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The Architecture of the Heart in Systole and Diastole

TECHNIQUE OF RAPID FIXATION AND ANALYSIS OF LEFT VENTRICULAR GEOMETRY

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ABSTRACT

Techniques for rapid fixation of the canine left ventricle in systole or diastole that have permitted analysis of ventricular geometry under known hemodynamic conditions are described. Six ventricles were arrested at end diastole, 7 at end ejection, and 7 in diastole following acute ventricular overdistension. The architecture of the ventricles was analyzed from measurements of the fixed ventricles and silicone-rubber casts of the ventricular cavities. In ventricles of matched weights, the average reduction, from end diastole to end ejection, of the apex to mitral valve distance was 4.6%, while that from apex to aortic valve was less than 1%. The minor internal equator was reduced by 26%, the midwall radius by 16%, and the outer radius by 8.5%. The ratio of the average end-diastolic volume minus end-systolic volume to the end-diastolic volume (analogous to stroke volume/end-diastolic volume) averaged 59%. The average wall thickness was 28% greater in systolic than in diastolic ventricles. The papillary muscle volume averaged 5.0% of ventricular volume at end diastole and 14.7% at end systole. The area of the mitral valve orifice averaged 28% less at end systole than at end diastole; this area was 39% more in the hearts subjected to over-transfusion than in those with normal filling pressures. These data provide a framework for construction of a geometric model suitable for use in analyses of the mechanics of left ventricular contraction. Moreover, the methods described offer the possibility of correlating ventricular geometry and ultrastructure with cardiac function in normal and in abnormal hearts.

ADDITIONAL KEY WORDS
dimensions of canine left ventricle
left ventricular volume glutaraldehyde casts of left ventricular cavity
anesthetized dogs

The recent application of the principles of muscle mechanics to the analysis of left ventricular contraction (1-3) has focused at-tention upon the need for detailed information concerning the anatomy of ventricular contraction. At present, many gaps exist in our knowledge of the changes in configuration of the muscular walls, the orientation of muscle fibers and the dimensions of the sarcomeres that occur continuously in the ventricle during the cardiac cycle. Such information is essential to the construction of
appropriate geometric models for application in mechanical analyses of ventricular contraction and also should provide basic insight into correlations between cardiac structure and function in the normal and the abnormal heart. Studies of the external and internal dimensions of the in situ left ventricle by dimension gauges and angiography have provided much important information concerning changes in the shape and volume of the left ventricle during the cardiac cycle, and studies in the isolated papillary muscle and excised left ventricle have investigated relations between sarcomere dimensions, muscle length, and the volume of the passive heart (4, 5). So far, however, there has been no correlative examination of gross anatomy and ultrastructure in the contracting left ventricle under known hemodynamic conditions.

The fixative glutaraldehyde does not produce contracture of isolated heart muscle (4), and this agent, therefore, offered the possibility of realizing this aim in the in situ heart. The present study describes a technique for the rapid fixation of the intact canine left ventricle, under known hemodynamic conditions in systole or diastole, and presents its application to an analysis of the geometry of the ventricular chamber, its muscular walls, and the papillary muscles. The ultrastructure of these ventricles is analyzed in the following article in this issue (7), and the dimensions of their sarcomeres are correlated with the phase of the cardiac cycle under normal conditions of contraction and relaxation, during acute left ventricular dilatation and during premature ventricular contractions.

Methods

Studies were carried out in dogs weighing 17.5 to 26.8 kg (avg 21.3 kg) anesthetized with sodium pentobarbital (30 mg/kg). A left thoracotomy was performed, ventilation with 100% oxygen was provided by a Harvard respiratory pump, and anticoagulation was provided with heparin, 3 mg/kg. Arterial pressure was measured through a catheter inserted into the femoral artery, and left ventricular pressure was measured through a short plastic cannula inserted through the ventricular apex and attached directly to a Statham P23Db transducer. In some experiments, left atrial pressure was measured through a catheter inserted into the left atrium via a segmental pulmonary vein. In most experiments, the sinus node was crushed and the heart rate maintained between 100 and 140 beat/min by electrical stimulation of the right atrium. The pressures and the electrocardiogram were recorded on a direct-writing oscillograph.

