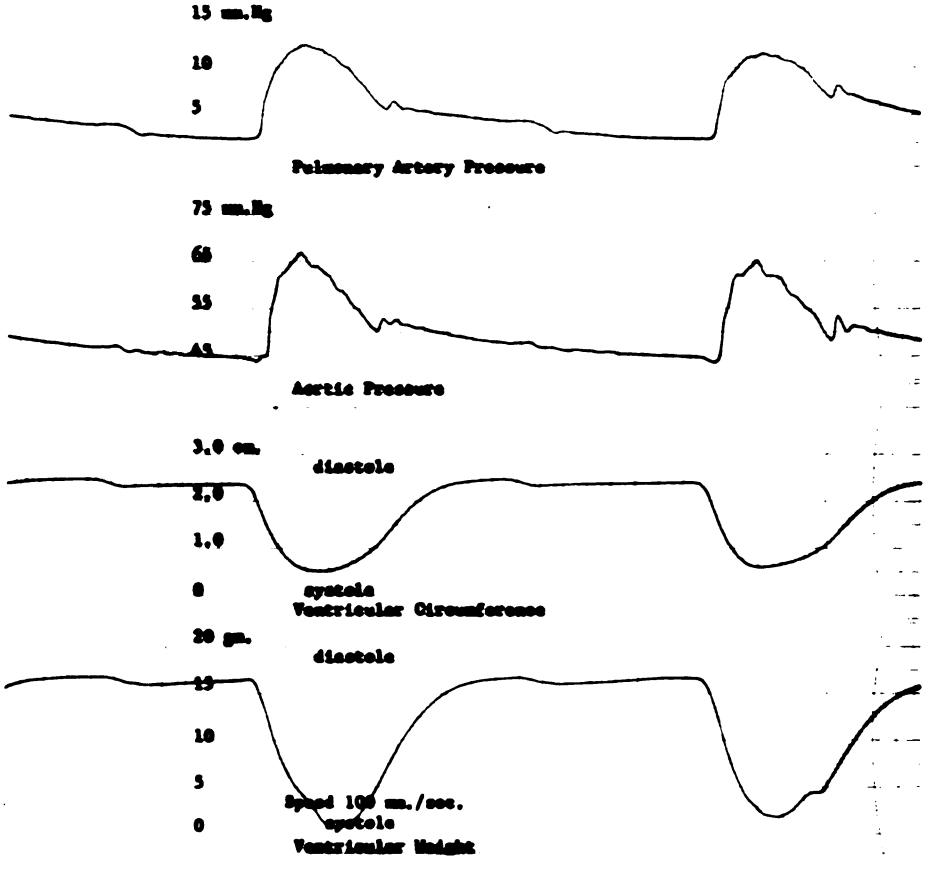
Top--Changes in contours of cardiac time curves 40 sec. after 20 μg./kg. of acetylcholine injection in the cat. From above downwards, pulmonary artery pressure, aortic pressure, and ventricular circumference recorded at a speed of 100 mm./sec.

Bottom--Changes in contours of ventricular function curves 10 sec. after 220 μg./kg. of acetylcholine infusion in the cat. From above downwards, pulmonary artery pressure, aortic pressure, ventricular circumference, and ventricular weight recorded at a speed of 100 mm./sec.



40 sec. after injection of 20 μg/Kg of acetylcholine Speed 100 mm./sec.

10 sec. after injection of 220 μg/Kg of acetylcholine



Speed 100 mm./sec.

Table 13

EFFECT OF VARIOUS DRUGS ON SYSTOLIC BLOOD PRESSURE AND PULSE RATE IN CATS

Treatment	Cat No.	Systolic Blood Pressure mm. Hg		Pulse Rate per min.		Time Lapse Between "Before" and "After" Recordings sec.
		Before	After	Before	After	
Adrenalin						
12 µg./kg.	4	60	117.5	120	100	60
10 µg./kg.	7	80	130	144	90	30
54 µg./kg.	8	50	100	165	90	40
9 µg./kg.	10	88	115	155	170	60
9 µg./kg.	10	15*	25*	155	170	60
9 µg./kg.	10	85	108	155	160	60
9 µg./kg.	10	15*	21*	155	160	60
20 µg./kg.	11	55	70	180	100	100
20 µg./kg.	11	24*	25*	180	100	100
12 µg./kg.	16	83	175	192	200	40
5 µg./kg.	17	110	140	192	216	30

Table 13 (Continued)

Treatment	Cat No.	Systolic Blood Pressure mm. Hg		Pulse Rate per min.		Time Lapse Between "Before" and "After" Recordings sec.
		Before	After	Before	After	
Acetylcholine						
16 μg./kg.	4	60	47.5	120	24	20
22 μg./kg.	10	84	74	160	160	30
22 μg./kg.	10	17*	14*	160	160	30
222 μg./kg.	10	84	68	160	36	10
222 μg./kg.	10	17*	7*	160	36	10
20 μg./kg.	11	55	50	180	144	40
20 μg./kg.	11	21*	17*	180	144	40
200 μg./kg.	11	38	28	168	130	60
200 μg./kg.	11	16*	16*	168	130	60
170 μg./kg.	13	90	58	132	20	20
170 μg./kg.	13	135	100	132	132	150

* Pulmonary artery pressure

Table 14

COMPARISON OF FIRST FOURIER COEFFICIENTS OF BASIC CARDIAC PARAMETERS UNDER VARIOUS CONDITIONS IN CATS

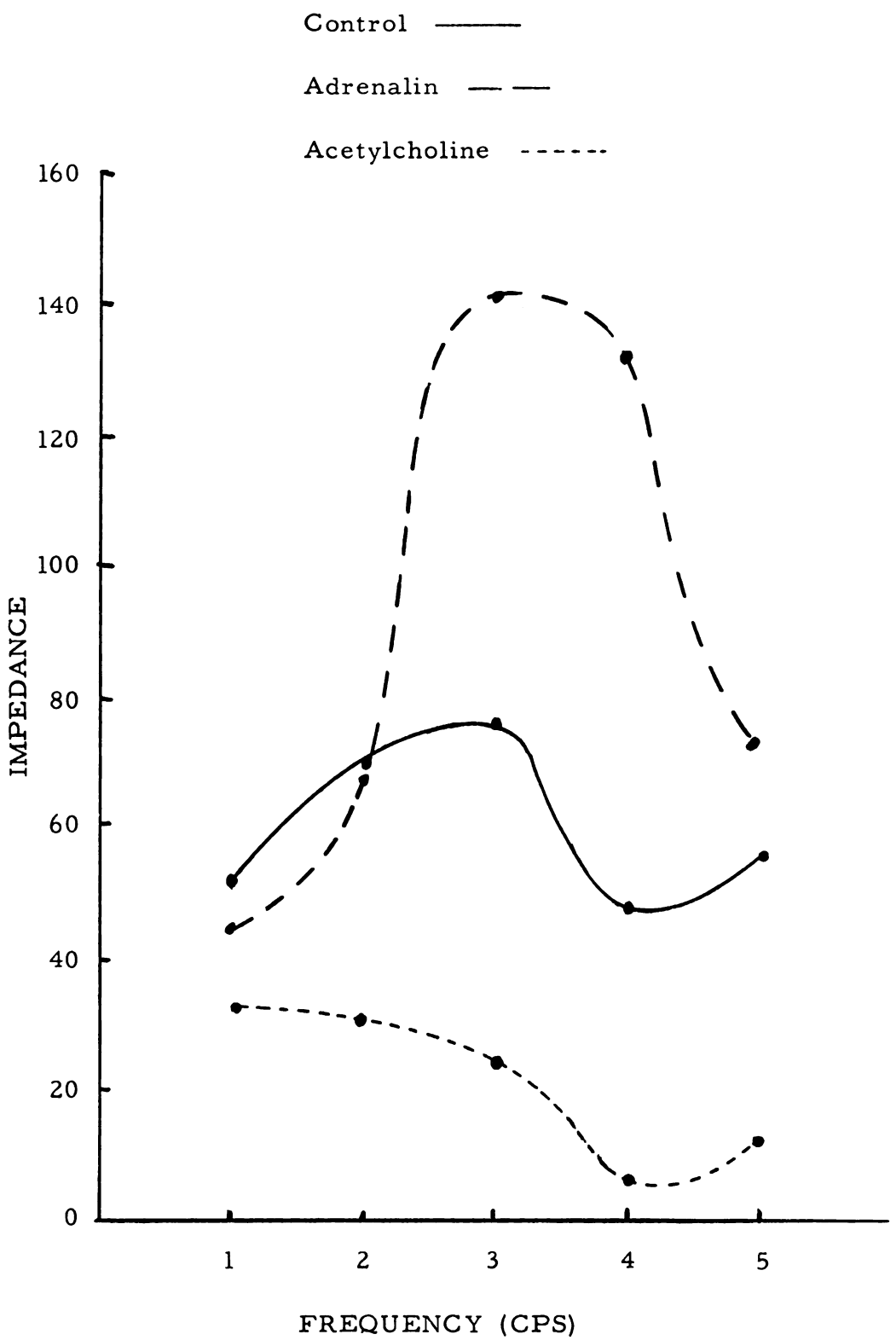
Treatment	Cat No.	Carotid Pressure A_o - mm. Hg		Aortic Pressure A_o - mm. Hg		Pul. Art. Pressure A_o - mm. Hg		Left Vent. Pressure A_o - mm. Hg		Vent. Circ. (ΔC.) A_o - cm.	
		Before	After	Before	After	Before	After	Before	After	Before	After
Adrenalin											
12 µg./kg.	4	10.88*	17.63*	-	-	-	-	74.75	113.00	-	-
10 µg./kg.	7	151.88	170.50	157.00	193.25	-	-	-	-	-	-
54 µg./kg.	8	44.50	115.90	60.88	131.25	-	-	-	-	1.53	1.46
9 µg./kg.	10	-	-	125.13	153.25	14.00	16.45	-	-	1.48	1.61
9 µg./kg.	10	-	-	125.13	142.38	14.00	18.25	-	-	1.48	1.37
12 µg./kg.	16	110.00	236.50	121.50	270.75	-	-	-	-	1.82	2.20
Acetylcholine											
16 µg./kg.	4	10.88*	17.13*	-	-	-	-	74.75	46.63	-	-
22 µg./kg.	10	-	-	115.60	100.70	16.90	13.50	-	-	2.96	2.56
222 µg./kg.	10	-	-	115.60	92.25	16.90	9.63	-	-	2.96	1.40
20 µg./kg.	11	-	-	55.75	42.30	11.95	9.90	-	-	1.85	1.50
200 µg./kg.	11	-	-	76.50	19.70	12.60	17.98	-	-	1.72	1.91
170 µg./kg.	13	135.13	80.25	132.40	63.00	-	-	-	-	0.84	0.29

* Pulse pressure

impedance amplitude and impedance phase angle spectra were constructed, some interesting aspects of the pharmacodynamic action of these drugs were observed. The variations of impedance of cat ventricles are shown in figure 15. Each curve represents six different experiments. In essence, all curves have the same contour distribution over the frequency analyzed. The adrenalin curve (broken line), in contrast to that of turtle, shows an initial decline in impedance (low frequency components), followed by a steady rise in impedance reaching its peak at approximately 3 cps. The observed delay in the rise of impedance might be attributed to the fact that, in the cat, adrenalin exerts its primary action on the ventricular conductive system, and secondarily on the myocardial fibers. On the other hand, in the turtle, which does not have a conductive system similar to that of cat, the primary action of adrenalin is on the muscle fibers. The acetylcholine curve (dotted line) in figure 15 shows a reduction in impedance (low frequency components) indicating a weak myocardial contraction and a diminished wave reflection due to peripheral vasodilation. There is no change in the frequency of the minimum impedance after acetylcholine (4 cps) as compared with control (4 cps). These results are not unusual, but rather fit well with other evidence obtained by entirely different experimental means. The author does not claim to have found new evidence for the mechanism of actions of these drugs. On the contrary, in applying a mathematical method to the cardiac time curves we have given additional insight to the hypothetical

FIGURE 15

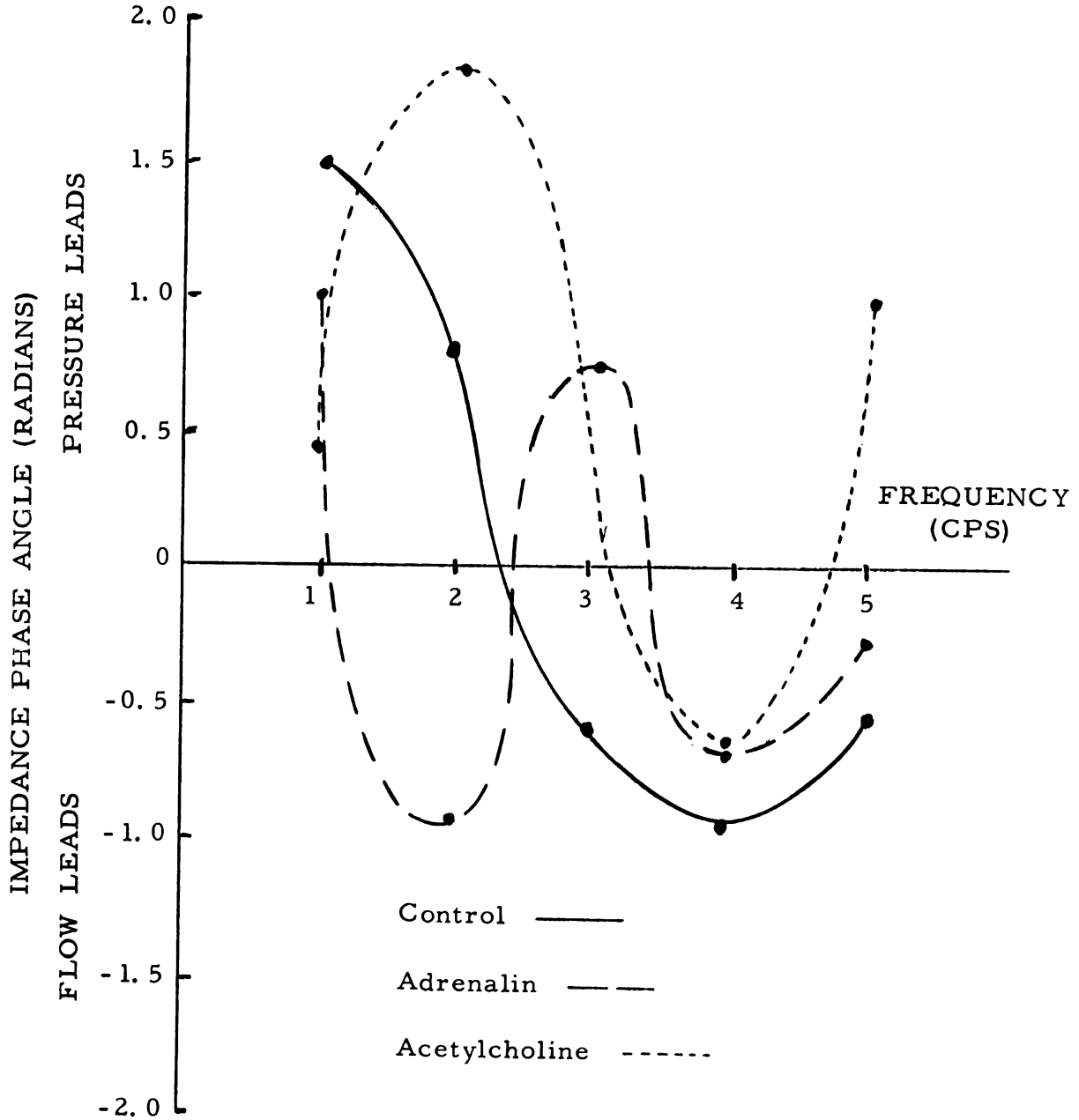
Variations of impedance with pulsating frequency of the cat ventricle under control conditions (solid line), after adrenalin injection (broken line), and after acetylcholine infusion (dotted line).


Control
Adrenalin
Acetylcholine
160
140
120
100
80
60
40
20
0
IMPEDANCE
1
2
3
4
5
FREQUENCY (CPS)

action of these drugs in the turtle and cat. Another interesting aspect of this mathematical method is that it unveils strikingly the time course of action of these drugs and the manner in which they affect the three parameters responsible for generation of the cardiac time curves, namely, mass, friction, and compliance (Peterson, 1954). This is illustrated in figure 16 which shows the impedance phase angle spectrum of cat ventricle. Under control conditions, the inertial force of cardiac contraction is expended to accelerate a mass of blood. This is shown by the segment of the curve in which the pressure fluctuations precede the flow. At approximately 2. 5 cps the inertial forces overcome the resistive forces (where phase angle fluctuations cross the abscissa) and flow leads the pressure. This indicates that at this frequency the elastic elements of the system set in. The acetylcholine curve (dotted lines) shows the time course of the above sequence. This is in accord with expectation, since acetylcholine is thought to raise the threshold for cardiac excitation, thus to prolong the contraction process. The phenomenon was also illustrated by the graphs of figure 15. In contrast, the adrenalin curve (broken line), as in the turtle, produces a reversal of the above sequence of action. Adrenalin brings about a rapid acceleration of the blood so that the inertial forces overcome the resistive forces much sooner. At approximately 1. 5 cps the elastic components of the system set in. Then, at 3 cps the system partly repeats itself. The reason for this repetition is not clear. This analysis of the time course of action of drugs in

FIGURE 16

Variations of impedance phase angle with pulsating frequency of the cat ventricle under control conditions (solid line), after adrenalin injection (broken line), and after acetylcholine infusion (dotted line).


