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AN ANALYSIS OF SEVERAL VARIABLES INFLUENCING THE LEFT VENTRICULAR DIASTOLIC PRESSURE-VOLUME RELATION IN THE ISOLATED CANINE HEART

by

JOSEPH STANLEY JANICKI

A DISSERTATION

Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Physiology and Biophysics in the Graduate School of the University of Alabama in Birmingham

BIRMINGHAM, ALABAMA

1974

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

LIST OF ABBREVIATIONS

Δ EDV	The amount of additional diastolic volume required to maintain diastolic pressure constant when increasing systolic pressure from an ejecting value to the isovolumic value.
Δ EDP	The decrease in diastolic pressure (constant diastolic volume) resulting from an increase in systolic pressure from an ejecting value to the isovolumic value.
EDP	Left ventricular diastolic pressure.
EDV	Left ventricular diastolic volume.
EP	Left ventricular mean ejection pressure.
HR	Heart rate.
LVP	Left ventricular pressure.
LVV	Left ventricular volume.
PMAX	Peak isovolumic left ventricular pressure.
P_o	Isovolumic contraction.
PV-curve	Left ventricular diastolic pressure-volume curve.
PV-relation	Left ventricular diastolic pressure-volume relation.
SV	Left ventricular stroke volume.
V_o	Left ventricular volume at zero filling pressure.

INTRODUCTION

The diastolic pressure-volume relationship of the left ventricle reflects the mechanical properties of the surrounding myocardium. An understanding and awareness of this relationship, for any given circumstance, would aid in the description of the functional state of the ventricular muscle. The Frank-Starling response of the heart, which relates the energy of contraction to the length muscle fibers attain just prior to contraction, is exemplary. The importance of this relation has again been re-emphasized in light of recent clinical observations, dealing with coronary artery disease, whereby significant alterations in ventricular stiffness were found to occur during myocardial ischemia and infarction (Covell and Ross, 1973; and Levine, 1972).

The role of the diastolic pressure-volume relation as a determinant of cardiac performance has been the subject of an extensive research effort for nearly a century. While these studies have contributed much to our understanding, several major obstacles have prevented the precise quantification of this relation. In particular, the inability to measure absolute volume directly and to control both the ejection and diastolic pressures accurately were critical limitations. Despite this fact, however, one unanimous observation was apparent, namely,

that the diastolic pressure-volume relation was altered by variations in developed systolic pressure irrespective of how this pressure was manipulated. The underlying cause of this phenomenon, however, remains controversial, primarily because of insufficient quantitative data.

Recently a pressure-servo system has been developed whereby the left ventricular diastolic and ejection pressures of the isolated canine heart are controllable and ventricular volume is measured directly and continuously (Janicki et al., 1974). Therefore, the purpose of this dissertation is to utilize this servo system to quantify the influence of ejection pressure on the left ventricular diastolic pressure-volume relation and thereby provide a better insight into the underlying mechanism. In addition the dependence of this relation on several other variables, including stroke volume and filling rate will be assessed.

The dissertation has been structured as follows: a) Part I consists of a review of terminology, relevant concepts and pertinent literature; b) Part II includes a detailed description of the servo system and the biological preparation utilized in the investigation together with the experimental protocol and data reduction techniques; c) Part III is devoted to the results; and d) Part IV is comprised of a discussion of these results.

PART I

CONCEPTS, TERMINOLOGY AND A REVIEW OF LITERATURE

CONCEPTS AND TERMINOLOGY

Cardiac muscle displays many elastic and viscoelastic properties (Alexander, 1962), and the relation between the diastolic pressure and volume of the ventricular chamber is primarily determined by these properties. Because this relation is a determinant of cardiac function (Frank-Starling principle), it has been the subject of an extensive research effort for nearly a century. A brief summary of the terminology and definitions commonly applied to this field of research would be appropriate before a review of the literature is presented. For a more detailed description the interested reader is referred to Remington's review article on muscle mechanics, which included a glossary of terms (Remington, 1962).

One method of characterizing the diastolic properties of the left ventricular myocardium requires a knowledge of its chamber pressure and volume. Ideally, volume should be measured directly. However, heretofore indirect assessments such as internal diameter, external circumference or radiographic techniques have been principally used. A typical plot of pressure and volume obtained from an arrested heart, shows the relation to be an almost perfect exponential function throughout the pressure range of 5 to 30 mm Hg (Diamond et al., 1971). In the contracting heart, the end of the filling period and its respective diastolic pressure (EDP) and volume (EDV) have conventionally been chosen to characterize these properties, because it is at this point in the cardiac cycle that a presumed equilibrium state exists devoid of viscous and inertial

effects. A graph of EDP versus EDV (PV curve) is similarly nonlinear. The slope of the PV curve ($\Delta P/\Delta V$) is the index of stiffness or elasticity of the myocardium and, because the PV curve is nonlinear, will be dependent on diastolic volume and the magnitude of ΔV. Stiffness or elasticity is the property of the muscle that determines the tendency of the stretched tissue to return to its prestretched state. The reciprocal of stiffness ($\Delta V/\Delta P$) represents an index of ventricular distensibility or compliance. Thus, if a given intervention caused a decrease in the slope of the PV curve, then for a given EDV this intervention would have resulted in a reduced stiffness or an increased distensibility. Other terms such as the coefficient of distensibility $\Delta V/(EDV \times \Delta P)$ have been used to compare the elastic properties between hearts of varying sizes. Alternatively, expressing the PV curve as a stress-strain relation would negate the need for such additional quantities since a characteristic volume (ideally the unstressed volume at zero filling pressure) could be used as a normalizing factor. Diastolic stress is the force (diastolic pressure × internal ventricular area) per cross-sectional area of the ventricular muscle. Strain is the fractional or percent change in a characteristic dimension (usually internal radius) from the original or unstressed dimension. This type of representation, however, does require a knowledge of chamber geometry and as a first order approximation a spherical shape has been assumed (Mirsky and Parmley, 1973).

Creep, hysteresis and stress relaxation are terms that have been used to describe the viscoelastic phenomena characteristic of

most biological tissue. Creep is the increase in tissue dimensions that occurs over the course of time under constant stress. For example, when papillary muscle is studied in vitro its homeostatic condition has been disturbed by resection (i.e., it remains unstressed for a long period of time). Restressing the muscle with a constant load will result in a gradual increase in length or creep (approximately 4% increase in 10 minutes). If the muscle is then again unloaded for a 5 minute period and the same constant load reapplied an increase in length of less than 1% will be observed in the same time period (Pinto and Fung, 1973). The authors refer to this procedure as preconditioning in a creep test. An equivalent preconditioning procedure in a stress-strain test would consist of repeated cycles of continuous loading and unloading. Hysteresis is the term used to describe the difference between the stress-strain curve obtained during loading (extension) and unloading (release). That is, the stress-strain curve does not traverse the same stress-strain path, but rather forms a loop with the release curve lying below the extension curve. Fung (1967) has demonstrated that the hysteresis loop is almost independent of the strain rate indicating that biological tissue is a nonlinear, viscoelastic material. If the tissue were linearly viscoelastic, the hysteresis loop would, by definition, vary directly with the strain rate. Stress relaxation refers to the time rate of decline in stress following an abrupt, but constantly applied, strain. Both the initial amount of stress and the subsequent rate of decline increase as the rate of strain is increased. Therefore,

depending on the magnitude of the viscoelastic behavior in the intact ventricle, it could be anticipated that the diastolic pressure-volume relation would be influenced by the rate of filling and the diastolic time interval.

In the older literature, the mechanical properties of the heart during diastole were considered with reference to a cardiac "tone". In reviewing this topic Meek (1927) defined tone to be "a sustained partial contraction independent of the systolic contractions, by virtue of which the muscle fibers resist distension during diastole more than they would because of their mere physical properties." Alexander (1962), in discussing the viscoelastic determinants of muscle contractility, reached the following conclusion: "The ghost of cardiac tone still lurks in our midst; it is time to probe more specifically into the influence of the passive physical system and possible tonic contractile mechanisms on cardiac function during diastole and systole." The cardiac tone concept was again resurrected and redefined by Burch and Giles (1970), "to mean the tightness due to active, biological (living) physiochemical phenomena with which the cardiac muscle squeezes or tightens on the blood within its respective chambers at the end of diastole". Thus, there has been considerable discussion concerning the exact definition of cardiac tone and, until some agreement is reached, this concept will remain controversial. Despite this controversy, there were a few investigators who described observed changes in the diastolic pressure-volume relation as alterations in diastolic tone (Barry

et al., 1974; Johnson and Katz, 1937; and Katz et al., 1955). Nevertheless, the major related research effort over the ensuing years has been, and still remains, based on demonstrating whether the diastolic pressure-volume relation of the ventricle can be altered without reference to the controversial tone concept.

HISTORICAL SURVEY

This section reviews the pertinent literature which specifically deals with the diastolic pressure-volume relation of the left ventricle and its influencing factors. To facilitate presentation, it is structured into 5 subsections: The first and second subsections enumerate the many types of experimental preparations and ventricular volume sensing techniques, respectively, employed in these studies; the third and fourth subsections discuss the various factors which have been found to influence the relation; and the fifth summarizes the literature.

PREPARATIONS

A review of the literature reveals that a variety of experimental preparations, ranging from the isolated, isovolumically beating ventricle to the instrumented conscious animal have been utilized to study the various factors influencing the ventricular diastolic pressure-volume relation. A detailed technical description of each would be impractical; however, some comment is appropriate.

In the isolated in situ or in vitro preparations, the left ventricular cavity was isolated from the remainder of the circulation, and the right ventricle unloaded. Coronary perfusion pressure was constant and nonpulsatile. The blood was oxygenated either artificially (e.g., Sonnenblick et al., 1966; and

Templeton et al., 1970) or by a support dog (e.g., Gilmore et al., 1966a, 1966b; and Monroe and French, 1961). Leach and Alexander (1965) on the other hand used an oxygenated Locke-Ringer solution as the perfusate. Those isolated preparations which were contracting isovolumically utilized an intraventricular balloon of known volume which could be varied, and preparations which were ejecting (no balloon) usually had the option for obtaining the isovolumic state. The advantage of this type of preparation was the ability to control pertinent variables such as heart rate and diastolic pressure or volume. In addition, when the heart was contracting isovolumically a knowledge of absolute volume, at all times, was obtainable.

With the instrumented conscious animal such control of these as well as other influencing variables was lacking. Three such studies which were specifically concerned with the diastolic pressure-volume relation were those of Adolph (1965), Noble et al. (1969) and Rushmer (1956). The acute thoracotomized preparation, with normal pulsatile coronary perfusion and a "nonisolated" ventricle, would appear to be situated somewhere between the isolated and conscious animal preparations with respect to the above discussion. Experiments of this type oftentimes incorporated modifications in order independently to control and vary specific hemodynamic variables, such as cannulating the aorta (Braunwald et al., 1960; and Wildenthal et al., 1969) or the atrial appendage (Hefner et al., 1961). Others lacking such provision were dependent on cruder techniques to induce responses in the cardiovascular system such

as aortic constriction using an adjustable clamp and intravenous saline infusion (e.g., Johnson and Katz, 1937). In general, all studies reviewed were performed without the pericardium. Furthermore, the majority were interested in various inotropic manipulations either to induce responses or specifically to study their effects on the diastolic pressure-volume relation.

VOLUME SENSING TECHNIQUES

A problem which has long plagued investigations of this nature has been the measurement of absolute ventricular volume. This is evidenced by the multitude of indirect techniques utilized in ejecting hearts. The most popular method has been the circumferential or mercury-in-silastic tubing gauge (Bianco et al., 1970; Braunwald et al., 1960; Gilmore et al., 1966a, 1966b; Hefner et al., 1961; and Rushmer, 1956). A closely related method is that used by Mitchell et al. (1960) whereby a myocardial segment length was measured with a strain gauge. A cardiometer or oncometer has been used to measure (1) the volume of both ventricles (Johnson and Katz, 1937; Katz et al., 1955; and Rosenblueth et al., 1959); and (2) the pressure-volume relation of the apical portion of the ventricle (Adolph, 1965). Radiographic techniques in conjunction with assumed ventricular geometrical configurations were employed by Noble et al. (1969) and Wildenthal et al. (1969). In the isolated preparation of Monroe and French (1961) and Monroe et al. (1968), the ventricle ejected air into a Krogh spirometer, which recorded stroke volume. Recently ultrasound was utilized by Morgenstern

et al. (1973) to study the effects of coronary pressure and flow on intracoronary blood volume and geometry of the left ventricle. Sandler and Alderman (1974), in reviewing these methods used to measure left ventricular size and shape, re-emphasized the limits of the current state of art with their statement: "At the present time, there is no method which allows a determination of the absolute amount of blood in a given cardiac chamber during life." They also discussed clinical echocardiography and radioisotope angiocardiography which are promising new techniques currently under investigation.

INFLUENCE OF CORONARY PERFUSION PRESSURE, PERICARDIUM, THE RIGHT VENTRICLE, HEART RATE, AND AUTONOMIC STIMULATION ON THE DIASTOLIC PRESSURE-VOLUME RELATION OF THE LEFT VENTRICLE

It is apparent that in many of the preparations the coronary pressure was nonpulsatile and constant, the pericardium removed, the right ventricle unloaded and the heart paced. These variables and the presence or absence of an intact pericardium certainly affect the diastolic pressure-volume relation of the left ventricle. For instance, Salisbury et al. (1960) demonstrated the effects of coronary artery pressure upon myocardial stiffness when concomitant changes in aortic and ventricular pressures were obtained with the heart beating isovolumically. Typically the diastolic ventricular pressure increased 5 mm Hg when coronary perfusion pressure was raised 70 mm Hg from a control value of 10 to 40 mm Hg. They referred to the increased stiffness as the "erectile"

response of the coronary tree. Spotnitz and Kaiser (1971) investigated the effects of the pericardium in arrested canine hearts and found that its presence elevated ventricular pressure and reduced volume over the entire range of pressure studied (0-20 cm H_2O). Removal of the pericardium at a filling pressure of 10 cm H_2O reduced the pressure an average of 4.6 cm H_2O and an additional average volume of 6.2 cc/100 gm of muscle was required to restore it. Hefner et al. (1961), on the other hand, using a thoracotomized preparation reported that the presence of a pericardium made essentially no difference for filling pressures less than 10 mm Hg.

The influence of right ventricular filling on left ventricular volume has been studied in canine hearts immediately post mortem (Laks et al., 1967; and Taylor et al., 1967). Laks and co-workers demonstrated that the volume accepted by the ventricles during a simultaneous biventricular infusion were significantly less (30%) than volumes determined with infusion into either ventricle individually. A lesser influence was reported by Taylor. Instead of simultaneous infusion as used by Laks, these investigators matched each level of left ventricular filling pressure with a right ventricular filling pressure found to coexist in vivo. At a left ventricular pressure of 20 mm Hg, left ventricular volume was 7.1% smaller with the right ventricle "full" (7.7 ± 1.4 mm Hg) than with it empty. This difference decreased with lower left ventricular pressures. Both groups attributed their observations to the presence of the common intraventricular septum.

Extreme tachycardia can also cause an apparent increase in stiffness (Braunwald et al., 1960; Meek, 1927; Mitchell et al., 1960; Monroe and French, 1961; Sonnenblick et al., 1963; and Templeton et al., 1972). This effect, however, was not observed until the heart rate exceeded 180 beats/min and was not attributed to a true change in viscoelastic properties but rather a decrease in the diastolic period to a critical point at which ventricular relaxation was incomplete. The fact that in vitro preparations are denervated does not appear to influence the left ventricular diastolic pressure-volume relation (Bianco et al., 1970; Mitchell et al., 1960; and Sonnenblick et al., 1963). These investigators have shown that cardiac sympathetic and vagal nerve stimulation had no effect (unless the heart rate exceeded 180 beats/min) on the relationship.

EFFECTS OF CATECHOLAMINES, PAIRED PACING AND INCREASED DEVELOPED PRESSURE ON THE DIASTOLIC PRESSURE-VOLUME RELATION

In the previous subsection, there was for the most part agreement as to the influence each factor had on the diastolic pressure-volume relation. Such is not the case with the pharmacological administration of catecholamines. For example, upon infusion of epinephrine or norepinephrine, Katz et al. (1955) reported an increased tone (or stiffness); others (Hefner et al., 1961; Leach et al., 1965; and Rushmer, 1956) observed a decrease in stiffness and there were those who

reported finding no change (Gilmore et al., 1966a; Monroe and French, 1961; Templeton et al., 1972; and Wildenthal et al., 1969). It should be noted that Gilmore and Wildenthal were careful to avoid concomitant peripheral vascular effects of norepinephrine by holding aortic pressure constant. Similarly, Templeton and co-workers, in discussing their results, stated that "when such extraneous factors were excluded, no changes in diastolic compliance were observed." One of the extraneous factors they referred to was a "large increase in tension development." Monroe in a recent publication (Monroe et al., 1968) using the same preparation, reported "a small increase in diastolic ventricular volume following the abrupt imposition of the load while end-diastolic pressure remained constant." Thus it appears that increases in developed tension may influence the diastolic pressure-volume relation.

This was the conclusion that Sonnenblick et al. (1966) arrived at when they demonstrated that paired pacing of the isovolumically contracting left ventricle increased peak systolic pressure 24 to 77 mm Hg, and associated with this increase was a decline of 0.25 to 1.5 mm Hg in end-diastolic pressure. The extent of the fall was dependent on the initial level of diastolic pressure with a greater decline occurring at higher end-diastolic pressures. Sonnenblick et al. (1966) as well as Bartlestone et al. (1965) were able to demonstrate a similar response in the isovolumically contracting right ventricle using either paired pacing or calcium infusion. Gilmore et al. (1966a) also reported a tendency for the diastolic pressure-volume curve to be shifted toward the right at higher

aortic pressures, and in another report (Gilmore et al., 1966b) concluded that in the ejecting left ventricle, paired pacing had no significant influence on stiffness when changes in developed tension were minimized. Braunwald et al. (1960) were not able to demonstrate a change in the diastolic pressure-volume relation with increments in developed systolic pressure; however, the fact that Braunwald and Ross co-authored the article with Sonnenblick in 1966, where changes were observed, leaves some question as to their original observations. The results of Templeton et al. (1972) concerning the influence of increased developed pressure are also somewhat confusing. At one point in the discussion they claimed that "in diastole, alterations in stiffness did occur." Later they implied, as previously mentioned, that data associated with large increases in tension development were excluded; and in their summary they emphatically stated that with noradrenaline infusion "there are no changes in left ventricular diastolic pressure at a fixed volume and no changes in diastolic stiffness or compliance." Despite these unsettled issues one can probably assume that the diastolic pressure-volume relation is influenced by increments in developed pressure. This assumption is further reinforced by similar observations in papillary muscle (Hoffman et al., 1968; and Sonnenblick et al., 1966).

The cause of this phenomenon is still controversial and precise quantification lacking. While it appears as Sonnenblick claimed, to be directly related to increases in developed pressure, Hoffman et al. (1968) concluded that the diastolic alterations were not necessarily related to either an increase or a decrease in

pressure developed during contraction. Instead they hypothesized "that a variable degree of persistent interaction between the contractile elements is responsible for some of the changes in diastolic compliance." Although they did not specifically mention the controversial tone concept, it appears to be implicit in their hypothesis. Before summarizing this section it should be noted that Wildenthal et al. (1969) tested the effects of propranolol and found that it did not alter stiffness. When severe cardiac depression was induced with a large dose, however, stiffness decreased. Noble et al. (1969) showed that in their chronic preparation increased serum calcium concentration or isoproterenol did not significantly alter the diastolic pressure-volume curve. Methoxamine, on the other hand, shifted the curve significantly to the left during early and late diastole.

SUMMARY TO THE HISTORICAL BACKGROUND

In summary, it is apparent that the left ventricular diastolic pressure-volume relation is influenced by many variables including developed pressure. In attempting to quantify the magnitude of these factors a wide variety of preparations have been utilized varying from the isolated, isovolumically beating heart to the instrumented conscious animal. The major obstacles to precise quantification in these research efforts have been the inability to measure absolute volume directly and continuously, and to control both the ejection and diastolic pressures accurately. While discrepancies exist, one can conclude that apparent stiff-

ness decreased as developed pressure was increased, regardless of how this pressure was raised. The cause of this phenomenon is still controversial, which may, in part, be related to the lack of quantitative data. With the recent development of a pressure-servo system which permits control of ejection and diastolic pressures and provides for the continuous monitoring of absolute ventricular volume in an ejecting, isolated canine heart (Janicki et al., 1974) such an analysis is now possible. The purpose of this study, therefore, is to utilize this servo system to quantify the influence of ejection pressure on the left ventricular diastolic pressure-volume relation and thereby provide a better insight into the underlying mechanism. In addition, the dependence of the pressure-volume relation on stroke volume and diastolic filling rate will be assessed.

PART II

EXPERIMENTAL METHODS

PRESSURE-SERVO SYSTEM

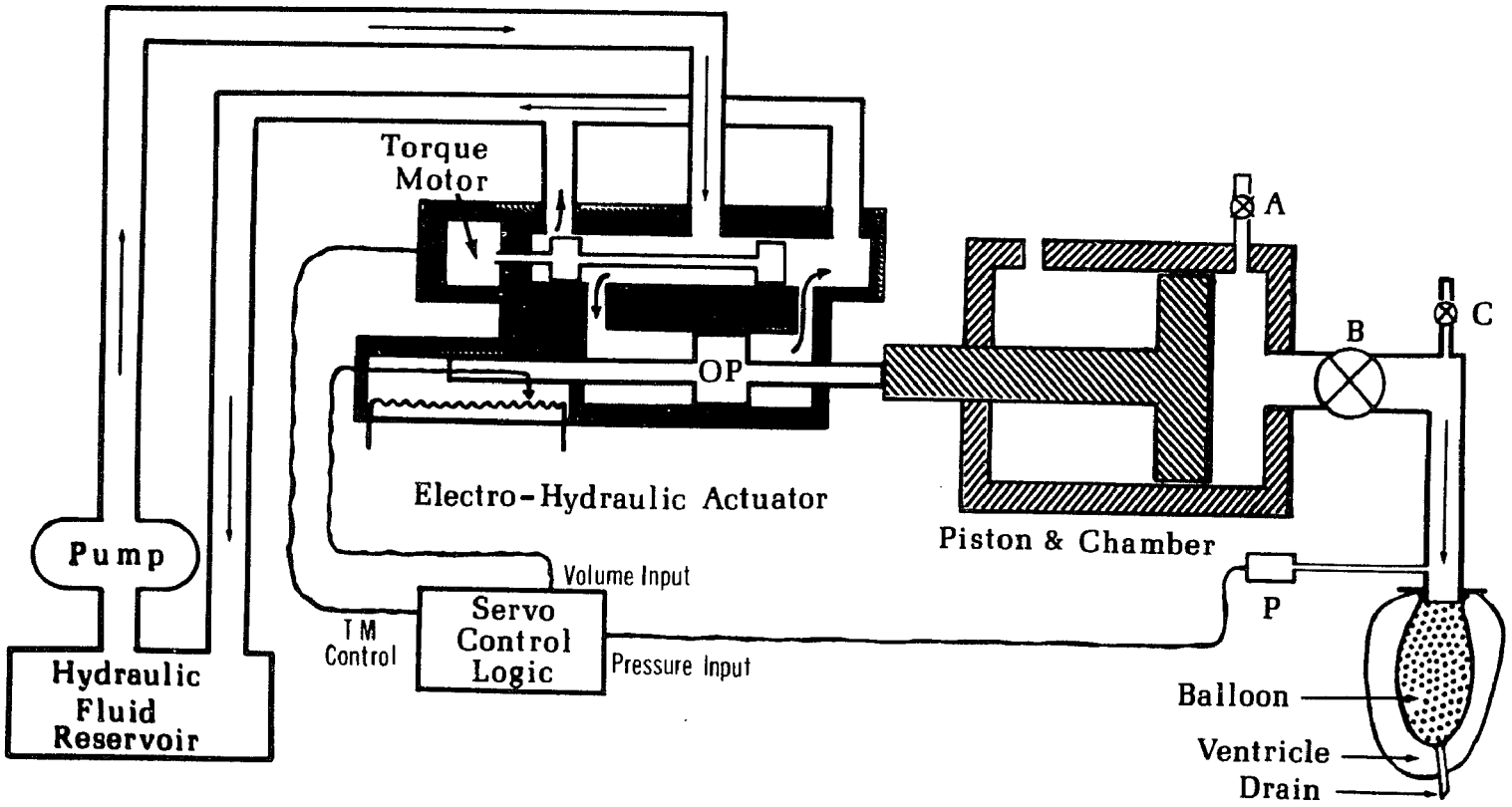
MECHANICAL SYSTEM

Figure 1 is a schematic representation of the mechanical system used to control diastolic and systolic pressure of the left ventricle and to measure its volume. The apparatus consists of a electro-hydraulic actuator (EHA) coupled to a piston in a cylinder, 8.4 cm in diameter, that has connected to its output port stainless steel tubing (1/2 inch ID) which terminates in a stainless steel cannula (1.3 cm ID and 1.9 cm OD) and to which a balloon is attached. The balloon positioned in the left ventricle is a #9 helium balloon chosen for its pressure-volume characteristics. That is, for volumes in the range of 0 to 60 cc the intra-balloon pressure remained at zero and at 80 cc this pressure increased only 1 mm Hg. For all dog hearts studied the largest ventricular volume ever encountered was 70 cc corresponding to a diastolic ventricular pressure of 30 mm Hg. The cylinder or chamber, connecting hardware and balloon are filled with Dowtherm SR-1, a fluid having a low CO_2 solubility coefficient and which is used to minimize the occurrence of cavitation when large fluid withdrawal rates are encountered (Christie, 1969). Chamber temperature is thermostatically controlled using a thermistor and heater resistors to maintain the fluid near 37.5°C.