The basic objective of the experimental preparation was to achieve rapid fixation of the left ventricles during systole at end ejection, and during diastole at a pressure close to that existing at end diastole. Cannulations of the coronary artery and cardiac fixation were achieved in 46 dogs. However, a number of these experiments were excluded from the present study because of uncertainty concerning the phase of the cardiac cycle during which fixation occurred; in some experiments fixation took place during contraction or relaxation, and in others it occurred during asynchronous contraction or relaxation, the contracted portion of the ventricle being clearly delimited from the remainder. Moreover, in some experiments in which the heart was fixed successfully in diastole, the phase of diastole could not be determined with certainty from the pressure tracing. Therefore, a separate cannulation and fixation technique, described below, was devised to permit reliable determination of the ventricular end-diastolic pressure during diastolic fixations. Several hearts were not included in this study because of an unusually large or small mass of the left ventricle.

Twenty-two ventricles were considered satisfactory for analysis. In each, the phase of the cardiac cycle was identified from the electrocardiogram, the pressure tracings, and the configuration of the ventricular cavity. The category "normal systole" represents those ventricles fixed at or near end ejection; "normal diastole" indicates ventricles fixed at or near the left ventricular end-diastolic pressure (LVEDP) observed immediately prior to fixation; "dilated diastole" includes ventricles fixed at an elevated LVEDP, induced acutely by the infusion of whole blood or dextran or both.

Fixation Methods

Two methods of cannulation were employed, the second being designed specifically for diastolic fixation.

Method 1 (Fig. 1A)

The left coronary artery was perfused through tubing leading from the femoral artery and attached to a modified Gregg cannula. The cannula was inserted via the left subclavian artery and its tip ligated firmly into the origin of the
RAPID FIXATION OF THE LEFT VENTRICLE


Preparations employed for rapid fixation of the canine left ventricle. For description see text.

A laterally placed, Luer-fitting and three-way stopcock was provided on the cannula, and tubing leading from a power syringe$^1$ was attached to this stopcock. A 40-ml syringe barrel was primed first with 35 ml of glutaraldehyde fixative$^2$ and the remaining 5 ml and the connecting tubing were then filled with a solution containing 20 mg/ml of acetylcholine and 2 mEq/ml of potassium chloride. The latter solution was found to reduce the incidence of premature ventricular contractions and ventricular tachycardia at the onset of the power injection. The syringe was programmed to fire at a preset interval following the R wave of the electrocardiogram, the interval being controlled by an electrical delay circuit provided on the power syringe. The delay between the R wave and the onset of the injection was 40 msec, and with a dial setting of 800 lb/in$^2$, the time required for complete delivery of the injectate was approximately 750 msec.

The primed connecting tubing leading from the power syringe was attached to the closed stopcock on the Gregg cannula. Just prior to the fixation the stopcock was opened, and coincident with the injection the coronary arterial perfusion line was clamped proximally to prevent retrograde flow of fixative (Fig. 1A). Immediately after the power injection, an additional 50 ml of glutaraldehyde was injected manually through the sidearm of the cannula. The heart was then excised and immersed in glutaraldehyde 6.25% for 2 to 3 hr, following which it was placed in phosphate buffer (pH 7.4) and refrigerated until sections for electron microscopy were taken. The heart was then permanently stored in 10% buffered formalin.

With this technique, fixation of the left ventricle in late systole was obtained by initiating the injection during the refractory period (Fig. 2). The hearts designated as end-systolic were selected on the basis of completed ejection, as shown by the arterial pressure pulse, failure of ventricular relaxation as reflected in a delayed downslope of the left ventricular pressure pulse, and little or no filling in diastole; that significant diastolic filling of the left ventricle had not occurred was apparent from the contracted state of the ventricle evident from the casts of the cavity (Fig. 5A) and, in particular, from an appropriate intracavitary volume relative to that of diastolic

$^1$Cordis Corporation, Miami, Florida.