IMPEDANCE PHASE ANGLE (RADIANS)
PRESSURE LEADS
FLOW LEADS
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2.0
1
2
3
4
5
FREQUENCY (CPS)
Control
Adrenalin
Acetylcholine

determining the sequence of the three basic physical forces responsible for the genesis of pressure pulse in cat have never been reported. It is evident that application of Fourier analysis made possible a different view of the action of these drugs.

Harmonic analysis of the left ventricular pressure under various conditions is shown in Table 21. There is a definite increase in the value of A_o (area under the curve) after adrenaline infusion. The modulus of the first harmonic, after adrenaline injection, shows a substantial increase over the control. However, the moduli of the second and third harmonics show a sign reversal which confirms the interpretations advanced earlier based on impedance phase angle spectrum. In addition, a marked decrease in the sine function of the adrenaline curve is observed. Both of these findings support the ideas suggested earlier that proper mathematical analysis, namely, Fourier transform, would yield more insight into the mechanisms and time course of cardiac function under control and experimental conditions.

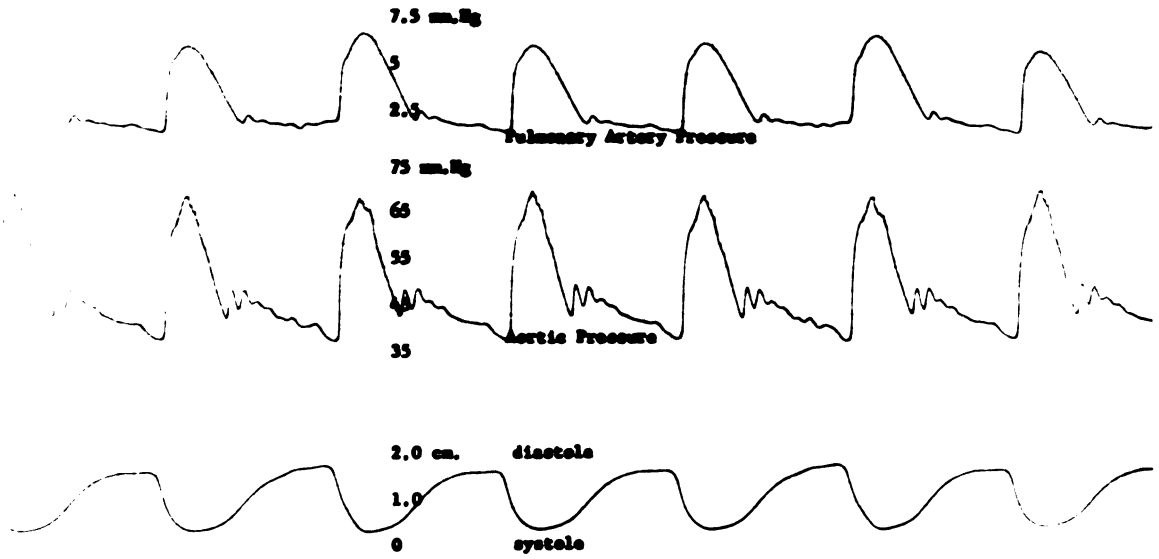
Harmonic analysis of the left ventricular pressure after acetylcholine infusion is presented in Table 21. Note the sustained decrease in the values of A_o, the moduli of the first, second, and third harmonics and the reduction in the argument of the sinusoidal functions. Fourier components for aortic pressure are shown in Table 22. There was a definite increase in the values of A_o, the moduli of the three harmonics, and a marked reduction in the argument of the sine functions after

adrenalin infusion. However, in contrast to the left ventricular pressure, no sign reversal was observed in the computed moduli. This dichotomy of the results tempts one to speculate on the difference in the mode of action of adrenalin on the heart and the vessels. Harmonic analysis of the aortic pressure curve after acetylcholine produced the expected changes (reduction in the values of moduli) but revealed no information on the difference in the mode of action of this drug on the heart and the blood vessels. However, Fourier components of ventricular circumference curves (Table 23) revealed some interesting results. There was an increase in the values of A_o after adrenalin injection. The relationship of this increase with respect to alteration of stroke volume output or the time course of contraction or relaxation of the heart is not clear. However, it can be noted that after adrenalin, the first harmonic becomes dominant and the contour of the ventricular circumference curve takes the form of a true sinusoid. This conclusion is partly confirmed by the contour of the ventricular circumference tracing (see figure 13, bottom photograph). Fourier components of the circumference curve after acetylcholine (Table 23) indicates a decrease in the value of A_o and the argument of the sine function, but relatively no change in the values of moduli of the three harmonics. In effect, these results support the contention advanced earlier (based on impedance amplitude and phase angle spectrum) that acetylcholine brings about a decrease in the force of contraction, prolongs the systolic phase of

FIGURE 17

Top--Changes in contours of cardiac time curves 40 sec. after 9 μg./kg. of adenylic acid injection in the cat. From above downwards, pulmonary artery pressure, aortic pressure, and ventricular circumference recorded at a speed of 100 mm./sec.

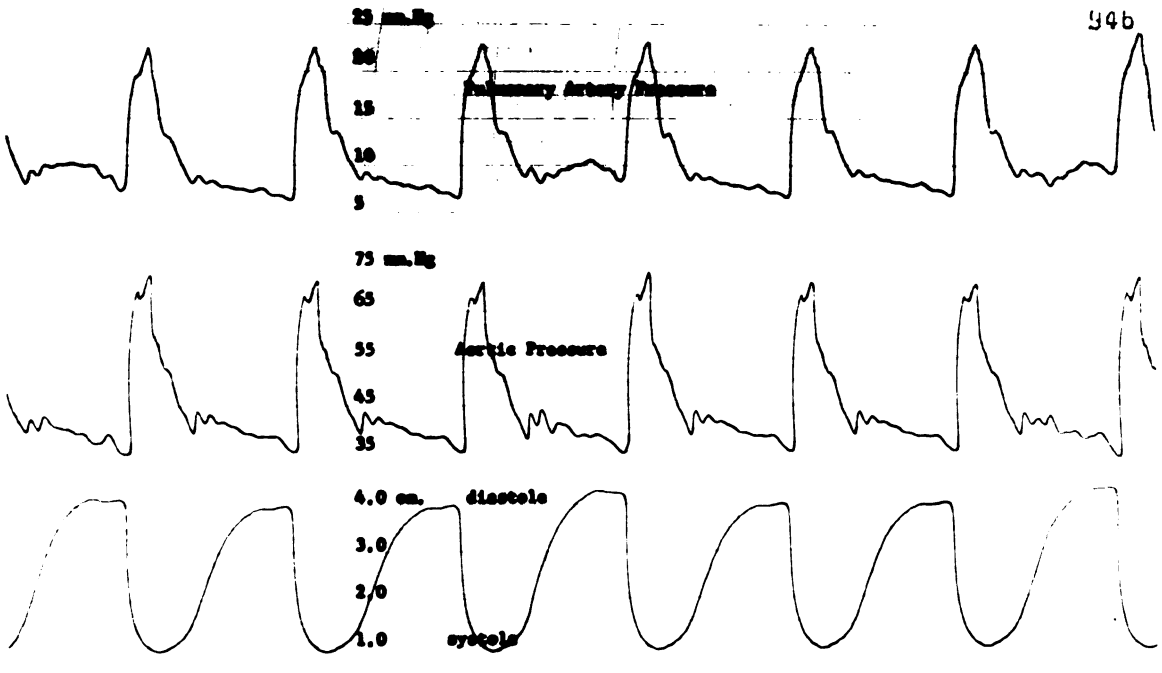
Bottom--Changes in contours of ventricular function curves 30 sec. after 120 μg./kg. of histamine infusion in the cat. From above downwards, pulmonary artery pressure, aortic pressure, and ventricular circumference recorded at a speed of 100 mm./sec.



Ventricular Circumference

40 sec. after injection of
9 µg/Kg of adenylic acid

Speed 100 mm./sec.



Ventricular Circumference

30 sec. after injection of
120 µg/Kg of histamine

Speed 100 mm./sec.

cardiac cycle, and produces peripheral vasodilation.

Changes in the contours of the cardiac time curves after injection of adenylic acid and histamine are shown in figure 17. When compared to controls (top photograph of figure 13) there are definite distortions of both systolic and diastolic segments of the recorded curves. Note the rapid rise in systolic pressure and the marked drop in the incisural pressure. This is in accord with the vasodilating effect of these drugs on the peripheral vascular bed (Alexander, 1953). Since the heart is completely filled and as a result of vasodilation has a lower aortic pressure to work against, its initial ejection is rapid and the systolic peak occurs early. Because of vasodilation the peripheral runoff of blood exceeds the amounts ejected by the heart in midsystole, hence the pressure starts to drop well in advance of the incisura and continues to drop steeply throughout diastole. These conclusions are adequately supported by the cardiac time curves tracings (top photograph of figure 17) and the impedance phase angle spectra (see figure 19). The shape of the recorded ventricular function curves after adenylic acid and histamine are similar to those observed by Alexander (1953) and Peterson (1954). The explanations offered by these investigators for the sources or possible causes of distortion of the contours are different. Alexander (1953) considers the shape of the pressure pulse to be the synthesis of two components, namely, the transmitted pulse and the reflected wave. On this basis, Alexander and Webb (1947) analyzed the differences in the contours of pressure

pulse in shock and hemorrhage. The difference in the two curves was considered to be due to the marked changes in the reflected waves. They concluded that, "While such a theoretical synthesis of pulse types does not in itself prove the mechanism of changes in pulse contour observed in the animal, it does offer a rational approach to the interpretation of pulse form." The interpretation of the changes in the pulse pressure contour based on the reflected or standing wave makes use of the assumption that the vascular system is free of damping (Hardung, 1962). Since the same authors and their colleagues have made significant contributions to the concept of existence of vascular damping, it is rather astonishing that they consider standing wave analysis of pulse pressure a "rational" approach. Peterson (1954), as described earlier, takes a different, and apparently logical approach, to the problem. Peterson synthesized the pulse pressure from the sum of contributions of three forces, namely, mass, friction, and compliance. There is little doubt that such forces do exist in the vascular system. However, the manner of their complex interaction is not known. Peterson (1954) believes that the information resulting from the interplay of these forces is coded within the shape of the pulse in a complex manner. Thus, Fourier analysis of these complex curves would be the logical and rational approach to the problem of decoding the recorded pulses.

Table 15 presents the data on the values of systolic blood pressure and pulse rate under control conditions, and after infusion of various

Table 15

EFFECT OF VARIOUS DRUGS ON SYSTOLIC BLOOD PRESSURE AND PULSE RATE IN CATS

Treatment	Cat No.	Systolic Blood Pressure mm. Hg		Pulse Rate per min.		Time Lapse Between "Before" and "After" Recordings sec.
		Before	After	Before	After	
Adenylic Acid						
11.4 µg./kg.	6	80	25	144	114	100
10 µg./kg.	7	80	75	144	120	30
9 µg./kg.	10	85	68	155	170	40
9 µg./kg.	10	15*	14*	155	170	40
8 µg./kg.	11	38	28	160	110	30
8 µg./kg.	11	18*	13*	160	110	30
7 µg./kg.	13	135	90	132	120	90
12 µg./kg.	16	70	63	180	168	30
Nor-adrenalin						
18 µg./kg.	10	85	160	144	156	60
18 µg./kg.	10	16*	23*	144	156	60
12 µg./kg.	16	70	155	180	198	30
Pitressin						
5.7 units/kg.	6	42.5	47.5	-	-	50
5.7 units/kg.	6	65	72.5	130	140	-
Histamine						
122 µg./kg.	10	85	70	160	180	20
122 µg./kg.	10	17*	21*	160	180	20

* Pulmonary artery pressure

drugs. The area under the pressure pulse curves for various cardiac parameters after drug infusion is shown in Table 16. The effect of various drugs on the carotid, aortic, and pulmonary artery pressure and stroke volume (change in ventricular circumference, ΔC) can easily be deduced from these two tables. Figure 18 shows the plot of variations of impedance amplitude of cat aorta under control, after nor-adrenalin and after adenylic acid infusion. Each curve represents five different experiments. In essence, all curves had similar contour distribution over the frequency analyzed. Note that nor-adrenalin curve (broken line) shows a definite increase in impedance at lower frequencies. This rise in impedance is due to an increase in the frequency of wave reflection from periphery which is the result of vasoconstriction. The Fourier treatment of the data makes this conclusion possible. At approximately 3 cps there is a further increase in impedance which falls off slowly. The adenylic acid curve (dotted line) shows a pattern which is somewhat similar to that of nor-adrenalin but it is displaced downward. The impedance spectra for these two drugs are in accord with their vasoconstricting and vaso-dilating action which were explained above.

Variations of impedance phase angle of cat aorta are shown in figure 19. The nor-adrenalin curve (broken line) shows that initially flow precedes the pressure fluctuations. However, shortly after 1 cps there is a rapid increase in inertial forces which indicate acceleration

Table 16

COMPARISON OF FIRST FOURIER COEFFICIENTS OF BASIC CARDIAC PARAMETERS UNDER VARIOUS CONDITIONS IN CATS

Treatment	Cat No.	Carotid Pressure A_o - mm. Hg		Aortic Pressure A_o - mm. Hg		Pul. Artery Pressure A_o - mm. Hg		Vent. Circ. (Δ C.) A_o - cm.	
		Before	After	Before	After	Before	After	Before	After
Adenylic Acid									
11.4 µg./kg.	6	-	-	44.25*	27.40*	-	-	2.30	1.62
10 µg./kg.	7	151.88	78.75	151.00	88.38	-	-	1.46	1.00
9 µg./kg.	10	-	-	125.13	82.85	14.00	9.88	1.48	1.10
8 µg./kg.	11	-	-	26.75*	23.40*	17.70	12.35	1.93	1.44
7 µg./kg.	13	190.00	114.50	193.00	110.40	-	-	1.37	0.70
12 µg./kg.	16	86.50	76.50	52.62	85.25	-	-	0.61	1.76
Nor-adrenalin									
18 µg./kg.	10	-	-	120.25	237.13	14.48	16.50	1.16	1.38
12 µg./kg.	16	86.50	191.25	52.62	115.77	-	-	0.61	0.48
Pitressin									
5.7 units/kg.	6	-	-	44.25*	59.25*	-	-	2.20	3.30
Histamine									
122 µg./kg.	10	-	-	115.60	81.20	16.90	18.43	2.96	2.62

* Pulse pressure

FIGURE 18

Variations of impedance of the cat aorta with pulsating frequency under control conditions (solid line), after nor-adrenalin injection (broken line), and after adenylic acid infusion (dotted line).