Figure 1

Servo Mechanical System

A diagrammatic representation of the mechanical system. A, B and C are hydraulic valves; P is an intraventricular pressure transducer communicating with the ventricular balloon via a catheter; OP, the output piston; and TM, the torque motor. The electro-hydraulic actuator alters the position of the piston which in turn displaces fluid into or out of the balloon. That is, the fluid within the chamber and the balloon is continuous. Arrows indicate direction of hydraulic fluid flow through the actuator during diastole when fluid is being added to the balloon (see text).


Torque
Motor
OP
A
B
C
Electro-Hydraulic Actuator
Piston & Chamber
Pump
Volume Input
TM
Control
Servo
Control
Logic
Pressure Input
P
Hydraulic
Fluid
Reservoir
Balloon
Ventricle
Drain

Chamber volume is controlled by the electro-hydraulic actuator (EHA, Moog #17-135) which utilizes an operating hydraulic pressure of 3000 PSI supplied by a variable volume hydraulic pump (Dennison - 600 Series). As shown in Figure 1 balloon volume is sensed within the EHA by means of a slide wire potentiometer, the output of which was calibrated in terms of volume using a 50 $\pm$ 0.05 cc burette. Potentiometer resolution was found to be 0.2 cc. Volume and intraventricular pressure (P, Statham P23Gb or Millar PC-480, in Figure 1) are used as inputs to the servo control logic, which will be discussed in the next subsection. The output of the servo logic (TM control, Figure 1) is an analog signal, which controls a torque motor within the EHA. This torque motor via a complex valving arrangement determines the position of the EHA output piston which in turn is directly coupled to the piston. As an aid in understanding the operation of the EHA, arrows indicating fluid flow through the EHA have been drawn in Figure 1 to depict the case when intraventricular volume is being increased during cardiac diastole. The EHA is capable of a maximum displacement of 3.5 cm and a maximum velocity of 16 cm/sec. This enables the system to have a maximum volume change of 197 cc and a maximum flow rate of 860 cc/sec. The first system developed utilized a stainless steel bellows that had an effective diameter of 5.9 cm and a maximum flow of only 440 cc/sec. In many hearts, however, this maximum flow was exceeded, especially following positive inotropic interventions; and, therefore, the larger area piston was incorporated into the

subsequent systems. The response characteristics of the EHA had an inherent time lag of 10-15 msec. Consequently, a circuit which compensates for this response-limiting lag (discussed in the next subsection) at the onset of ventricular ejection was included in the servo control logic.

The valves A, B and C (Figure 1) are required during an experiment. Valve C is used to initially fill and de-bubble the balloon (Valve B closed). To the outflow port of Valve A is attached a fluid filled tube (not shown) which then terminates under fluid contained in a flask. Vacuum is applied above the fluid so that when Valve A is opened the fluid within the chamber is de-bubbled. Following de-bubbling, the vacuum is removed and fluid allowed to replace any resultant empty space within the chamber. The piston is positioned so that once the ventricle is filled the actuator can still operate around its mid-point. The volume reading of the system, at this position, is corrected for the volume displaced by the balloon (usually 4 cc) and used as zero reference throughout the experiment. Finally Valve A is closed, Valve B is opened and the servo control logic activated.

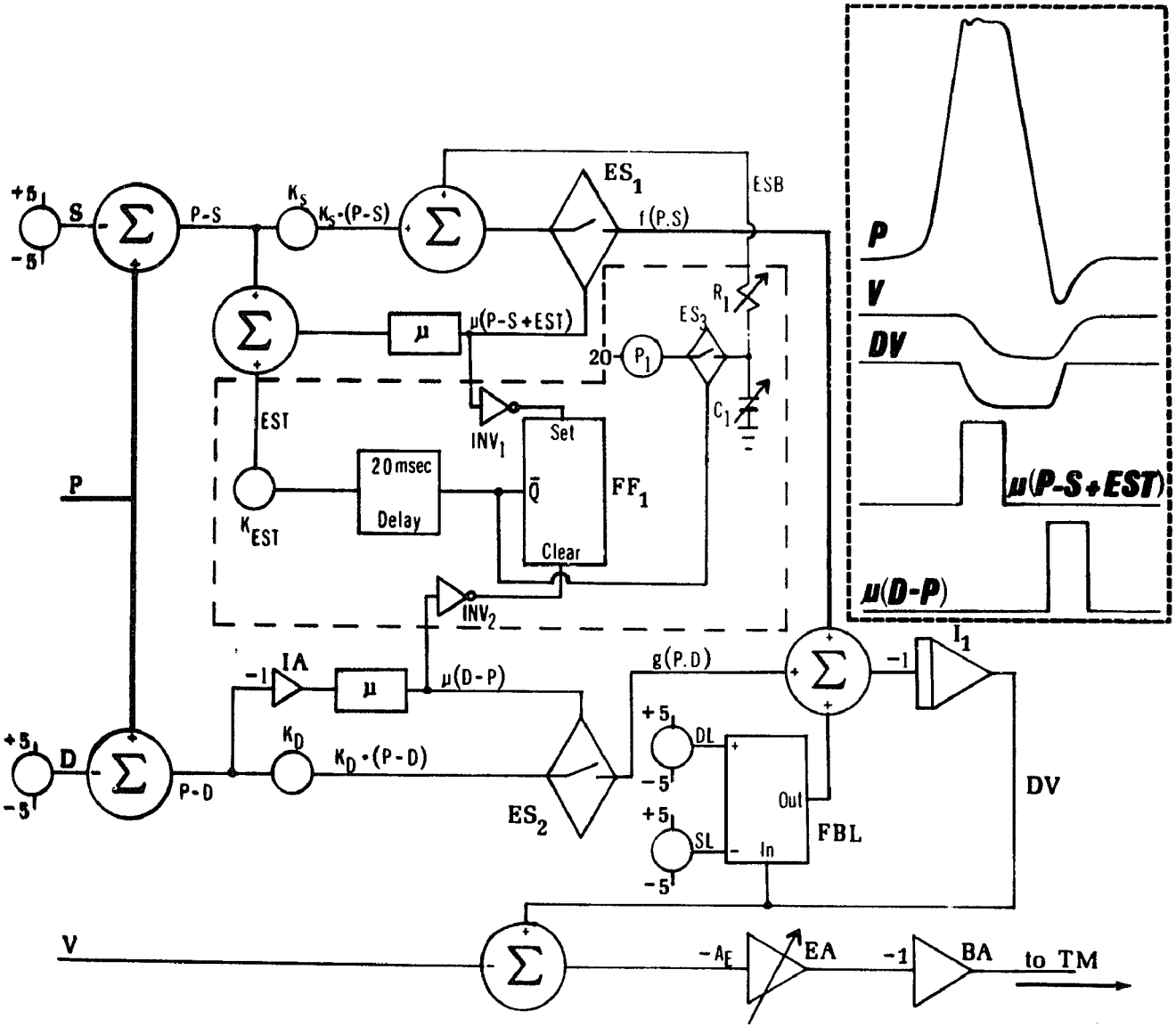
SERVO CONTROL LOGIC

The servo control logic is shown in Figure 2 with representative signals given in the insert. System operation can be described as follows:

Figure 2

Servo Control Logic

Servo control logic where P and V are intraventricular pressure and volume inputs; S and D systolic and diastolic threshold pressures; Σ's summing amplifiers with inputs labeled as to polarity; K_S and K_D adjustable systolic and diastolic gain potentiometers; IA_S a unity gain inverting amplifier; μ, f and g functions defined in the text; ES_1, ES_2 and ES_3 electronic switches; I_1 negative integrating amplifier; FBL feedback limiter with positive and negative inputs representing a diastolic volume limit (DL) and a systolic volume limit (SL); EA error amplifier with an adjustable gain of $-A_E$; BA current booster amplifier with a voltage gain of -1; and TM electro-hydraulic actuator torque motor. The early trigger circuit enclosed by the dashed line is composed of logic inverting amplifiers INV_1 and INV_2, a flip flop FF_1 (Q standard inverted output), a delay circuit, potentiometer P_1, electronic switch ES_3, variable capacitor C_1 and resistor R_1. This circuit provides an early systole trigger pressure EST, determined by the potentiometer K_{EST} setting, and a high amplitude short duration signal ESB to the above primary logic circuit. Pressure and volume are scaled so that -5 to +5 volts equals 0-200 mm Hg and 0-200 cc respectively. The insert illustrates typical P, V, desired volume DV and unit step functions $\mu(P-S+EST)$ and $\mu(D-P)$ curves measured over a cardiac cycle.


+5
S
-5
P-S
K_S
$K_S \cdot (P-S)$
ES_1
ESB
f(P.S)
P
V
DV
$\mu(P-S+EST)$
R_1
ES_3
20
P_1
C_1
μ
$\mu(P-S+EST)$
EST
INV_1
Set
$\bar{Q}$
FF_1
Clear
20 msec
Delay
K_{EST}
P
INV_2
$\mu(D-P)$
$\mu(P-S+EST)$
$\mu(D-P)$
IA
-1
μ
$\mu(D-P)$
g(P.D)
I_1
-1
+5
D
-5
K_D
$K_D \cdot (P-D)$
P-D
ES_2
+5
DL
-5
+5
SL
-5
Out
In
FBL
DV
V
$-A_E$
EA
-1
BA
to TM

$$DV = V + \Delta V \tag{1}$$

where DV is the desired intraventricular volume; V, intraventricular volume and ΔV, the change in intraventricular volume as defined below.

$$\Delta V = -\int \Big(f(P,S) + g(P,D) \Big)\, dt \tag{2}$$

Here P is intraventricular pressure; S, the preset systolic threshold; D, the preset diastolic threshold and f and g are functions determining ΔV during systole and diastole, respectively, given by:

$$f(P,S) = \begin{cases} K_s \times (P-S) + ESB & \text{for } (P+EST-S) > 0 \\ 0 & \text{for } (P+EST-S) \leq 0 \end{cases} \tag{3}$$

$$g(P,D) = \begin{cases} K_D \times (P-D) & \text{for } (D-P) > 0 \\ 0 & \text{for } (D-P) \leq 0 \end{cases} \tag{4}$$

K_s is systolic gain and K_D, diastolic gain. EST is an adjustable early systole trigger pressure, and ESB is an adjustable signal required to accelerate piston movement during early systole. As seen in Figure 2, the input to the negative integrator I_1 is determined by electronic switches ES_1 and ES_2 which are controlled by unit step functions (μ) defined by:

$$\mu(X) = \begin{cases} 1 & \text{for } X > 0 \\ 0 & \text{for } X \leq 0 \end{cases} \tag{5}$$

The electronic switches are open when the controlling input is 0 and closed when the controlling input is 1.

In order to eliminate any variability in end-diastolic volume due to pressure noise and to prevent balloon aspiration into the piston chamber and possible tearing, particularly during a potentiated post-premature ventricular contraction, the system is constrained by adjustable diastolic (DL) and systolic (SL) volume limiters so that at any given time:

$$SL \leq V \leq DL \tag{6}$$

This is accomplished by placing a feedback limiter (FBL) circuit around the integrator I_1 with the diastolic and systolic volume limiters as positive and negative inputs respectively (see Figure 2).

For the purpose of understanding system operation a brief description of the actuator control logic is given. The insert to Figure 2 exemplifies P, V, $\mu(P-S+EST)$, $\mu(D-P)$ and DV recorded for a cardiac cycle with the early triggering circuit (enclosed in dashed lines in Figure 2) intact. The operation of the logic will first be discussed without the early triggering circuit, in which case EST and ESB in Equation 3 will be 0. During the isovolumic contraction and relaxation phases of the cardiac cycle $D \leq P \leq S$, and $\mu(P-S) = \mu(D-P) = 0$ and ES_1 and ES_2 are open, keeping ΔV at 0. At the onset of ejection (P–S) becomes greater than 0, $\mu(P-S)$ becomes 1 and ES_1 is closed, causing ΔV to be $-\int K_s(P-S)dt$. Since ΔV is negative, DV and V are reduced, and, as seen in Figure 2, V is decreased at a rate

determined by A_E (error amplifier gain). A_E is set at a value so that actuator response is adequate and the systolic gain K_S is set to a value which is sufficient to keep P close to the threshold S but not high enough to cause oscillations around S. As diastole begins, (D-P) becomes greater than 0, $\mu(D-P) = 1$ and ES_2 is closed causing ΔV to be $-\int K_D(P-D)dt$. Since ΔV is positive, DV and V are increased. Diastolic gain K_D is set at a value high enough to keep P close to the threshold D in early diastole but not so high as to cause overshoot in late diastole.

In order to compensate for the previously mentioned time lag inherent to the actuator and in order to start changing V at the correct time with sufficient magnitude, it was necessary to add a compensating circuit (enclosed in dashed lines in Figure 2). This circuit transiently lowers true systolic threshold by EST, where EST is given by K_{EST}x(100 mm Hg) during diastole and early systole (for 20 msec after onset of ejection) and is 0 during the remainder of systole. EST is typically 0-20 mm Hg and is dependent on dP/dt. This circuit also generates ESB, a high amplitude short duration signal, which is sent to integrator I_1 and hence to the actuator a few milliseconds (5-15, depending on EST) before true threshold is reached.

In practical operation, the P-V loop is continuously displayed on an X-Y oscilloscope and K_S, K_D, A_E, EST, ESB, DL and SL manually adjusted to yield the desired waveform.

In Figure 2 only those elements required to describe the servo control logic during normal operation were presented. Two additional modes of operation are available: namely, the instantaneous isovolumic mode and the external control mode. Since both were used to obtain data, a brief description of how they interrupt the normal servo logic mode is necessary. Instantaneous isovolumic contractions are defined as those which occur when DV remains at the diastolic volume (EDV) throughout the cardiac cycle. As seen in equation (1) this would be the case when ΔV and V are equal to 0 and EDV, respectively. Electrically, this was accomplished by inserting a manual switch (not shown) between the μ(P-S+EST) control and the electronic switch ES_1 (Figure 2). As long as this manual switch remained closed the system operated in its normal fashion as described above. However, if during diastole the manual switch was opened, then filling would be unaltered and throughout systole ES_1 would remain open keeping ΔV at 0 and V at EDV. Under these conditions, the heart would beat isovolumically and continue to do so until the manual switch was again closed.

The external mode of operation provided an additional input (not shown) to the DV and V summing amplifier (Figure 2) which, when used, effectively bypassed the servo control logic and transferred control to an external, desired intraventricular volume function. Therefore, any electrical signal could be used to drive the system. For example, if the signal was a sine wave, the system would respond by sinusoidally moving fluid in and out of the balloon. Three experiments using potassium arrested hearts were performed using this external mode together with a recorded volume signal from one

of the isolated (ejecting) heart experiments. These three experiments will be discussed in greater detail in the Results section (Part III).

SURGERY AND THE PERFUSION SYSTEM

Mongrel dogs (17-29 kg) were anesthetized with intravenous ketamine (14-20 mg/kg) and succinylcholine (3.4-5.8 mg/kg) or pancuronium bromide (0.04-0.06 mg/kg) and ventilated (Harvard Model 607 Respirator) following endotracheal intubation.

The chest was entered through a median sternotomy and the pericardium incised longitudinally. The azygous vein was ligated and the inferior and superior vena cavae, pulmonary artery and thoracic aorta proximal to the first intercostal artery were isolated. A polyethylene cannula (20 F) was inserted into the left subclavian artery and extended to the aortic arch and was used to perfuse the heart both during its removal from the chest and during the experimental procedure. The brachiocephalic artery was cannulated with a polyethylene catheter (8 F) for subsequent monitoring of aortic root perfusion pressure (Statham P23Gb). Following vessel ligation, the heart was isolated using a modification of a previously described technique (Geis et al., 1971) which permits removal of the heart without the sinus node. During the isolation procedure, the aortic root was continuously perfused with autologous blood from a separate reservoir suspended above the heart (80 cm H_2O).

Prior to its attachment to the perfusion apparatus, a vent line was inserted through the left ventricular apex and an approximate

heart weight was obtained. Normally it took one hour from the time the heart was removed from the chest to the beginning of data acquisition and 4 to 5 hours to complete the protocol. At the conclusion of the experiment, the heart and left ventricle were again weighed. Once attached to the apparatus, as shown in Figure 3, nonpulsatile aortic root pressure was maintained at 80-100 mm Hg, and total coronary flow measured using an extracorporeal electromagnetic flow probe (Biotronex). Bipolar pacing leads excited by a Grass stimulator (Model S4) and epicardial ECG leads were sewn to the interatrial septum above the tricuspid valve and the right ventricular outflow tract respectively. The chordae tendineae of both the anterior and posterior left ventricular papillary muscles were severed and the competence of the aortic valve assessed. The collapsed balloon attached to the coupling cannula was then placed in the left ventricle through the mitral valve opening. The cannula was secured in position at the mitral annulus with a purse string suture. The perforated ridge of the cannula, shown in Figure 3, permitted additional securement to the annulus and left atrium by silk sutures.

As seen in Figures 3 and 4, a support dog was used to oxygenate the blood. Anesthesia of the support dog was maintained with a ketamine (1.0 mg/min) and pancuronium bromide (1.0 mg/hr) mixture; and the animal ventilated with a volume-cycled respirator (Harvard, Model 613) and supplemental oxygen (0_2) with periodic sighing to 25 cm H_2O. Venous blood from the collection reservoir was returned to the internal jugular vein of the support dog using a roller pump (Sarns, Model 350). Arterial blood was taken from the femoral

Figure 3

Isolated Heart Preparation

Diagram of the isolated heart being supported by a support dog. S_1 and S_2 are arterial and venous blood sampling ports respectively; AP is the aortic perfusion pressure catheter; LVP, left ventricular pressure gauge catheter; and LV, left ventricle (see text).

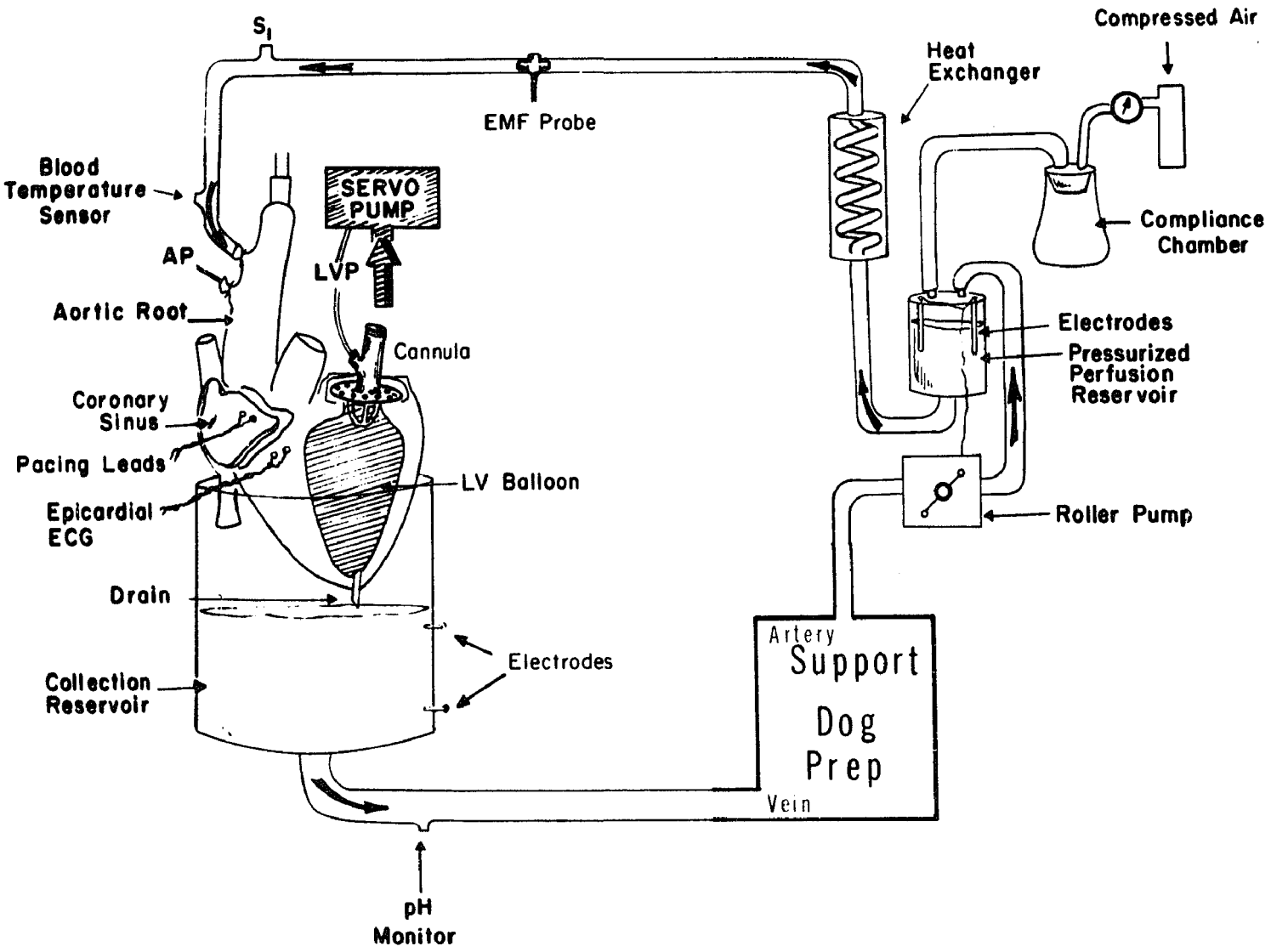
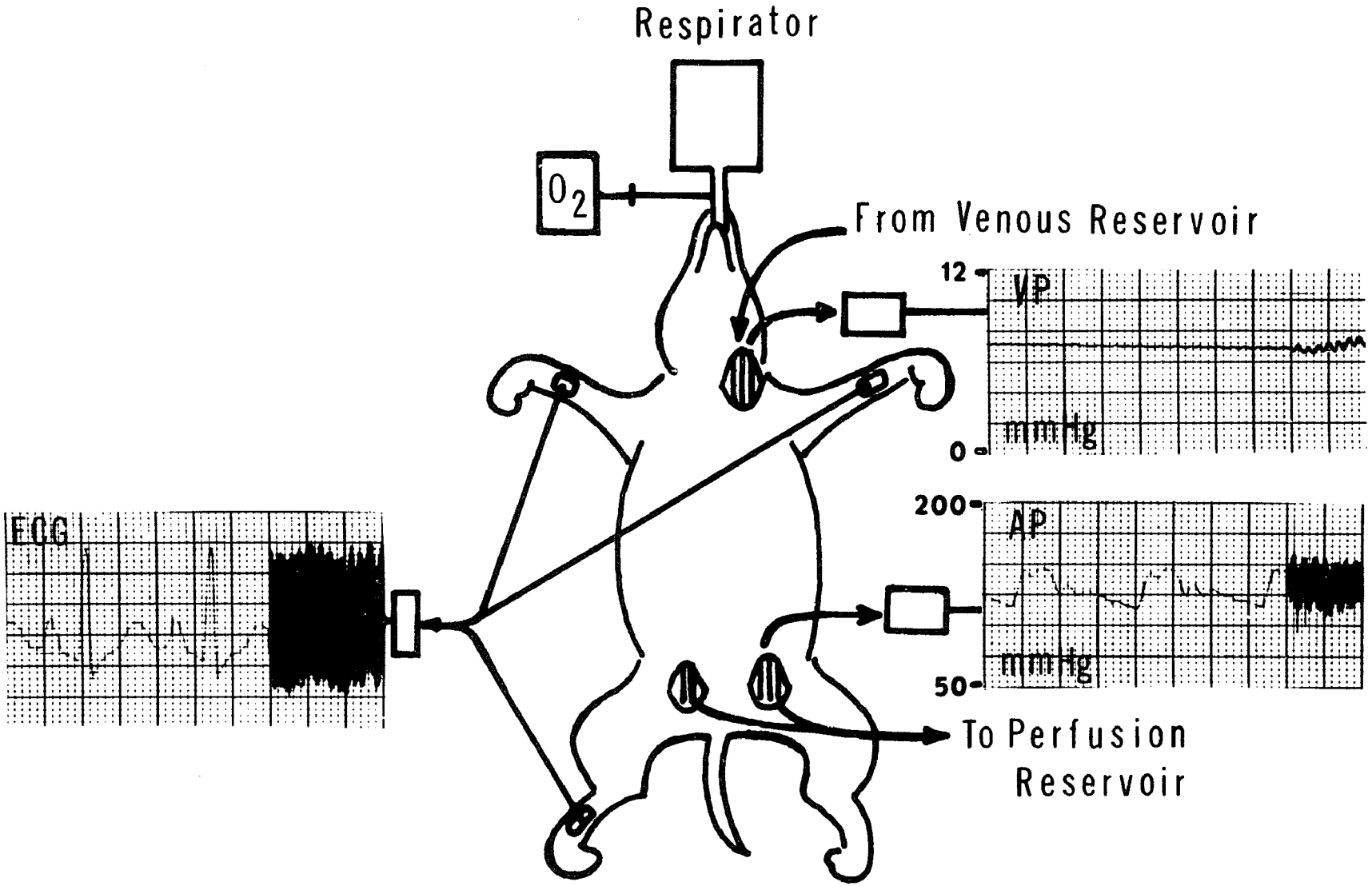

S_1
EMF Probe
Heat Exchanger
Compressed Air
Blood Temperature Sensor
SERVO PUMP
LVP
AP
Aortic Root
Cannula
Compliance Chamber
Electrodes
Pressurized Perfusion Reservoir
Coronary Sinus
Pacing Leads
LV Balloon
Epicardial ECG
Roller Pump
Drain
Electrodes
Collection Reservoir
Artery
Support
Dog
Prep
Vein
pH Monitor

Figure 4

Support Dog Preparation

Diagram of the support dog preparation used to oxygenate the blood. Venous blood from the venous collection reservoir was returned to the internal jugular vein and arterial blood was withdrawn via the femoral arteries and pumped to the perfusion reservoir. As indicated, the electrocardiogram (ECG), and arterial (AP) and venous (VP) pressures were monitored and recorded throughout the experiment.