$^2$Glutaraldehyde 25% (diluted to 6.25% with phosphate buffer), North-Strong, Inc.

Circulation Research, Vol. XXI, October 1967
ventricles of equal weight, giving a ratio of systolic to end-diastolic volume consistent with complete ejection (Fig. 6). Therefore, while it is clear that fixation was not instantaneous, the evidence is strong that fixation was achieved after ejection and before significant diastolic filling had occurred. Since no significant change in sarcomere lengths would be expected to occur during the isovolumic period after ejection, the sarcomere lengths represent effectively those at end-ejection. In some experiments the right ventricle produced several contractions after fixation of the left ventricle by selective left coronary arterial injection (two such contractions are reflected in the high-sensitivity left ventricular pressure tracing in Fig. 2); however, since these contractions occurred after left ventricular fixation, they did not appear to affect volume of the left ventricle. In a few experiments using method 1, arrest and fixation near end diastole was achieved by initiating the injection in early diastole; however, this approach to diastolic fixation generally proved unreliable and the second preparation was devised.

**Method 2 (Fig. 1B)**

A large-bore (no. 20 French) cannula having end and side holes was inserted via the left subclavian artery into the ascending aorta, and loose tapes were passed around the aortic arch and the brachiocephalic artery. A catheter was inserted into the left atrium for measurement of pressure,
RAPID FIXATION OF THE LEFT VENTRICLE

and a second large-bore catheter (PE no. 200) was also positioned in the left atrium. The latter was attached to a three-way stopcock and was used for adjusting the volume of fluid in the left atrium and left ventricle after cardiac arrest. The catheter positioned in the ascending aorta was attached to the power syringe through a three-way stopcock. A 60-ml syringe barrel and the tubing leading to the three-way stopcock were primed with glutaraldehyde fixative. A 100-ml syringe was then filled with 90 ml of dextran and 10 ml of 25% potassium citrate and attached to the other arm of the stopcock (Fig. 1B).

For diastolic fixation, the potassium-dextran solution was first injected manually as rapidly as possible until the heart was arrested. Partial constriction of the brachiocephalic artery and aorta was performed during this maneuver to facilitate perfusion of the coronary arteries with the arresting solution. At the moment of cardiac arrest, the aorta and brachiocephalic arteries were cross-clamped, and the left atrial pressure was rapidly adjusted by withdrawal or infusion of saline to a level approximating the LVEDP in the beating heart. The power injector was then activated at 800 lb/in². An additional 50 to 100 ml of glutaraldehyde was subsequently infused manually, the heart was excised, and treated as described earlier. With this method the leaflets of the aortic valve must close with the power injection for effective perfusion of the coronary arteries, and both ventricles are arrested and fixed.

METHODS OF MEASUREMENT

After storage in buffered glutaraldehyde solution, the left ventricular cavity was thoroughly washed to rid it of residual blood clots; the great vessels, the atria, and the free wall of the right ventricle and its papillary muscles were dissected away, and the left ventricle was weighed. The intracavitary volume was then determined by filling the left ventricular cavity with water to the level of the annuli of the mitral and aortic valves, and the contained fluid volume was measured in a graduated cylinder. Care was taken to remove air bubbles from beneath the leaflets of the mitral and aortic valves, and the volume was measured several times until reproducible within 1.0 ml. The external circumference of the fixed left ventricle was measured with a string midway between the mitral valve and the ventricular apex.

A cast was made of the cavity of each left ventricle by filling the chamber with liquid, room temperature vulcanizing silicone rubber. Measurements were then made with calipers directly from the hardened rubber casts, as shown diagrammatically in Figure 3, and are represented by the following abbreviations:

- AB = distance from ventricular apex to the base of the aortic leaflets; AM = distance from apex to the mitral annulus; C = circumference at 1/2 AM; X = horizontal diameter at C, avoiding the papillary muscle depression; Y = vertical diameter at C.