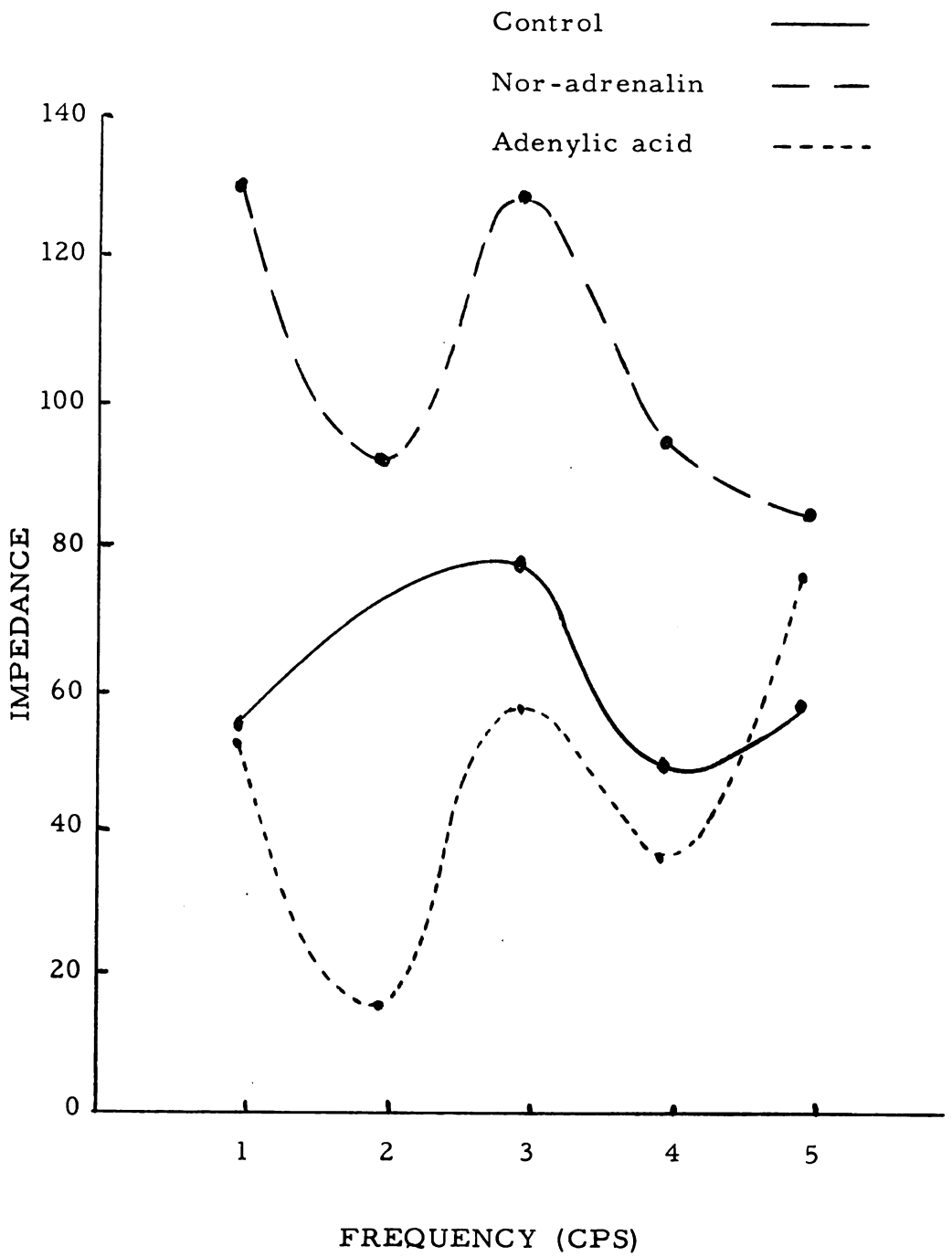
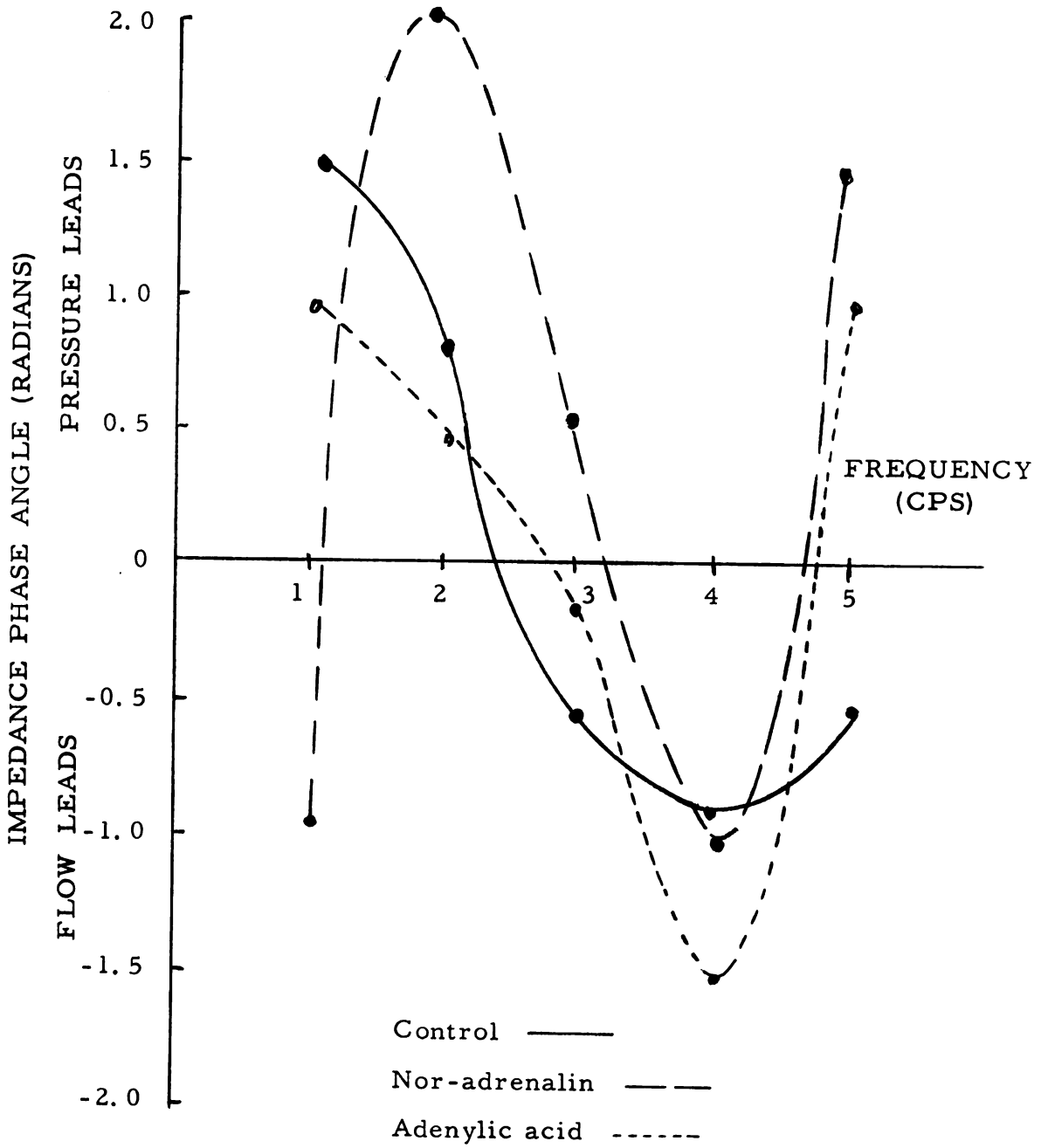

Control
Nor-adrenalin
Adenylic acid
140
120
100
80
60
40
20
0
IMPEDANCE
1
2
3
4
5
FREQUENCY (CPS)

FIGURE 19

Variations of impedance phase angle with pulsating frequency of the cat aorta under control conditions (solid line), after nor-adrenalin injection (broken line), and after adenylic acid infusion (dotted line).

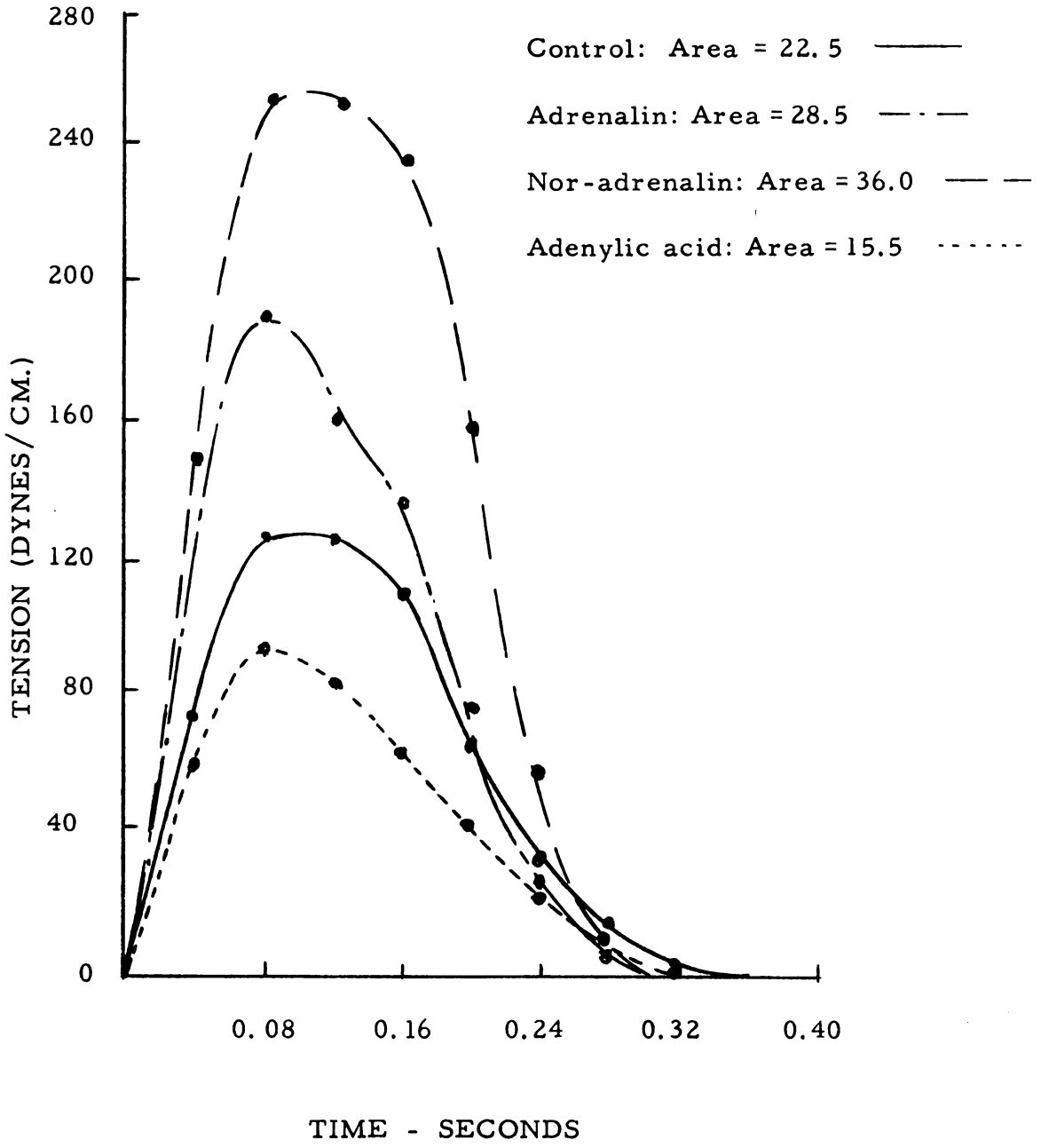

IMPEDANCE PHASE ANGLE (RADIANS)
PRESSURE LEADS
FLOW LEADS
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2.0
1
2
3
4
5
FREQUENCY (CPS)
Control
Nor-adrenalin
Adenylic acid

of blood in the vascular system. At approximately 3 cps the elastic elements of the system set in, as indicated by the segment of the curve in which flow fluctuations precede pressure fluctuations. The adenylic acid curve (dotted line) shows a mixed pattern resembling the initial half of the control curve and the second half of nor-adrenalin curve. The overall effect of adenylic acid, as interpreted by this curve, is the prolongation or persistance of the compliance characteristics of the system. This implies that adenylic acid, acting as a vasodilator, decreases vascular impedance and results in a flow under a reduced pressure gradient.

Comparison of the time course of tension of cat aorta under control, after adrenalin, nor-adrenalin, and adenylic acid infusion is shown in figure 20. Note the changes in the ascending limb, the summit, and the descending limb of the tension curve under various conditions. Each curve in figure 20 represents a minimum of five experiments. The area under each curve, as calculated by the trapezoidal method of integration, shows a 40% increase in aortic tension with nor-adrenalin as compared with only 26% with adrenalin. This indicates that the greater vasoconstricting effect of nor-adrenalin is accompanied by the expenditure of additional energy by the vessel. In contrast, the aortic tension during adenylic acid infusion showed a 40% reduction. These data provide further support to the conclusions reached from Fourier analysis of cardiac time curves after drug infusion.

FIGURE 20

Comparison of the time course of tension of the cat aorta under control conditions (solid line), after adrenalin injection (centered line), after nor-adrenalin injection (broken line), and after adenylic acid infusion (dotted line).


280
240
200
160
120
80
40
0
TENSION (DYNES/CM.)
0.08
0.16
0.24
0.32
0.40
TIME - SECONDS
Control: Area = 22.5
Adrenalin: Area = 28.5
Nor-adrenalin: Area = 36.0
Adenylic acid: Area = 15.5

Fourier components of aortic pressure and ventricular circumference after adenylic acid infusion are presented in Tables 22 and 23, respectively. Note a significant decrease in the value of A_o, the argument of the sinusoidal function, and moduli of the three harmonics of the aortic pressure curve as compared to control. The marked reduction of these values indicates the peripheral vasodialating effect of this drug as explained earlier.

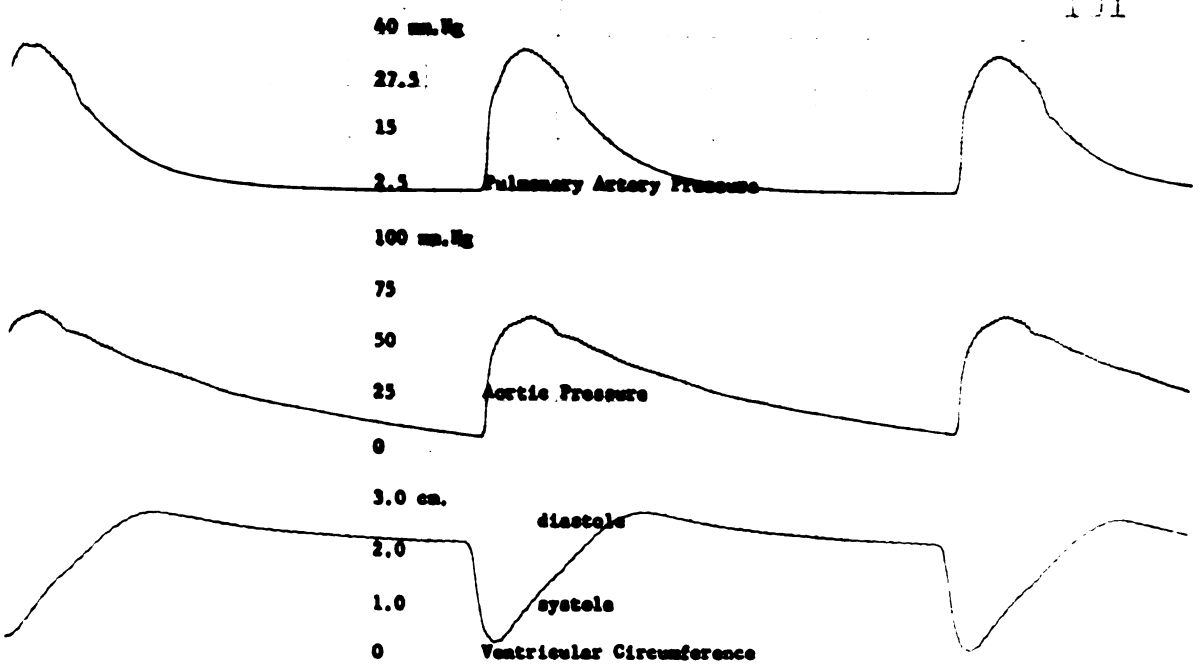
Fourier components of the circumference curve show no significant change in values as compared with control. This clearly supports the contention (Alexander, 1953) that adenylic acid has little or no effect on the heart. These conclusions regarding the action of adenylic acid based on Fourier analysis of pressure and circumference curves reported here provide strong evidence for the use and application of Fourier transform in deducing cardiac function from the pressure pulse contour.

