Factors Altering the Filling of the Isolated Left Ventricle of the Dog Heart

Effects of Epinephrine and Norepinephrine

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Ventricular filling was studied in an isolated left ventricle preparation, and mechanical impedance of the ventricular wall was computed throughout the filling period. Changes in work load or heart rate were accompanied by changes in intraventricular pressure curve contours and in the time-course of the mechanical impedance throughout filling. The filling pattern is characteristically altered as work load or heart rate increases, and after the administration of epinephrine or norepinephrine.

We have studied the filling of the left ventricle of the dog heart using a technic similar to that recently reported but in which only the left ventricle performs external work.

The mechanical impedance to the inflow of blood, which depends on mass, viscosity and elasticity, was calculated from the intraventricular pressure-inflow relationship throughout diastolic filling. This was used to relate the effects of work load, heart rate and sympathomimetic drugs to the physical properties of the ventricle wall which determine impedance.

Methods

The Isolated Left Ventricle Preparation

The left ventricle of a small dog heart is functionally isolated by filling it directly from a venous reservoir through an inflow cannula tied into the left atrium. The ventricle empties through a cannula in the brachiocephalic branch of the aorta, below which the thoracic aorta is ligated. The external circuit consists of a collapsible rubber reservoir in a water bath of large surface area and a Starling peripheral resistance unit. The coronary system of this heart is supplied by the working left ventricle. Oxygenation of the blood was maintained by supplying the reservoir with blood recirculated through a donor dog or by re-establishing the standard heart-lung circuit alternately as described below. Blood reaching the right ventricle by coronary drainage is siphoned during the period of measurements, when the right ventricle is to perform no external work. The work of the left ventricle is then determined by the variable hydrostatic head of blood and the variable aortic resistance.

The details of the procedure are: A standard heart-lung preparation is made, and a venous inflow cannula is then tied into the left atrium as close to the atrioventricular ring as possible (to prevent normal auricular filling) without completely obstructing pulmonary venous return. A drainage tube (closed) is then inserted through the right atrium into the right ventricle. When functioning as a standard heart-lung circuit, the venous inflow to the left ventricle and the right ventricular drainage tube are clamped. When functioning as an isolated left ventricle the venous inflow to the right atrium is clamped, and the right ventricular drainage tube and venous inflow to the left ventricle are opened. In about half of the preparations made a donor dog was used to recirculate and reoxygenate the blood, without detectable difference in results. Venous inflow and peripheral resistance are adjusted for the left ventricle, which requires a higher filling pressure than the right ventricle.

Blood volume was 500 to 1000 ml. and blood temperature was kept at 35 to 37°C, with only 0.5°C variation during a given procedure.

In eight of fifteen preparations simultaneous records of left ventricular pressure and volume changes and aortic pressure and outflow were made on a Hathaway oscillograph at a paper speed of 100 mm. per second, with time lines every .01 second. (Cardiometer and flowmeter tracings were obtained as in the isolated right ventricular preparation.)
the ventricular volume changes being measured from a zero set by allowing the left ventricle to empty as completely as possible.) In the other seven preparations only intraventricular and aortic pressures were recorded. These were registered by Statham arterial pressure transducers attached to a 13-gage needle inserted through the arterial cannula. Left ventricular pressure was amplified by a Sierra DC amplifier for ease of record analysis.

In all experiments, aortic outflow was measured by timed collections into a graduated cylinder.

Calculations

The performance of the left ventricle was evaluated from calculations of stroke output (aortic outflow/heart rate) and the stroke work done to develop pressure on the volume of blood ejected from the ventricle (stroke output X mean aortic pressure). These data will not be reported since they were used only as a guide to ventricular performance.

In the analysis of intraventricular pressure curves each filling period was divided into three phases: an early phase (e) from the instant that the decreasing pressure falls below the hydrostatic pressure head to the onset of the level diastolic pressure; a middle phase (m) during which intraventricular pressure is constant; and a late phase (l) from the instant that pressure begins to rise in late diastole to the instant that it rises above the hydrostatic pressure head (fig. 1). Cardiac cycle length (r), duration of diastolic filling (f) and of the midfilling phase (m) were measured. The ratio m/f was calculated.

The mechanical impedance of the ventricular wall was calculated from the ratio of intraventricular pressure to inflow at various times throughout filling. Blood entering the ventricle under hydrostatic pressure ($P_h$) is opposed by the resistance of the inflow tubing and cannula ($R_c$) and by the mechanical impedance of the ventricular wall ($I$). Since the resistance of the external circuit is measured separately for each inflow circuit used, the flow ($F$) may be calculated from $P_h - P_v$ where $P_v$ is the pressure inside the ventricle. Inflow is further opposed by the physical properties of the ventricle. Since this mechanical impedance of the ventricular wall opposes the pressure to which the wall is subjected, it may then be calculated from the ratio $P_v/F$.