Respirator
O_2
From Venous Reservoir
12
VP
mmHg
0
200
AP
mmHg
50
ECG
To Perfusion
Reservoir

arteries and pumped (Sarns) to the pressurized perfusion reservoir. Throughout the experiment the support dog's electrocardiogram (ECG) and arterial (AP) and venous (VP) pressures were monitored and recorded (Hewlett Packard #7848A recorder). Both pressures were measured with Statham (Model P23 Series) transducers.

The perfusion reservoir fluid level was held constant via fluid level sensors with feedback control to the roller pump. Similar control of the collection reservoir level was incorporated. Blood temperature was maintained at 37.5°C with a heat exchanger. The vent line drainage (i.e., Thebesian flow) and coronary sinus spill-over from the right ventricle drained into the collection reservoir. Arterial perfusate was circulated through an Instrument Laboratories blood gas analyzer (Model 113) at a rate of 1.5 cc/min using a Holter pump for the continuous monitoring of pO_2 and pCO_2. An indwelling, semi-micro combination pH electrode (Corning) in the "venous" line was used for continuous pH monitoring. The ranges of pO_2, pCO_2 and pH were 90 to 120 mm Hg, 32-37 mm Hg and 7.40-7.45, respectively.

PROTOCOL

Prior to data collection, balloon volume was first slowly increased and then decreased so that diastolic pressure (EDP) varied in the range 0 to 15 mm Hg. The heart was subjected to three such cycles in an attempt to minimize hysteresis effects (Patel et al., 1969), and in addition it was reasoned that this procedure would aid in the conformation of the balloon to the internal shape of the ventricle. The heart was then allowed to stabilize for a period of 10 to 20 minutes with an EDP of 8 mm Hg and an ejection pressure (EP) at a value that allowed for a stroke volume of approximately 10 cc. During this "conditioning" period, the slowest, paced heart rate was established.

Three methods were utilized to study the effects of varying EP on the diastolic pressure-volume relation. Method 1 consisted of fixing and maintaining the diastolic volume (EDV) constant and incrementally increasing EP to the isovolumic contraction (P_o). Data were recorded at each EP value after allowing sufficient time (1-2 minutes) for steady state. Oftentimes this procedure of incrementally varying EP was reversed (i.e., starting at P_o and reducing EP). In Method 2 the EDP was held constant as EP was incrementally varied. As described in more detail in the Results, this required the addition or subtraction of volume depending on whether EP was being increased or decreased, respectively.

Method 3 refers to the procedure whereby instantaneous isovolumic contractions were obtained (see page 30) for each measurement.

Data to be presented were obtained from a total of 20 experiments which can be divided into two series. In the first series (9 experiments) Methods 1 and 2 were used. In each experiment ejection pressure was varied at a minimum of 4 EDP values in the range 5 to 30 mm Hg. Method 3 was used in the second series (11 experiments) although in each experiment Method(s) 1 and/or 2 were also randomly included. In this latter series the range of EDP studied was primarily 0 to 12 mm Hg using increments of 2 mm Hg with the ejection pressure held constant.

Depending on the condition of the preparation, inotropic interventions (calcium chloride, norepinephrine or propranolol) were included late in the protocol. The only objective in using these drugs was further to vary experimental conditions and, therefore, a systematic study of the effects of these drugs on the diastolic pressure-volume relation was not part of the protocol. These drugs were infused, into the perfusate, at a constant rate using a Harvard Infusion-Withdrawal pump (Model 909). If, after a period of time, a steady state was achieved, the "control" protocol was repeated.

DATA ANALYSIS

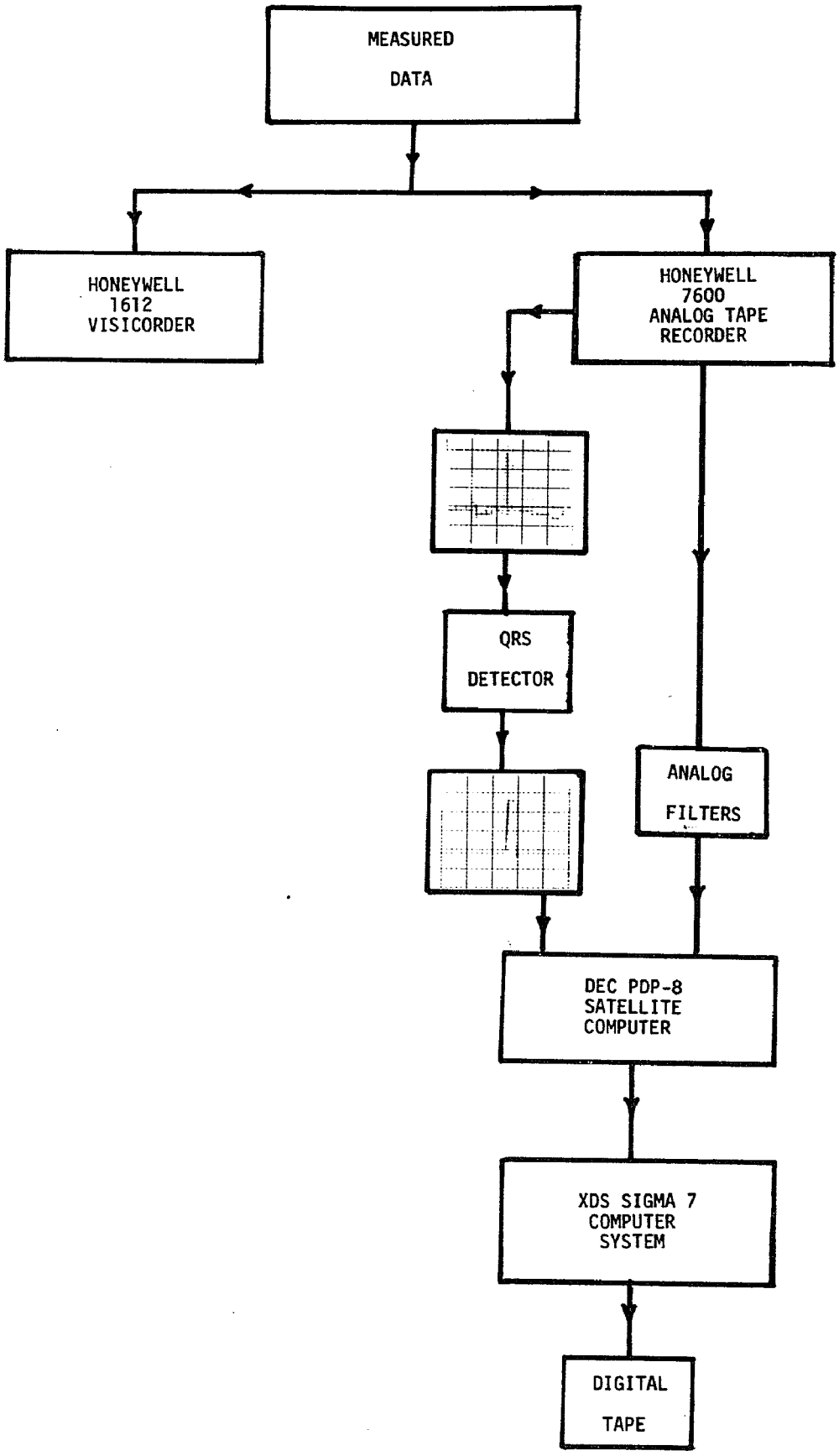
A block diagram illustrating the arrangement of the equipment used in the recording and subsequent computer analysis of the measured data is presented in Figure 5. The data were simultaneously recorded on Kodak Linagraph Direct Print paper (Type 1895) using a Honeywell 1612 visicorder oscillograph and on analog tape using a Honeywell 7600 analog tape recorder. The tape recording speed was 3 3/4 inches per second permitting the recording of data in the bandwidth of 0 to 2500 Hz (extended mode). At a later date the analog data were converted to digital data (A/D) at a sampling rate of 500 samples per second per data channel via a Dec PDP-8 satellite computer time shared with a XDS Sigma 7 computer system and stored on digital tape. Prior to conversion, the electrocardiogram (ECG) signal was transformed, using an analog QRS wave detection device, into a signal which remained at 0 volts until a QRS complex was detected, whereupon a short duration square wave (0 to 15 volts) was generated. The use of this instrument permitted accurate computer definition of a cardiac cycle without the use of a sophisticated ECG pattern recognition computer program.

The satellite computer is located approximately 150 feet from the laboratory and consequently electrical noise interference approximately 40 millivolts peak to peak was a problem. This was

Figure 5

A Flow Diagram of the Equipment Used for Recording and Digitally Converting the Data

(see text)


MEASURED
DATA
HONEYWELL
1612
VISICORDER
HONEYWELL
7600
ANALOG TAPE
RECORDER
QRS
DETECTOR
ANALOG
FILTERS
DEC PDP-8
SATELLITE
COMPUTER
XDS SIGMA 7
COMPUTER
SYSTEM
DIGITAL
TAPE

particularly bothersome because of the ± 1 volt input constraints of the satellite computer. For example, zero left ventricular pressure corresponded to - 1 volt and 200 mm Hg to + 1 volt, so that electrical noise amounted to 4 mm Hg peak to peak. Thus, all data, except ECG, were filtered at the satellite computer. The frequency response curves of these filters are given in Figure 6. Plotted are decibel (db) versus $\log_{10}$ frequency where:

$$db = 20 \log_{10} (\text{Volts out/Volts in}) \qquad (7)$$

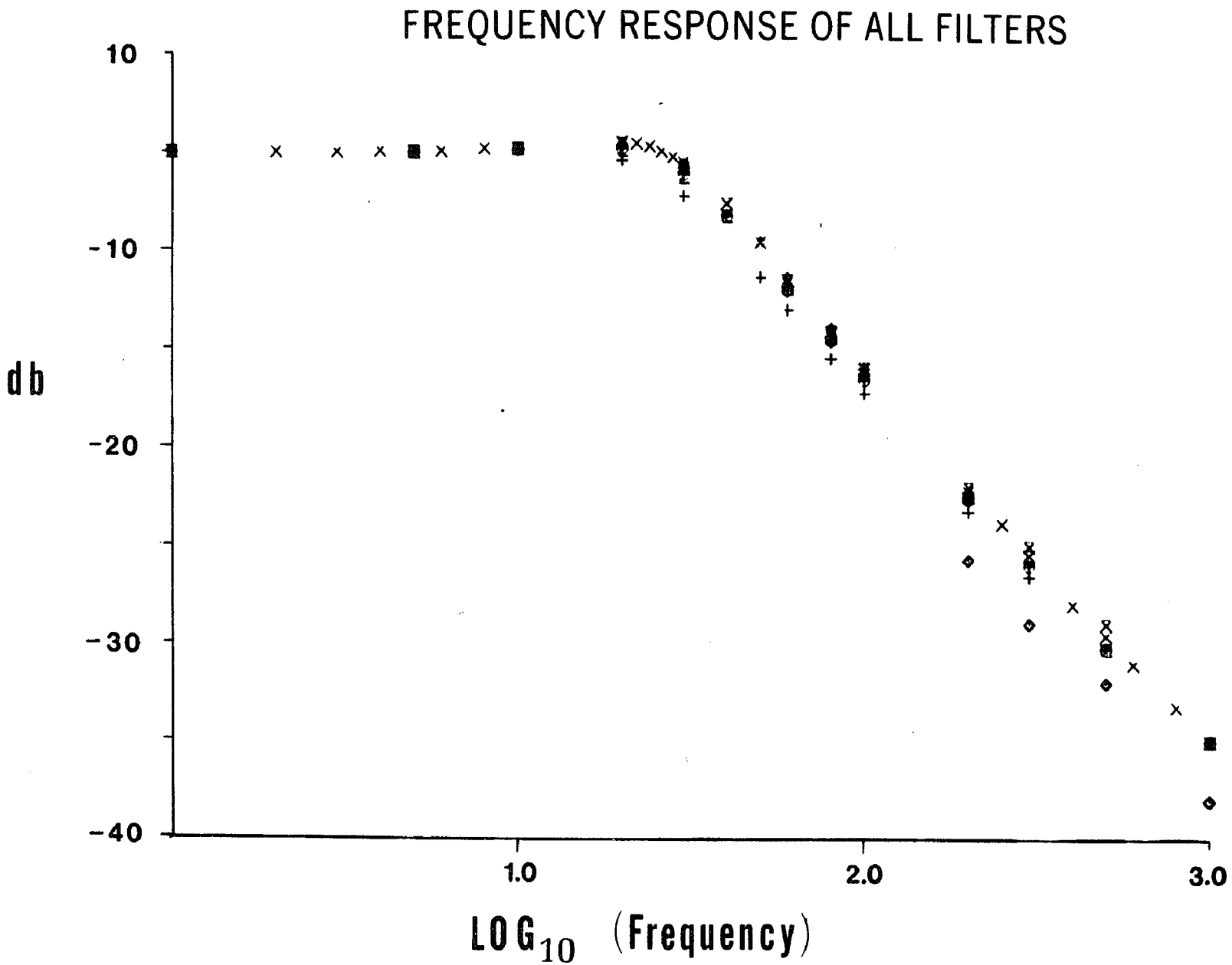
These filters had a flat response within 1 db up to 25 Hz, were down 3 db at 35 Hz and thereafter decreased 12 db per octave. The 90° phase shift occurred at approximately 30 Hz. All frequencies greater than 200 Hz were effectively removed (98% attenuated); and since the folding frequency associated with the sampling rate was 250 Hz, errors due to aliasing (Attinger et al., 1966) were thus avoided.

The residual 60 Hz noise which was inadvertently converted was eliminated, during data reduction, by using a fast Fourier transform (FFT) subroutine on each measured event for each cardiac cycle analyzed. This subroutine transforms a periodic event from the time domain to the frequency domain. That is, the time varying event is expressed as a finite series consisting of a constant term, plus harmonically related sine and cosine terms, where each harmonic is an integer multiple of the fundamental frequency, (i.e., frequency of the cardiac cycle). The number of terms or harmonics is one-half the number of points sampled. For example, assuming the heart rate to be 120 beats/min and the sampling rate 500 samples per second,

Figure 6

Frequency Response of All Filters

A graph of decibel (db) versus the logarithm to the base 10 of frequency for all analog filters, with each filter distinguished by a symbol.


FREQUENCY RESPONSE OF ALL FILTERS
10
-10
-20
-30
-40
db
1.0
2.0
3.0
LOG10 (Frequency)

each cycle would contain 250 points and the Fourier transform would return 125 harmonics. If 60 Hz noise were present it would then be associated with the 30th harmonic. Therefore, in this example, deleting the 30th harmonic, before resynthesizing the original event, eliminates the noise. Resynthesis is accomplished by taking the inverse of the Fourier transform.

When resynthesizing a periodic cardiac event it is not necessary to use all of the harmonics. According to Gersh et al. (1971), left ventricular pressure could be accurately resynthesized using the first 6 harmonics. In this study all harmonics corresponding to frequencies greater than 35 Hz were removed before taking the inverse Fourier transform. An example of a resynthesized left ventricular pressure and volume curve is given in Figure 7. As seen, no apparent extraneous noise is present. Furthermore, a visual comparison between these curves and the analog (unfiltered) curves illustrated in Figures 9, 10 and 11 indicates that the overall integrity of the filtered curves was maintained.

The FFT subroutine, a standard systems program, was utilized in an extensive program developed, by the author, to analyze the data. The major programming steps involved in the data reduction are summarized in Figure 8. A data set refers to a series of converted cardiac cycles having constant diastolic and ejecting pressures. A data set is read from the A/D digital tape (Figure 5) and a search for the beginning and end of a cardiac cycle is initiated. That is, the computer searches for two consecutive square waves which are the analog of two consecutive QRS complexes

Figure 7

Example of Resynthesized Data

An example of resynthesized left ventricular pressure (LVP) and volume (EDV) curves, using digitized data and removing all frequency components greater than 35 Hz.

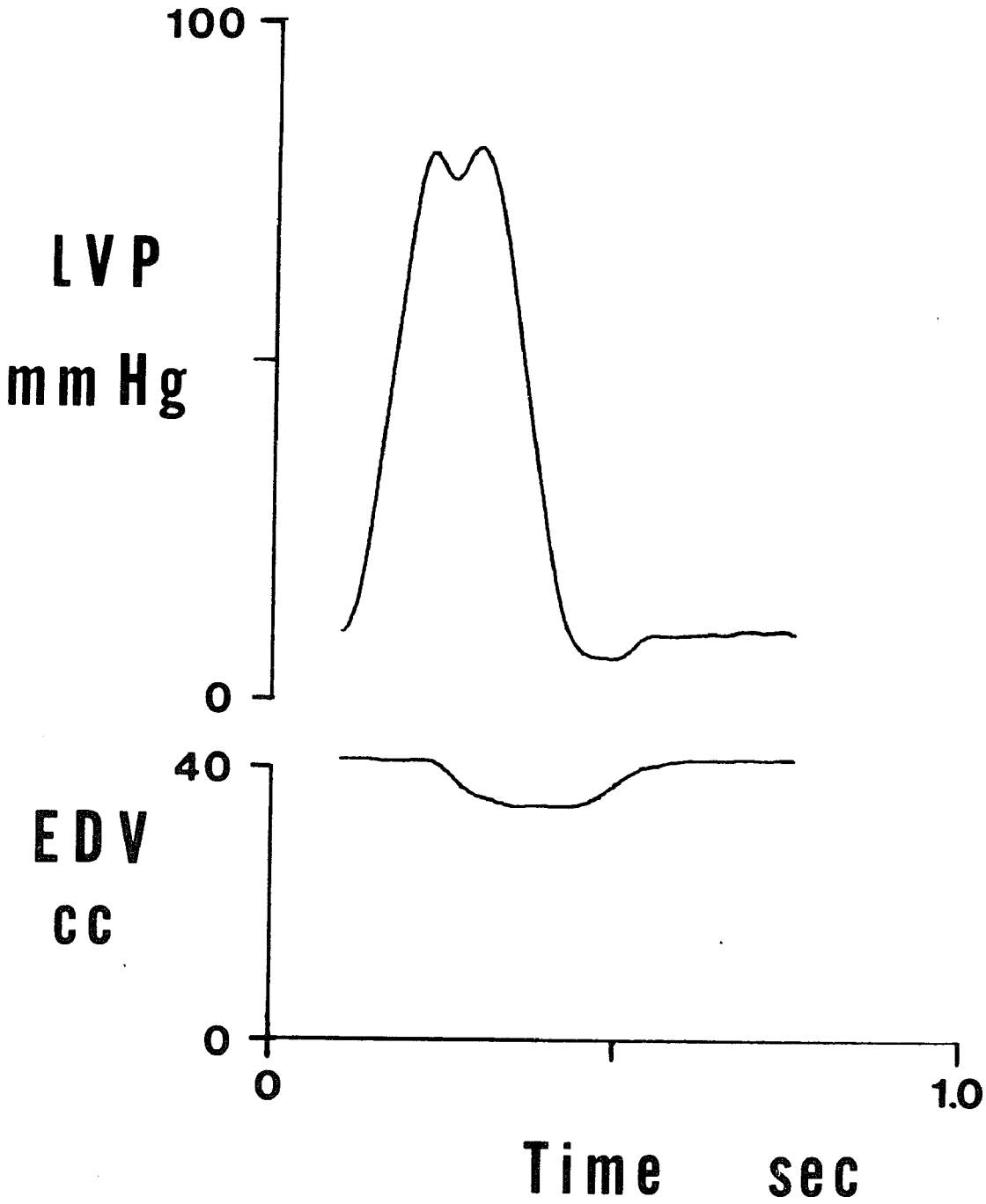
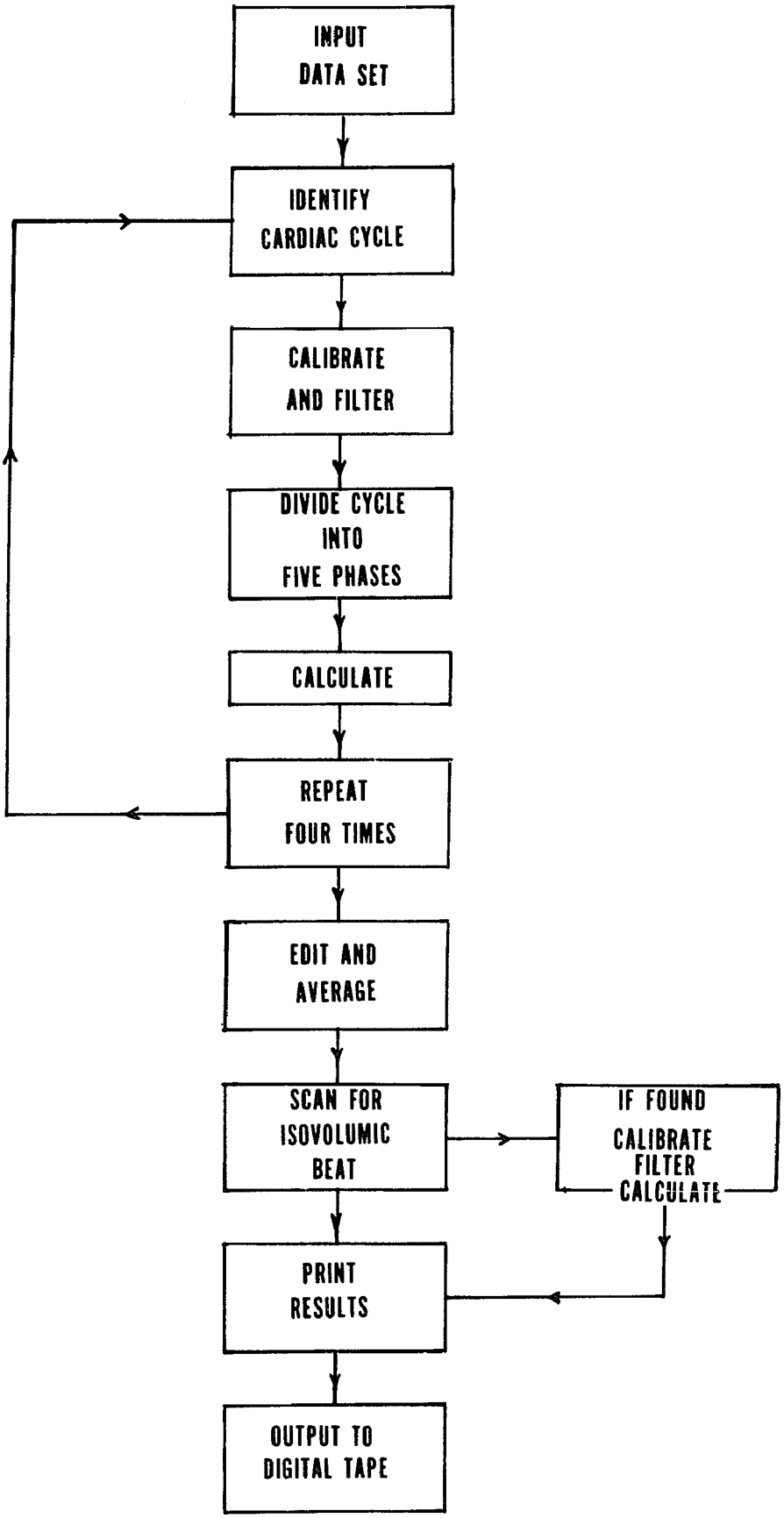

100
LVP
mm Hg
0
40
EDV
cc
0
0
1.0
Time sec

Figure 8

A Flow Diagram of the Computer Program

(see text)


INPUT
DATA SET
IDENTIFY
CARDIAC CYCLE
CALIBRATE
AND FILTER
DIVIDE CYCLE
INTO
FIVE PHASES
CALCULATE
REPEAT
FOUR TIMES
EDIT AND
AVERAGE
SCAN FOR
ISOVOLUMIC
BEAT
IF FOUND
CALIBRATE
FILTER
CALCULATE
PRINT
RESULTS
OUTPUT TO
DIGITAL TAPE

(Figure 5). Once found, the data within the cardiac cycle are calibrated from arbitrary A/D units to their respective physical units and the 60 Hz noise removed as previously discussed using FFT. Following this the ejecting cardiac cycle is subdivided into 5 phases, namely: 1) isovolumic contraction, 2) ejection, 3) isovolumic relaxation, 4) filling and 5) diastole. The program then obtains and stores diastolic pressure (EDP) and volume (EDV), mean ejection pressure (EP) and end systolic volume (ESV). From these data heart rate (HR), stroke volume (EDV-ESV) and ejection fraction (stroke volume/EDV × 100%) are calculated and stored. The above is repeated for 4 subsequent ejecting cardiac cycles. Once 5 ejecting cardiac cycles have been analyzed, the next step is to compare their respective heart rates, ejection pressures, and diastolic pressures and volumes. If any of these 4 quantities deviated more than one standard deviation from the average, the cardiac cycle with which it was associated was rejected. The acceptable ejecting beats were then averaged. At this point the program scanned all remaining data in the set for an instantaneous isovolumic beat (Method 3). If found, its heart rate, peak pressure (PMAX) and diastolic pressure and volume were obtained. The final programming steps were to print all results and store them on another digital tape for further analysis and plotting. Thus, the final digital tape contained for each data set: an average ejecting left ventricular pressure and volume curve and its average HR, EP, EDP, EDV, ESV, stroke volume and ejection fraction; and if

measured an instantaneous isovolumic left ventricular pressure curve along with its HR, PMAX, EDP and EDV. The program, therefore, in addition to supplying the results to be presented, reduced the data to a readily accessible form for analyses concerned with other aspects of ventricular function (e.g., Weber et al., 1974).