Cardiac responses to faradic stimulation of intact vago-sympathetic trunk were studied in three cats. Figure 21 depicts the changes in the contour of ventricular function curves during right vagus (top photograph) and left vagus (bottom photograph) stimulation. Stimulus was applied by means of an electrodyne stimulator at a frequency of 25 to 30 cps. Note the marked drop in systolic pressure after right vagus stimulation followed by a slow fall in the diastolic pressure. The ventricular circumference curve, after vagus stimulation, shows a definite decrease in systolic ejection and a marked increase in diastolic filling. The changes

FIGURE 21

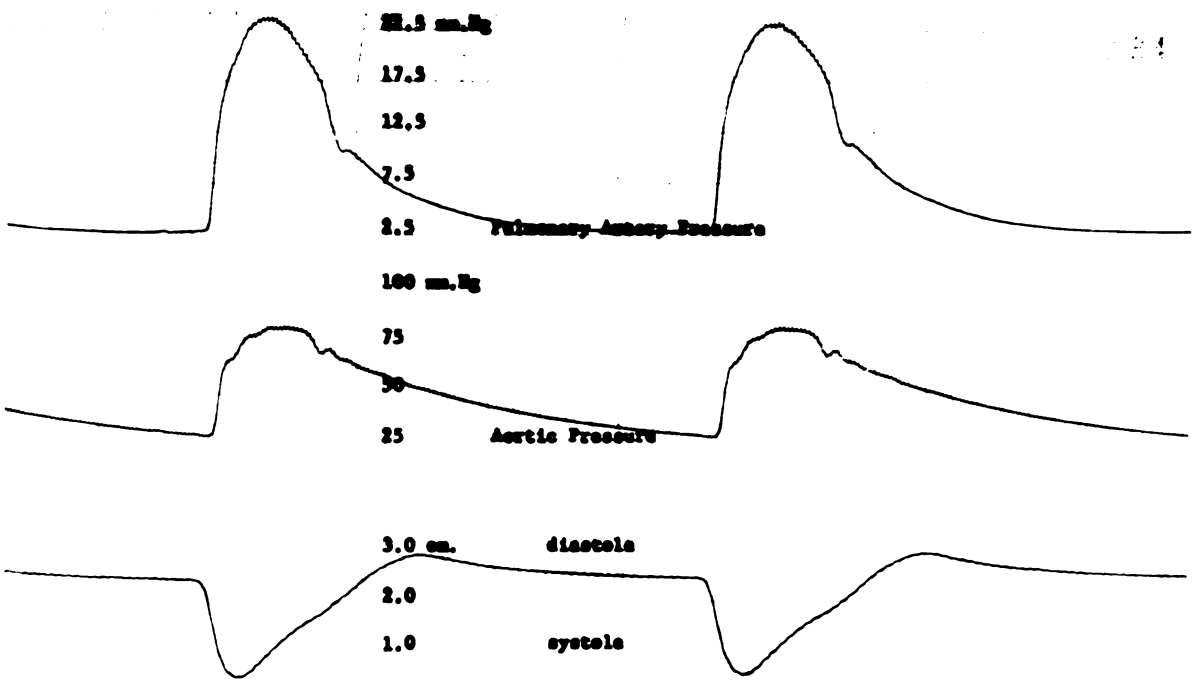
Top--Changes in contours of cardiac time curves during stimulation of right intact vago-sympathetic trunk in the cat. From above downwards, pulmonary artery pressure, aortic pressure, and ventricular circumference recorded at a speed of 100 mm./sec.

Bottom--Changes in contours of cardiac function curves during stimulation of left intact vago-sympathetic trunk in the cat. From above downwards, pulmonary artery pressure, aortic pressure, and ventricular circumference recorded at a speed of 100 mm./sec.



During Stimulation of Right Vagus
With 30 Volts

Speed 100 mm/sec.



During Stimulation of Left Vagus
with 30 Volts

Speed 100 mm./sec.

in blood pressure and heart rate are shown in Table 17. The area under the various cardiac curves as computed by the first coefficient of Fourier transform, is presented in Table 18. Note a decrease in the stroke volume (change in ventricular circumference, ΔC), after vagus stimulation as compared with control.

In order to determine the time course of vagus depression of the heart the graphical records such as those shown in figure 21 were subjected to Fourier analysis. The variation of impedance amplitude of cat aorta under control conditions, after acetylcholine injection, and during right vagus stimulation is shown in figure 22. Note that both the acetylcholine infusion and the right vagus stimulation show approximately the same qualitative pattern of impedance spectra. Both curves indicate slight modification of initial impedance followed by a sharp reduction of impedance at frequencies between 2 to 4 cps. The decrease in impedance at these frequencies indicates a reduction in wave reflection due to peripheral vasodilation. The marked difference in the quantitative values of impedance at various frequencies can be interpreted as follows. Stimulation of the vago-sympathetic trunk produces its effect primarily on the heart, hence a smaller reduction in impedance of the aorta thus indicating little or no peripheral vasodilation. However, acetylcholine acts as a vasodilator and produces a marked reduction in the impedance due to peripheral dilation. Fourier analysis has provided a quantitative difference in the action of acetylcholine and the vago-sympathetic trunk

Table 17

CHANGES IN SYSTOLIC BLOOD PRESSURE AND PULSE RATE UNDER VARIOUS CONDITIONS IN CATS

Treatment	Cat No.	Systolic Blood Pressure mm. Hg		Pulse Rate per min.		Time Lapse Between "Before" and "After" Recordings sec.
		Before	After	Before	After	
Cessation of Artificial Respiration	4	65	99	120	120	50
	6	-	-	-	-	-
	9	110	125	228	210	50
	10	88	145	192	180	30
	10	15*	23*	192	180	30
	10	85	133	180	165	40
	10	15*	34*	180	165	40
	17	110	130	198	153	60
Stimulation of Right Vagus, 30 Volts	7	113	90	144	60	10
	10	85	70	180	110	10
	10	17*	17*	180	110	10
	11	98	70	175	65	5
	11	34*	33*	175	65	5
Stimulation of Left Vagus, 30 Volts	11	105	88	162	60	5
	11	22*	24*	162	60	5

* Pulmonary artery pressure

Table 18

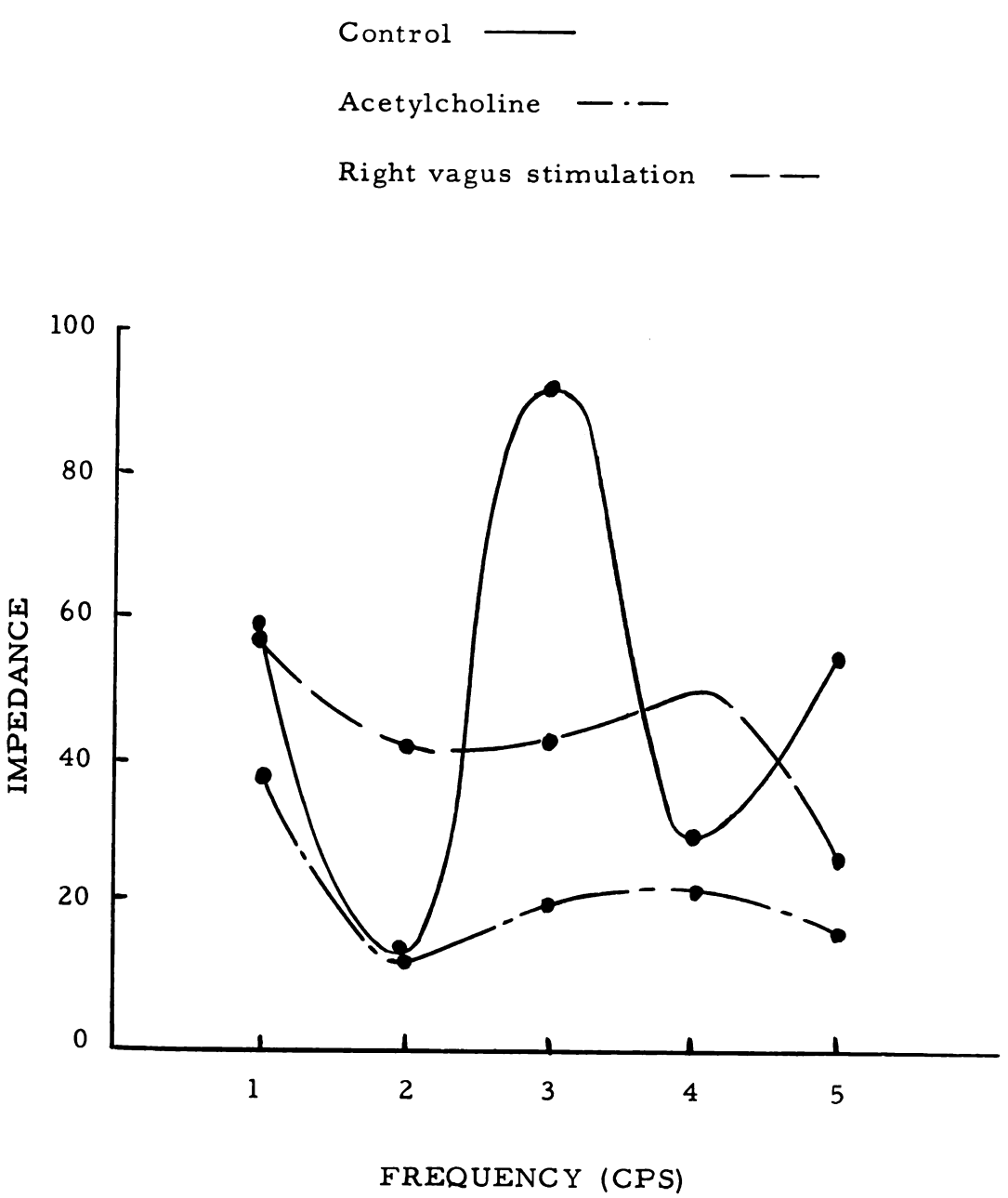
COMPARISON OF FIRST FOURIER COEFFICIENTS OF BASIC CARDIAC PARAMETERS UNDER VARIOUS CONDITIONS IN CATS

Treatment	Cat No.	Carotid Pressure A_o - mm. Hg		Aortic Pressure A_o - mm. Hg		Pul. Art. Pressure A_o - mm. Hg		Left Vent. Pressure A_o - mm. Hg		Vent. Circ. (Δ C.) A_o - cm.	
		Before	After	Before	After	Before	After	Before	After	Before	After
Cessation of Artificial Respiration	4	9.70*	18.70*	-	-	-	-	67.94	100.70	-	-
	6	-	-	44.25*	40.40*	-	-	-	-	2.20	3.90
	9	-	-	133.00	-	-	-	81.00	89.00	0.91	1.10
	10	-	-	115.13	211.38	14.54	20.51	-	-	1.13	0.88
	10	-	-	114.50	185.75	14.44	27.19	-	-	0.99	0.68
	17	76.00	114.00	106.15	155.00	-	-	-	-	-	-
Stimulation of Right Vagus -- 30 Volts	7	151.88	89.93	157.00	90.13	-	-	-	-	1.46	1.00
	10	-	-	114.30	123.80	16.65	14.90	-	-	3.10	2.65
	11	-	-	129.40	66.00	33.00	17.40	-	-	1.24	1.37
Stimulation of Left Vagus -- 30 Volts	11	-	-	151.75	96.00	51.20	14.30	-	-	1.22	0.90

* Pulse pressure

FIGURE 22

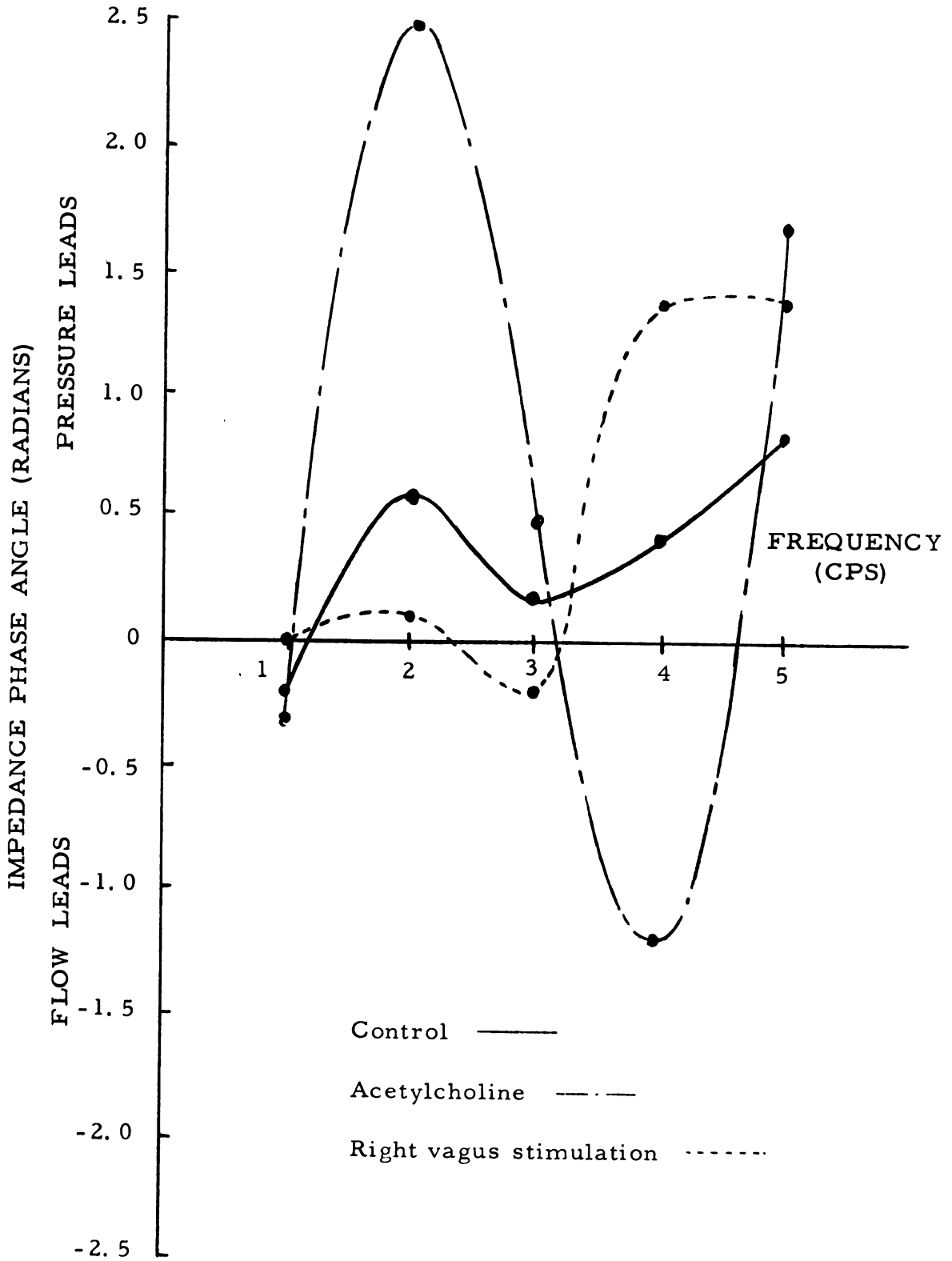
Variations of impedance with pulsating frequency of the cat aorta under control conditions (solid line), after acetylcholine injection (centered line), and during right vagus stimulation (broken line).


Control
Acetylcholine
Right vagus stimulation
100
80
60
40
20
0
IMPEDANCE
1
2
3
4
5
FREQUENCY (CPS)

stimulation with respect to generation and propagation of the pressure pulse. Figure 23 depicts the changes in impedance phase angle of cat aorta with pulsating frequency. The acetylcholine curve (centered line) shows a marked exaggeration of the effects of the inertial components of the system as compared to the control. Since the inertial characteristics of the system represent that aspect of cardiac energy which accelerates the blood, then cardiac inhibition by acetylcholine might be manifested in the decrease in blood velocity and hence exaggeration of the inertial characteristics of the system. In the interval of 3 to 5 cps the acetylcholine curve shows an increase in the elastic characteristics of the system. This is indicated by that segment of the curve where flow precedes the pressure fluctuations. This is attributed to the peripheral vasodilation due to the action of acetylcholine. The impedance phase angle during right vagus stimulation shows a decrease in the inertial characteristics of the system, between frequencies of 1 to 3 cps, as compared to the control and acetylcholine curves. Furthermore, vagus stimulation curve shows a marked augmentation of the effects of the inertial components of the system between frequencies of 3 to 5 cps. This is in contrast to the acetylcholine curve at these frequencoes. These observations confirm the conclusions stated above (based on the analysis of impedance spectrum) on the differential action of acetylcholine and stimulation of vagus nerve.

FIGURE 23

Variations of impedance phase angle with pulsating frequency of the cat aorta under control conditions (solid line), after injection of acetylcholine (centered line), and during right vagus stimulation (dotted line).


IMPEDANCE PHASE ANGLE (RADIANS)
PRESSURE LEADS
FLOW LEADS
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2.0
-2.5
1
2
3
4
5
FREQUENCY (CPS)
Control
Acetylcholine
Right vagus stimulation

Fourier components of aortic pressure and ventricular circumference under control and during right vagus stimulation are shown in Tables 22 and 23, respectively. The changes in the various parameters of Fourier components of aortic pressure and circumference curves are self-explanatory and confirm the conclusions reached based on amplitude and phase impedance spectra.

Changes in Peripheral Resistance and Venous Return

In order to study the dynamic alteration of cardiac time curves during acute changes of peripheral resistance and venous return three different experiments were performed. Acute alteration of pulmonary and systemic resistances was produced by stopping artificial respiration and occluding thoracic aorta, respectively. Venous return to the heart was altered by acute occlusion of pulmonary artery and both vena cavae and saline infusion. Changes in systemic and pulmonary pressures after varied periods of stopping the artificial respiration are shown in Table 17. The area under the curve, as computed by the first coefficient of Fourier transform, for various cardiac parameters are presented in Table 18. Note an increase in both systemic and pulmonary artery pressures. The increase in pulmonary artery pressure is attributed to the increased pulmonary resistance due to collapse of the lungs and hypercapnia. These conclusions are in accord with those of Nisell (1951) who studied the influence of blood gases on the pulmonary vessels

of the cat. Using an isolated perfused lung, Nisell observed that increasing CO_2 concentration of perfusing air resulted in an increased resistance and increased pulmonary artery pressure. He attributed the increase in pulmonary resistance to dilation of arterioles and constriction of pulmonary venules.