To construct impedance-time plots (fig. 1), impedance was calculated at comparable short intervals throughout the filling period. It should be noted that the method employed for calculation of inflow assumes that blood enters the ventricle during all phases of filling, since a pressure gradient exists, up to the moment of reopening of the atrio-ventricular valve.

![Diagram](image_url)

**Fig. 1.** Effects of increasing hydrostatic filling pressure (H), on intraventricular pressure and the time-course of mechanical impedance (dog 25). Ventricular pressure curves are marked to show onset and end of the filling period, and duration of the midfilling phase. Horizontal lines are record baselines. Impedance units (I) are $\text{dyne sec} \cdot \text{cm}^2$ (DSC).
Plan of Experiment. The venous return to the left ventricle was varied by changing the hydrostatic head within the upper range of filling pressures found for open-chest dogs (10 to 20 mm. Hg). Records were taken at constant aortic pressure and heart rate after the ventricle had attained equilibrium with respect to each new input load. Each equilibrium was characterized by reproducible pressure and volume curves from beat to beat (where recorded).

The heart rate was increased from spontaneous rates of 90 to 120 to rates of 130 to 160 by electric stimulation in the region of the sinoatrial node, using a technic reported elsewhere. Records were taken at constant filling and aortic pressures.

Aortic pressure was altered by varying the air pressure in the Starling peripheral resistance unit over ranges above and below average aortic pressures found for normal open-chest dogs (40 to 180 mm. Hg). The lower range was used to demonstrate effects of low coronary perfusion pressure. Records were taken at constant filling pressure and heart rate after the ventricle had attained equilibrium with respect to each new output load. Again, each equilibrium was characterized by reproducible pressure and volume curves from beat to beat.

The effects of sympathomimetic drugs were studied, using doses of .002 mg. synthetic epinephrine (Suprarenin*) and .001 mg. l-norepinephrine (Levophed*) per dog. Records were made during and after chronotropic effects, at intervals for 20 minutes. Criteria for a positive inotropic effect were increased stroke work, output and decreased diastolic volume.

RESULTS

The isolated left ventricular preparation was evaluated by comparing the general performance of 15 such preparations with that of 7 Starling and 5 Evans heart-lung preparations using the same equipment. Increasing work load resulted in increased work output over comparable ranges and there was no remarkable difference in diastolic behavior. However, comparison of the intraventricular pressure curves showed that pressure remained constant during the greater part of the filling period in the isolated left ventricle at all but the fastest heart rates. In 5 left ventricular preparations the left atrial cannula was placed in the tip of the atrial appendage rather than close to the atrioventricular ring. In these cases intraventricular pressure curves were obtained exactly like those from heart-lung preparations, i.e., pressure gradually rose in late diastole. This is apparently related to the function of the relatively intact atrium.

Thus evaluation of the isolated left ventricle's performance demonstrated that the more complicated dissection had not interfered with ventricular function.

Ventricular Filling at Work Equilibrium. As in the right ventricle, analysis of records taken during work equilibrium at constant heart rate reveals the uniformity of ventricular behavior during a series of consecutive beats. The duration of filling and of the early, middle and late phases of filling does not change. The extent of filling (diastolic volume) and the time course of ventricular mechanical impedance do not change. This suggests that there is a fixed response of the physical properties of the ventricular wall during filling at work equilibrium.

Each impedance-time plot in figures 1 to 4 illustrates the typical variation of ventricular mechanical impedance throughout the filling period. In each plot the very high impedance characteristic of the earliest and latest times during filling is not shown. These values must necessarily approach infinity at the onset and

* Kindly supplied by Winthrop-Stearn Co.
end of filling. From the opening of the atrio-
ventricular valve impedance decreases very
rapidly to a level which is maintained constant
throughout most of the filling period. Impen-
dance then increases suddenly and is in-
finitely high at the closure of the atrioventricu-
al valve. This typical pattern for the
pressure-inflow relationship during filling char-
terizes work equilibrium at all but the
fastest heart rates. In the latter case, no
constant ventricular pressure or impedance is
observed.