Circulation Research, Vol. XXI, October 1967

3A similar solution has been employed previously to arrest the human heart during surgical procedures (6).
OT = plane through outflow tract of the left ventricle; X = horizontal diameter of OT; and Y = vertical diameter of OT.
MV = plane of mitral valve annulus; X = horizontal diameter; and Y = vertical diameter.

The circumference of the cast at plane C was also measured using a string. The thickness of the wall at plane C was taken as the difference between the radii calculated from the measured external circumference of the fixed ventricle and that of the cast. The directly measured radii of the casts were used to compare the X/Y ratio in plane C in systole and diastole. The areas of OT and MV were calculated from the measured diameters, using the formula for area of an ellipse. The volumes of the papillary muscles were determined by filling the depressions left by these muscles in the casts with clay (Fig. 5) and measuring volume of the clay by fluid displacement.

Results
Pertinent hemodynamic data and the information derived from measurements on the 22 left ventricles and their casts are summarized in Table 1. A photograph of a heart arrested and fixed in diastole (method 2) is shown in Figure 4, and views of 3 casts made from ventricles fixed at end diastole, end systole, and at end diastole following infusion are reproduced in Figure 5.

"NORMAL DIASTOLE"
The left ventricular (LV) diastolic pressures at fixation ranged from 2 to 12 mm Hg; these pressures were matched as closely as possible to the LV end-diastolic pressures that existed during previous contractions (Table 1). The left ventricular weights averaged 95.5 g (range 82 to 107 g), and the cavity volumes averaged 51.6 ml (range 40 to 62.1 ml).
Silicone rubber casts of the left ventricular cavities of hearts arrested in systole at end ejection (panel A), “normal end diastole” (panel B), and in diastole, following infusions (panel C). The photographs on the left are views of the left aspect of the casts, the depressions left by the papillary muscles being visible in the center of each cast. The photographs in the middle are views of the apices of the casts. The photographs on the right are views of the right lateral aspect of the casts. Each set of casts is viewed from the same distance and at equal magnification.

The volume occupied by the two papillary muscles averaged 2.2 ml (range 1.2 to 2.7 ml), and averaged 4.3% of the end-diastolic ventricular volumes. The dimensions measured from the casts (Fig. 3) showed a circumference at C averaging 12.6 cm (range 11.2 to 13.5 cm).
Hemodynamic and Geometric Data in the Rapidly Fixed Canine Left Ventricle

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LV pr S/ED = left ventricular pressure, systolic/end-diastolic; Fix pr = pressure at which fixation occurred; C = circumference; Calc = calculated; Meas diam = measured diameter; Ext diam = external diameter; Midw diam = mid-wall diameter; WT = wall thickness; Pap m = papillary muscles; % = percent of ventricular volume. The dimensions AM, AB, OT, MV, X and Y are shown in Figure 3, and are defined in the text. All dimensions are in centimeters, areas in square centimeters.

The external diameter at C of the fixed ventricles averaged 5.67 cm (range 5.14 to 6.18 cm) and the calculated wall thickness at C averaged 0.84 cm (range 0.66 to 1.08 cm).

**NORMAL SYSTOLE**

The end-diastolic pressures prior to fixation ranged from 1 to 9 mm Hg (Table 1). The left ventricular weights averaged 102.4 g (range 90 to 125 g) and the volumes of the left ventricular cavities averaged 20.2 ml (range 17 to 25 ml).

The volume of the two papillary muscles averaged 2.93 ml (range 2.0 to 4.1 ml) and averaged 14.5% of the end-systolic ventricular volume.
RAPID FIXATION OF THE LEFT VENTRICLE

Measurements of the casts showed a circumference at C averaging 8.8 cm (range 8.2 to 10.1 cm) and the calculated diameter at C averaged 2.80 cm (range 2.62 to 3.22 cm). AM averaged 5.29 cm (range 4.7 to 6.0 cm) and AB averaged 6.4 cm (range 5.8 to 6.7 cm). The area of OT averaged 1.36 cm² (range 0.92 to 1.74 cm²) and the MV area averaged 3.71 cm² (range 2.94 to 4.91 cm²).