Fourier components of aortic and pulmonary artery pressures and ventricular circumference curves are shown in Tables 21, 22, and 23, respectively. The area under the pulmonary artery pressure (Table 21) shows a marked increase over the control. The moduli of the three harmonics are substantially greater than the controls. However, little or no change occurred in the argument of the sinusoidal function. Similar changes were observed in the harmonic components of aortic pressure (Table 22). The area under the ventricular circumference curve (Table 23) decreased indicating a reduced stroke volume output. The changes in the Fourier components of the various cardiac time curves, during cessation of artificial respiration, support and confirm the works of Nisell and those reported here that the rise in systemic and pulmonary pressure were due to increased pulmonary resistance.

I. Occlusion of Vessels

The cardiac response to sudden changes of systemic resistance was studied in two cats by acute occlusion of thoracic aorta. Such a constriction of the aorta produces marked changes in the contour of the

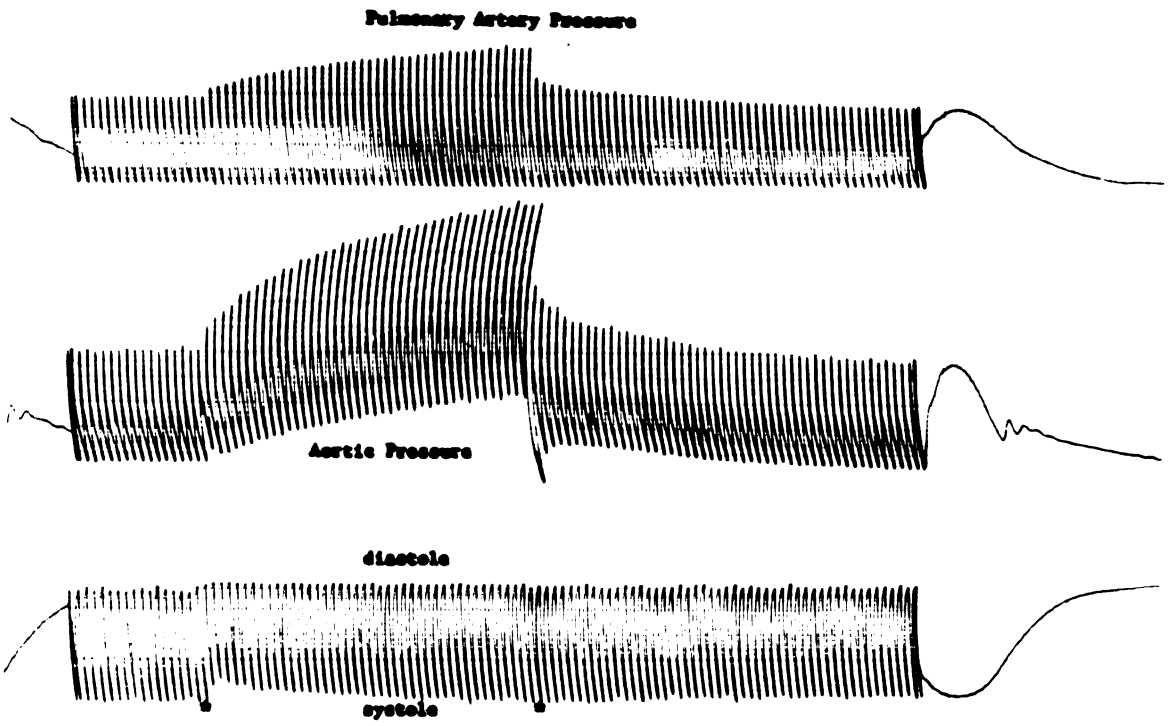
aortic pressure pulse as shown in figure 24. By scanning this record (bottom photograph) from right to left, a number of alterations in the detailed contours are noted. The initial systolic upstroke shows a marked increase in amplitude. In addition, the systolic pulse which is well rounded in the control pulse, tends to peak and results in a higher incisura. The increase in the incisural pressure is clearly evident from the top photograph of figure 24. The changes in systolic pressure during aortic occlusion are shown in Table 19. The values for area under the various cardiac time curves are shown in Table 20. The ventricular circumference tracing shows a marked alteration in both amplitude and contour (figure 24). Since the ventricular transducer records changes in both chambers of the heart, no definite conclusion as to the time course of the left ventricular volume can be made.

The influence of changes in venous return to the heart was studied in three cats by sudden occlusion of pulmonary artery. The constriction of the pulmonary artery caused an acute reduction in venous return to the left ventricle. Analysis of the changes in the aortic pressure pulse contour revealed a marked reduction in both amplitude and rate of the initial systolic upstroke. This is demonstrated by the reduction of systolic pressure (Table 19) which could be explained as a consequence of decreased myocardial contraction due to a reduced diastolic filling. Such deductions are in accord with observations and conclusions of Alexander (1953) on similar experiments in dogs.

FIGURE 24

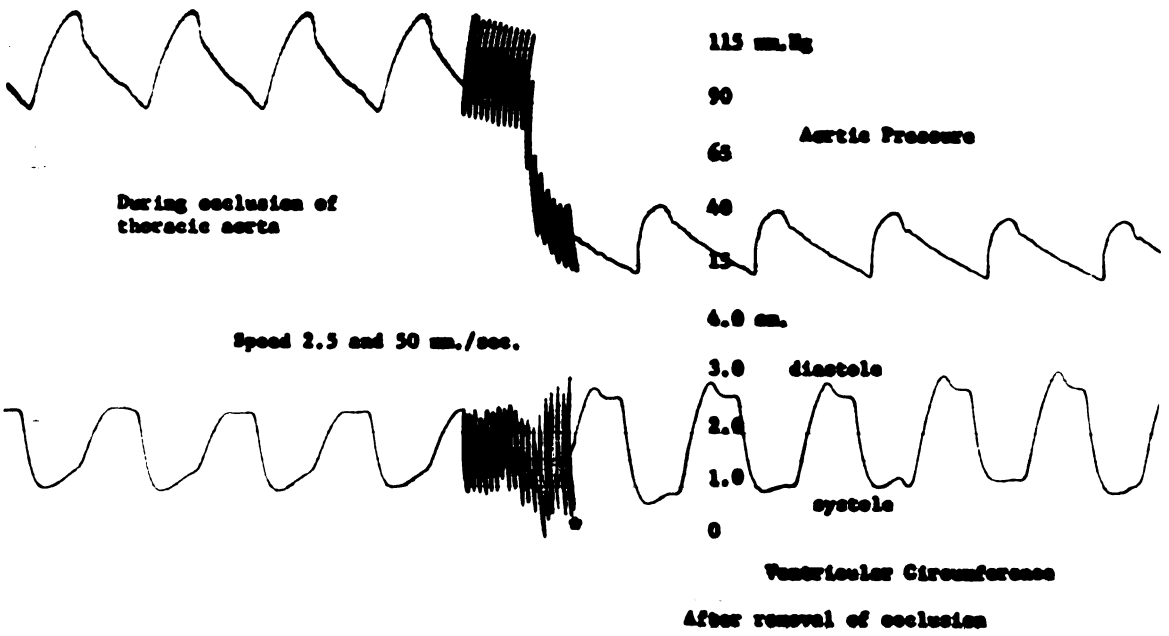
Top--Changes in cardiac time curves during occlusion of thoracic aorta in the cat. Aorta occluded at the left side of the record as indicated by the star (*) and occlusion removed at the right side of the record as shown by a star (*). From above downwards, pulmonary artery pressure, aortic pressure, and ventricular circumference recorded at a speed of 2.5 mm./sec.

Bottom--Changes in contours of cardiac function curves during occlusion of thoracic aorta in cat. From above downwards, aortic pressure and ventricular circumference recorded at a speed of 50 mm./sec.



Occlusion of Thoracic Aorta

Speed 2.5 mm./sec.



Speed 2.5 and 50 mm./sec.

After removal of occlusion

Table 19

CHANGES IN SYSTOLIC BLOOD PRESSURE AND PULSE RATE UNDER VARIOUS CONDITIONS IN CATS

Treatment	Cat No.	Systolic Blood Pressure mm. Hg		Pulse Rate per min.		Time Lapse Between "Before" and "After" Recordings sec.
		Before	After	Before	After	
Occlusion of Vessels						
Thoracic	6	85	130	144	150	5
Aorta	7	78	113	225	240	5
Pulmonary	9	130	65	228	225	20
Artery	10	85	53	180	90	20
	10	15*	53*	180	90	20
	13	105	63	150	150	5
Superior	6	38**	33**	144	162	30
Vena Cava	6	80	73	144	162	30
Inferior	6	38**	13**	144	156	30
Vena Cava	6	90	25	144	156	30
Both	6	38**	13**	144	156	30
Vena Cavae	6	90	25	144	156	30
	7	78	25	250	240	20

Table 19 (Continued)

Treatment	Cat No.	Systolic Blood Pressure mm. Hg		Pulse Rate per min.		Time Lapse Between "Before" and "After" Recordings sec.
		Before	After	Before	After	
Left Carotid Artery	7	78	110	210	210	30
Infusion of Saline (50 ml.)	7	78	115	210	192	30
	13	90	98	132	132	40
	13	90	143	132	132	100
	13	90	130	132	128	400

* Pulmonary artery pressure

** Pulse pressure

Table 20

COMPARISON OF FIRST FOURIER COEFFICIENTS OF BASIC CARDIAC PARAMETERS UNDER VARIOUS CONDITIONS IN CATS

Treatment	Cat No.	Carotid Pressure A_o - mm. Hg		Aortic Pressure A_o - mm. Hg		Vent. Circ. ($\Delta C.$) A_o - cm.	
		Before	After	Before	After	Before	After
Occlusion of Vessels							
Thoracic Aorta	6	-	-	115. 25	189. 88	2. 30	1. 50
	7	96. 25	139. 63	97. 45	142. 63	0. 94	1. 38
Pulmonary Artery	9	-	-	133. 00	-	0. 91	1. 57
	10	-	-	114. 50	80. 38	0. 99	1. 73
	13	140. 25	81. 10	153. 40	86. 90	1. 50	3. 78
Superior Vena Cava	6	-	-	44. 25*	38. 25*	2. 20	1. 50
Inferior Vena Cava	6	-	-	115. 25	30. 60	2. 30	1. 73
Both Vena Cavae	6	-	-	115. 25	36. 10	2. 30	1. 75
	7	72. 75	23. 00	79. 00	24. 80	-	-
Left Carotid Artery	7	93. 75	137. 75	96. 38	141. 38	1. 14	1. 64
Infusion of Saline							
50 ml.	7	96. 25	144. 63	97. 45	150. 63	-	-
	13	135. 13	136. 00	132. 40	131. 50	0. 84	1. 14
	13	135. 13	205. 75	132. 40	212. 00	0. 84	2. 76
	13	135. 13	182. 50	132. 40	187. 63	0. 84	1. 56

* Pulse pressure

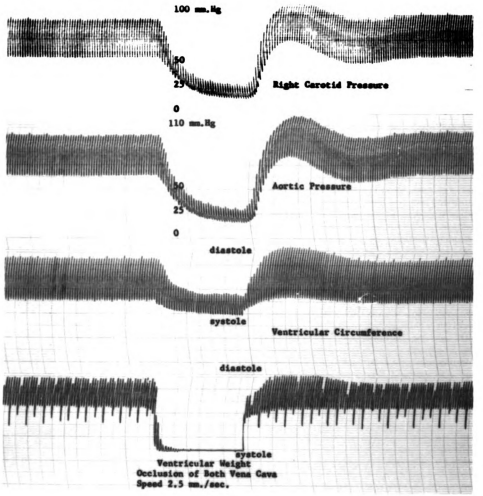
The response of the heart to sudden reduction of venous return was studied in two cats by acute occlusion of both vena cavae. The over-all changes in the various cardiac time curves during the occlusion are shown in figure 25 (top photograph). Note the marked changes in right carotid and aortic pressures and stroke volume output. The dynamic alterations in the contours of aortic pressure and ventricular circumference during occlusion are shown in the bottom photograph of figure 25. Scanning this record from left to right, a number of changes in the detailed contours are noted. The initial systolic upstroke of the pulse becomes reduced in both amplitude and rate. This can be explained on the basis of a smaller and less vigorous myocardial contraction due to a reduced diastolic filling. The systolic peak is markedly reduced and tends to a lower incisura. This is evident from a close examination of the data presented in Tables 19 and 20.

In order to ascertain the time course of cardiac response to changes in venous inflow and peripheral resistance graphical records such as those shown in figures 24 and 25 were subjected to Fourier analysis. Variations of amplitude impedance of cat aorta with pulsating frequency are depicted in figure 26. Impedance curves for thoracic aorta and pulmonary artery occlusion show, qualitatively, similar contour distribution over the frequency analyzed. However, the impedance spectrum shows a marked change after occlusion of both vena cavae. The changes in impedance phase angle of cat aorta are shown in figure 27.

FIGURE 25

Top--Ventricular time curves during occlusion of both vena cavae in the cat. From above downwards, right carotid pressure, aortic pressure, ventricular circumference, and ventricular weight recorded at a speed of 2.5 mm./sec.

Bottom--Changes in contours of ventricular function curves during occlusion of both vena cavae in the cat. From above downwards, aortic pressure and ventricular circumference recorded at a speed of 50 mm./sec.


100 mm.Hg
50
25
Right Carotid Pressure
0
110 mm.Hg
50
25
Aortic Pressure
0
diastole
systole
Ventricular Circumference
diastole
systole
Ventricular Height
Occlusion of Both Vena Cava
Speed 2.5 mm./sec.

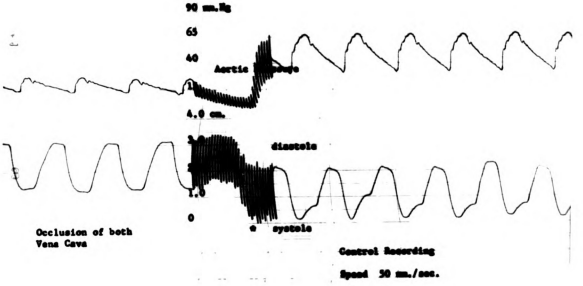

90 mm.Hg
65
40
Aortic
4.0 cm.
diastole
1.0
0
systole
Occlusion of both
Vena Cava
Control Recording
Speed 50 mm./sec.

FIGURE 26

Variations of impedance with pulsating frequency of the cat aorta under control conditions (solid line), after thoracic aorta occlusion (broken line), after pulmonary artery occlusion (dotted line), and after both vena cavae occlusion (centered line).