Effects of Work Load or Heart Rate Changes
on Ventricular Mechanical Impedance. Data
were obtained on 15 dog hearts (42–100 gms.).
At constant aortic pressure and heart rate,
successive increases in filling pressure were
accompanied by longer midfilling phases,
lower inflow rates and higher impedance levels.
At constant filling pressure and heart rate,
successive increases in aortic pressure were
accompanied by shorter midfilling phases,
decreased inflow rates and higher impedance
levels. At constant aortic and filling pressures,
successive decreases in cycle length were ac-
companied by shorter midfilling phases, de-
creased inflow rates and higher impedance
levels. These data are comparable to those
previously reported for the right ventricle.1

Ventricular pressure curve contours from
typical experiments are presented in figures 1,
2 and 3, together with the time-course of
ventricular mechanical impedance throughout
diastole.

Increasing the filling pressure (fig. 1) is ac-
compained by (1) a steeper fall of impedance
in early filling, (2) a lower midfilling im-
pedance and (3) a longer midfilling period
(phase of lowest impedance).

Increasing the mean aortic pressure (fig. 2)
above 80 mm. Hg is accompanied by (1) a
faster rate of impedance fall in early filling,
(2) a higher midfilling impedance and (3) a
shorter midfilling period.

Increasing the heart rate (fig. 3) is likewise
accompanied by (1) a steeper fall of imped-

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**Fig. 3.** Effects of increasing heart rate on intraventricular pressure and the time-course of me-
chanical/impedance (dog 17). Ventricular pressure curves are marked to show onset and end of the
filling period and duration of the midfilling phase. Horizontal lines are record baselines. Impedance
units (1) are \( \text{dyne cm}^{-1} \) (DSC).
FILLING OF THE ISOLATED LEFT VENTRICLE

TABLE 1.—Inotropic Effects of Epinephrine and Norepinephrine on Left Ventricular Behavior During Midfilling.

<table>
<thead>
<tr>
<th>RECE</th>
<th>P (mm Hg)</th>
<th>F (cc/sec)</th>
<th>I (dyne sec/cm² X 10⁶)</th>
<th>c (sec)</th>
<th>m/c</th>
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<tr>
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<tr>
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<td>.62</td>
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<tr>
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<tr>
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<td>.53</td>
<td>.04</td>
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</tbody>
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P = left ventricular pressure during midfilling.
F = left ventricular inflow during midfilling.
I = ventricular mechanical impedance during midfilling.
c = cardiac cycle length.
m = duration of the middle phase of filling.
C = control.
E = epinephrine.
N = norepinephrine.

Fig. 4. Effects of epinephrine (left) and norepinephrine (right) on the time-course of ventricular mechanical impedance (dog 27, table 1). Data obtained during a positive chronotropic effect are presented to emphasize the lengthening of the time available for filling when impedance is lowest. Solid lines, control; dash lines, after epinephrine (left) and norepinephrine (right). Impedance units (I) are dyne sec/cm². c = (I/sec).

ance in early filling, (2) a higher midfilling impedance and (3) a shorter midfilling period.

We had observed a variable change in midfilling impedance when mean pulmonary artery pressure was increased in the isolated right ventricle preparation, and had obtained some evidence that this might be related to decreases in coronary flow. This was confirmed by observations on the left ventricle, in which decreasing the mean aortic pressure below 60 mm. Hg (which eventually leads to decreased coronary flow) is accompanied by a slower rate of impedance fall and a lower midfilling impedance level.

Effects of Epinephrine and Norepinephrine on Ventricular Mechanical Impedance. Data were obtained on seven dog hearts (65 to 93 Gm.). Both drugs decreased the intraventricular pressure and impedance and increased the inflow during the midfilling period. Both drugs produced a transient positive chronotropic effect in all hearts studied. Analysis were made both during and after a chronotropic effect and the changes in ventricular impedance were found to persist. Table 1 shows the drug effects after heart rate had returned to the control value.

The time course of ventricular mechanical impedance throughout filling in representative experiments is shown in figure 4. During the early phase of filling, after epinephrine or norepinephrine injection, impedance decreased more rapidly to a lower midfilling level. Data presented were obtained during the chronotropic effect. Contrary to the results on electrical stimulation of the S-A node, administration of these drugs produces a longer midfilling time even in the presence of a positive chronotropic effect.