The external diameter at C of the fixed ventricles averaged 5.18 cm (range 4.94 to 5.32 cm), and the calculated wall thickness at C averaged 1.19 cm (range 1.07 to 1.28 cm).

**Comparison Between "Normal End Diastole" and "Normal End Systole"**

For these comparisons, ventricles of precisely matched weights were selected, those in diastole ranging from 101 to 107 g (experiments 41, 42, and 46) and those in systole ranging from 103 to 108 g (experiments 6, 22, and 24). With the exception of the change in calculated wall thickness, however, the average percent change from diastole to systole in dimensions and volumes of these selected ventricles differed little from those for the entire group of "normal" hearts (Table 1).

The average change in left ventricular volume from the diastole (48.5 ml) to the end systole (20.7 ml) was 31.0 ml, and the ratio of this change to the end-diastolic volume (analogous to the stroke volume to end-diastolic volume ratio) was 59.9%.

In comparing hearts fixed at end diastole
with those fixed at end systole, the internal circumference at C decreased from an average of 12.3 to 9.0 cm; the external diameter at C (Fig. 3) decreased by an average of 0.50 cm (average decrease 8.5%), the midwall diameter by 0.76 cm (average decrease 16%), and the internal diameter at C decreased by 1.03 cm (average decrease 26%). The calculated wall thickness at C increased from an average value of 0.96 cm at end diastole to an average of 1.23 cm at end systole, the increase in wall thickness at C, therefore, averaging 28% of the end-diastolic value.

The distance AM decreased by 0.27 cm (average decrease 4.6%) while the distance AB diminished by only 0.04 cm (average decrease 0.7%). The ratio of the major ventricular axis AM to the minor axis C averaged 1.49 in the diastolic hearts and 1.93 in systolic hearts, reflecting the relatively greater extent of shortening in the minor axis. The ratio of the two measured diameters at C (X and Y, Fig. 4) was 0.91 at end diastole and 0.99 at end systole. The difference between these two ratios was not significant statistically.

The area of the outflow tract decreased by
RAPID FIXATION OF THE LEFT VENTRICLE

0.68 cm² from end diastole to end systole, an average reduction of 30.8%. The area of the mitral valve diminished by 1.40 cm², an average decrease of 28%. The volume of the two papillary muscles averaged 5.0% of the end-diastolic ventricular volume, and 14.7% of the end-systolic ventricular volume.

These comparisons between the end-diastolic and end-systolic ventricles of matched weights are summarized in Figure 6.

DILATED DIASTOLE

In the ventricles acutely overdistended by infusions, the end-diastolic pressures immediately prior to fixation ranged from 20 to 40 mm Hg; at the time of fixation they ranged from 24 to 40 mm Hg (Table 1). The left ventricular weights averaged 108.3 g and the left ventricular volumes averaged 72.1 ml (range 54.8 to 83 ml). A cast obtained in a dilated ventricle is shown in Figure 5C.

The dimensions at C, AM, and AB were larger than at normal end diastole (Table 1). The average wall thickness at C was slightly less than that at normal end diastole, averaging 0.79 cm (range 0.67 to 0.59 cm). The average area of the outflow tract was the same as that in the normal diastolic hearts, while the area of the mitral valve was considerably larger, averaging 6.73 cm², an average increase of 31%. (Table 1). With acute distension of the ventricle, the circular shape of the ventricular cavity in plane C was not preserved, the X/Y ratios averaging 0.77 (range 0.73 to 0.84), compared with an average value of 0.91 at normal end diastole.