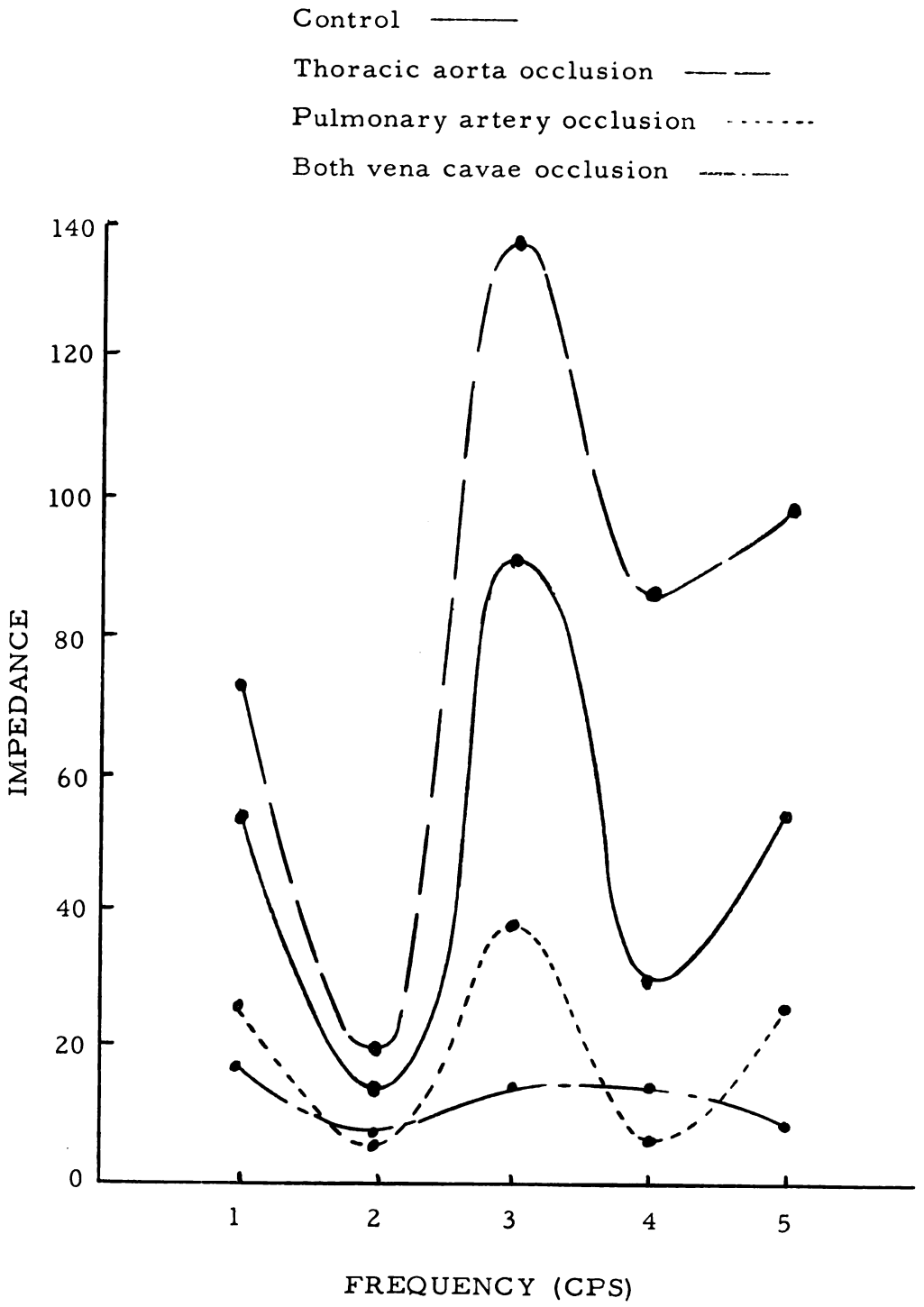
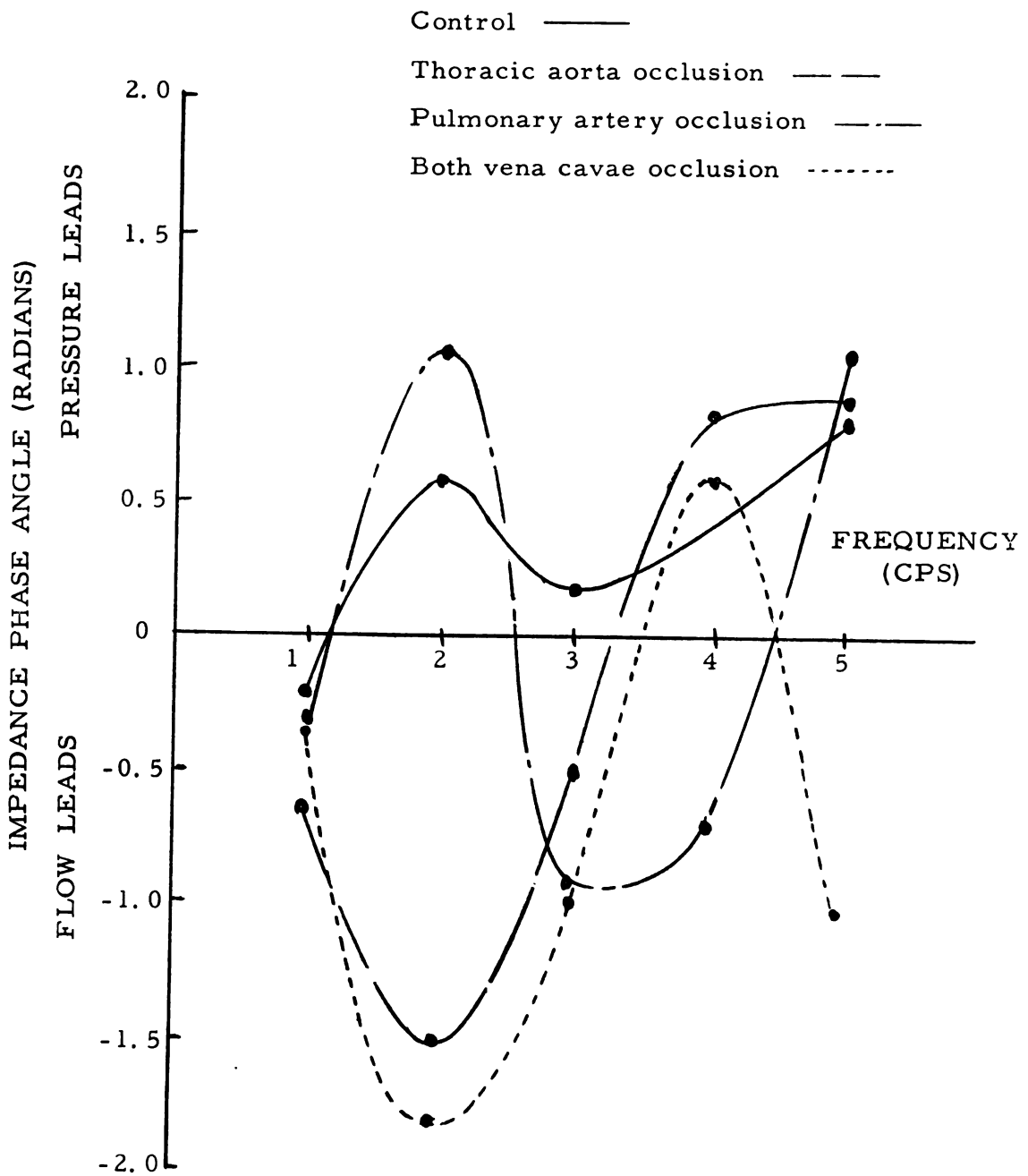

Control
Thoracic aorta occlusion
Pulmonary artery occlusion
Both vena cavae occlusion
140
120
100
80
60
40
20
0
IMPEDANCE
1
2
3
4
5
FREQUENCY (CPS)

FIGURE 27

Variations of impedance phase angle with pulsating frequency of the cat aorta under control conditions (solid line), after thoracic aorta occlusion (broken line), after pulmonary artery occlusion (centered line), and after both vena cavae occlusion (dotted line).


Control
Thoracic aorta occlusion
Pulmonary artery occlusion
Both vena cavae occlusion
IMPEDANCE PHASE ANGLE (RADIANS)
PRESSURE LEADS
FLOW LEADS
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2.0
1
2
3
4
5
FREQUENCY
(CPS)

After thoracic aorta occlusion, there is a marked change in the characteristics of the system. Constriction of the aorta changes the inertial characteristics of the system into a predominantly compliant characteristics. The same changes seem to occur after vena cavae occlusion. In both cases there is a definite delay in the frequency at which resistive forces are overcome, that is when curves cross the abscissa and pressure and flow fluctuations come into phase. The similarity in the impedance phase angle spectra after thoracic aorta and venal caval occlusion could be explained as a result of the similarity of physiological effect of occluding these vessels. Occlusion of thoracic aorta would bring about a reduction in the venous return. The same results are obtained following occlusion of both vena cavae. Therefore, it is not surprising that Fourier analysis of occlusion of these vessels depicts the similar response evoked by the heart. The effect of pulmonary occlusion upon the variation of impedance phase angle is somewhat different. Initially, there is a marked exaggeration of the inertial characteristics of the system. However, after approximately 3 cps the elastic elements replace the inertial components of the system. It is difficult to relate spectral changes to the physiological phenomena during the course of such experiments. However, the significance of the contour distortion (spectral changes) can be appreciated if two things are kept in mind. First, the components of the pulse proceed in time with different speeds, and changing the phasic relations between the

components. Second, the amplitudes of the components are damped in a different way; because the components with higher frequencies undergo a higher damping than the components with the lower frequencies (Hardung, 1962).

Harmonic analysis of the aortic pressure and ventricular circumference curves under control and during occlusion of various vessels are presented in Tables 22 and 23, respectively. The area under the pulmonary artery pressure, after occlusion of the same vessel, shows approximately a 4-fold increase over the control (Tables 22 and 21). There was a corresponding increase in the moduli of the three harmonics, but relatively little or no change occurred in the argument of the sinusoidal function. The area under the aortic pressure, after occlusion of the same vessel, showed a marked increase as compared to the control (Table 22). A significant increase in the moduli of the three harmonics was observed also. But little or no change occurred in the argument of the sine function. In the case of the occlusion of vena cavae, the area under the curve, the moduli of the three harmonics, and the argument of the sine function showed a marked decrease as compared to control. Table 23 shows the harmonic analysis of the ventricular circumference curves under control and during occlusion of various vessels. The area under the curve, after pulmonary occlusion, shows a marked increase over the control. The observed changes in the various parameters of cardiac harmonics demonstrate the importance of the

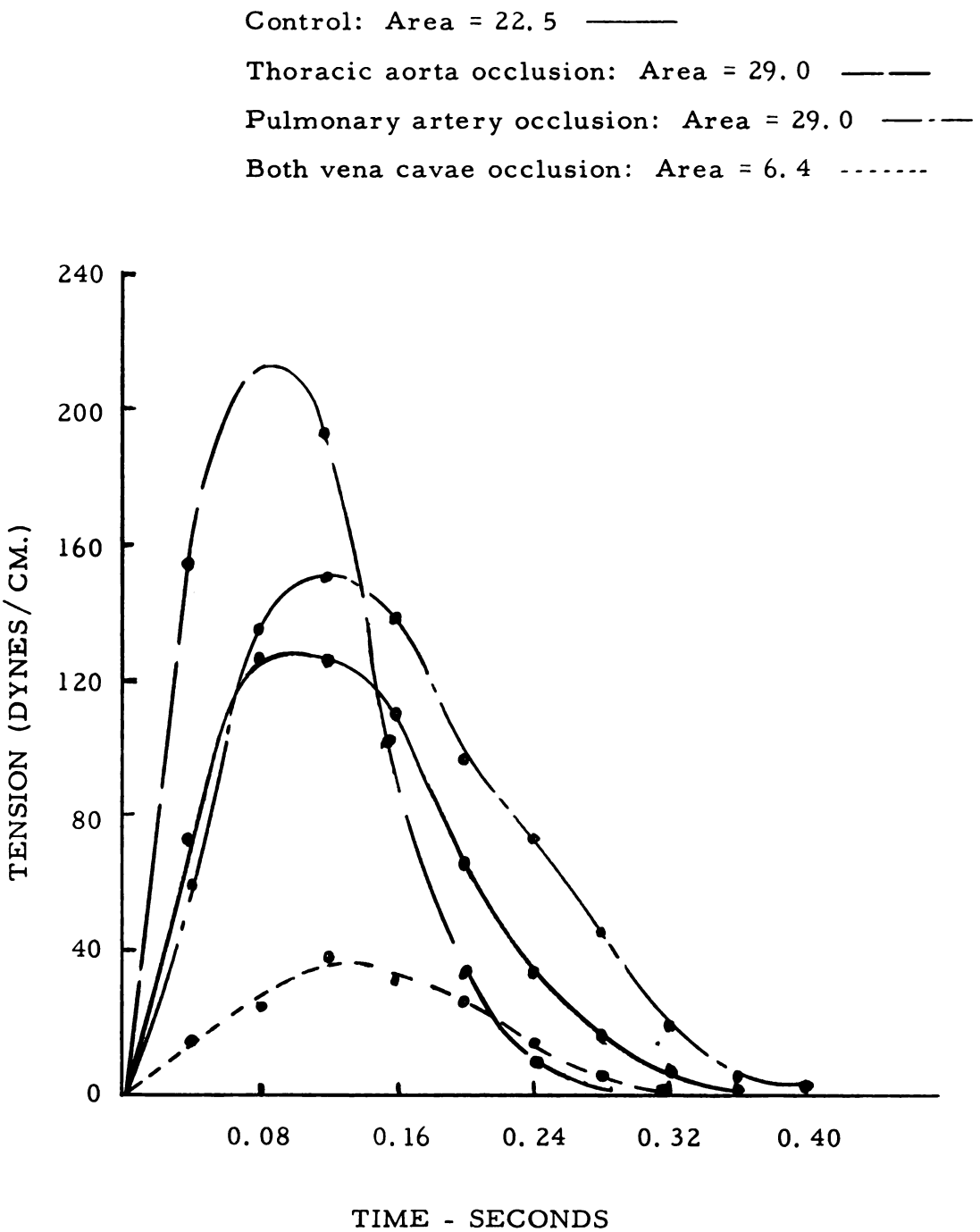
interplay of the amplitude and phase relations of the various components of the pulse.

Comparison of the time course of tension of the cat aorta is presented in figure 28. Note the rapid initial rise in tension after occlusion of thoracic aorta. The tension-time curve after pulmonary artery occlusion shows, qualitatively, a similar contour distribution as compared with the control. There was approximately a 30% increase in the tension after thoracic aorta or pulmonary artery occlusion. There was, on the average, an 80% reduction in the aortic tension after occlusion of both vena cavae.

From a comparative standpoint, it should be noted that tension developed by myocardium during the cardiac cycle, as computed from the area under the curve, shows a marked difference between the turtle and the cat. On the average, the turtle heart developed some 50% more tension than the cat heart (figures 10 and 20). However, it should be noted that, on the average, cats used in this study had a mean pressure of approximately 50% greater than the mean blood pressure of the turtle. Since oxygen consumption of the heart is directly related to the amount of tension developed by the myocardium (Burton, 1957), then one would find it difficult to account for the development of such a tension by turtle heart. It is commonly believed that the turtle, being a cold blooded animal, consumes less oxygen as compared with mammals. Therefore, the observed contradiction, in the relation of oxygen consumption to

FIGURE 28

Comparison of the time course of tension of the cat aorta under control conditions (solid line), after thoracic aorta occlusion (broken line), after pulmonary artery occlusion (centered line), and after both vena cavae occlusion (dotted line).


Control: Area = 22.5
Thoracic aorta occlusion: Area = 29.0
Pulmonary artery occlusion: Area = 29.0
Both vena cavae occlusion: Area = 6.4
240
200
160
120
80
40
0
TENSION (DYNES/CM.)
0.08
0.16
0.24
0.32
0.40
TIME - SECONDS

tension and the latter to pressure, could be explained as a consequence of the geometry and mechanics of the turtle heart as compared with cat heart. The relation of tension to pressure and geometry of the heart is elegantly described by Laplace's surface tension law (Burton, 1957). Since the geometrical configuration of the heart is the primary factor in determining the total tension developed, then the high value of tension of the turtle heart over the cat heart could be related to the shape and not to the difference in oxygen consumption.

II. Venous Infusion

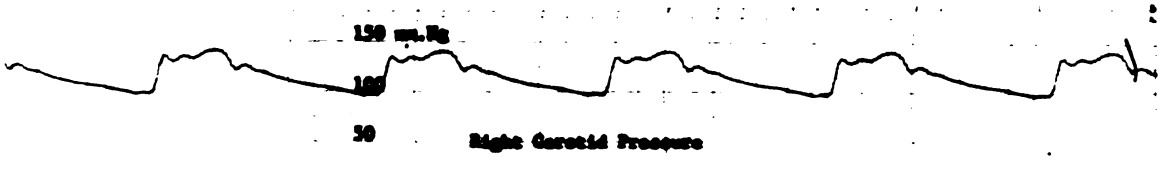
The influence of changes in the venous inflow on cardiac function was studied by means of intravenous infusion of saline in three cats. There are two objections to the use of saline infusion as a means of increasing venous inflow to the heart. First, saline infusion causes a reduction in blood viscosity, thus augmenting the volume flow. Second, infusion of saline dilutes the blood, hence reducing the oxygen carrying capacity of the blood (Katz, 1927). Since the immediate effects of increased venous inflow were of interest here, the disadvantages of saline infusion were considered to be of no great consequence.

The effect of a sudden increase in venous inflow on the contour of the various cardiac time curves is shown in figure 29. Note the marked alteration in the systolic uptake and diastolic drainage segments of the pressure curve as compared to the control (figure 13, top photograph).

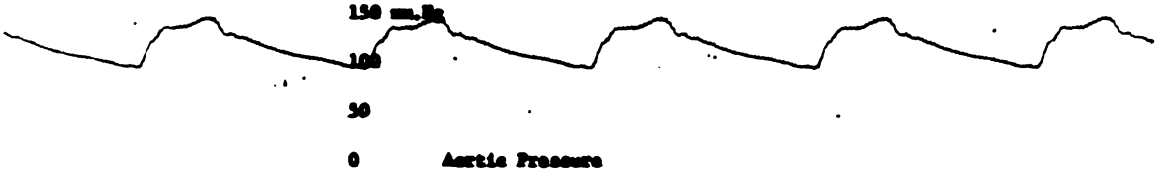
FIGURE 29

Top--Changes in the contours of ventricular function curves 100 sec. after 50 ml. of saline infusion in the cat. From above downwards, right carotid pressure, aortic pressure, and ventricular circumference recorded at a speed of 100 mm./sec.