PART III

RESULTS

Development of the servo system and the isolated heart technique required 28 separate biological experiments. The results discussed below were obtained in a subsequent series of 20 experiments. An illustration of hemodynamic data exemplary of the latter series of experiments is given in Figure 9, which shows epicardial electrocardiogram (ECG), left ventricular pressure (LVP) and volume (LVV) obtained with a heart perfused by a support dog and paced at 110 beats/min. The diastolic pressure (EDP) was set and maintained at 5 mm Hg (Panel A) or 13 mm Hg (Panel B) which corresponded to diastolic volumes (EDV) of 45 and 63 cc respectively. Two variably afterloaded ejection beats and an isovolumic contraction (P_o) for each EDP were generated by raising the ejecting pressure (EP) from 62 to 78 to 95 mm Hg in Panel A and from 80 to 122 to 142 mm Hg in Panel B. It can be noted that for each pre-set systolic pressure mean ejection pressure was held constant within $\pm$ 3 mm Hg. In general, at lower ejecting to peak isovolumic pressure ratios (< 0.3), the control of ejection pressure was less effective; however, the maximum variation was rarely greater than $\pm$ 5 mm Hg.

Basic data for each experiment are summarized in Table 1. Included are the following: left ventricular (LV) weight measured at the end of the experiment; initial left ventricular volume (V_o) obtained at a diastolic pressure of 0 mm Hg; the slowest paced heart rate (HR) obtained; an estimate of performance at the onset of the

Figure 9

Exemplary Hemodynamic Data

Data obtained from an isolated heart preparation (SD517) paced at 110/min illustrating the ability of the servo system to maintain diastolic and ejection left ventricular pressure (LVP) at constant pre-set levels. Also shown are the epicardial electrocardiogram (ECG) and the left ventricular volume (LVV). Panel A consists of data corresponding to three ejection pressures including an isovolumic pressure (P_o) obtained at a diastolic pressure of 5 mm Hg, and Panel B shows similar data obtained at a diastolic pressure of 15 mm Hg.

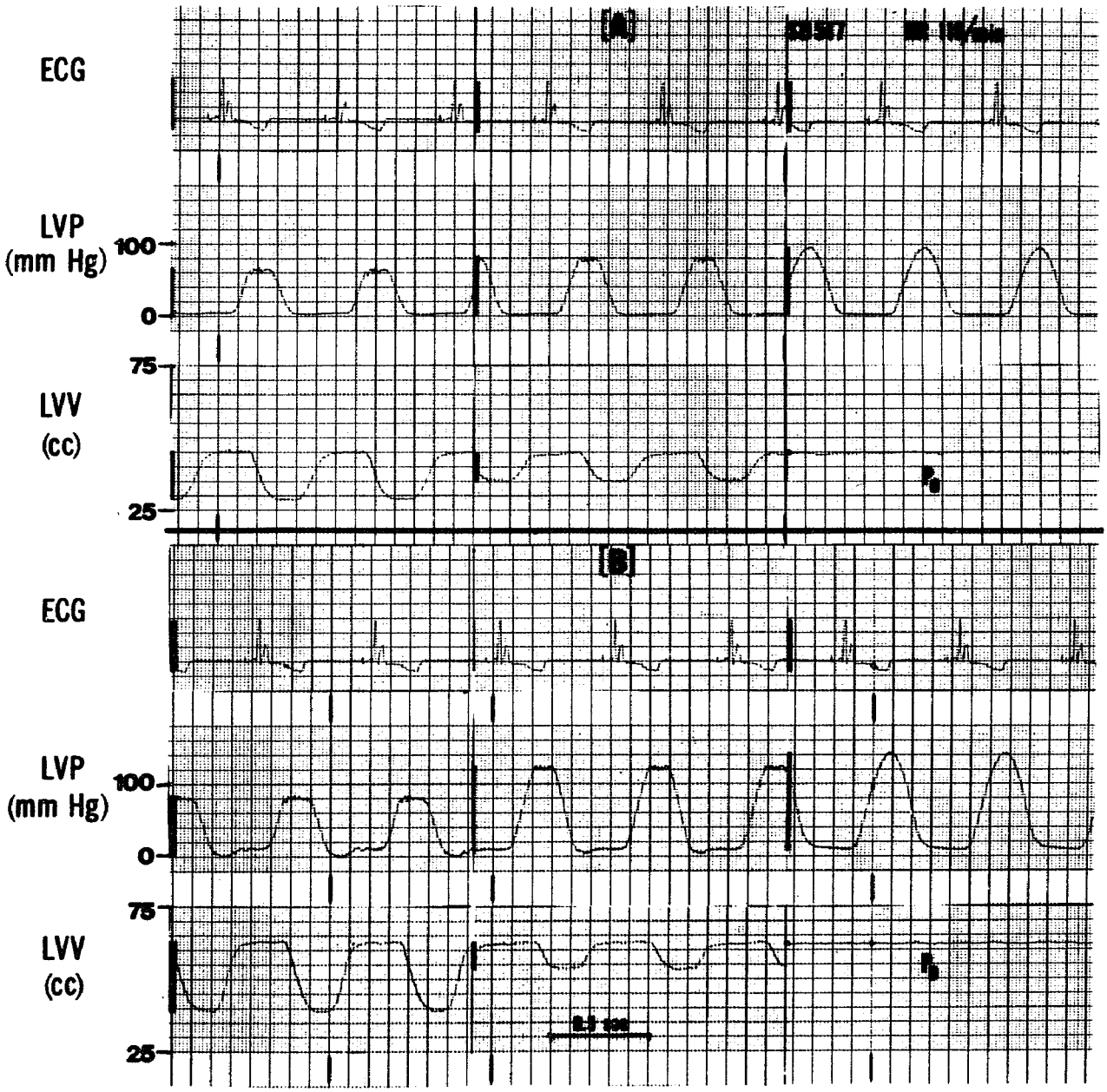

ECG
LVP
(mm Hg)
100
0
75
LVV
(cc)
25
[A]
ECG
LVP
(mm Hg)
100
0
75
LVV
(cc)
25
[B]

TABLE 1

SUMMARY OF BASIC DATA FOR EACH EXPERIMENT

SERIES	EXPERIMENT #	LV WEIGHT(g)	V_o (cc)	HR (Beat/Min)	PMAX (mm Hg)	DRUGS
I	51	135	15.0	115	128	PROPRANOLOL
I	523	171	14.5	100	136*	
I	517	147	24.5	100	102*	
I	6153	182	30.0	165	130	
I	6203	93	19.5	110	162*	
I	6223	172	19.6	115	96	CALCIUM PROPRANOLOL
I	763	152	23.5	80	148	
I	7103	130	14.5	110	110	CALCIUM PROPRANOLOL
I	7123	169	24.0	95	144*	CALCIUM PROPRANOLOL
II	7253	155	29.1	60	93	PROPRANOLOL
II	9123	108	14.5	130	190	PROPRANOLOL
II	9193	115	21.0	120	> 200	
II	11133	87	10.3	110	> 200	
II	1243	132	16.3	90	91	NOREPINEPHRINE
II	12183	135	15.9	55	96	NOREPINEPHRINE
II	1154	143	16.2	65	101	NOREPINEPHRINE
II	1244	169	15.6	90	118	
II	254	132	20.6	85	> 200	NOREPINEPHRINE
II	2144	132	11.5	100	150	NOREPINEPHRINE
II	2214	132	12.8	130	158	

* Obtained at EDP in the range 7 to 12 mm Hg.

experiment as given by the peak isovolumic pressure (PMAX) developed at an EDP in the range of 10 mm Hg; and the notation of whether inotropic (drugs) interventions were made. Those PMAX entered as > 200 mm Hg indicate pressures which exceeded the recording capabilities, according to the pre-established recording sensitivity. A PMAX value followed by an asterisk implies that it was obtained at an EDP in the range 7 to 12 mm Hg with all others measured at 10 mm Hg. In those studies where calcium was administered the blood levels were increased from a control range of 8-10 mg % to 12-18 mg %. The range of norepinephrine and propranolol infusion rates were 0.4-1.4 μgm/min and 0.1-0.5 mgm/min, respectively. The first 9 experiments listed are referred to as Series I and the remaining 11, as Series II as discussed in Part II (p. 40). This table, in addition to providing some basic data concerning the cavity size and weight of the ventricles, indicates that the results to be presented were derived from data obtained under a variety of conditions. In addition the spectrum of experimental conditions was further broadened by including those experiments where inotropic interventions were made and heart rates and performance altered. For example in experiment 12183 the paced heart rate had to be increased from 55 to 90 beats/min and the PMAX at an EDP of 10 mm Hg increased from 96 to 140 mm Hg when norepinephrine was infused at a constant rate of 1 μgm/min. In two experiments, 2144 and 2214, the hearts became edematous during data collection as reflected by increases of 60 and 66% respectively in total heart weight, and represent still another set of experimental conditions examined. The average percent total weight gain, however, for the remaining 18 experiments was only 13% (± 3 SEM).

EFFECTS OF VARYING EJECTION PRESSURE ON THE DIASTOLIC PRESSURE-VOLUME RELATION

As discussed in Part II (p. 39), three methods were used to study the alterations in the diastolic pressure-volume relation (PV-relation) which occurred when ejection pressure was varied. Examples of these maneuvers are presented in Figures 10, 11 and 12. Shown in Figure 10 are data, obtained from experiment 254, consisting of epicardial electrocardiogram (ECG), and three superimposed left ventricular pressure (LVP) and volume (VOL) curves. The LVP curves, all obtained at a constant EDV of 36 cc (Method 1), consist of two ejecting curves having ejection pressures of 40 and 80 mm Hg (a and b in Figure 10, respectively) and an isovolumic beat of 137 mm Hg peak pressure (c in Figure 10). EDP declined as EP was increased with the total decrease in EDP being 20% from a value of 9.3 mm Hg for the lowest ejection pressure to 7.4 mm Hg for the isovolumic beat. Figure 11 (experiment 51) illustrates an example where EDV was increased to maintain EDP constant at 10 mm Hg (Method 2) during increments in EP. The amount of filling volume added as a result of increasing EP from 58 to 98 mm Hg (labeled a and b respectively) was 1.7 cc with an additional amount of 1.6 cc added during the isovolumic beat where PMAX was 122 mm Hg (curve c).

A demonstration of the typical response obtained following an instantaneous isovolumic beat (Method 3) is given in Figure 12

Figure 10

Effect of Varying Ejection Pressure
on the Diastolic Pressure

Data, obtained from experiment 254 paced at 90/min, consisting of epicardial electrocardiogram (ECG), and three superimposed left ventricular pressure (LVP) and volume (VOL) curves. The LVP curves, all obtained at a constant diastolic volume, consist of two ejecting pressures (curves a and b) and an isovolumic contraction (curve c). As ejection pressure was increased the diastolic pressure decreased indicating an alteration in the diastolic pressure-volume relation.

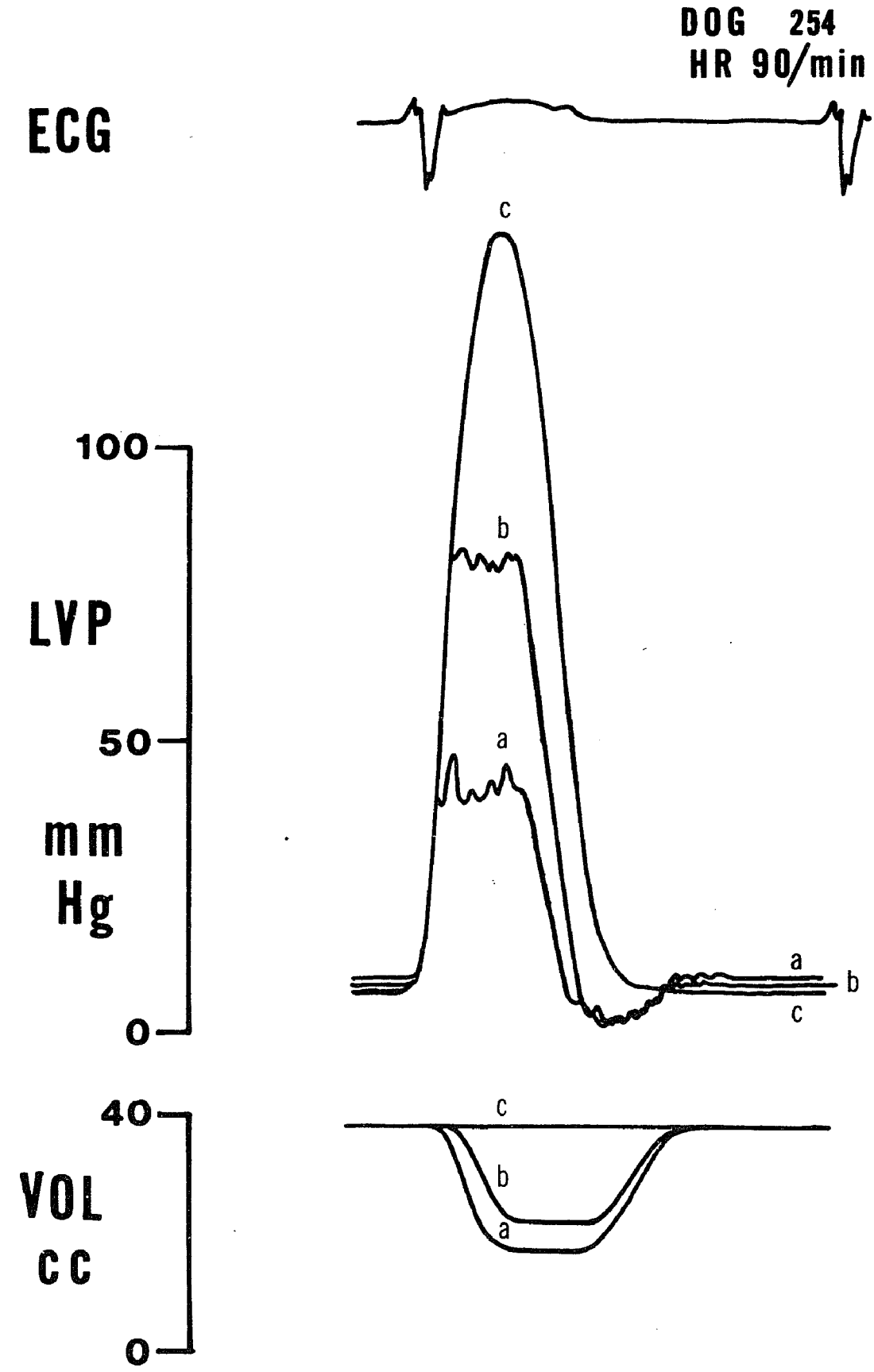

DOG 254
HR 90/min
ECG
100
LVP
50
mm
Hg
0
40
VOL
cc
0
c
b
a
a
b
c
c
b
a

Figure 11

Effect of Varying Ejection Pressure
on the Diastolic Volume

Data, obtained from experiment 51 paced at 113/min, consisting of epicardial electrocardiogram (ECG), and three superimposed left ventricular pressure (LVP) and volume (VOL) curves. The LVP curves, all obtained at a constant diastolic pressure, consist of two ejecting pressures (curves a and b) and an isovolumic contraction (curve c). As ejection pressure was increased the diastolic volume had to be increased to maintain the diastolic pressure constant, indicating an alteration in the diastolic pressure-volume relation.

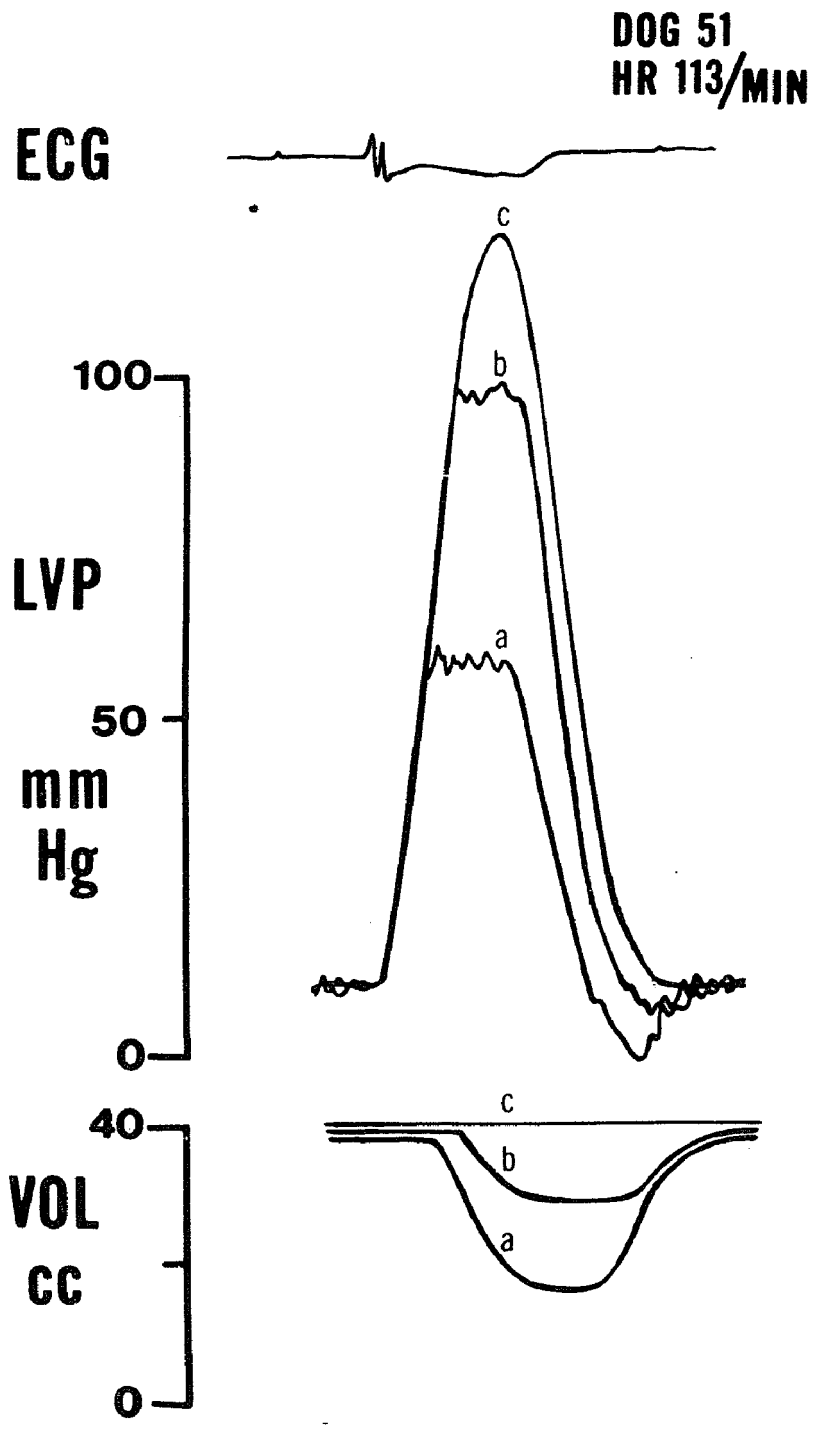
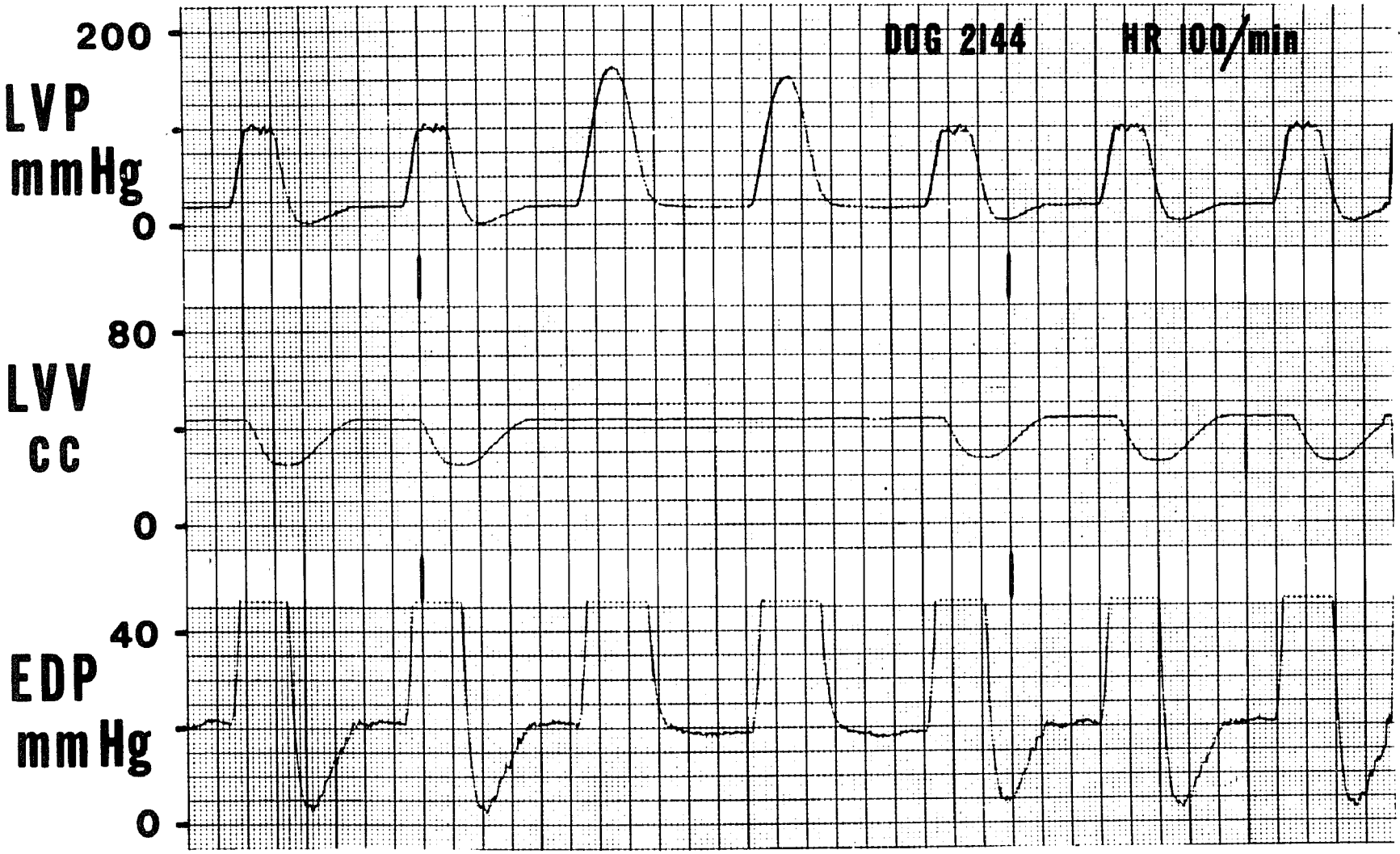

DOG 51
HR 113/MIN
ECG
c
b
a
100
LVP
50
mm
Hg
0
c
40
b
VOL
a
cc
0

Figure 12

Diastolic Pressure Response Following
an Instantaneous Isovolumic Contraction

Data obtained from an isolated heart preparation (Dog 2144) paced at 100/min illustrating the decrease in diastolic pressure (EDP) following the sudden imposition of an isovolumic state. Upon removal of this isovolumic condition EDP returned to its original value following two ejecting beats. Also shown are the left ventricular pressure (LVP) and volume (LVV).


DOG 2144
HR 100/min
200
LVP
mmHg
0
80
LVV
cc
0
40
EDP
mmHg
0

(experiment 2144). Shown are recordings of LVP, left ventricular volume (LVV) and augmented diastolic pressure (EDP). Initially the EP and EDP were 100 and 21 mm Hg, respectively, and the EDV remained at 44 cc throughout. Immediately after the first isovolumic beat (PMAX of 162 mm Hg) EDP had decreased to 19 mm Hg. Furthermore, after removal of the isovolumic condition EDP had returned within 2 cardiac cycles to its pre-isovolumic value. These latter observations would tend to negate, as a possible explanation, phenomena which require a relatively longer time constant such as alterations in coronary flow, the development of myocardial ischemia and catecholamine depletion. Thus, it was possible via increases in ejection pressure, either in a steady state fashion (Figures 10 and 11) or transiently (Figure 12), to produce a change in the PV-relation such that: (1) for a constant EDV the EDP decreased, or (2) for a constant EDP the EDV increased. This occurred, without exception, in all of the experiments listed in Table 1 including those with inotropic manipulations or marked increments in heart weight.