Any apparent difference between the effects of these two drugs may be due to variations in timing and effective concentration, and should not be regarded as significant in the present report.
DISCUSSION

The Mechanical Impedance of the Ventricular Wall Throughout Diastolic Filling. During work equilibrium at constant heart rate, filling pressure and aortic pressure, filling of the isolated left ventricle is characterized by a constant pattern of inflow, volume, and intraventricular pressure for an indefinite number of consecutive cardiac cycles. When this relationship has been examined throughout the filling period while ventricular volume is enlarging, many investigators have seen that (1) inflow increases rapidly while intraventricular pressure is falling in early filling, (2) ventricular pressure and inflow become constant for much of the filling period and (3) inflow decreases rapidly while intraventricular pressure is rising steeply at the end of filling. Although we are aware of the unreliability of cardiometer records it is apparent that the ratio of ventricular pressure to inflow is independent of ventricular volume throughout the midfilling period, as was shown previously for the right ventricle.1

We have considered that the intraventricular pressure-inflow ratio is a result of the balance between stress on the ventricular wall and its opposition to the stress, and that the ratio therefore expresses the mechanical impedance of the ventricular wall. Calculation of impedance throughout the filling period has emphasized the constant ventricular behavior at constant heart rate and work load. Considering that impedance depends upon the mass, elasticity and viscosity of the ventricular wall and assuming that ventricular mass remains constant during a given experiment, it should be possible to describe changes in the viscoelastic properties of the ventricle by the time course of its mechanical impedance. The increasing mass of blood in the ventricle has been neglected.

Examination of a typical impedance-time plot indicates first a rapid decrease in impedance early in diastole. This is probably related to changes in elasticity and viscosity of the structural components of the ventricle during the process of relaxation. It is probable that any stimulus speeding the rate of relaxation of the ventricle would speed the rate of impedance fall.

Continuing into mid-diastole the constant impedance may be explained as a result of (1) the changing geometrical configuration of an expanding elastic shell and (2) the continuous strain-free expansion of a viscous shell.

At end-diastole impedance rises precipitously, probably corresponding to changes in elasticity and viscosity of the structural components of the ventricular wall beginning contraction.4 It may well be that the only limit to filling is the onset of the next systole, as demonstrated by records obtained at very slow heart rates.

Effects of Work Load and Heart Rate on Ventricular Filling. When the input load is increased at constant heart rate and aortic pressure, the change in pattern of the impedance-time plots consists of a more rapid decline of impedance to a lower level, and a longer midfilling period. Thus there is more time available for filling when impedance is lowest. These observations could be a consequence of an increased rate of relaxation. Lundin4 and Dudel and Trautwein* have found that cardiac muscle, subjected to sudden shortening from a moderately longer stretch, subsequently relaxes faster.

When the output load is increased at constant heart rate and filling pressure, the change in pattern of the impedance-time plot consists of a faster fall of impedance to a higher level and a shorter midfilling period. From the experiments of Lundin4 on releasing a load from contracting cardiac muscle, it might be concluded that a ventricular wall which has been subjected to the larger "afterload" of higher output pressure might lose its tension more rapidly when this load is released as the aortic valve opens. This could account for an increased rate of decline of impedance. An explanation of the higher midfilling impedance is not apparent to us. As Wiggers found earlier,7 systole becomes proportionately longer under high output loads, which would account for the shorter time available for filling when impedance was lowest.

When the heart rate is increased at constant
filling and aortic pressures, the change in pattern of the impedance-time plot consists of a more rapid impedance fall to a higher level and a markedly shortened midfilling period. As the onset of systole is earlier, there is proportionately less time available for filling when impedance is lowest. The more rapid impedance fall may be related to the more rapid rate of cardiac muscle relaxation found at faster rates of electrical stimulation. The higher level of midfilling impedance may be related to the less complete relaxation which was observed in isolated ventricular strips subjected to faster rates of electrical stimulation.

Effects of Epinephrine and Norepinephrine on Ventricular Filling. The positive inotropic effects of epinephrine and norepinephrine have been recently studied in cat papillary muscle preparations, perfused mammalian hearts, and open-chest intact dogs. Increased force and amplitude of contraction, increased systolic pressure and decreased diastolic pressure have been noted. The observations of Opdyke on the effects of epinephrine on the intraventricular pressure curve obtained from the empty beating right ventricle led to his conclusion that the drug speeds the rate of relaxation of the heart. We have been interested in the effects on the intraventricular pressure-inflow relationship.

Examination of the impedance-time plots in figure 4 reveals that the mechanical impedance of the left ventricle falls more rapidly in the early phase of filling to a lower level in midfilling, and that the midfilling period is lengthened after the administration of either epinephrine or norepinephrine. These changes were found both during and after a positive chronotropic effect. Although the augmentation of systolic pressure and amplitude of contraction have been reported to last only 2 to 3 minutes after comparable doses of these drugs, our observations indicate a more persistent inotropic effect (about 10 minutes) when diastolic intraventricular pressure and inflow are studied. The persistence of a positive inotropic effect after the peak of a transitory chronotropic effect supports the suggestion of Lands and Howard that a different mechanism is involved in the inotropic and chronotropic activity of these drugs.