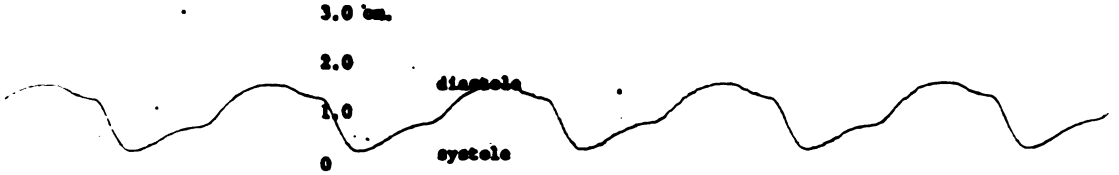
Bottom--Changes in the contours of cardiac time curves 400 sec. after 50 ml. of saline infusion in cat. From above downwards, right carotid pressure, aortic pressure, and ventricular circumference recorded at a speed of 100 mm./sec.



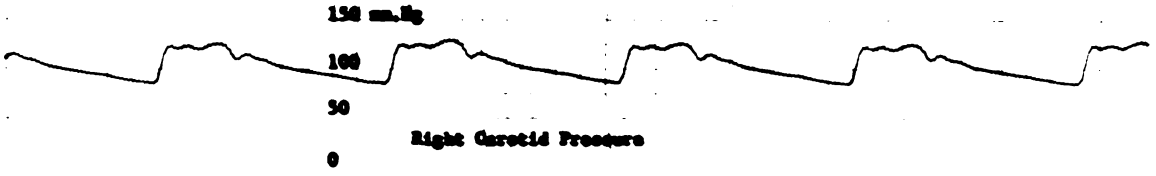
Right Carotid Pressure



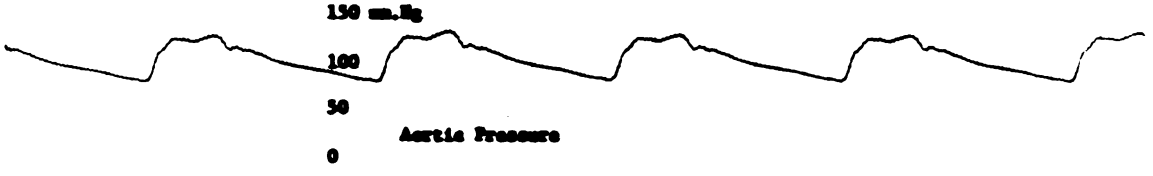
Aortic Pressure



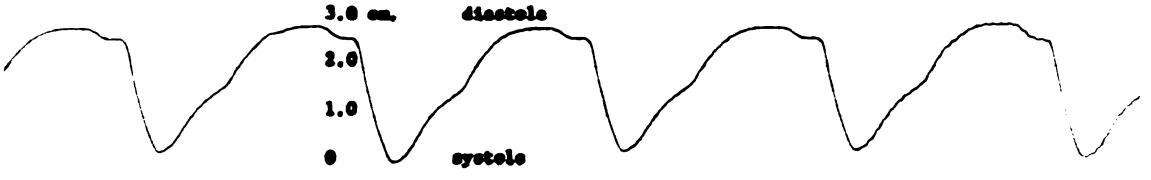
Ventricular Circumference
100 sec. after infusion of
50 ml. of saline
Speed 100 mm./sec.



Right Carotid Pressure



Aortic Pressure



Ventricular Circumference
400 sec. after infusion of
50 ml. of saline
Speed 100 mm./sec.

The pattern of the ventricular contraction, as reflected by the time course of the circumference record, shows a definite alteration in both amplitude and contour. There was a marked increase in stroke volume output after saline infusion which was maintained for approximately 5 minutes. To ascertain the time course of cardiac response to sudden increase in venous inflow, a series of pressure and circumference records, obtained at intervals of 40, 100, and 400 sec. after saline infusion, were subjected to Fourier analysis. The variations in amplitude impedance of the cat aorta are shown in figure 30. Note that immediately after infusion there is a rise in vascular impedance. However, as systole progresses there is a decline in the magnitude of impedance at 2 cps. Furthermore, it is interesting to note that approximately 100 sec. after infusion the impedance spectrum returns to normal. In fact, the curve depicting the time course of ventricular function 100 sec. after saline infusion shows crests and troughs similar to the control curve. In contrast, the characteristics of the cardiac response, 400 sec. after infusion, show close resemblance to that of 40 sec. after infusion. The delayed increase in the vascular impedance, as shown 400 sec. after infusion, could be explained as a consequence of myocardial adaptability to the increased circulatory load, causing a more vigorous contraction against the high vascular impedance. The variations of impedance phase angle after infusion are shown in figure 31. Following saline infusion there is a definite alteration in the time course

FIGURE 30

Variations of impedance with pulsating frequency of the cat aorta under control conditions (solid line), 40 sec. after 50 ml. saline infusion (centered line), 100 sec. after 50 ml. saline infusion (broken line), and 400 sec. after saline infusion (dotted line).

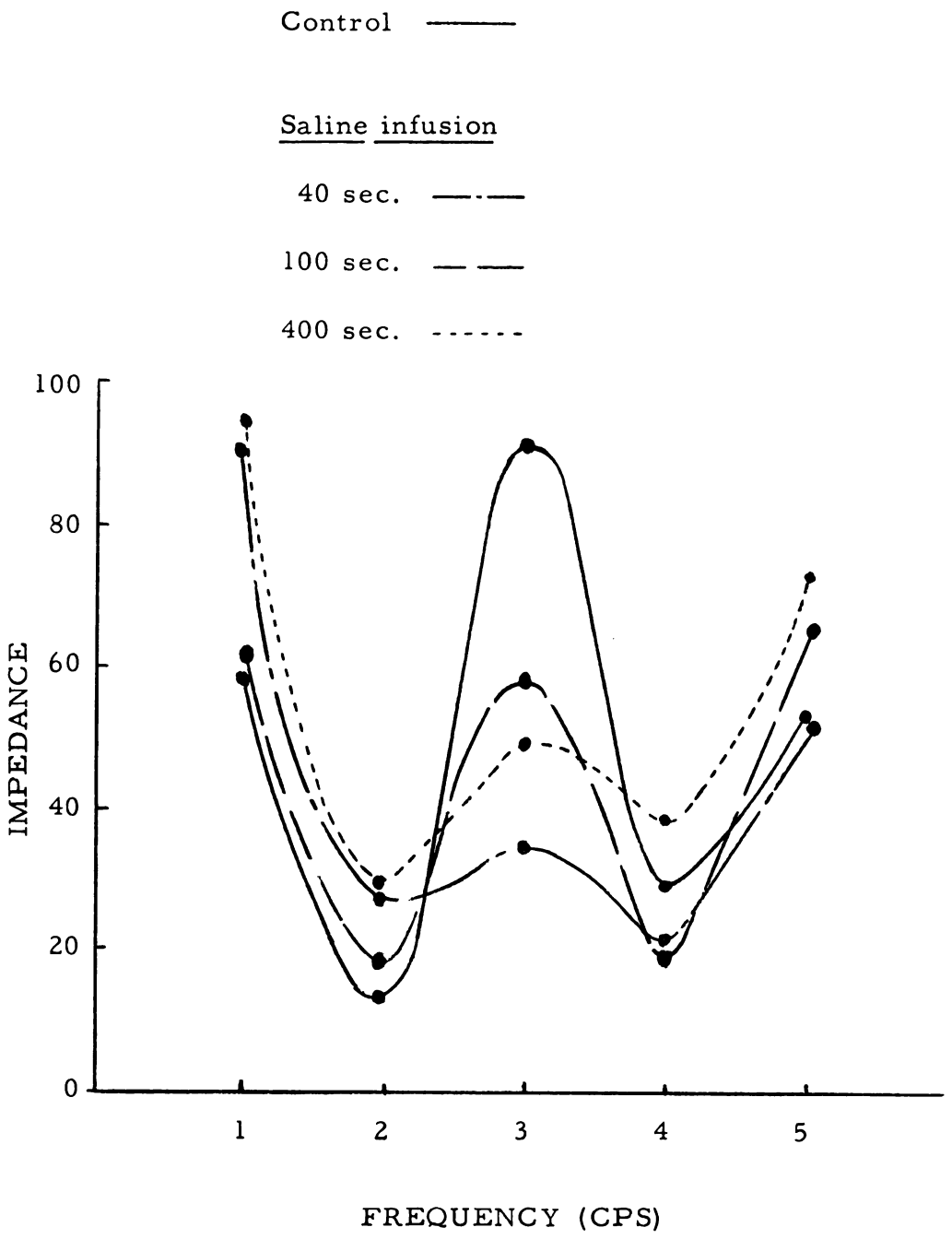
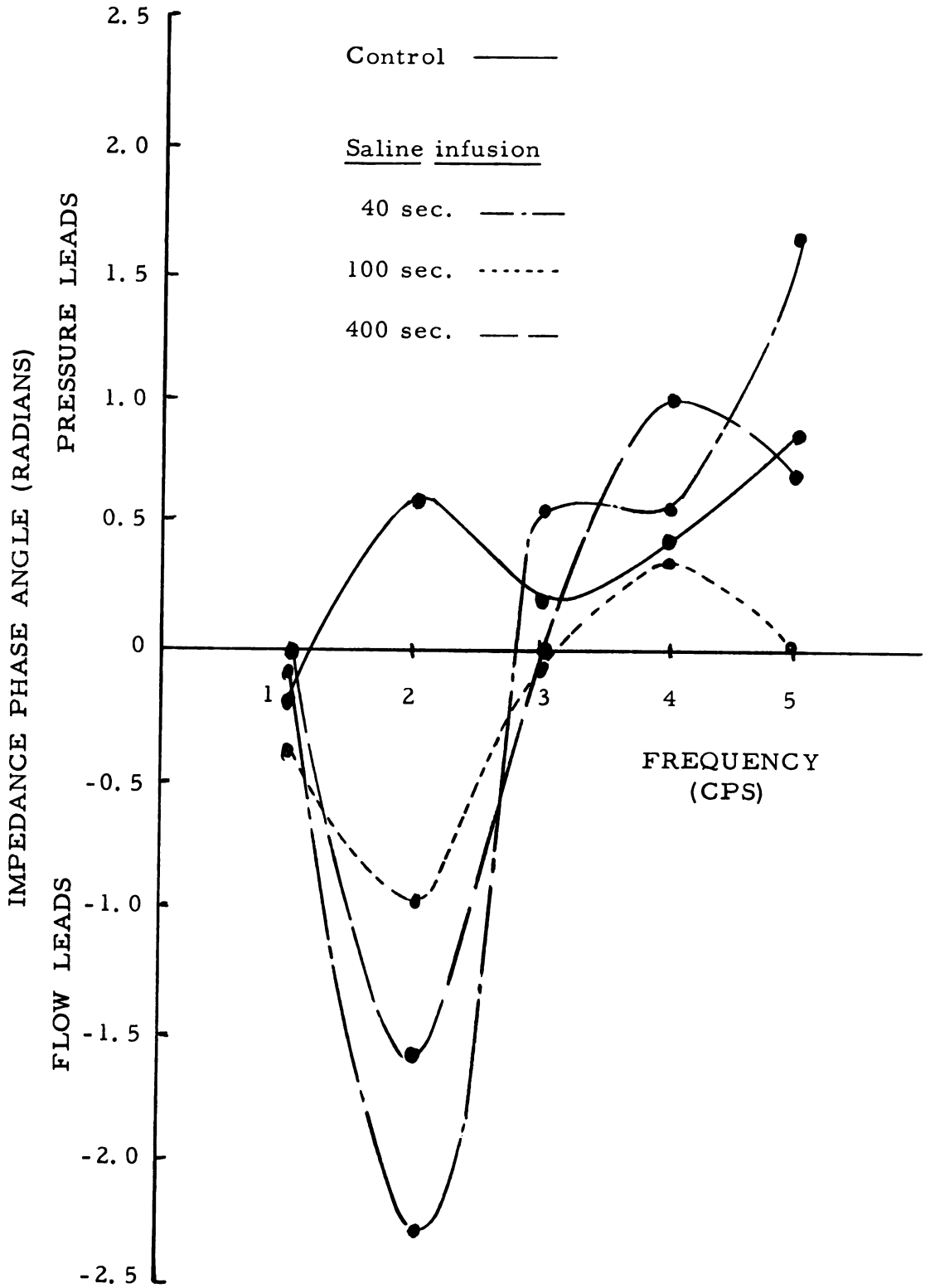

Control
Saline infusion
40 sec.
100 sec.
400 sec.
100
80
60
40
20
0
IMPEDANCE
1
2
3
4
5
FREQUENCY (CPS)

FIGURE 31

Variations of impedance phase angle with pulsating frequency of the cat aorta under control conditions (solid line), 40 sec. after 50 ml. saline infusion (centered line), 100 sec. after 50 ml. saline infusion (dotted line), and 400 sec. after 50 ml. saline infusion (broken line).


Control
Saline infusion
40 sec.
100 sec.
400 sec.
IMPEDANCE PHASE ANGLE (RADIANS)
PRESSURE LEADS
FLOW LEADS
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2.0
-2.5
1
2
3
4
5
FREQUENCY
(CPS)

of interplay of the three basic circulatory forces, namely, mass, friction, and distensibility. All three infusion curves show a definite phase reversal between frequencies 1 to 3 cps. It should be noted that at these frequencies the compliant characteristics (when flow precedes pressure) replace the inertial characteristics (when pressure precedes flow) of the system. This phase reversal is interpreted as an indication of an increase in vascular capacity necessary to accommodate the augmented blood volume following saline infusion. At approximately 3 cps, the inertial characteristics of the system predominate indicating an increase in venous return during the diastolic phase of the cardiac cycle.

Fourier components of the ventricular function curves after saline infusion are shown in Tables 22 and 23. There is a marked increase in the area under the aortic pressure curves after infusion of saline (Table 22), as compared to the control. The moduli of the first and the third harmonics of all three curves show a definite increase over the control values. In addition, there is a change in the sign of the second modulus of the 100 and 400 sec. after infusion curves. This sign reversal and the marked reduction in the argument of the sinusoidal function confirm the conclusions stated above (based on analysis of impedance amplitude and impedance phase angle spectra) on the nature of cardiac response to increased venous return.

Table 21

FOURIER COMPONENTS FOR LEFT VENTRICULAR AND PULMONARY ARTERY PRESSURES UNDER VARIOUS CONDITIONS IN CATS

Treatment	No. of Animals	A_o Mean ± S. D.	First Harmonic	Second Harmonic	Third Harmonic
Left Vent. Pressure					
Control	5	77 ± 6	+116. 5 sin 8.5t	+55 sin 17t	+14.8 sin 25.5t
After adrenalin injection	5	113 ± 8	+199. 2 sin 6.3t	-26.4 sin 12.6t	-54.4 sin 18.9t
After acetylcholine injection	6	44. 5 ± 4	+70 sin 5. 2t	+20.4 sin 10.4t	+3 sin 15. 6t
Occlusion of pulmonary artery	2	37 ± 4	+55. 7 sin 12.5t	+29. 1 sin 25t	+11.4 sin 37.5t
Cessation of artificial respiration	3	95 ± 5	+132. 6 sin 9.2t	+84 sin 18. 4t	+23.8 sin 27.6t
Pulmonary Art. Pressure					
Control	7	14. 2 ± 2	+19. 6 sin 9.5t	+7. 7 sin 19. 0t	+6. 7 sin 28. 5t
After adrenalin injection	4	17. 4 ± 5	+25. 5 sin 8.7t	+10.5 sin 17.4t	+6.2 sin 25.1t
Cessation of artificial respiration	4	23. 8 ± 4	+31. 6 sin 9. 8t	+12.5 sin 19.6t	+10.1 sin 29.4t

Table 22

FOURIER COMPONENTS FOR AORTIC PRESSURE UNDER VARIOUS CONDITIONS IN CATS

Treatment	No. of Animals	A_o Mean ± S. D.	First Harmonic	Second Harmonic	Third Harmonic
Control	14	107. 6 ± 17	+140 sin 11.2t	+11.6 sin 22.4t	+38.3 sin 33.6t
After adrenalin injection	5	178.2 ± 57	+250 sin 5.9t	+14.8 sin 11.8t	+61 sin 16.7t
After adenylic acid injection	4	88. 8 ± 7	+120 sin 5.3t	+3.4 sin 10.6t	+28 sin 15.9t
Saline Infusion					
After 40 sec.	3	141 ± 8	+190 sin 8.3t	+6.5 sin 16.6t	+39 sin 24.9t
After 100 sec.	3	212 ± 14	+291 sin 7.1t	-17.4 sin 14.2t	+55.9 sin 21.3t
After 400 sec.	3	187.6 ± 9	+263 sin 7t	-7.7 sin 14t	+46 sin 21t
Vessel Occlusion					
Pulmonary artery	2	80.4 ± 6	+98.3 sin 9.8t	+3.4 sin 19.6t	+30.5 sin 29.4t
Thoracic aorta	2	142.6t ± 4	+165.2 sin 12t	+9.3 sin 24t	+55 sin 36t
Both vena cavae	2	30 ± 8	+43 sin 9.8t	+0.7 sin 19.6t	+6.6 sin 29.4t
Left common carotid	2	141.4 ± 5	+172.6 sin 11.2t	+10.6 sin 24.4t	+48.2 sin 33.6t
Right Vagus Stimulation	2	93.3 ± 10	+131.2 sin 4.2t	-1.3 sin 8.4t	+42.5 sin 12.6t
Cessation of Artificial Respiration	2	198.6 ± 11	+251 sin 9. 8t	+29 sin 19.6t	+70 sin 29.4t