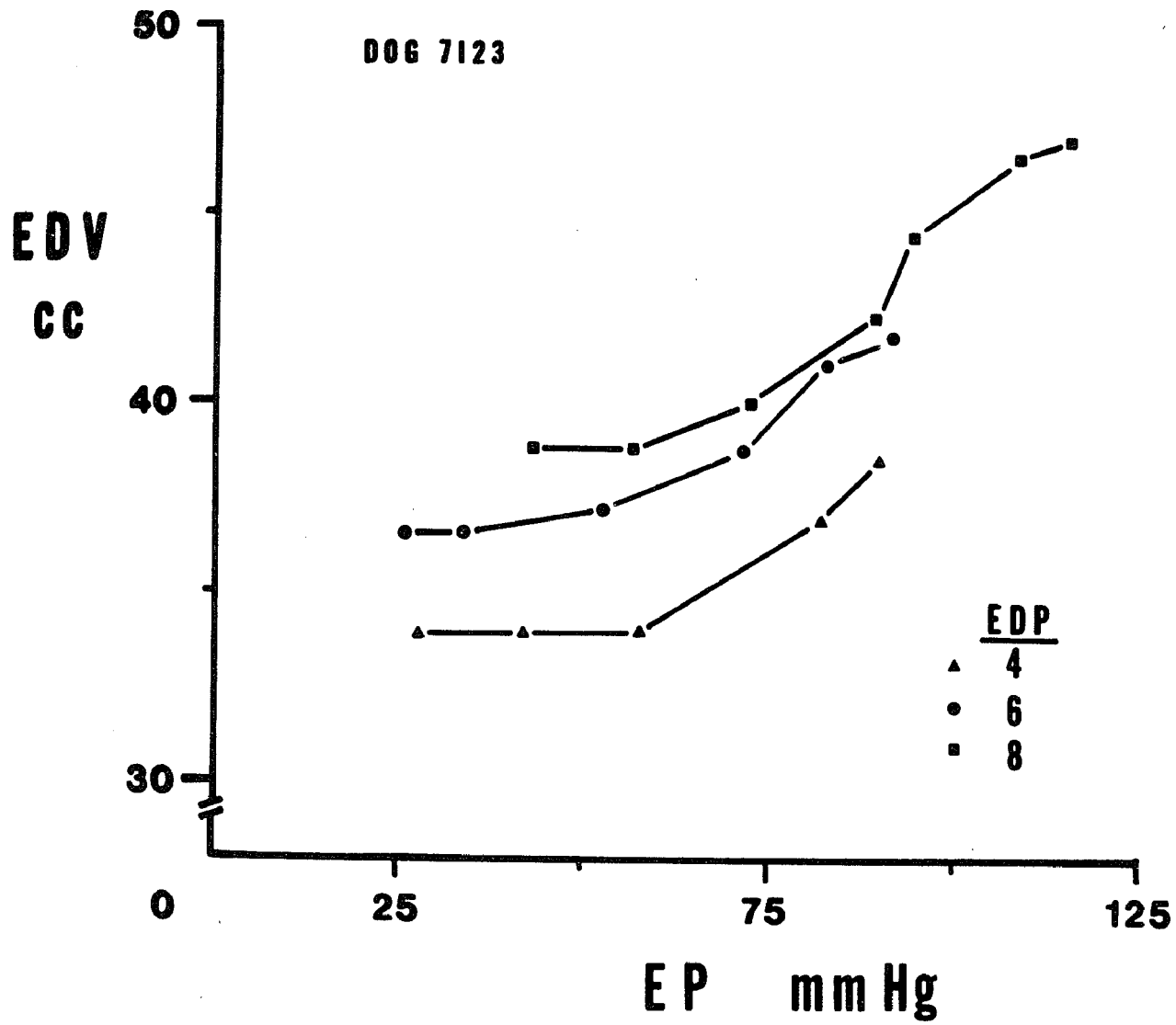
CORRELATION BETWEEN MAGNITUDE OF CHANGE IN THE DIASTOLIC PRESSURE-VOLUME RELATION AND EJECTION PRESSURE

The above results demonstrate that the PV-relation is dependent on ejection pressure. The following analyses were designed to investigate the magnitude of change in the PV-relation and its relationship to ejection pressure. During data acquisition, using Method 1 or 2 at any given EDP, it became apparent that for a range of ejection pressures significantly less than PMAX the PV-relation was relatively insensitive to changes in EP. That is, little or no change in the PV-relation occurred as EP was raised or lowered. For greater EP, outside this range, alterations in the PV-relation became progressively greater. Subsequent analyses verified this observation and are described below. An example (experiment 7123) of such is given in Figure 13 where EDV is plotted versus EP for 3 constant EDP values (Method 2). The total increments in EDV required to keep EDP constant at 4, 6 and 8 mm Hg as EP was increased, were 4.6, 5.2 and 8.2 cc, respectively. This pattern of behavior suggested that the magnitude of the shift in the PV-relation was in some manner related to the difference between peak isovolumic and ejection pressures. However, it did not rule out the possibility of a direct relation with EP. These two possibilities were further investigated using regression analyses on all Method 2 data.

Figure 13

Effect of Varying Ejection Pressure
on the Diastolic Volume

Presented is a graph of diastolic volume (EDV) versus ejection pressure (EP) for three constant diastolic pressures (EDP), using data from Dog 7123. For low EP, the EDV remained constant. As EP was further increased, the EDV, required to keep EDP constant, increased nonlinearly.


DOG 7123
50
40
30
0
25
75
125
EDV
CC
EP mm Hg
EDP
4
6
8

Before proceeding with the results of these analyses, an example of how these data were manipulated prior to regression analysis is presented in Table 2. The first two columns list EP and EDV data which correspond to the 8 mm Hg EDP curve plotted in Figure 13. The next column contains the accumulated change in EDV (Δ EDV) with respect to the largest EDV obtained during the isovolumic beat. This quantity is the amount of additional volume required to keep EDP constant when going from a particular EP to the isovolumic beat. The fourth column (PMAX-EP) is the pressure difference between an isovolumic and an ejecting beat and the final column (EP/PMAX) expresses EP as a percent ratio of PMAX.

A graphic display of all data (116 points) plotted as ΔEDV versus EP is given in Figure 14 including the calculated regression line. The correlation coefficient (r) of -0.40 was significantly different from zero ($P < 0.01$). The PMAX associated with this regression line (Δ EDV = 6cc - 0.32cc/mm Hg x EP) was 185 mm Hg. Thus in going from an EP of 20 mm Hg to 185 mm Hg it would be predicted that an additional 5 cc would have to be added to keep EDP constant. The absolute value of the slope indicates the average volume change in going from one EP value to another. The data plotted in Figure 14 were associated with a PMAX range of 60 to 160 mm Hg. Within this range, however, an insignificant ($P > 0.3$) correlation ($r=0.23$) was obtained when total Δ EDV was correlated with PMAX. Presenting all data in this fashion gives some idea as to its magnitude.

TABLE 2

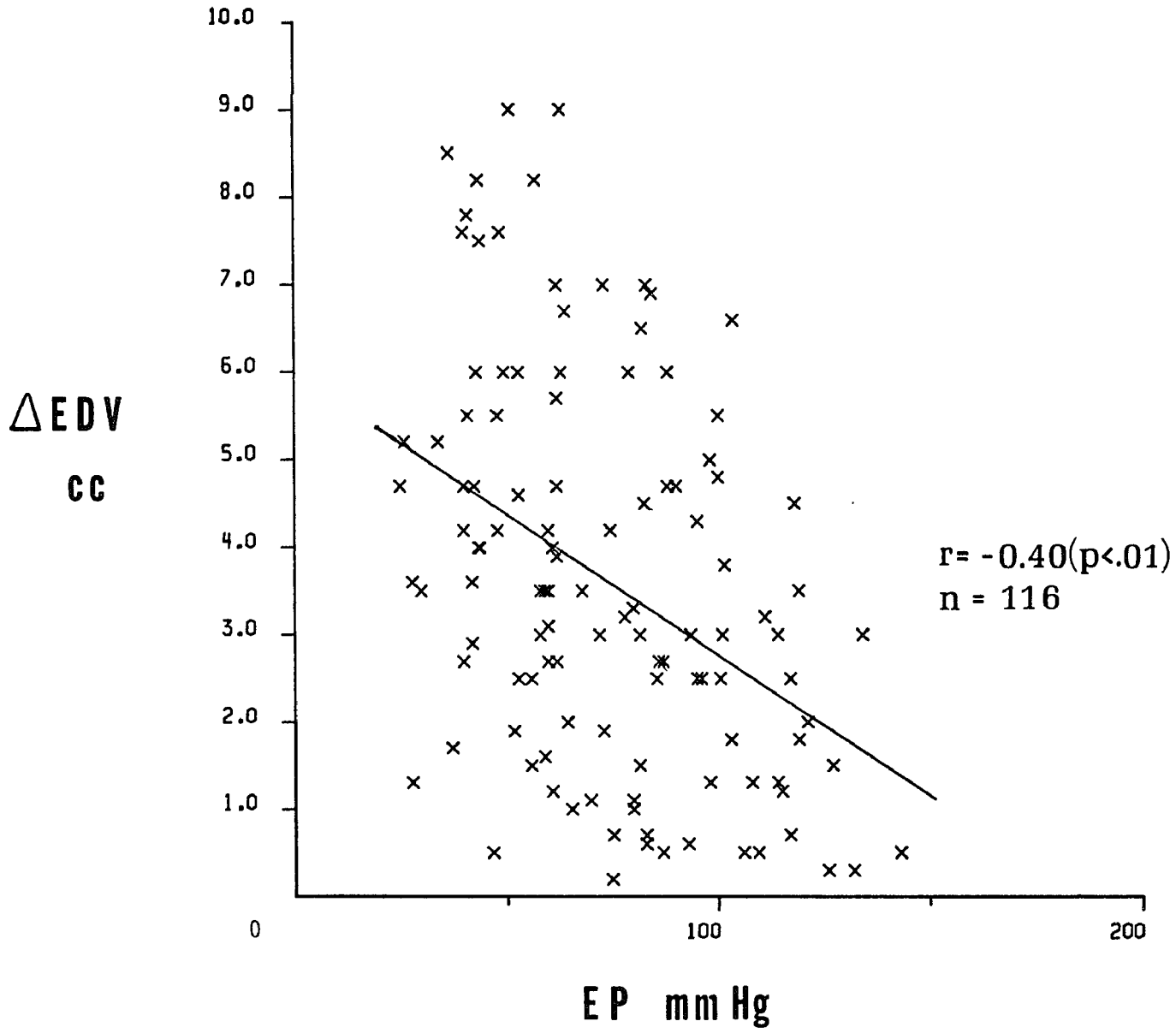
DATA FROM EXPERIMENT 7123 AND EXAMPLES OF
CALCULATED QUANTITIES USED FOR SUBSEQUENT ANALYSES

EP (mm Hg)	EDV (cc)	EDV (cc)	PMAX-EP (mm Hg)	EP/PMAX x 100%
43.5	38.8	8.2	73.0	37.3
57.0	38.8	8.2	59.5	48.9
73.0	40.0	7.0	43.5	62.7
90.0	42.3	4.7	26.5	77.2
95.0	44.5	2.5	21.5	81.5
109.5	46.5	0.5	7.0	94.0
116.5	47.0	0	0	100

Figure 14

Correlation of Accumulated Change
in Diastolic Volume With Ejection Pressure

A graphic display of all data (116 points) plotted as accumulated change in diastolic volume (ΔEDV) versus ejection pressure (EP), including the calculated regression line. The correlation coefficient (r) of -0.40 was significantly different from zero ($P < 0.01$).


ΔEDV
cc
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
100
200
EP mm Hg
r= -0.40(p<.01)
n = 116

Another method (class intervals) of displaying these "pooled" data is illustrated in Figure 15. Here, class intervals of 10 mm Hg were used, and all ΔEDV corresponding to EP within an interval were averaged. The average ΔEDV was then assigned an EP value corresponding to the interval midpoint. Therefore, Figure 15 consists of average ΔEDV for each 10 mm Hg interval versus the interval's midpoint EP. The standard error of the mean (SEM) was calculated for each average and is indicated as $\pm$ SEM by the vertical bars. Below each SEM bar is the number of data points included in the average. Not shown are end point averages obtained from 3 or less data points. In order to compare these two methods of data representation the regression line is again given in Figure 15. This latter method of representation will also be utilized in Figures 16, 17 and 18.

Average ΔEDV is plotted versus PMAX-EP in Figure 16. The regression line (not shown) analysis produced a significant ($P < 0.01$) correlation coefficient of 0.62. Of further interest is the non-linear tendency particularly for PMAX-EP values greater than 40 mm Hg. This tends to reconfirm earlier statements concerning the existence of a range of lesser EP within which the PV-relation was relatively insensitive to EP changes. One advantage of grouping data according to class intervals is that the resultant means can then be statistically compared using the "t" test of significance, in this case, between unpaired variates. Sequentially numbering the points from left to right and comparing successive points indicated: (a) a significant difference between points 2-3 ($P < 0.01$); (b) no difference ($P > 0.4$) between points 3-4, 5-6, 6-7, 7-8, 8-9 and 9-10;

Figure 15

Example of Class Interval Method
of Representing Pooled Data

A graph of accumulated change in diastolic volume (ΔEDV), averaged for each 10 mm Hg interval, versus the interval's midpoint ejection pressure (EP), including the calculated regression line. Vertical bars indicate $\pm$ standard error of the mean, with the number of data points included in each average given below the bars. Not shown are end point averages obtained from 3 or less data points.

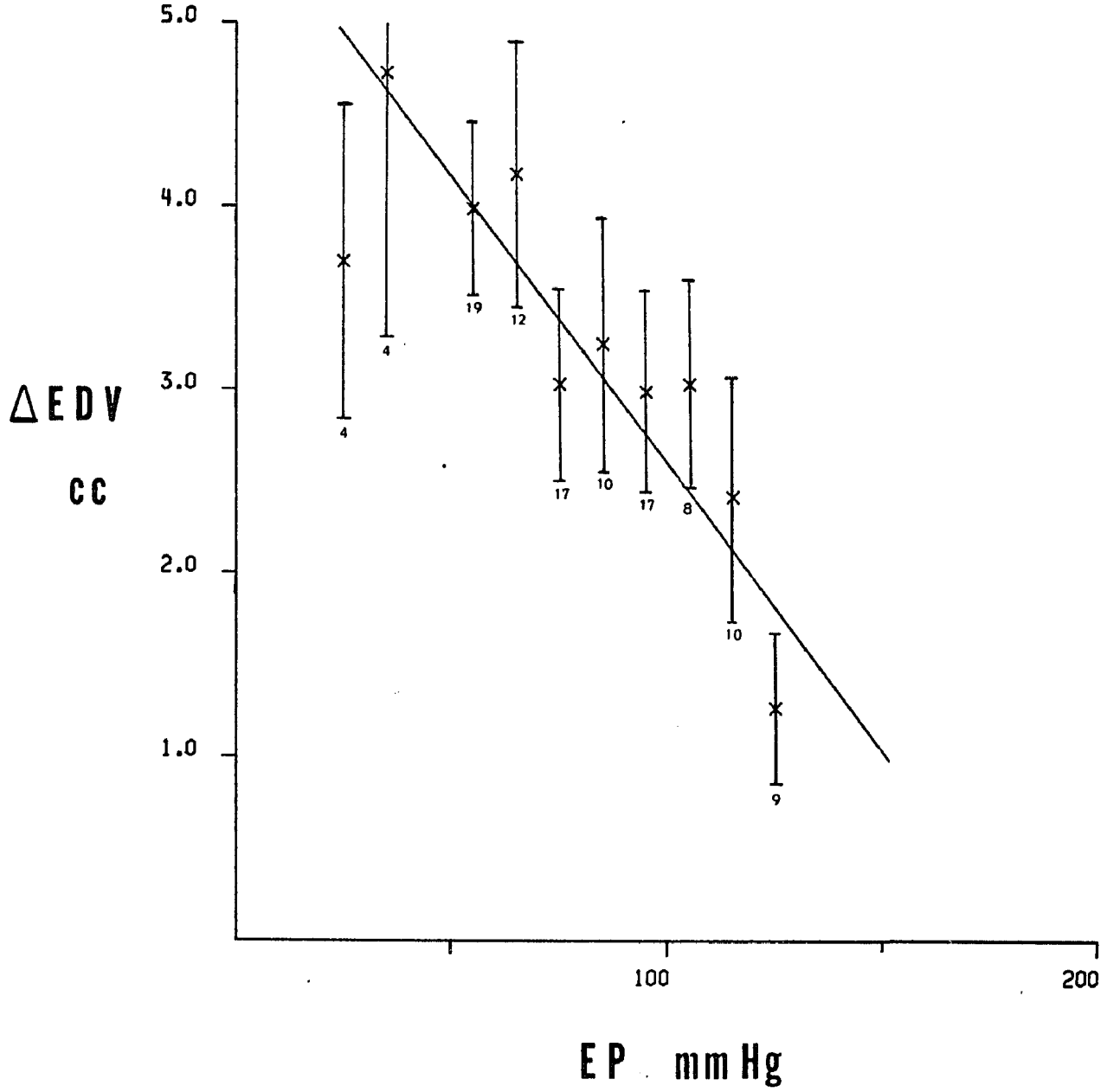
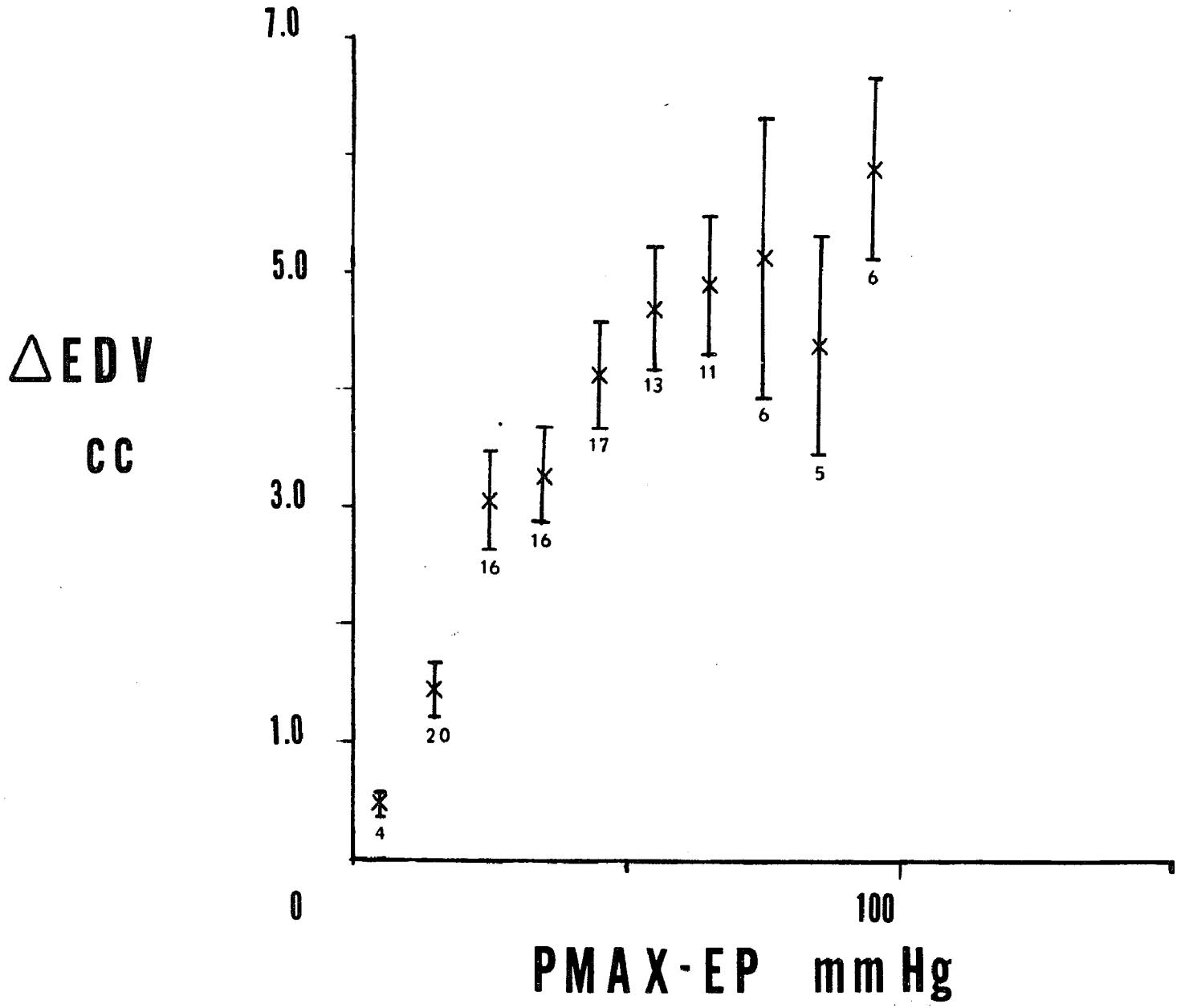

5.0
4.0
3.0
2.0
1.0
ΔEDV
cc
4
4
19
12
17
10
17
8
10
9
100
200
EP mm Hg

Figure 16

Accumulated Change in Diastolic Volume Versus Difference Between Peak Isovolumic and Ejection Pressures

A graph of accumulated change in diastolic volume (ΔEDV), averaged for each 10 mm Hg interval, versus the interval's midpoint value of the difference between peak isovolumic and ejection pressures (PMAX-EP). Vertical bars indicate $\pm$ standard error of the mean, with the number of data points included in each average given below the bars. Not shown are end point averages obtained from 3 or less data points.


7.0
5.0
3.0
1.0
0
ΔEDV
cc
4
20
16
16
17
13
11
6
5
6
100
PMAX-EP mm Hg

and (c) a "borderline" level of difference ($0.2 > P > 0.1$) between points 4-5. Points 1-2 did not satisfy the null hypothesis of equal variances (F-test) and, therefore, were not compared. Thus, for PMAX-EP values greater than 40 mm Hg the slope (or rate of change) of this relation was sufficiently reduced such that for successive 10 mm Hg increments the average Δ EDV did not significantly differ from the preceding point. Therefore, with 40 mm Hg as a dividing point, the average rates of change, using all data, were calculated to be 0.0915 cc/mm Hg (significantly different from zero, $P < 0.01$) for PMAX-EP less than or equal to 40 mm Hg and 0.0272 cc/mm Hg (marginally different, $0.1 > P > 0.05$) for PMAX-EP greater than 40 mm Hg.

A comment concerning the arbitrary choice of a class interval of 10 mm Hg would be appropriate. Obviously, with these data, it is possible to choose a sufficiently smaller or larger interval such that no significant difference existed between resulting, averaged points. The only justification for choosing a 10 mm Hg interval is that repeating this analysis using a 20 mm Hg interval did not affect the overall results in that significant differences between successive points were obtained for PMAX-EP values in the range 0 to 40 mm Hg while no significant differences were obtained for values greater than 40 mm Hg. Using an interval of 5 mm Hg resulted in more average Δ EDV points, each obtained from fewer data, which could not be meaningfully compared.

Plotted in Figure 17 is average ΔEDV versus EP/PMAX x 100% (% EP/PMAX). The regression line (not shown) analysis between these two variables produced an r value of -0.60 ($P < 0.01$). A similar line of reasoning, as described above, was applied to this relation with the results of the "t" test comparison indicated between each point. NS indicates that the difference between the means was not significant with P being greater than 0.4 in all cases. S implies significance with $P < 0.01$ and MS, marginal signficance with the P value indicated in the legend. The average rate of change calculated for all data within the range $20 < \%EP/PMAX < 50$ was 0.0266 cc/%, and not different from zero ($0.7 > P > 0.6$). On the other hand, for all data corresponding to % EP/PMAX > 50, the average rate of change (-0.55 cc/%) was significantly different ($P < 0.01$). Therefore, normalizing ejection pressure with respect to PMAX takes into account the fact that PMAX is also a variable, and permits one to conclude that when EP is varied in the range 20 to 50% of its associated PMAX value little, if any, change in the PV-relation occurs.

ΔEDV could also be normalized in a similar manner by dividing each ΔEDV by the total observed change in volume in raising EP from a low level to PMAX. Using experiment 7123 as an example (see Table 2) this would be equivalent to dividing each ΔEDV by 8.2 cc and multiplying this ratio by 100%. Thus the ΔEDV associated with the lowest EP will always be 100%. These results are presented in Figure 18 where the average, normalized ΔEDV (% ΔEDV) is plotted versus % EP/PMAX. The r value for these two variables was -0.82 ($P < 0.01$), and the results of the "t" test are indicated as in

Figure 17

Accumulated Change in Diastolic Volume
Versus Normalized Ejection Pressure

A graph of accumulated change in diastolic volume (ΔEDV), averaged for each 10% interval, versus the interval's midpoint value of the percent ratio of ejection to peak isovolumic pressures (% EP/PMAX). Vertical bars indicate $\pm$ standard error of the mean, with the number of data points included in each average given below the bars. The results of statistically comparing successive points are given between points with NS representing no significant difference ($P > 0.4$); S, significant difference ($P < 0.01$); and MS, marginal significant difference ($0.1 > P > 0.05$).

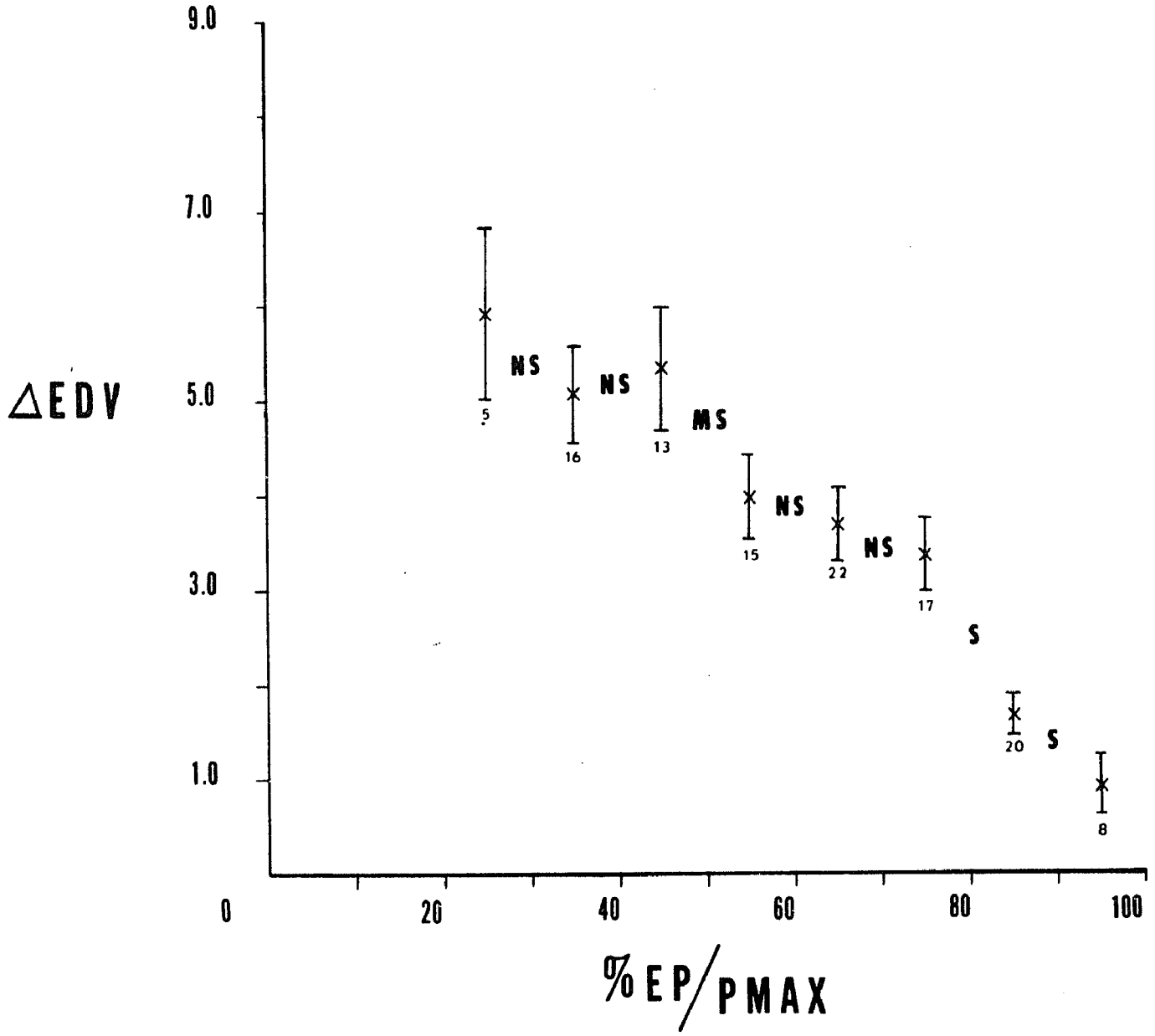

9.0
7.0
5.0
3.0
1.0
ΔEDV
0
20
40
60
80
100
%EP/PMAX
NS
NS
MS
NS
NS
S
S
5
16
13
15
22
17
20
8

Figure 18

Normalized Change in Diastolic Volume
Versus Normalized Ejection Pressure

A graph of accumulated change in diastolic volume (ΔEDV) expressed as percent of total observed ΔEDV(% ΔEDV), averaged for each 10% interval, versus the interval's midpoint value of the percent ratio of ejection to peak isovolumic pressures (% EP/PMAX). Vertical bars indicate $\pm$ standard error of the mean, with the number of data points included in each average given below the bars. The results of statistically comparing successive points are given between points with NS representing no significant difference ($P > 0.3$); S, significant difference ($P < 0.01$); and MS, marginal significant difference ($0.2 > P > 0.1$).