Discussion

The methods described for rapid fixation of the canine left ventricle in systole or diastole have permitted an analysis of the geometry of the ventricular cavity and wall under known hemodynamic conditions. Information gained by the use of these direct measurements and from other, dynamic techniques, should allow the development of appropriate geometrical models for application in analyses of the mechanical properties of ventricular contraction. Changes in ventricular shape, volume, and wall thickness require a continuously variable model which, when correlated with pressure and flow determinations, should eventually permit precise calculation of stress distribution and fiber shortening throughout the cardiac cycle.

It is apparent from the pressure tracings reproduced in Figure 2 that truly instantaneous fixation of the heart is not achieved with the present techniques. Nevertheless, arrest and fixation at a controlled diastolic pressure can readily be accomplished with method 2, and systolic fixation can be obtained using method 1. Thus, it was found empirically that by programming the injection to commence during the QRS complex of the electrocardiogram, the left ventricle usually failed to relax after ejection, and the yield of ventricles fixed at end ejection proved adequate. Verification that fixation was completed by end systole was shown by complete ejection on the arterial pressure pulse, a delayed downslope of the ventricular pressure tracing, and a systolic configuration and volume of the cast of the ventricular cavity. The rapid pressure-injection technique does not appear to damage the myocardium, as evidenced by the well preserved ultrastructure (7).

The comparison between left ventricles arrested at end diastole and those arrested at end systole supports the conclusion that the ventricles were actually fixed at these phases of the cardiac cycle. Thus, the average changes in ventricular dimensions resemble those which occur in the intact, beating heart analyzed by means of dimension gauges or angiography (8-10), the apex to mitral annulus distance (AM) at end ejection being shorter than that at end diastole by 5%, the internal diameter at plane C being reduced by 26%, the midwall diameter diminished by 16%, and the outer diameter by 8.5%. It is of interest that whereas AM diminished by nearly 5%, there was little change in the distance from apex to the base of the aortic valve (AB), perhaps reflecting lack of shortening, or probably an actual lengthening of the outflow tract region accompanying ejection (see Fig. 5). The average ratio of the difference between the end-diastolic and the end-systolic vol-
umes averaged 59%, a value comparable to the stroke volume to end-diastolic volume ratios determined by angiographic methods (10), although somewhat higher than those obtained with the indicator-dilution technique (11, 12). The X-Y ratio in plane C was near unity in the normal diastolic and systolic hearts and provides experimental support for the technique used by Fry et al. (1), and recently applied in this laboratory in human subjects, in which a slice of muscle in the minor ventricular axis was treated as a cylinder. It is of interest that during acute overdistension of the ventricle this minor axis did not remain circular, but expanded more in the vertical direction than the horizontal (Fig. 5C), the X-Y ratio therefore being considerably reduced. Preliminary findings indicate, however, that in chronically overdistended hearts, this plane again assumes a circular shape.

The areas of the LV outflow tract and the mitral valve orifices were substantially lower at end systole than at end diastole (Fig. 6). Angiographic measurements have indicated that the outflow tract is at its widest during early systole (13), and therefore, it may be surmised from the present study that progressive narrowing of this region occurs throughout ejection. Whether the sizeable reduction of the area of the mitral valve orifice from end diastole to end systole, presumably due to contraction of the ventricular muscle adjacent to the annulus, is of importance in maintaining closure of the mitral valve throughout ventricular ejection is uncertain. With acute distension of the heart, there was a further (30%) increase in the area of the mitral valve orifice over that of the normal diastolic hearts, a factor that would clearly favor the development of mitral regurgitation.

Further studies will be undertaken on these ventricles to study the important problem of changes in muscle fiber orientation and distribution that occur across the ventricular wall during diastole and systole. The present methods are potentially applicable to the study of experimental cardiac disease, and they should permit comparisons between the geometrical and ultrastructural characteristics and the functional states of normal and abnormal hearts.

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RAPID FIXATION OF THE LEFT VENTRICLE


The Architecture of the Heart in Systole and Diastole: Technique Of Rapid Fixation And Analysis Of Left Ventricular Geometry

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