The increased heart rate observed after the administration of epinephrine or norepinephrine was accompanied by a lower midfilling impedance and a longer time available for filling when impedance was lowest. This was in marked contrast to the results obtained when the heart rate was increased by electrical stimulation in the sinoatrial node region. Similar interesting differences in the excitability of the dog ventricle have been observed by Siebens and co-workers, who reported almost no change in the periods of absolute and relative refractoriness upon increasing the heart rate with epinephrine or norepinephrine, in contrast to the decreased refractoriness upon increasing the heart rate by electrical stimulation. Since both types of procedure have been found to augment coronary artery flow, the differences cannot be explained on this basis.

The foregoing discussion supports our previous conclusions based upon the study of other inotropic drugs, work load and heart rate in the isolated right ventricle. The stroke output is determined early in diastole by conditions which may be partly measured in terms of mechanical impedance during filling. Thus whenever a ventricle has been observed to increase its stroke output, an increased ease of filling was also evident in the decreased mechanical impedance and increased duration of the midfilling period.

With due regard to the different ranges of physiologic performance, the left and the right ventricle appear to behave similarly with respect to the phenomena reported here.

Summary

Ventricular filling has been studied in a modified heart-lung preparation in which only the left ventricle performs external work. The ratio of intraventricular pressure to inflow, termed the mechanical impedance of the ventricle, was calculated throughout the filling period. This impedance characteristically de-
creases rapidly during the early part of filling, to a constant low level during the middle of the filling period and rises rapidly during the last part of the filling period.

Increases in hydrostatic filling pressure are accompanied by a decreased midfilling impedance and a lengthened time available for filling when impedance is lowest.

Increases in aortic pressure or in heart rate are accompanied by an increased midfilling impedance and a shortened time for filling when impedance is lowest.

Epinephrine or norepinephrine administration is followed by a transient chronotropic and a persistent inotropic effect. Both effects are accompanied by a decreased midfilling impedance and a lengthened time available for filling when impedance is lowest.

Changes in stroke output appear to be closely related to changes in the ease and duration of filling.

Acknowledgments

The authors gratefully acknowledge the technical assistance of Joan Gould and Ernest Porter.

SUMMARIO IN INTERLINGUA

Le processo del plenamento ventriculare esseva studiate in un modificate experimento cardio-pulmonar in que solmente le ventriculo sinistre executava labor externe. Le proportion de pression intraventricular a influxo (appellate le impedantia mechanic del ventriculo) esseva calculate pro le integre curso del periodo del plenamento. Le impedantia exhibi un reduction characteristic durante le prime parte del plenamento, mantene un constant nivele basse durante le periodo intermediari del plenamento, e monta rapidemente durante le ultime parte del plenamento.

Augmentos del hydrostatic pression del plenamento es accompaniante per un reducece impedantia in le phase central del plenamento e un reducete tempore disponibile pro le plenamento quando le impedantia es le plus basse.

Augmentos de pression aortic o de frequentia cardiac es accompaniante per un elevate impedantia in le phase central del plenamento e un reducete tempore disponibile pro le plenamento quando le impedantia es le plus basse.

Le administration de epinephrina o norepinephrina es sequite per un transiente efecto chronotropic e un persistente efecto inotropic. Ambes es accompaniante per un reducece impedantia in le phase central del plenamento e un prolongate tempore disponibile pro le plenamento quando le impedantia es le plus basse.

Alterationes in volume per pulso es apparentemente in stricte relation con alterationes del facilitate e duration del plenamento.

REFERENCES


Statistics and Common Sense

An increasing number of investigators have gained a knowledge of elementary principles and therefore feel impelled to examine every bit of data they obtain. It is therefore healthy to be reminded that statistical analysis is not a wonder tool by which meaningful conclusions can be drawn from faulty experimentation or observation. "Statistical methodology is the application of logic to experimental data, formalized by applied mathematics. They give logical results, if the application is proper. Every procedure should be used with a little common sense and a statistical procedure is no exception."

Statistical techniques are no substitute for good experimental techniques or sound professional judgment. The size of samples required depends on the reliability of the data and on the magnitude of discrepancy tolerated by the problem investigated. Indeed, if the sample is too large, differences of a size that are not pertinent to the problem may be discovered. Common sense must therefore be used in estimating the source and reliability of material and the use to which the results are to be put. Time spent in statistical analysis is wasted if the conclusions are obvious or if discrepancies are not of a size to be of practical importance. The time to consult a statistician is before a research is planned. Statistical knowledge is better adapted to aid in designing experiments than to extract reliable information from questionable data. As stated, "If one sentence could summarize what was said, it would be: Common sense is the best approach to the use of statistical tools."

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