Table 23

FOURIER COMPONENTS OF VENTRICULAR CIRCUMFERENCE UNDER VARIOUS CONDITIONS IN CATS

Treatment	No. of Animals	A_o Mean ± S. D.	First Harmonic	Second Harmonic	Third Harmonic
Control	15	2. 3 ± 0. 7	+3. 5 sin 8. 5t	+1. 4 sin 17t	+0.2 sin 25.5t
After adrenalin injection	6	3. 0 ± 0. 5	+4. 9 sin 6. 3t	+0.4 sin 12.6t	-
After acetylcholine injection	6	1. 5 ± 0. 1	+3. 2 sin 5. 2t	+1.6 sin 10. 4t	+0. 58 sin 15.6t
After adenylic acid injection	6	2. 4 ± 0. 5	+3. 5 sin 5. 3t	+0.85 sin 10.6t	+0.6 sin 15. 9t
Saline Infusion					
After 40 sec.	3	2. 8 ± 0. 4	+4. 1 sin 8.3t	+1.2 sin 16.6t	+0.8 sin 24.9t
After 100 sec.	3	2. 8 ± 0. 2	+4.6 sin 7. 1t	+1.1 sin 14.2t	-0.6 sin 21.3t
After 400 sec.	3	1. 6 ± 0. 1	+2.6 sin 7t	+1.2 sin 14t	-0.3 sin 21t
Vessel Occlusion					
Pulmonary artery	4	4. 5 ± 1	+6. 3 sin 9.8t	+0.8 sin 19.6t	+0.7 sin 29.4t
Thoracic aorta	4	2. 0 ± 0. 1	+3.0 sin 12t	+1.2 sin 24t	-
Both vena cavae	4	1.3 ± 0. 1	+2.0 sin 9.8t	+0.5 sin 19.6t	-
Right Vagus Stimulation	4	2. 1 ± 0. 2	+3.0 sin 4.2t	+0.7 sin 8.4t	+1.1 sin 12.6t
Cessation of Artificial Respiration	4	1.7 ± 0. 2	+2.1 sin 9.8t	+ sin 19.6t	+0.6 sin 29.4t

SUMMARY AND CONSLUSIONS

Graphic records of cardiac function curves of the turtle and the cat under a variety of experimental conditions were subjected to Fourier analysis. The conditions and assumptions upon which the application of Fourier transform to cardiac pulses is based and the difficulty in interpretation of the data are discussed. It is pointed out that a requirement for application of Fourier analysis to cardiac time curves is that the system should be in a "steady state" condition. This implies that any alteration in frequency must be allowed to settle down before Fourier method is applied. One of the fundamental difficulties in applying Fourier transform is the fact that circulatory system is non-linear. The consequence of this non-linearity is that one cannot relate, with absolute accuracy, the harmonics of pressure with those of flow. However, since the effect of such a non-linearity is small and negligible in a first approximation, one could justify the use of Fourier analysis in such a non-linear system.

The results obtained from Fourier analysis of cardiac curves, as processed by a 160-A Fortran Control Data Digital Computer, are twofold. First, plots of amplitude impedance and phase angle impedance spectra were constructed in order to provide graphical illustration of the time course of cardiac function curves under various experimental conditions. Secondly, the first three harmonics of various cardiac

time curves were computed. Within the limits of the experimental and analytical techniques of obtaining data from graphical records, the first three harmonics were sufficient to synthesize the original curve. This was verified by the computer.

Spectral and harmonic analyses of the cardiac waveforms obtained in the present study indicate that:

1. Adrenalin stimulated the turtle heart muscle directly, whereas its action on the cat heart was initially on the conductive system and secondarily on the myocardium. This conclusion was based on the difference in the distribution of the cardiac impedance of these two species in response to adrenalin infusion. In addition, adrenalin resulted in an increase in the distensibility of both the turtle and cat hearts. This inference was bsed on the comparison of the cardiac impedance phase angle under control conditions and after adrenalin injection.

2. Acetylcholine infusion in the turtle resulted in decreased force of contraction and prolonged the ejection phase of the cardiac cycle. This was deduced from a sustained reduction of cardiac impedance after the drug. However, in the cat, injection of acetylcholine produced, in addition to cardiac depression, vasodilation of blood vessels. This conclusion was based on decreased impedance at lower frequencies indicating a reduction in wave reflection due to peripheral vasodilation. The marked difference in the quantitative values of vascular impedance at various frequencies, after vagus stimulation as compared to

acetylcholine infusion, were interpreted to indicate that stimulation of vagus nerve produces its effect primarily on the heart. This was based on a smaller reduction in the impedance of the aorta. Therefore, Fourier analysis of cardiac function curves provided a quantitative difference in the action of acetylcholine and the stimulation of vagus with respect to generation and propagation of the pressure pulse.

3. Adenylic acid infusion resulted in a reduced vascular impedance and persistance of the compliance characteristics of the system. This implied that adenylic acid, acting as a vasodilator, decreases vascular impedance and results in a flow under a reduced pressure gradient.

4. Alteration of the total peripheral resistance, by acute occlusion of the cat aorta, produced a marked increase in vascular impedance and distensibility.

5. Reduction in the venous return to the left heart, by occluding pulmonary artery increased the inertial characteristics of the vascular system. This was in contrast to decreased effects of inertial components of the aorta when both vena cavae were occluded. Occlusion of thoracic aorta and vena cavae resulted in similar impedance phase angle spectra. This similarity was attributed to the similarity of the physiological effects of occluding these vessels. Occlusion of aorta would bring about a reduction in the venous return. The same results are obtained following occlusion of both vena cavae. Therefore, it is not surprising that Fourier analysis of such occlusion curves depicts the similar response evoked

by the heart.

6. Sudden augmentation of the venous inflow, by saline infusion, produced a definite increase in the distensibility of the elastic components of the vascular system. This was interpreted as an indication of an increase in vascular capacity necessary to accommodate the augmented blood volume following saline infusion.

A modification of Laplace's surface tension law was used to compute tension-time curves for hearts and aortae under various experimental circumstances. On the average, the turtle heart developed 50% more tension than the cat heart. Since oxygen consumption is directly related to the amount of tension developed by the myocardium, then the high value of tension of the turtle heart, as compared to the cat heart, was attributed to the shape and not to the difference in the oxygen consumption.

In the course of this investigation it was assumed that the heart is a black box generating a periodic waveform whose contour reflects the interplay of the various physical forces. Therefore, by subjecting the signals from the vascular system to Fourier analysis it was hoped to establish spectral patterns which would help to identify the physical components of the system. In this respect the effort was successful. However, since the nature of the interaction of the physical forces which produce the cardiac signals is very complex, the information obtained was not quite sufficient to warrant definite conclusions as to the

mechanisms of interaction of these physical forces. This is attributed to the fact that the cardiovascular model chosen in this study was too simplified. It included mass, friction and distensibility but not flow.

In conclusion, Fourier transform is considered to be a suitable method for analyzing cardiac waveforms. It is suggested that further study and application of the method should provide a better understanding of the dynamics of cardiovascular physiology. By this means more detailed information becomes available, and at the outset, one is not forced to assume a particular model of the vascular system.

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APPENDICES

APPENDIX A

AN INTRODUCTION TO THE USE OF COMPUTERS

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I. General

The computer is a device which, in general, performs on stored data four different operations, namely, addition, subtraction, multiplication, and division, and is capable of making a decision, that is, whether the sum of given numbers is zero, positive, or negative. There are two general types of computers. First, an analogue computer which involves no explicit use of special "language." Analogue data are represented by magnitudes of physical quantities, such as length, voltage, pointer deflection, etc. Such quantities, in general, have a continuous range of values which are obtained through readings or measurements. The recorded analogue physical variables are converted into voltages in the computer and related to each other by arbitrary scale factors. Second, the digital computer in which physical variables are represented by a finite number of characters or symbols, such as the decimal number system, the binary number system, and the alphabet. Most instruments used in biomedical research display their output in analogue form. Very often a transducer of some sort is employed to convert the quantity being measured into electrical signals. Therefore, it is necessary to use an analogue-to-digital converter to make useful arithmetical operations on the stored data. The fundamental difference between the two types of computers is one of speed. The advantage of the analogue

computer is that it allows the analysis and synthesis of a system with speed and efficiency. However, there are certain types of problems which can be solved with greater accuracy with a digital computer than with an analogue computer. Therefore, the type of computer used depends on the type of problem to be solved.

II. Components of a Computer

A modern computer consists of five constituent parts: input, output, control, arithmetic, and memory units. The input unit serves as a device for presenting the raw data to the computer in the form of punched-card or tape. The output unit presents the results to the investigator in the desired form, as card, tape, or paper print-out. The control unit is a device which orders the activities of the computer from a set of instructions in a previously written program. The arithmetical component is designed basically to perform the operations of addition, subtraction, multiplication, and division. However, in new computers, the arithmetical unit can perform logical as well as discriminatory operations. The final component of the computer, namely, memory or storage unit is the most important part of the machine. It is capable of retaining large amounts of coded information. The storage unit is constructed, at the present, almost exclusively from magnetic materials of different forms: (1) magnetic tape for relatively slow speed but large capacity records, (2) a magnetized surface on a rotating drum

for less extensive storage but faster speed, and (3) high speed storage utilizing small cores of rectangular loop ferrite materials.

III. Applications

The major advantage of the digital computer is its versatility accruing from the fact that it is basically a symbol manipulator. The analogue computer, in contrast, has a limited application. The most significant use of the analogue computer is the solution of differential equations, including simultaneous nonlinear differential equations. The input and output of the analogue computer can both be time function variables. However, this property of the analogue computer is shared by the digital computer. When using the digital computer to solve various types of differential equations we must resort to some methods of numerical analysis. This method generally involves converting the analogue signals to digital form, sampling the physical variables at an appropriate rate, and quantifying each sample to form a number. The digital computer is then capable of performing all the necessary calculations in the interval between samples, and then delivering a result which can be reconverted to analogue form when desired. This application of the digital computer requires additional analogue-to-digital and digital-to-analogue converters which are quite expensive. In general, all digital computers have a high basic cost, whereas analogue computers may be built to solve special problems at a reasonable cost.

Computers can be programmed to perform a wide variety of operations. Since the solution of any physical problem can be reduced to simple operations, such as addition, subtraction, multiplication, and division, then, theoretically, any problem no matter how difficult can be solved by the computers. The advantage of the computer over human brain is the reliability of its memory and its speed. Some of the general applications of computers are listed below:

1. Computers are able to read and write.
2. Computers are able to memorize information in coded form for long or for short periods of time.
3. Computers are able to follow instructions precisely.
4. Computers are able to operate rapidly, accurately, and usually, more economically than men assigned to perform identical tasks.

IV. Communication with a Computer

The set of ordered instructions given to computers before inputting the raw data is called the program. Complete programming requires three things:

1. The problem must be completely defined and every logical eventuality within the scope of the problem must be preconceived.
2. A method or methods of solving the problem must be known. However, the computer may be instructed to choose the best solution under a given set of boundary conditions.

3. The method of solution must be "known" to the computer. This involves the complete set of ordered instruction or program. It should be noted that a programmer is not always a problem solver.

V. Types of Programs

The degree of sophistication of programming language is increasing continuously. In general, there are three types of languages used for programming. One language is the so-called machine-oriented language, by means of which each step of a machine operation is executed. Another language is the symbolic language which has a one-to-one correspondence with the machine language and replaces the numerical instructions with alphabetical symbols. The third type of language is the problem-oriented language which requires a special compiler to translate the terms into symbolic and machine language. The compiler itself is a computer program that gives the computer the instructions required to convert the initial instructions into the numeric language of the computer. The problem-oriented languages require different compilers for each type of machine with which the program is to be run. One such problem-oriented language that is in use is FORTRAN, which is a mathematical, or formula-translaring, language. Another problem-oriented language is COBOL, which is used in business calculations. From one program statement in COBOL or FORTRAN, a compiler will

generate several machine instructions by which that segment of the program can be carried out. When the entire program has been written on cards or tape, it can then be fed into the computer, for which a compiler program has also been written.

In compiling this introduction the author has made extensive use of the following three references:

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2. Moyer, J. H. (Editor). 1962. Application of Computers in Cardiovascular Disease. New York: The American Heart Association, Inc.

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APPENDIX B

A PROGRAM AND DETAILED INSTRUCTIONS FOR COMPLETE FOURIER ANALYSIS ON 160-A FORTRAN

The following is the detailed FORTRAN program for complete Fourier analysis with a typical set of data used.

```
*     ESMAIL KOUSHANPOUR DOCTORAL THESIS
C     PROGRAM ESMAIL KOUSHANPOUR
      DIMENSION X(10), BETA(10), TIME(10), A(10), B(10), C(10), D(10)
   1  FORMAT (1H9, 4F15.5)
   2  FORMAT (F7.3)
   3  FORMAT (1HO,F10.5)
   4  FORMAT (I3)
   5  FORMAT (1H1, 19H ESMAIL KOUSHANPOUR/1HO,44H FOURIER ANALYSIS OF
     1 CARDIAC TIME CURVES)
   6  FORMAT (3H2 AO)
   7  FORMAT (8H2 A, B, C, D)
      PRINT 5
      READ 4,NO
      DO 16 JJ=1,NO
      READ 2, T, (TIME(I), I=1,10)
      DO 16 II=1,3
      READ 2, (X(I), I=1,10)
      AO = 0.5*(X(I) + X(10))
      FIELD = 0
      DO 11 I = 1,9
  11  FIELD = x(I) + FIELD
      FIELD = 2.0*FIELD
      AO = (AO + FIELD)*.1
      PRINT 6
      PRINT 3, AO
      DO 15 N=1,10
      DO 12 J=1,10
```

```
 12   BETA(J) = (3.14*TIME(J))/T
      A(N) = 0.5*(X(1)*COSF(N*BETA(1)) + X(10)*COSF(N*BETA(10)))
      SORT = 0
      DO 13 I=2,9
 13   SORT = X(I)*COSF(N*BETA(I))+ SORT
      SORT = SORT*2.
      A(N) = (A(N) + SORT)*.2
      B(N) = .5*(X(1)*SINF(N*BETA(1) + X(10)*SINF(N*BETA(10)))
      SORT = 0
      DO 14 I=2,9
 14   SORT = X(I)*SINF(N*BETA(I)) + SORT
      SORT = SORT*2.
      B(N) = (B(N) + SORT)*.2
      C(N) = (A(N)*A(N) + B(N)*B(N))**.5
 15   D(N) = ATANF(A(N)/B(N))
      DO 16 I=1,10
      PRINT 7
      PRINT 1, A(I), B(I), C(I), D(I)
 16   CONTINUE
      END
3              Number of Data Set
 .400          Cycle Length
 .040          t1
 .080          t2
 .120          t3
 .160          t4
 .200          t5
 .240          t6
 .280          t7
 .320          t8
```

.360 t_9

.400 t_{10}

Aortic Pressure Pulse (mm. Hg)

15.000

12.500

7.500

25.000

37.500

42.500

32.500

30.000

25.000

20.000

Ventricular Circumference (cm.)

1.700

1.900

2.400

3.700

3.700

3.350

3.150

3.150

2.300

1.600

Change in Ventricular Circumference (cm.)

.100

.300

.800

2.100

2.100
1.750
1.550
1.550
.700
.000

The integration scheme employed in this program is the well-known trapezoidal method.

Instruction for Use of Program and Data Preparation

The first data card indicates to the computer the number of times the entire calculation should be repeated. For example, in the case of the above data, the entire operation will be repeated 3 times. The second data card indicates the cycle length (T) in seconds for each individual pulse curve. The next 10 data cards are the time intervals starting from $t_1 = .040$ to $t_{10} = T = .400$. The remainder of 30 cards are the actual values obtained from the pulse curves after dividing each one into 10 equal time intervals in the manner shown in figure 6.

This program is written for a special case in which there are only 10 points on the curve. If it is desired to divide the pulse curve or any periodic phenomenon into more or less than 10 points the program requires a minor modification.