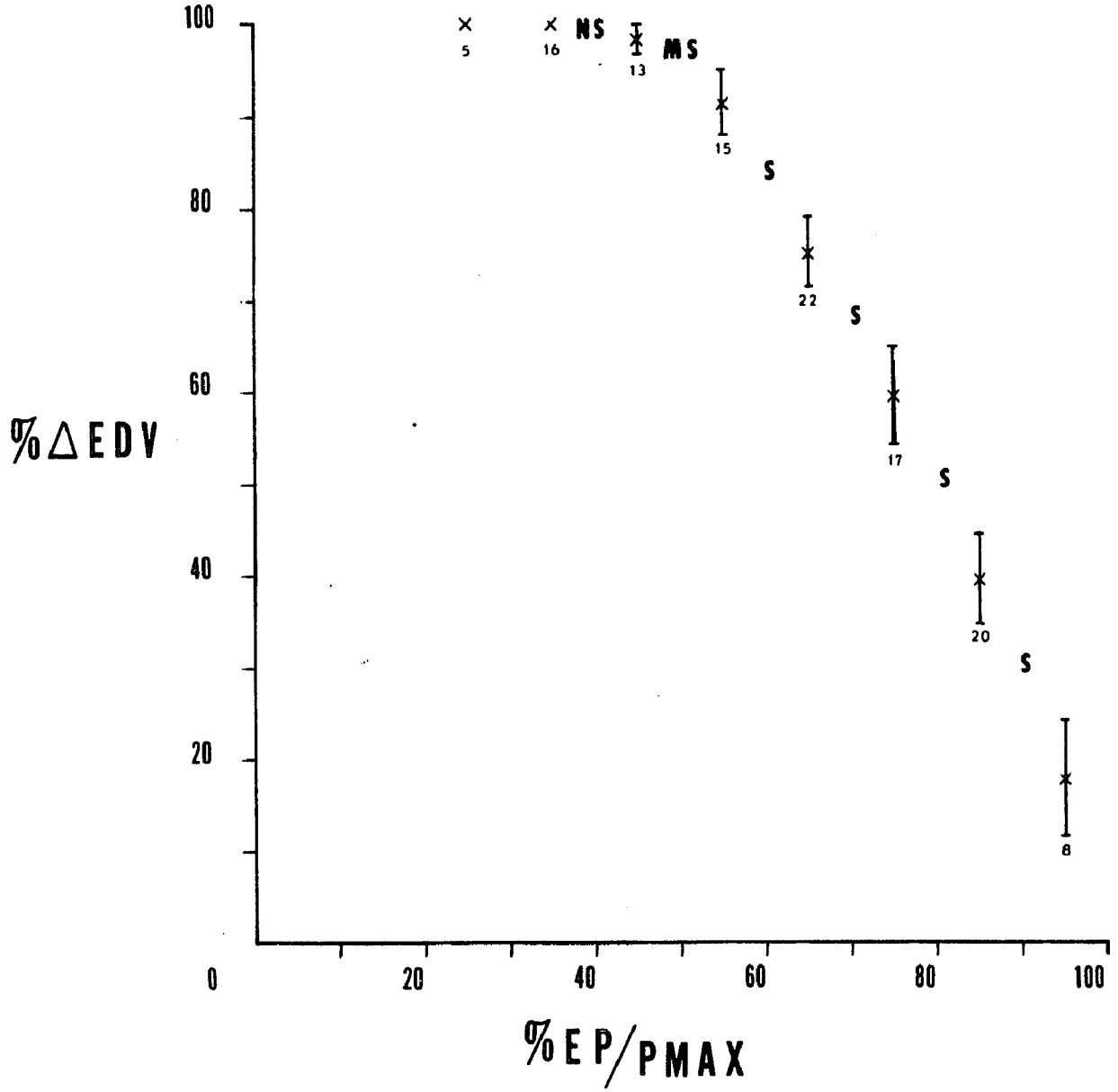

100
80
60
40
20
0
20
40
60
80
100
%ΔEDV
%EP/PMAX
NS
MS
S
S
S
S
5
16
13
15
22
17
20
8

Figure 17. Expressing the data in this manner clearly indicates that, when EP is varied in the range 50 to 100% of PMAX, significant alterations in the PV-relation occur. Correlating % ΔEDV with EP and PMAX-EP increased their respective r values to -0.63 and 0.76.

All of the above analyses utilized pooled Method 2 data. A similar analyses sequence was performed using pooled Method 1 data. Figure 19 and Table 3 summarize these results. Plotted in Figure 19 is the accumulated change in EDP (ΔEDP), calculated in a similar manner as was ΔEDV (Table 2), versus % EP/PMAX. That is, ΔEDP is the decrease in EDP, keeping EDV constant, one would obtain in going from a particular EP to its associated PMAX. The primary purpose of presenting this information is to indicate the magnitude of these data. Given in Table 3 are: the types of correlations using regression analysis; the resulting correlation coefficient; and whether it significantly differed from zero. In general these correlation coefficients were smaller than those obtained using Method 2 data. However, the conclusion concerning the insensitivity of the PV-relation to EP changes in the range 20 to 50% of PMAX is still valid, based on the average rate of change (-0.006 mm Hg/%), in this range, not being significantly different from zero ($0.6 > P > 0.5$). For % EP/PMAX greater than 50, the average rate of change (-0.020 mm Hg/%) was significantly different ($P < 0.01$).

Finally ΔEDV and normalized ΔEDV were correlated with left ventricular ejection fraction (EF), which itself is a normalized quantity; the resulting r values were 0.57 and 0.79, respectively.

Figure 19

Correlation of Accumulated Change in Diastolic Pressure
With Normalized Ejection Pressure

A graphic display of all data (160 points) plotted as accumulated change in diastolic pressure (Δ EDP) versus percent ratio of ejection to peak isovolumic pressures, including the calculated regression line. The correlation coefficient of -0.39 was significantly different from zero ($P < 0.01$).

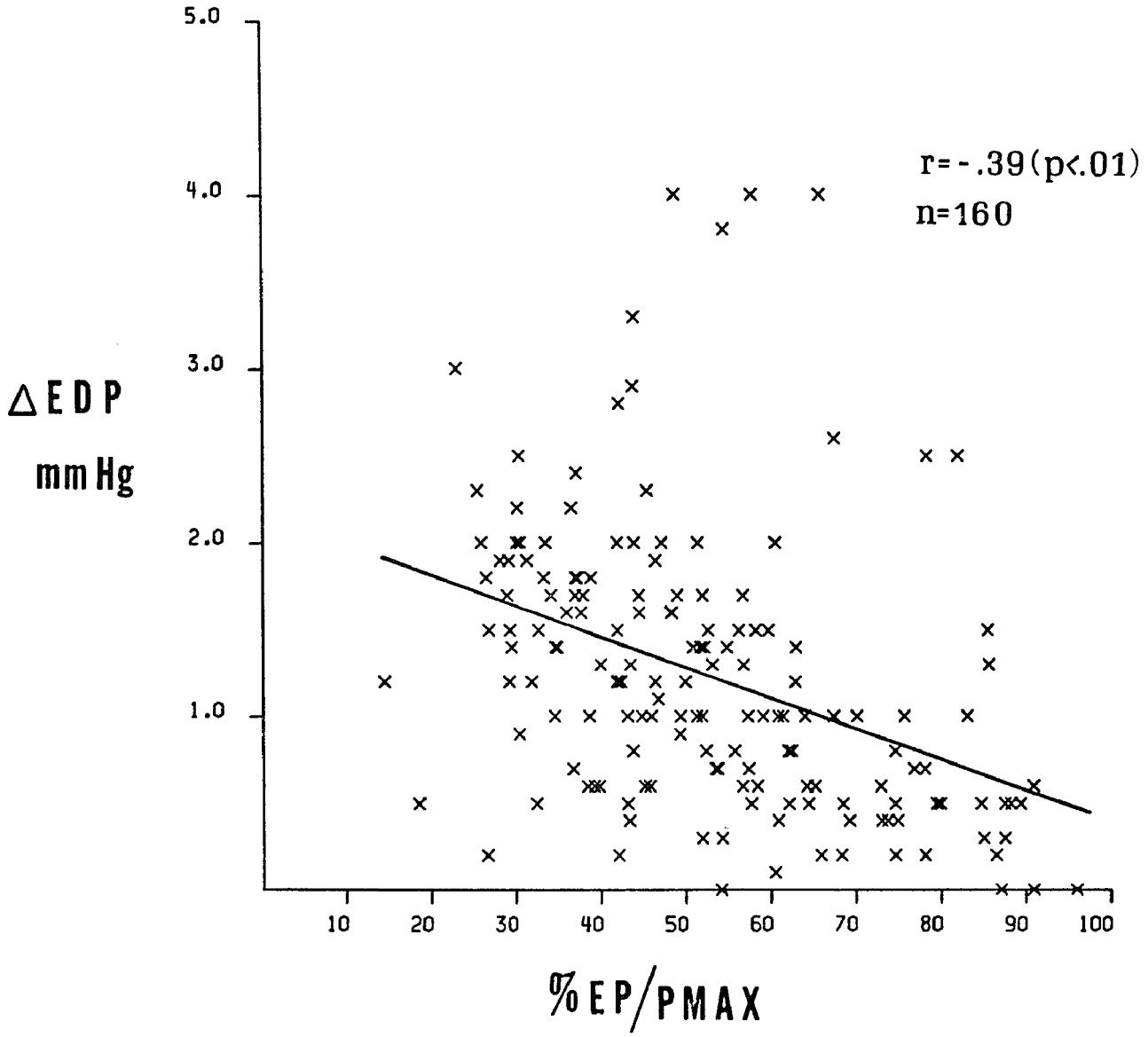

r=-.39(p<.01)
n=160
5.0
4.0
3.0
2.0
1.0
ΔEDP
mmHg
10
20
30
40
50
60
70
80
90
100
%EP/PMAX

TABLE 3

SUMMARY OF REGRESSION ANALYSIS ON METHOD 1 DATA

VARIABLES CORRELATED	CORRELATION COEFFICIENT	P VALUE
ΔEDP - EP	-0.46	< 0.01
Total ΔEDP - PMAX	0.40	> 0.2
ΔEDP - (PMAX - EP)	0.46	< 0.01
ΔEDP - EP/PMAX x 100%	-0.39	< 0.01
NORMALIZED ΔEDP - EP	-0.62	< 0.01
NORMALIZED ΔEDP - (PMAX - EP)	0.64	< 0.01
NORMALIZED ΔEDP - EP/PMAX x 100%	-0.74	< 0.01

Ejection fraction at a given diastolic pressure is inversely related to ejection pressure. Therefore, the purpose of these analyses was to define a range of EF, corresponding to that of EP, within which the PV-relation was essentially unaltered. Chosing class intervals of 10% and sequentially comparing the averaged data points, this range was determined to be 45 to 65%. When ejection fraction was less than 45% significant changes in the PV-relation were obtained.

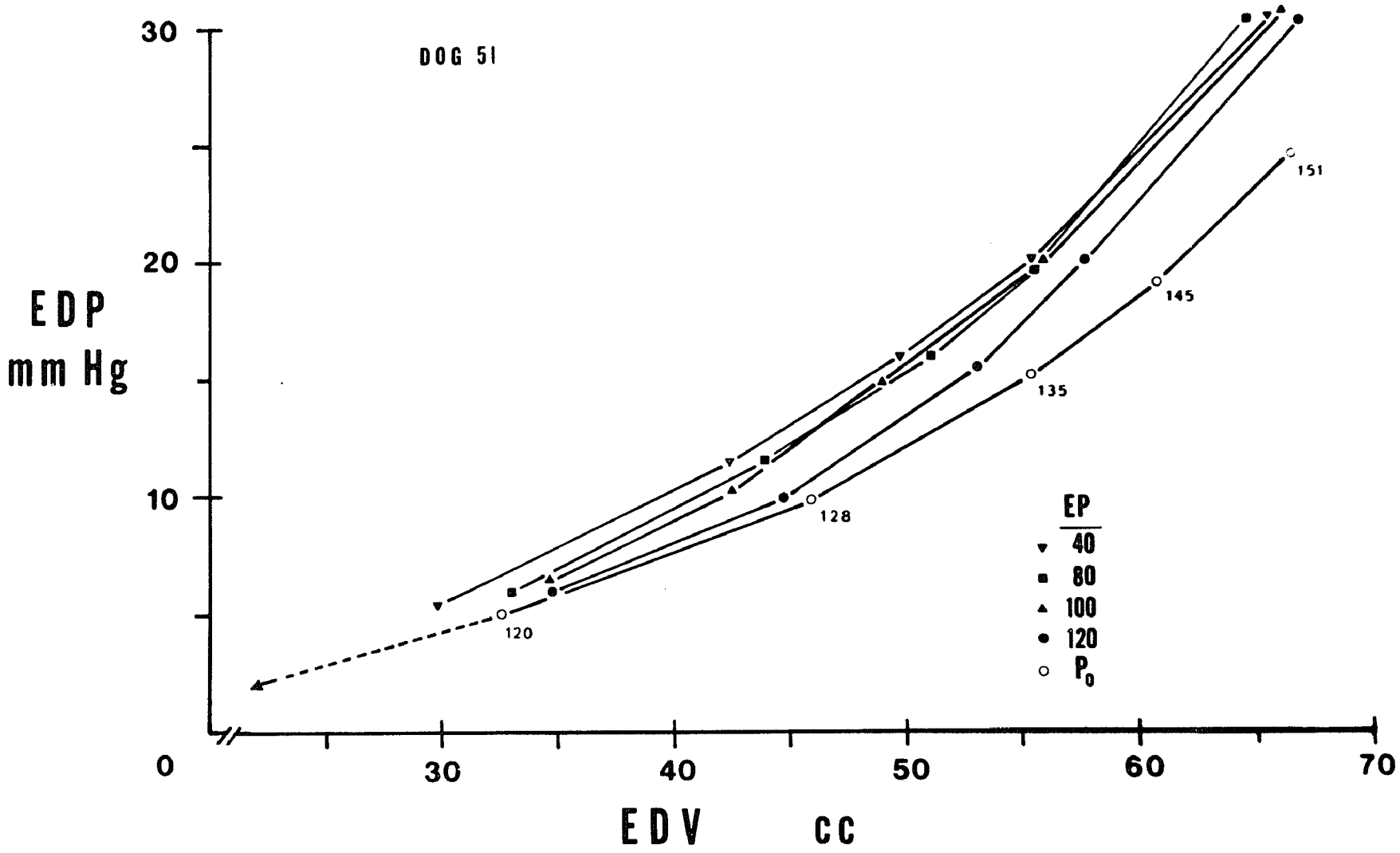
THE RELATION BETWEEN THE DIASTOLIC PRESSURE-VOLUME CURVE AND EJECTION PRESSURE

Up to this point the effects of varying ejection pressure on absolute diastolic pressure and volume values have been considered, but the diastolic pressure-volume relation referred to only in general terms. It will now be shown that increasing the ejecting pressure does indeed shift the diastolic pressure-volume curve either downwards (Methods 1 and 3) or to the right (Method 2) when EDP is plotted versus EDV. The next question therefore concerns itself with the relative relations between the diastolic pressure-volume curves (PV curve) obtained at different (but constant) ejection pressures. Figures 20 and 21 present such comparisons. Data obtained in experiment 51 using Method 2 are graphed in Figure 20. Plotted are PV-curves corresponding to ejection pressures (EP) of 40, 80, 100, 120 mm Hg and the isovolumic state (P_o). The isovolumic or PMAX values are given with their corresponding EDP-EDV points; the dashed line represents a linear extension to the point (not shown) which corresponded to an EDP and EDV of 0 mm Hg and 15 cc respectively. At this point the PMAX value was measured to be 48 mm Hg. Further inspection of the figure reveals that for EDV less than 45 cc each PV-curve is distinct. In addition, the slopes of the ejecting PV-curves are such that the curves tend to originate from the isovolumic PV-curve and thereafter diverge. In fact the point of

Figure 20

Effect of Varying Ejection Pressure
on the Diastolic Pressure-Volume Curve
Dog 51

Presented is a graph of diastolic pressure (EDP) versus diastolic volume (EDV), using data from Dog 51. Each curve corresponds to either a constant ejection pressure (solid symbols) or the isovolumic state (open circles). The peak isovolumic pressure values are given below their corresponding EDP-EDV points. The dashed line represents a linear extension to the isovolumic point (not shown) which corresponded to an EDP and EDV of 0 mm Hg and 15 cc respectively.


DOG 51
30
20
10
0
EDP
mm Hg
30
40
50
60
70
EDV cc
120
128
135
145
151
EP
40
80
100
120
P_0

origin for the PV-curve associated with an EP of 120 mm Hg appears to be the point at which the ejecting and isovolumic pressures are equal. As EDV is increased above 45 cc the ejecting PV-curves, particularly those obtained at lower EP, begin to converge and tend to follow the same path. Based on the previously presented results this convergence is indicative of approaching the region in which the PV-relation is relatively insensitive to changes in ejection pressure.

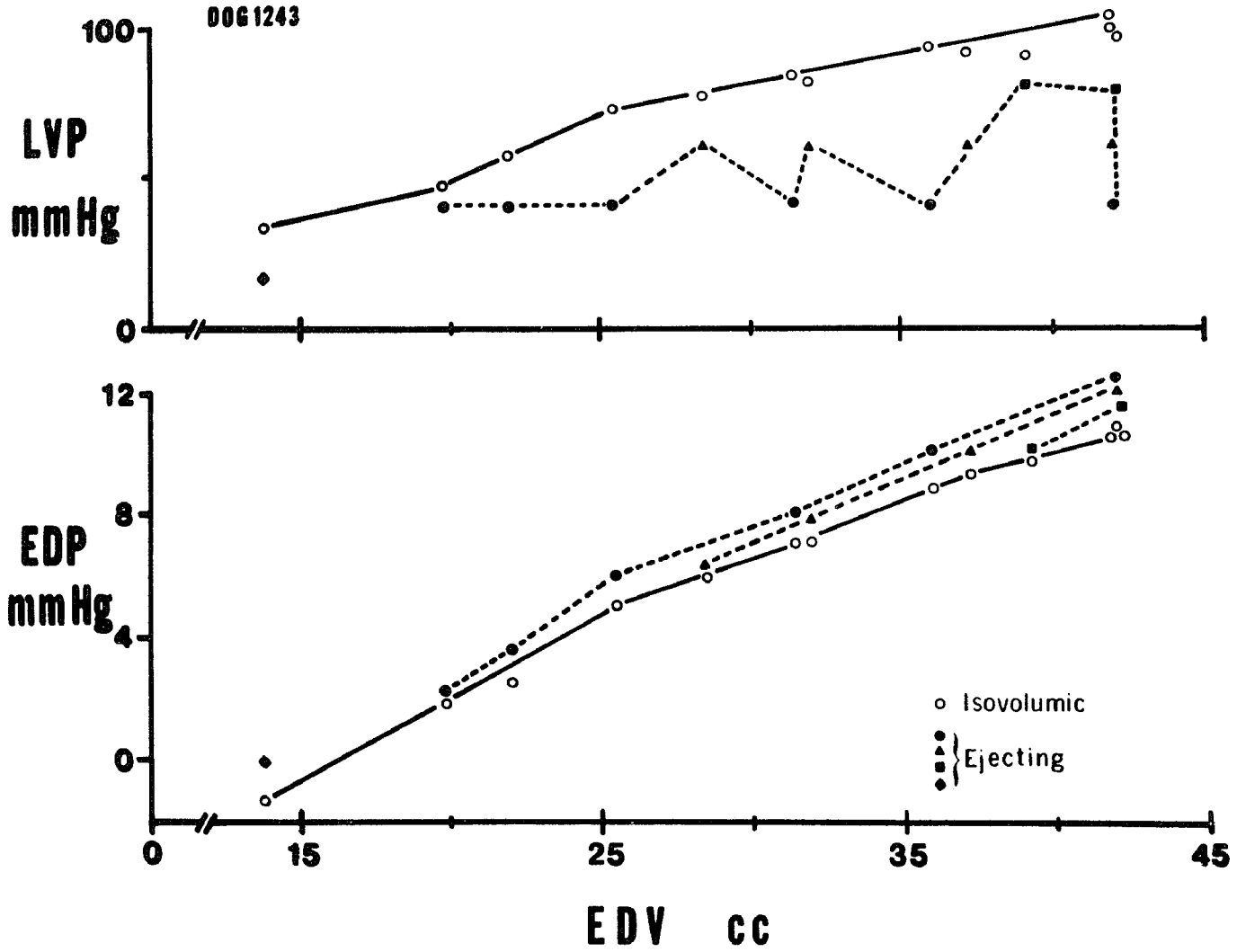
Within the range of EDV presented in Figure 20, the EP of 40 mm Hg was always less than 50% of PMAX. Therefore, the PV-curve obtained at this EP can be thought of as the upper limit. Similarly, the PV-curve associated with the isovolumic state can be considered as the lower limit. A PV-curve obtained at some constant EP greater than 40 mm Hg would then fall within these two limiting curves, originating somewhere on the lower limiting curve and eventually converging with the upper limiting curve. These two limiting curves were found to be significantly different ($0.02 > P > 0.01$) using the "t" test of significance between two sample means. That is at each of the 5 diastolic volumes where data were obtained for the upper limit curve the EDP was taken, together with an EDP interpolated from the lower limit curve, and the two treated as paired variates (paired data analysis).

Another example of the influence of EP on the PV-curve using data obtained from experiment 1243 is given in Figure 21. The experimental protocol shown here differed from that of experiment 51 (Figure 20) and in addition at each data point Method 3 was used to obtain the isovolumic values. Depicted are developed pressure (LVP)

Figure 21

Effect of Varying Ejection Pressure
on the Diastolic Pressure-Volume Curve
Dog 1243

Depicted are the developed pressure (LVP) and diastolic pressure (EDP) versus diastolic volume (EDV) for both ejecting (solid symbols) and isovolumic (open circles) contractions, using data from Dog1243. The dashed lines, in the lower graph, join those diastolic points associated with the same LVP.


DOG 1243
100
LVP
mmHg
0
12
8
EDP
mmHg
4
0
Isovolumic
Ejecting
0
15
25
35
45
EDV cc

and diastolic pressure (EDP) versus diastolic volume for both ejecting and isovolumic contractions. The dashed lines join those diastolic points associated with the same EP. The EP of 40 mm Hg (solid circles) did not become less than 50% of PMAX until the EDV was approximately 30 cc, so that for lesser volumes the two PV-curves converge until they coincide at an EDV of 17 cc. The LVP curves similarly coincide at this EDV. At EDP values of 6, 8 and 10 mm Hg the EP was raised from 40 to 60 mm Hg (solid triangles) and Methods 2 and 3 were used, resulting in a shift of the PV-relation to the right. Also, at an EDP of 10 mm Hg the EP was further increased to 80 mm Hg (solid squares) and the EDP-EDV point shifted even further to the right (Method 2). Finally at a constant EDV of 42 cc, EP was lowered by 20 mm Hg decrements from 80 to 40 mm Hg, and the corresponding EDP-EDV points shifted upwards. The 3 isovolumic points obtained at this EDV give some idea of the reproducibility of Method 3.

Another interesting feature of this figure is furnished by the diastolic points obtained at an EDV of 14 cc when EDP was zero mm Hg. The diastolic volume obtained at zero filling pressure (V_o) is referred to as the unstressed volume and may be used to normalize the diastolic volumes when PV-curves are expressed as stress-strain relations or when one heart is compared to another. However, V_o too is dependent on ejection pressure (solid diamonds) and perhaps it would be more consistent to use the unstressed volume determined from the isovolumic PV-curve. All of the V_o values presented in this section in fact were obtained isovolumically.

Experiment 1243 used in Figure 21 can be classified as a "weak" preparation according to the relatively low peak isovolumic pressures developed (Table 1). Figure 22, on the other hand, is presented for contrast. Plotted are similar data obtained from experiment 11133, which had a peak isovolumic pressure curve more representative of a "normal" functioning heart. Here again the ejecting and isovolumic PV-curves begin to converge as EP approaches PMAX. The two PV-curves, however, were significantly different ($P < 0.01$). Figures 20, 21 and 22 are examples from three separate experiments which illustrate the differences observed between the ejecting and isovolumic PV-curves. Each of the three experiments represented separate levels of performance as evidenced by the peak isovolumic pressures that were developed at a common EDP.

At this time it would be appropriate to introduce and discuss methods by which the two limiting diastolic PV-curves obtained in one experiment could be compared with equivalent curves from other experiments. One possible approach would be to calculate the percent difference or decrease in diastolic pressure between the two limiting curves at each measured diastolic volume where data were obtained. For example, Table 4 includes this calculation for the three aforementioned experiments. Also given are: (1) the diastolic volume (EDV), at which the calculated percent difference or decrease in EDP (% difference) between the two limiting curves was obtained, and (2) the average of these % differences. As can be seen, the % difference remains relatively constant as EDV is increased, despite the fact that

Figure 22

Effect of Varying Ejection Pressure
on the Diastolic Pressure-Volume Curve
Dog 11133

Depicted are the developed pressure (LVP) and diastolic pressure (EDP) versus diastolic volume (EDV) for both ejecting (solid circles) and isovolumic (open symbols) contractions, using data from Dog 11133. The open circles with a dot indicate LVP greater than 200 mm Hg.

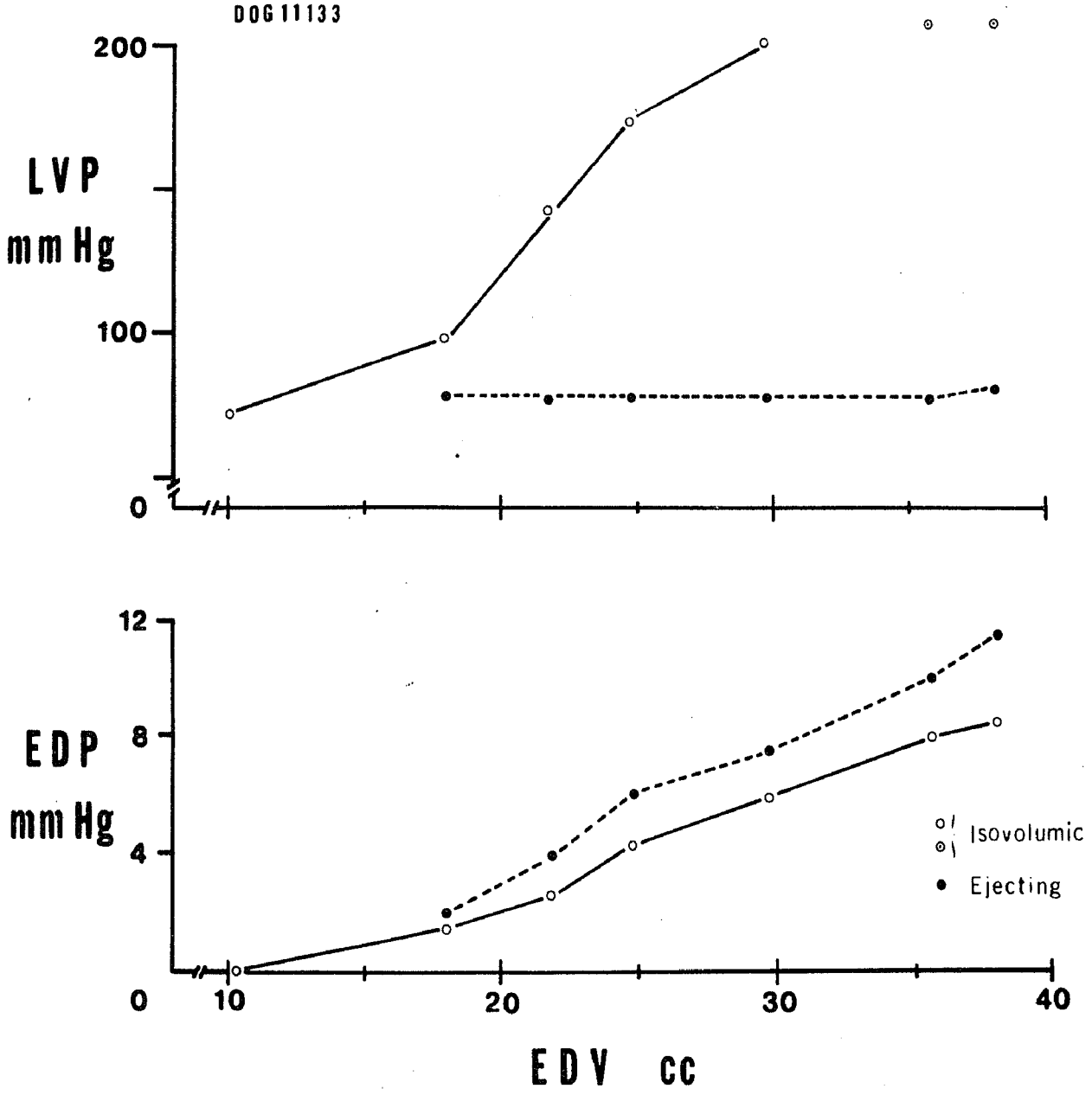

DOG 11133
200
LVP
mm Hg
100
0
12
EDP
mm Hg
8
4
0
10
20
30
40
EDV cc
Isovolumic
Ejecting

TABLE 4

EXAMPLE OF METHOD FOR COMPARING DIFFERENCE BETWEEN TWO LIMITING PRESSURE-VOLUME CURVES

EXPERIMENT	EDV - cc	% DIFFERENCE	AVERAGE % DIFFERENCE
51	29.8	20.0	23.2
	42.5	25.2	
	49.9	25.0	
	55.7	24.0	
	65.9	21.9	
11133	24.8	28.3	23.9
	29.8	21.3	
	35.8	20.0	
	38.2	26.1	
1243	25.5	16.7	14.0
	31.5	12.5	
	36.0	12.0	
	42.1	14.6	

the algebraic difference between the limiting curves increases. Thus the average percent difference could serve as an index, for a given experiment, which would reflect the average change in EDP (or wall stress since the two EDP values were obtained at the same EDV) one could expect to occur by varying the ejection pressure from a value 50% of PMAX to PMAX, while holding EDV constant.

This average percent difference or decrease in diastolic pressure was obtained for all of the Series II experiments and has been included in Table 5 with the following additional information: (1) average stiffness ($\Delta P / \Delta V$) for the ejection (EP) and isovolumic (P_o) diastolic PV-curves; (2) heart rate (HR); (3) peak isovolumic pressure (PMAX) developed at an EDP of 10 mm Hg; and (4) isovolumic unstretched volume (V_o) obtained at an EDP of 0 mm Hg. In addition, within any given experiment, if other PV-curves were obtained during either control conditions or during the steady state response to inotropic interventions, these data are given. Because of the non-linear nature of the PV-curve, stiffness is a function of diastolic volume and, therefore, only the average stiffness is given for qualitative comparison purposes. It was obtained by first evaluating the quantity $(EDP_j - EDP_i) / (EDV_j - EDV_i)$, where $j = i + 1$ and i is a PV-curve data point. This quantity, which represents the slope of the line joining two consecutive diastolic pressure-volume points, was then calculated for all (n) data points defining the PV-curve. That is, i was incremented by one, from 1 to n-1 and the slope or stiffness obtained for each increment. Finally, the calculated slopes were

TABLE 5

SUMMARY OF METHOD 3 DATA AND RESULTS

EXP	COMMENT	% DECREASE IN EDP	AVG ΔP/ΔV (mm Hg/cc) EP	P_o	HR	PMAX (mm Hg)	V_o (cc)
2214	CONTROL 1	66.7	2.08	1.15	130	158	12.8
	CONTROL 2	53.3	2.13	1.72	170	159	12.6
	CONTROL 3	14.4	2.27	1.78	120	127	14.9
2144	CONTROL	18.0	0.83	0.72	100	150	11.5
	NOREPINEPHRINE	19.6	1.64	1.52	100	118	14.6
254	CONTROL 1	11.9	0.46	0.42	85	> 200	20.6
	CONTROL 2	6.0	0.61	0.56	80	152	21.2
	NOREPINEPHRINE	14.5	0.94	0.85	80	148	21.9
1244	CONTROL	17.2	1.04	0.84	90	118	15.6
1154	CONTROL	17.8	1.23	1.09	65	101	16.2
	NOREPINEPHRINE	18.2	1.42	1.12	120	142	18.6
12183	CONTROL	17.2	0.65	0.56	55	96	15.9
	NOREPINEPHRINE 1	20.2	0.55	0.47	90	140	15.9
	NOREPINEPHRINE 2	26.1	0.49	0.38	100	184	16.5
1243	CONTROL 1	14.0	0.49	0.40	90	91	16.3
	CONTROL 2	16.9	0.68	0.56	90	86	19.9
	NOREPINEPHRINE	19.6	0.81	0.54	100	150	18.5
	CONTROL 3	13.8	0.94	0.79	100	62	18.0
11133	CONTROL 1	23.9	0.51	0.35	110	> 200	10.3
	CONTROL 2	15.9	0.62	0.57	110	164	15.5
9193	CONTROL	22.0	0.62	0.54	120	> 200	21.0
9123	CONTROL	17.0	0.78	0.57	130	190	14.5
	PROPRANOLOL	16.4	0.89	0.81	130	120	19.6
7253	CONTROL	19.1	0.64	0.56	60	93	29.1
	PROPRANOLOL	32.4	0.66	0.62	90	78	34.0

averaged to obtain the average stiffness for the PV-curve. As is apparent from the Series II data the average percent decrease in EDP varied from 6% (experiment 254, control 2) to 66.7% (experiment 2214, control 1). In the latter experiment (2214) the heart was edematous as previously mentioned and could be excluded on this basis. It is interesting to note that this particular heart was also the "stiffest" having an average $\Delta P/\Delta V$ of 2.1 mm Hg/cc. The other edematous heart was experiment 2144. It too had a relatively large $\Delta P/\Delta V$ (1.64 mm Hg/cc) but only later in the experiment and during norepinephrine infusion. Perhaps on the basis of this temporal difference in stiffness between the control and norepinephrine observations one could conclude that the edema occurred after the control and before the norepinephrine data were obtained.

Excluding 2214, the next highest percent difference (32.4%) was obtained in experiment 7253 during propranolol infusion and the highest percent difference during "control" conditions was 23.9% (experiment 11133). As can be seen from Table 5, there was no significant correlation between percent difference and heart performance as reflected in PMAX measurements. For example, considering control runs only, experiment 254 had a peak isovolumic pressure >200 mm Hg and a percent difference of 11.9% while experiment 7253 had values of 93 mm Hg and 19.1%, respectively. Contrariwise, experiment 11133 had values of >200 mm Hg and 23.9% while experiment 1243 values were 91 mm Hg and 14.0%. Two other points concerning this table are noteworthy: first, in those experiments where norepinephrine was

given the percent difference in EDP increased. However, this increase was significant ($P < 0.05$) in only 2 experiments (254 and 12183). The increase with propranolol in experiment 7253 was not significant. Secondly, in all experiments except 12183, where more than one set of data was obtained, the average $\Delta P/\Delta V$ for both the ejecting and isovolumic curves increased.

Finally, the unstressed isovolumic volume (V_o) was included in Table 5 to give some idea of the creep phenomenon. In all experiments with more than one set of data the V_o obtained toward the end of the experiment was larger than that found at the onset. This increase in V_o ranged from 0.6 cc (experiment 12183) to 5.2 cc (experiment 11133) and the average value was 2.9 cc. In experiment 1243 upon infusion of norepinephrine V_o decreased from that of preceding control but was still larger than the initial V_o. It is not clear whether this was due directly to the action of the drug or some other process.

Thus, from the summary of data presented in Table 5 the following generalizations can be drawn. The average $\Delta P/\Delta V$ of the isovolumic pressure-volume curve is always less ($P < 0.02$) than that of the ejecting (ejection pressure constant) pressure-volume curve. When all of the experimental control data were compared (experiment 2214 excluded because of edema) the average percent decrease in diastolic pressure in going from an ejecting beat, that had an ejecting pressure less than 50% of PMAX, to an isovolumic beat was in the range of 6 to 21.8% with an average value of 16.5% ($\pm$ 1.2 SEM). On the whole there was no correlation between the percent decrease in diastolic pressure and

performance, as gauged by the peak isovolumic pressure developed at a common diastolic pressure of 10 mm Hg. Finally, over the course of several hours, each heart tended to become stiffer (except experiment 12183) and larger.

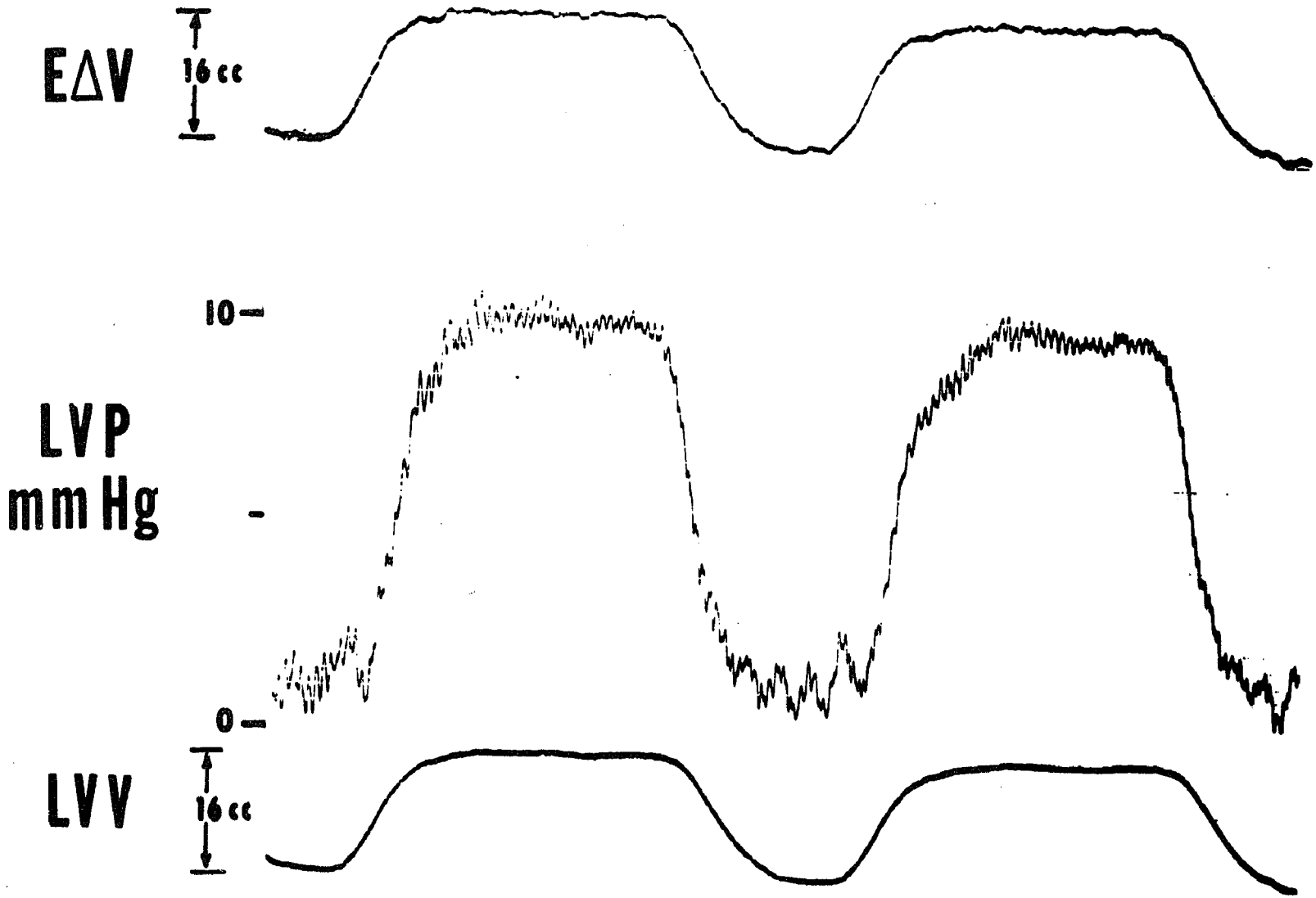
EFFECTS OF STROKE VOLUME AND FILLING RATE ON THE PRESSURE-VOLUME RELATION IN THE POTASSIUM ARRESTED HEART EXPERIMENTS

The fact that the diastolic pressure-volume curve was related to ejection pressure does not necessarily imply a direct "cause and effect" relationship. For example, as ejection pressure is increased, stroke volume and diastolic filling rate are noted to decrease (Figures 10 and 11); and these latter variables, rather than the former, may be the primary influencing factors. Because of their interrelation, however, one cannot dissociate these variables in the beating heart. This was demonstrated when accumulated diastolic volume change (Δ EDV) and ejection fraction were found to correlate equally as well as Δ EDV and the ejection pressure to peak isovolumic pressure ratio (p. 81 and 86). Therefore, in an attempt to study the effects of stroke volume and rate of filling in the absence of ejection pressure, a potassium arrested heart (K^+ heart) was attached to the apparatus and subjected to the same volume changes as was experiment 1243. This was accomplished using the external mode of operation (Part II p. 30) and the time varying volume signal recorded on analog tape (during the course of experiment 1243) as the external, desired intraventricular volume function. Figure 23 is an example of such a maneuver. Shown are recorded volume or external, desired intra-

Figure 23

Exemplary Potassium Arrest Experimental Data

Example of using the external mode of operation and the time varying volume signal (E Δ V) recorded during the course of experiment 1243. LVP and LVV are the resulting pressure and volume data respectively, using a potassium arrested heart.


EΔV
16 cc
10
LVP
mm Hg
0
LVV
16 cc

ventricular volume function (E Δ V), and resulting volume (LVV) and pressure (LVP) changes. Three such experiments were performed. Initially volume was either added or withdrawn so as to adjust each K^+ heart to have approximately the same diastolic pressures as experiment 1243.

Data analyses consisted of obtaining, for each data set (see p. 47), the average pressure (EDP) and volume (EDV) from the LVP and LVV curves, respectively, during the time period which corresponded to late diastole in the ejecting heart. The results of these three experiments (K-1, K-2 and K-3) are presented in Figure 24 as EDP plotted versus EDV. In addition the EDP-EDV data obtained during experiment 1243, which were previously discussed (see p. 94) and presented in Figure 21, are given. In order to present all four curves on the same graph and facilitate comparison, volumes for the K^+ hearts were adjusted so that equivalent data were vertically aligned. In addition, so as not to have overlapping curves, the data for each K^+ heart PV curve were shifted upwards by adding a constant value. The translation values for both volume and pressure are indicated in the legend to the figure. The alternating pattern of solid and open circles is also used as a comparison aid. For example, the third point (solid circle) from the left on curve 1243 was obtained with the ejection (EP) and diastolic (EDP) pressures set at 40 and 6 mm Hg, respectively, and the resultant stroke (SV) and diastolic (EDV) volumes were 9.0 and 25.5 cc, respectively. Therefore, the solid circles directly above this point represent the EDP-EDV values (when corrected for the shift factors) which

resulted from subjecting the potassium arrested hearts to this particular volume signal. Table 6 lists the experiment 1243 data for the eleven 1243 points plotted (points are numbered sequentially starting from the left in Figure 24). In addition the mean filling rate (Mean dV/dt), calculated by dividing stroke volume by filling time, is included.

As can be seen in Figure 24 the steplike feature of the 1243 curve is absent from the K-1, K-2 and K-3 curves. For example, in experiment 1243, when EP was increased from 40 to 80 mm Hg (points 8, 9 and 10), 3.3 cc had to be added to maintain EDP constant at 10 mm Hg, while this additional volume in the K^+ hearts resulted in a higher EDP. This maneuver was associated with a decrease in stroke volume and mean filling rate of 10.5 cc and 36.8 cc/sec; respectively (Table 6). Technical difficulties prevented the reproduction of an equivalent instantaneous isovolumic contraction (i.e., constant volume) in the first two K^+ hearts studied. In the third experiment these problems were circumvented with additional electronic circuitry. In this experiment no difference was found between the EDP-EDV values obtained after filling and those associated with the isovolumic condition.

The data presented in Figure 24 indicate that subjecting the potassium arrested heart to analogous stroke volumes and diastolic filling rates, within the ranges indicated in Table 6, did not produce similar alterations in the pressure-volume relation as were obtained in the ejecting heart. A comparison of the dynamic PV-curves during diastolic filling from experiment 1243 with equivalent curves from

Figure 24

Comparison of Pressure-Volume Curves

Pressure (EDP)-Volume (EDV) curves from three potassium arrest experiments (K-1, K-2 and K-3) are compared with that from experiment 1243. To facilitate comparisons the potassium arrest EDP-EDV curves were shifted, with the shift factors given below; and the alternating pattern of solid and opened circles was used (see text).

	EDV	EDP
K-1	-17	10.0
K-2	- 1	3.5
K-3	-16	5.0

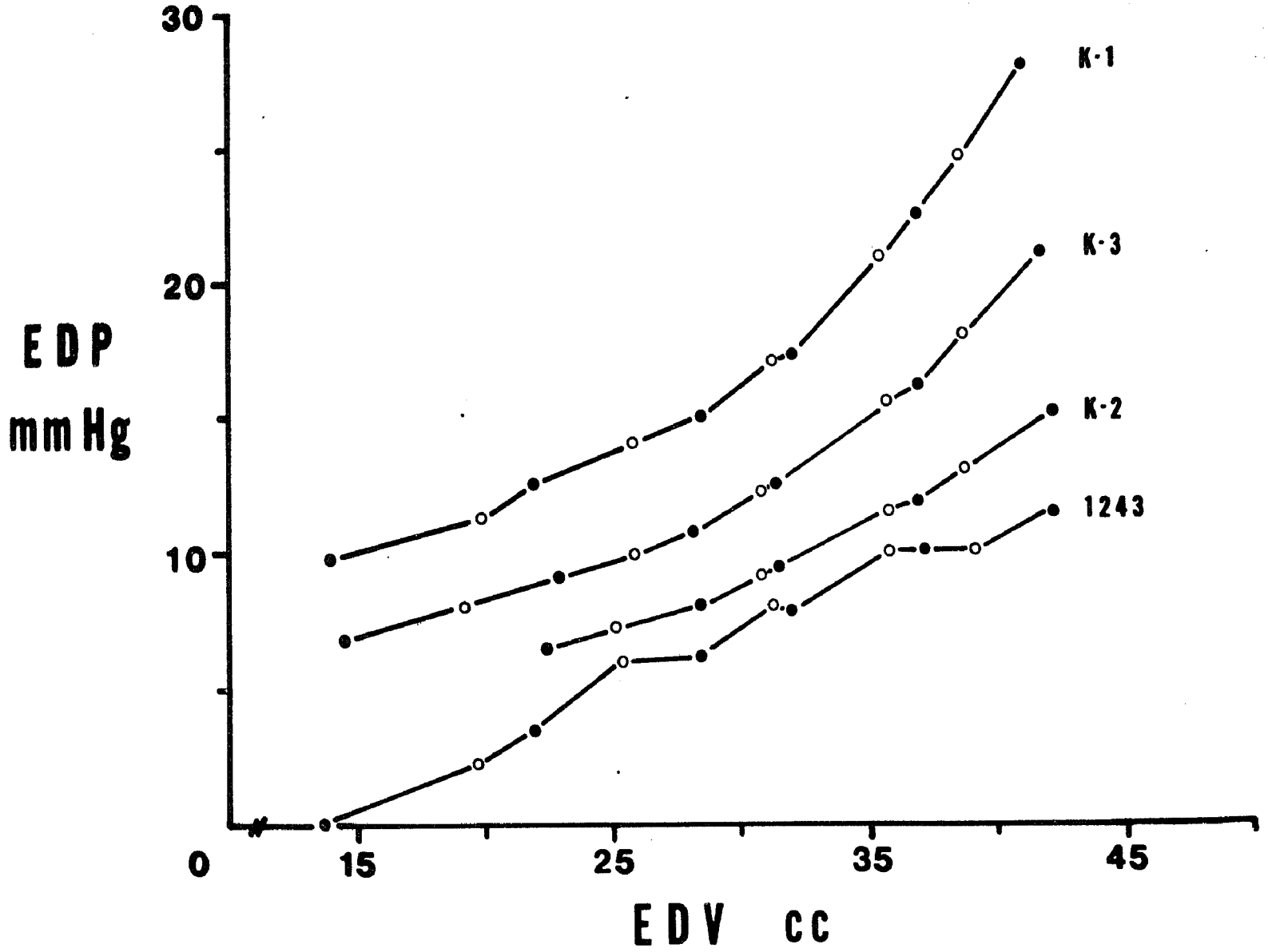

30
20
10
0
EDP
mm Hg
15
25
35
45
EDV cc
K-1
K-3
K-2
1243

TABLE 6

HEMODYNAMIC DATA FROM EXPERIMENT 1243

Point Number	Diastolic Pressure (mm Hg)	Diastolic Volume (cc)	Ejection Pressure (mm Hg)	Stroke Volume (cc)	Mean dv/dt (cc/sec)
1	0.1	13.8	18	1.7	8.3
2	2.2	19.8	40	3.1	22.0
3	3.5	22.0	40	5.5	25.9
4	6.0	25.5	40	9.0	52.3
5	6.2	28.5	60	5.0	36.8
6	8.0	31.5	40	13.0	62.5
7	7.7	32.0	60	7.0	44.9
8	10.0	36.0	40	14.0	62.5
9	10.0	37.3	60	9.0	38.8
10	10.0	39.3	80	3.5	25.7
11	11.5	42.0	80	6.0	38.5

the K^+ hearts provides further evidence. Such comparisons are made in Figure 25 and 26 where EDP is plotted versus EDV. In both figures, Panel A and Panel B are associated with experiment 1243 and a K^+ heart experiment, respectively, and equivalent curves are identified by letters (A, B and C). The legends indicate the ejection pressure (EP) of each curve. Figure 25 corresponds to that portion of experiment 1243 where EP was increased from 60 to 80 mm Hg and EDP was maintained at 10 mm Hg and Figure 26, to that portion where EDV was held constant at 42 cc and EP reduced from 80 to 40 mm Hg. The K^+ heart curves, in both figures, essentially follow the same path. In Figure 25 (Panel B), curve B terminates at a higher EDP corresponding to the increased EDV, and in Figure 26 (Panel B) all curves have the same EDP since EDV was constant. On the other hand, the curves in Panel A (both figures), in addition to the diastolic pressure-volume relation being altered, are contrastingly different to K^+ heart counterparts in that they did not follow the same path. Instead the curves shifted to the right as EP was increased.

Thus, assuming that arresting a heart in diastole with potassium does not alter its viscoelastic properties, one can conclude that the previously described alterations in the PV-relation, documented in the beating heart, are not directly influenced by stroke volume or the diastolic filling rate. Furthermore, other viscoelastic phenomena such as stress relaxation and pressure-volume hysteresis can be ruled out as possible causes if the same assumption concerning potassium arrest is made. That is, these phenomena are also passive properties of myocardium.

Figure 25

Comparison of Pressure-Volume Curves
During Diastolic Filling

Constant Diastolic Pressure

Pressure (EDP)-Volume (EDV) curves (A and B), obtained during diastolic filling, from Dog 1243 (Panel A) are compared with equivalent curves from a potassium arrest experiment (K^+ Heart - Panel B) (see text).

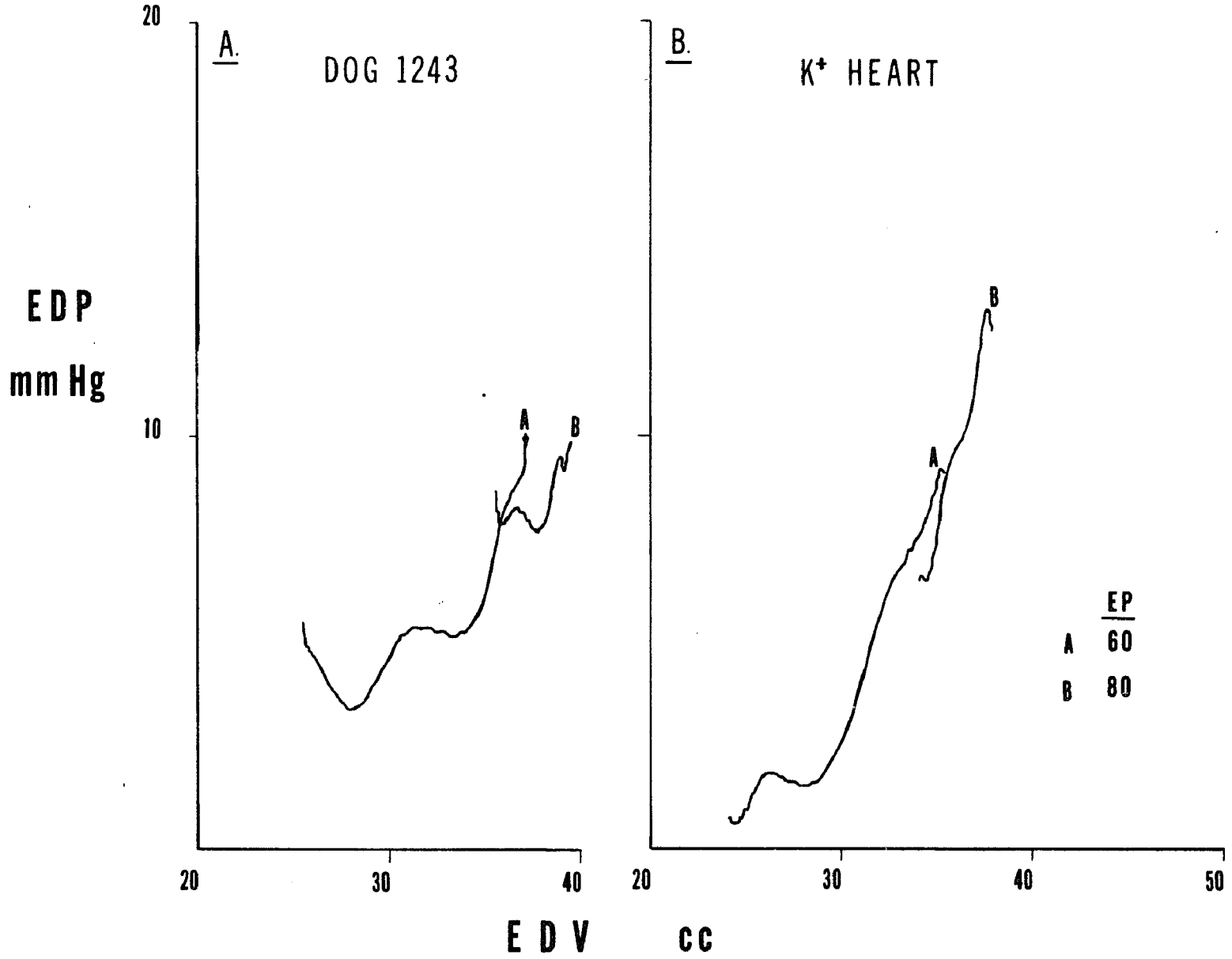
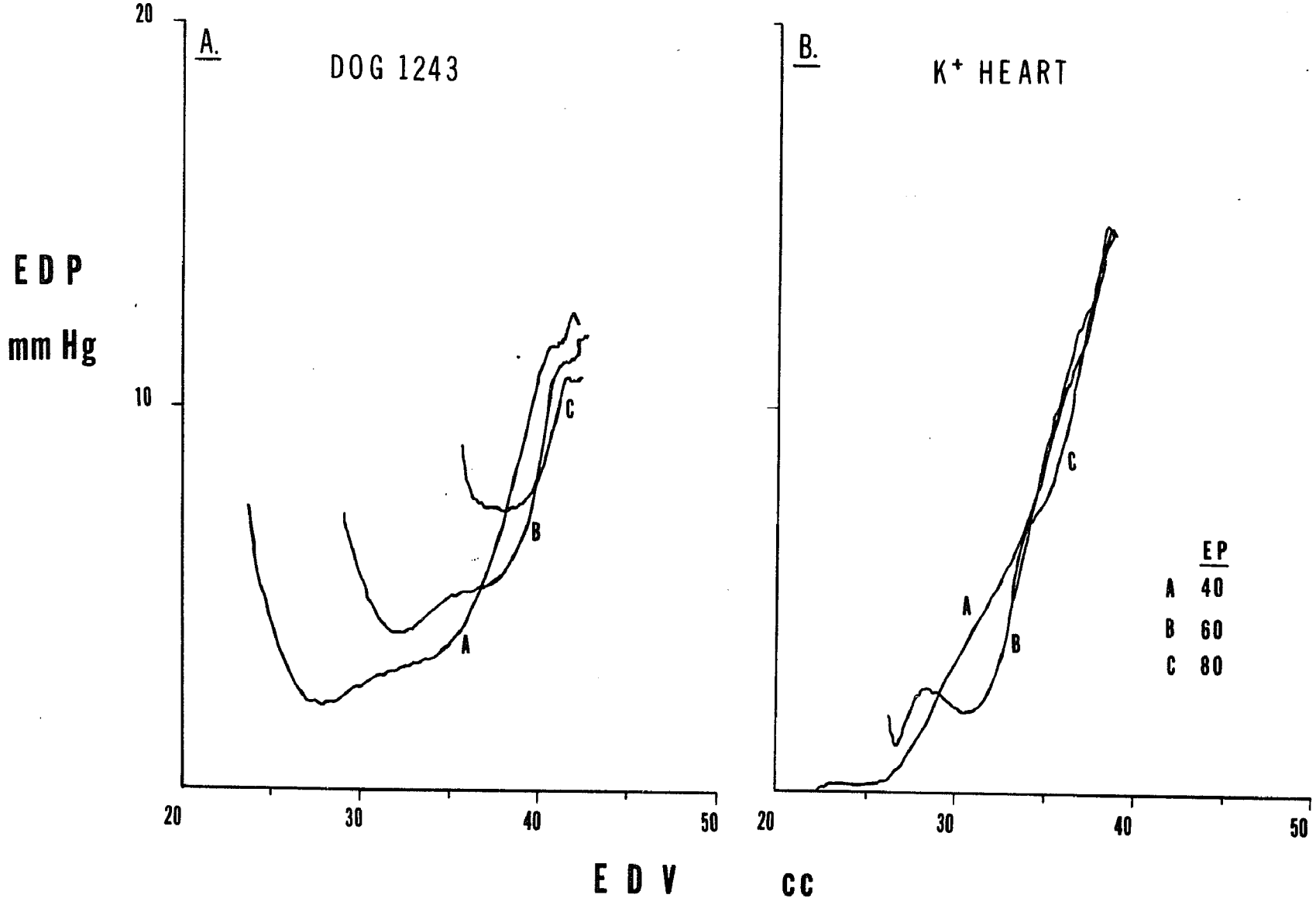

A.
DOG 1243
B.
K+ HEART
EDP
mm Hg
20
10
A
B
20
30
40
EDV
cc
20
30
40
50
EP
A 60
B 80

Figure 26

Comparison of Pressure-Volume Curves
During Diastolic Filling

Constant Diastolic Volume

Pressure (EDP)-Volume (EDV) curves (A, B and C), obtained during diastolic filling, from Dog 1243 (Panel A) are compared with equivalent curves from a potassium arrest experiment (K^+ Heart - Panel B) (see text).


A.
DOG 1243
B.
K+ HEART
EDP
mm Hg
20
10
20
30
40
50
EDV
cc
A
B
C
EP
A 40
B 60
C 80

PART IV

DISCUSSION

DISCUSSION OF RESULTS

An analysis of the factors influencing the left ventricular diastolic pressure-volume relation of the ejecting and isovolumically contracting heart requires that one be able to monitor left ventricular volume and control filling pressure. The pressure-servo system and its logic together with the intraventricular balloon were utilized to assess the effects of ejection pressure, stroke volume and filling rate on the left ventricular diastolic pressure-volume relation in paced, isolated canine hearts.

Before the experimental results are discussed, several comments and qualifying statements relevant to the stability of the biological preparation and the use of the servo system would appear appropriate. Data collection began following extirpation and a one hour period of perfusion during which time the balloon was inserted and the heart allowed to stabilize. Within the subsequent 4 to 5 hour data acquisition period, there was on the average a tendency for stroke volume to decrease 14% per hour for constant diastolic (EDP) and ejection (EP) pressures and heart rate. Peak isovolumic pressure (PMAX), when similarly checked for reproducibility, was also found to decrease, but to a lesser amount of 8% per hour. These reproducibility checks were usually made following 1 to 3 hours of data collection after which time calcium, norepinephrine or propranolol

were administered. In all hearts following the administration of calcium, stroke volume increased significantly and exceeded the initial control value. The summary presented in Table 5 indicates that norepinephrine likewise increased PMAX to a value greater than its control in 3 of the 5 experiments. Also shown in this table is the tendency for each heart to become stiffer and larger with time. The range of PMAX (90 to > 200 mm Hg) listed in Table 1 is similar to that measured by others (Abel and Reis, 1970; Clancy et al., 1968; and Monroe et al., 1966) in thoracotomized dogs or support dog perfused hearts (100 to 150 mm Hg for EDP approximately 10 mm Hg). Other indirect evidence of satisfactory performance were: the demonstration late in the experiment of a hyperemic response of the coronary circulation after a 10 second cessation of coronary flow and the small amount of total heart weight gain.

The servo system was capable of maintaining ejection pressure constant within $\pm$ 3 mm Hg of a given pre-set value when the ratio of systolic pressure to peak isovolumic pressure was greater than 0.3. At lower ratios, the pressure variations typically were within $\pm$ 5 mm Hg. The effect of these fluctuations on the resultant stroke volume was difficult to assess but more than likely inconsequential. System operation during diastolic filling was adequate, with the capability of achieving a maximum filling rate of 790 cc/sec. In these experiments, the filling rate was adjusted so that essentially all filling took place during the initial one third of diastole (rapid filling phase), with the

resulting rate rarely exceeding 400 cc/sec. Noble et al. (1969) reported a mean filling rate range of 30 to 410 cc/sec and a mean increase in volume of 0.63 cc/kg during the rapid filling phase of diastole in conscious dogs. In addition their results indicated: 1) a mid-diastolic period of relatively little filling (0.12 cc/kg); and 2) an appreciable amount of filling (0.30 cc/kg) during atrial systole. The servo system did not have the capability to simulate the atrial systolic contribution to ventricular filling and, consequently, the results presented herein were lacking in this respect. However, this was not considered to be a serious shortcoming, since others (Gilmore et al., 1966a; Hefner et al., 1961; and Rushmer, 1956) have reported similar variations in the PV-relation using preparations in which the left atrium remained functional.

In all experiments (Table 1) it was possible to alter the diastolic pressure-volume relation (PV-relation) by varying the ejection pressure. The direction of change associated with either steady state or transient increments in EP may be summarized as follows: for a constant diastolic volume (EDV), the diastolic pressure decreased as EP was increased, or stated differently, EDV increased for a constant EDP following increments in EP. The average total change in EDV required to keep EDP constant was 5.5 cc ($\pm$ 0.7 SEM). The corresponding total change in EDP was 1.5 mm Hg ($\pm$ 0.1 SEM). These values represent the largest change one would expect to measure with significant increments in ejection pressure (50% of PMAX). For lesser increments, they would concomitantly decrease and conceivably go undetected or be misinterpreted as insignificant when

using indirect methods of sensing volume (see Part II, VOLUME SENSING TECHNIQUES).

Subjecting pooled data to a regression analysis is a first order approximation to determine how much of the total variance, as indicated by the correlation coefficient squared (r^2) is due to regression. For example, when the accumulated change in EDV (Δ EDV) was correlated with EP the r value was - 0.4 indicating that the regression line accounted for only 16% of the total variance, and when ΔEDV was correlated with EP expressed as a percent of PMAX, 38% of the total variance was due to regression. Thus the latter represented a stronger correlation in that it accounted for an additional 22% of the total variance; and one then could possibly conclude that Δ EDV was in some manner better related to the pressure difference between PMAX and EP rather than EP alone. However, as seen in Table 3 when similar correlations using the accumulated change in EDP (ΔEDP) were obtained, the two equivalent r values were approximately the same (i.e., -0.46 for Δ EDP versus EP and -0.39 for Δ EDP versus EP/PMAX x 100%). Therefore, interpretation of these data simply on the basis of correlation coefficients was inconclusive. On the other hand, class interval analysis was more productive, indicating the nonlinear nature of the ΔEDV to EP/PMAX relation and providing a statistical justification for using the EP/PMAX value of 50% as a dividing line. For all data within the EP/PMAX range 20 to 50%, the average rate of change of this relation was not significantly different from zero. Therefore, it can be concluded that within this range, the PV-relation

was relatively insensitive to changes in ejection pressure.

This latter form of analysis statistically verified for the data collectively an observation consistently made during each experiment and permitted the subsequent interpretation of the diastolic pressure-volume curves obtained at various constant ejection pressures. The existence of two limiting PV-curves where the upper limit was obtained with EP less than 50% of PMAX and the lower limit, with the heart beating isovolumically, is an observation heretofore unreported. It is not clear how this two limiting curve concept would have been modified in those experiments (e.g. Bartlestone et al., 1965 and Sonnenblick et al., 1966) where alterations in the PV-relation were obtained in the isovolumic isolated canine heart using either paired stimulation or augmented perfusate calcium (increased contractility). That is, with respect to the two limiting curves, would these interventions have shifted the isovolumic curve further to the right and the average percent difference in EDP (% decrease) increased, or would both limiting curves have equally shifted to the right, thereby keeping the % decrease constant?

The fact that steady state norepinephrine infusion in the studies reported herein significantly increased the average % difference in 2 experiments (Table 5) tends to support the former possibility; implying some degree of dependence on the contractile state. However, this does not necessarily imply a direct relation between average % decrease in EDP and the inotropically, augmented PMAX. For example, when the Series 2 experiments were compared in Table 5 no apparent correlation between the average % decrease in EDP and

performance (PMAX) was indicated; and furthermore, comparing both the total change in diastolic volume and the total change in diastolic pressure with PMAX (Series I experiments) resulted in correlation coefficients that were not significantly different from zero. Therefore, for a given heart, the degree of dependence between the average % decrease in EDP and performance is still open to question and warrants further investigation. In any event, the conclusion concerning the existence of two limiting PV-curves should be modified accordingly. That is, for a given contractile or inotropic state there exist two limiting diastolic pressure-volume curves where the upper limit was obtained with the ejection pressure less than 50% of the peak isovolumic pressure, and the lower limit with the heart beating isovolumically.

DISCUSSION OF POSSIBLE MECHANISMS RESPONSIBLE FOR DIASTOLIC PRESSURE-VOLUME VARIABILITY

The results of this study quantitatively confirm the observations of others (Bartlestone et al., 1965; Gilmore et al., 1966a and 1966b; Hefner et al., 1961; Leach and Alexander, 1965; Monroe et al., 1968; Sonnenblick et al., 1966; and Rushmer, 1956) leaving little doubt that alterations in the diastolic pressure-volume relation occur with increments in ejection pressure. While the explanation of this phenomenon is not entirely clear the demonstration, in this study, of instantaneous decreases in EDP when EP was transiently increased tends to negate phenomena associated with longer time constants such as: alterations in coronary flow, the development of myocardial ischemia and myocardial catecholamine depletion.

Absent from the potassium arrested experiments were the systolic changes in ventricular geometry which accompanied the development of pressures and the corresponding ejected volumes. Thus, these experiments, where changes in the diastolic pressure-volume relation were not seen, suggest that such alterations are associated with the active development of pressure and shortening. Therefore, the statement, that concomitant changes in stroke volume and filling rate were not directly responsible for alterations in the PV-relation, does not imply that concomitant geometrical changes (in the beating heart), such as stroke diameter or end systolic configuration, are similarly

inconsequential. However, pressure-volume hysteresis being related to stroke volume and stress relaxation to filling rate can be eliminated as possible mechanisms. Furthermore, with regards to stress relaxation, Leach and Alexander (1965) specifically studied its response to epinephrine and could not detect any evidence that it was altered, even though the diastolic pressure-volume curve significantly shifted to the right.

The hypothesis of Hoffman et al. (1968) concerning this phenomenon is unique in that the role of increased developed pressure as a direct cause is questioned. They concluded that the diastolic alterations were not necessarily related to either an increase or a decrease in pressure developed during contraction, but instead were due to a variable degree of persistent interaction between the contractile elements. It is difficult to assert whether the results of this study confirm or deny their conclusions. The fact that the observed total changes in diastolic volume and pressure did not correlate with the peak isovolumic pressure or ventricular performance as previously discussed, and the observed existence of two limiting PV-curves for a given contractile state tend to indicate that indeed something other than developed pressure may be influencing the PV-relation. However, their alternative explanation is vague and reminiscent of the controversial tone concept.

Other possibilities, based on observations made in the course of this study, which may warrant future consideration include the following: It can be seen in Figures 10 and 11 that, in addition to the ejection pressure being increased, the time spent in systole is also

increased. Further inspection reveals that the time rate of decrease in pressure during isovolumic relaxation is less for curve (a) than for curves (b) and (c). Alternatively, diastolic pressure-volume alterations may in some way be related to the dynamic geometry of the ventricle. For instance, the mid-length internal diameter (ID) increases from its diastolic value during the isovolumic contraction phase of systole (Webster et al., 1974). The amount of this increase in ID is directly proportional to the ejection pressure. Furthermore, during an isovolumic contraction the diameter continues to increase until peak isovolumic pressure is reached, and then gradually returns to its diastolic value. That is, unlike the ejecting beats, the internal diameter did not decrease below its diastolic value during isovolumic contractions (unpublished observations). Thus, if indeed pressure is proven not to be the direct or sole cause, then other possibilities such as these should be investigated.

Another point of uncertainty concerning the diastolic pressure-volume relation is where in the cardiac cycle do these pressure induced alterations occur. The data obtained in this study provide little, if any, insight. In addition, an independent method of quantifying elasticity after each pressure increment is required. The technique of Templeton et al. (1970) would be ideal for such an assessment. Using an isovolumic, isolated preparation they were able to superimpose on the isovolumic pressure recording, small sinusoidal pressure responses to a sinusoidal volume perturbation of 1 cc. The perturbation frequency was 30 Hz. Thus they could measure stiffness which reflects the viscoelastic properties throughout the

cardiac cycle, in addition to the diastolic pressure-volume relation. Applying their technique to the ejecting heart would further aid in the understanding of the mechanism responsible for these diastolic pressure-volume alterations.

SIGNIFICANCE OF RESULTS

The results of this study indicate that the diastolic pressure-volume relation is a physiological variable that must be considered as one determinant of cardiac performance before the functional state of the ventricle can be fully understood. Furthermore, the observation that an increase in the pressure resisting shortening alters this relation, such that the ventricle could receive more volume without an increase in filling pressure, suggests that this phenomenon may serve as a compensatory mechanism. That is, according to the Frank-Starling response, the increased volume and fiber length would, at this increased systolic pressure, either increase or maintain the amount of shortening and thereby cardiac output. However, the new steady state would ultimately be determined by the complex inter-relationship between cardiac function, peripheral circulation and neurohumoral control.

Some idea as to the magnitude of this compensatory mechanism, in the absence of peripheral circulation and neurohumoral influence, can be obtained from the results of Weber et al. (1974), who demonstrated a linear, inverse relation between stroke volume (SV) and ejection pressure (EP) when the diastolic pressure was maintained constant. If, however, EDP was allowed to decrease (i.e., EDV maintained constant), as EP approached the isovolumic state, the SV to EP relation became nonlinear; in this nonlinear region, the

stroke volume was reduced for any EP. In one such example, the largest stroke volume difference between the two relations was 3 cc, which corresponded to a cardiac output of 420 cc/min.

The results of Weber and co-workers as well as those described herein were obtained under similarly controlled conditions, and whether they are part of the phenomenon, observed in the intact circulation, and termed the "Anrep" effect by Sarnoff and Mitchell (1961) is an intriguing possibility. A brief description of this effect is as follows: As a result of elevating aortic pressure the ejected fraction of the subsequent contraction decreases, thereby increasing the diastolic volume (EDV) and pressure (EDP). This increase in EDV, causes, via the Frank-Starling mechanism, a more forceful contraction of the following beat which in turn lowers EDV and EDP. This sequence continues until a "new" steady state is reached, where the heart might eject the same stroke volume as it did before elevation of the aortic pressure at approximately the original EDP. However, the EDV in the new steady state is disproportionally higher indicating an alteration in the PV-relation has occurred. That is, as the new steady state is approached, the EDP decreases to its original level while EDV also decreases, but to a lesser extent so that a net increase in EDV is realized. Clancy et al. (1968) concluded the major increase in performance, associated with this effect, results from the operation of the Frank-Starling mechanism; and in addition Monroe et al. (1968) measured the net increase in EDV to be 1 to 2 cc and concluded that this augmented

volume, in part, could account for the increased or constant output following an elevation in aortic pressure.

The observations made in this study also re-emphasize the limitations to the assumption that left ventricular diastolic pressure is a reliable index of diastolic myocardial length. Ventricular pressure measurements, compared to the measurement of volume, are relatively easy and accurate, and, consequently, have frequently been used both experimentally and clinically as an index of volume or myocardial length. As pointed out by Levine (1972) such an assumption could result in an erroneous conclusion concerning the cause of the elevated filling pressure. Finally, the findings of this study emphasize the importance of controlling developed pressure when studying the effects of inotropic interventions, particularly drugs, on the diastolic pressure-volume relation.

SUMMARY

A pressure-servo system was utilized to study the effects of ejection pressure on the diastolic pressure-volume relation in 20 isolated, ejecting, paced canine hearts. Three independent methods were utilized: where for two of the methods, either diastolic volume (1) or pressure (2) was maintained constant and the ejection pressure incrementally varied in a steady state fashion; the third method consisted of instantaneous isovolumic contractions obtained at a constant diastolic volume. In addition, 3 potassium arrested hearts were utilized to determine whether analogous stroke volumes and diastolic filling rates affected the passive pressure-volume relation. The results indicate that it was possible to alter the diastolic pressure-volume relation by varying the ejection pressure with the direction of change summarized as follows: for a constant diastolic volume, the diastolic pressure decreased as ejection pressure was increased. Stated differently, diastolic volume had to be increased in order to keep diastolic pressure constant following increments in ejection pressure. For large increments in developed pressure (50% of peak isovolumic pressure), the average total change in diastolic volume required to keep diastolic pressure constant was 5.5 cc ($\pm$ 0.7 SEM); and the total change in diastolic pressure for constant diastolic volume was 1.5 mm Hg ($\pm$ 0.1 SEM).

A comparison of diastolic pressure-volume curves obtained at various constant ejection pressures revealed that for a given contractile or inotropic state there exist two limiting diastolic pressure-volume curves where the upper limit was obtained with the ejection pressure less than 50% of the peak isovolumic pressure and the lower limit, with the heart beating isovolumically. Each diastolic pressure-volume curve associated with a constant ejection pressure, greater than 50% of the peak isovolumic pressure, characteristically originated on the lower limit curve and eventually converged with the upper limit curve. The point of origin was associated with that diastolic volume at which the ejection pressure equalled the peak isovolumic pressure. The average percent decrease in diastolic pressure between the upper and lower limit curves was 16.5% ($\pm$ 1.2 SEM). The absolute magnitude of this decrease was dependent on the initial level of diastolic pressure, a greater decline occurring at higher diastolic pressures.

With regards to possible mechanisms responsible for this phenomenon, the results negate alterations in coronary flow, the development of myocardial ischemia and myocardial catecholamine depletion as possible factors. Furthermore, the potassium arrested experiments demonstrate that these diastolic pressure-volume alterations are associated with the active development of pressure and shortening of muscle fiber. Finally, the fact that the observed total changes in diastolic volume and pressure did not correlate with the peak isovolumic pressure or performance indicates that increments in developed pressure may not be the sole cause of the observed variability in the diastolic pressure-volume relation.

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