Effect of Inotropic Agents on Distensibility of the Isolated Cat Heart (36132)

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(Introduced by S. Solomon)
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Previous studies have indicated that diastolic pressure–volume or initial length–tension relationships of mammalian cardiac muscle can be altered by inotropic influences such as paired stimulation, catecholamines, digitalis, and calcium (1–3). Such inotropic intervention results in lowering of the end-diastolic or initial tension, suggesting an increase in compliance or distensibility.

The mechanism and significance of these changes have been disputed. Sonnenblick *et al.* (2) have indicated that positive inotropic interventions do not induce a change in initial length–tension relationships of heart muscle unless they result in increased systolic force. They propose that when force of contraction is augmented, elongation of a series viscous component results in reduction of initial tension at any given initial muscle length (2).

Hoffman *et al.* (3) have presented data to show that changes in compliance may result from alterations in extensibility of the contractile element and are not dependent on increased active tension developed by the preceding contraction.

In a previous study, we observed that intraventricular pressure of fibrillating hearts was lowered by epinephrine in spite of the absence of phasic contraction and relaxation cycles (1). If the nonbeating heart exhibited changes in compliance similar to those seen in the beating heart, it would suggest that such changes were not related to increased contractile force. The present study was designed to test this hypothesis.

Methods. Isolated cat hearts, perfused by a modified Langendorff technique were arranged for isovolumetric pressure recording with a balloon in the left ventricle as previously described (1). The hearts were perfused with modified Locke–Ringer solution (4) to which 1.2% dextran was added to prevent cardiac edema (5).

Two glass tubes were inserted into a stopper in the mouth of the perfusion reservoir. To one of these, a gas dispersion tube was attached for oxygenation of the perfusion fluid. The other tube was connected to the side arm of a U-tube mercury manometer, the open end of which was fitted with a small rubber tube. A screw clamp on the rubber tube allowed for a constant pressure leak so that the pressure in the reservoir could be controlled. Two such reservoirs connected by a Y-tube to the perfusion apparatus allowed for rapid changing of perfusion fluid so that the heart could be alternately perfused with control solution or with solution containing inotropic agents.

Systolic and diastolic pressures were recorded at different sensitivities by means of Sanborn Model 1280 transducers connected to a Sanborn direct writing recorder. The hearts were allowed to beat spontaneously, were stimulated with an American Electronics stimulator (Model 104A) by means of an electrode catheter inserted into the right ventricle, were arrested or were put into ventricular fibrillation according to the design of the particular experiment.

Anoxic arrest was induced by allowing the cannulated heart to remain nonperfused until it stopped beating. It was then perfused with unoxygenated perfusion fluid, perfusion

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pressure being maintained by administration of compressed air into the perfusion reservoir. Hearts were put into ventricular fibrillation by stimulating at a rate of 5 to 10 cps.

Fluid was injected into, and withdrawn from, the balloon by means of a constant-speed injection pump (Sage), while pressures were continuously recorded. Injection time varied from 15 to 40 sec depending on the volume injected.

Pressure–volume curves were recorded during perfusion with Locke–Ringer solution with, and without, added epinephrine or norepinephrine. After determining the rate of flow of the perfusate these agents were added to the reservoirs in sufficient amounts to perfuse the heart with 0.5–1 μg of epinephrine or norepinephrine/min. For the ouabain experiments, 0.125 mg of ouabain was injected into the aortic cannula allowing the ouabain to directly enter the coronary arteries.

Results. A. Beating heart. As previously noted, positive inotropic agents caused a lowering of the end-diastolic pressure (1). In all cases, this was associated with increased systolic pressure.

Figure 1 shows changes in systolic and diastolic pressures after the addition of ouabain, without change in intraventricular volume. Associated with the increasing inotropic effect of the ouabain, as indicated by the increasing systolic pressure, there was a lowering of the end-diastolic pressure.

In Fig. 2, are pressure–volume curves of a perfused beating heart before, and after, administration of ouabain. Ouabain, as noted in Fig. 1, resulted in increased systolic and decreased diastolic pressure with the same initial volume. Addition of identical volume to the balloon before and after ouabain resulted in increasing systolic and diastolic pressure. The diastolic pressure remained lower, and the systolic pressure higher in the ouabain-treated heart, suggesting increased distensibility or compliance, as well as increased contractility. Similar results were noted with epinephrine and norepinephrine.

B. Arrested heart. Figure 3 shows pressure–volume relationships in the arrested heart perfused without, and with, epinephrine. The pressure–volume and stress relaxation curves are essentially parallel, indicating no difference in ventricular compliance or distensibility.

C. Ventricular fibrillation. Figure 4 depicts a similar experiment on a fibrillating heart. Again, it was noted that there was no significant difference in the slope of the pressure–volume or stress–relaxation curves in the presence or absence of epinephrine.

Pressure–volume relationships of the arrested and fibrillating hearts were analyzed statistically. The pressure–volume relation-

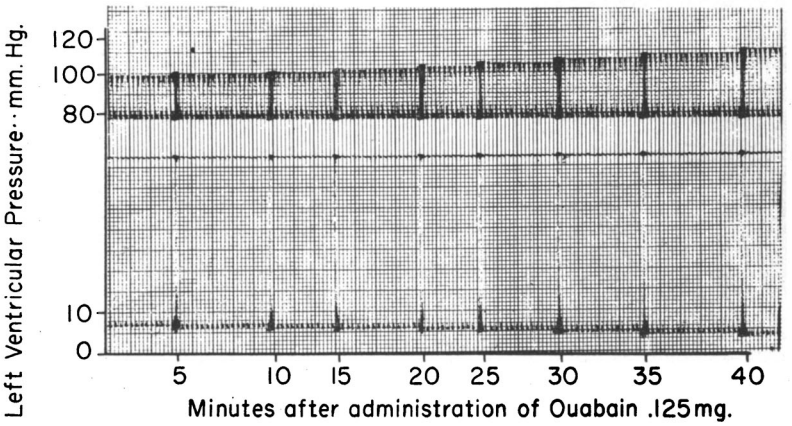

FIG. 1. Increased systolic and decreased diastolic pressure following administration of ouabain to the beating isovolumetric heart: volume of fluid in balloon constant. Pressure recorded at 2.5 mm/sec every 5 min for 40 min after administration of ouabain (0.125 mg) directly into the aortic cannula; (upper channel) systolic pressure; (lower channel) diastolic pressure.

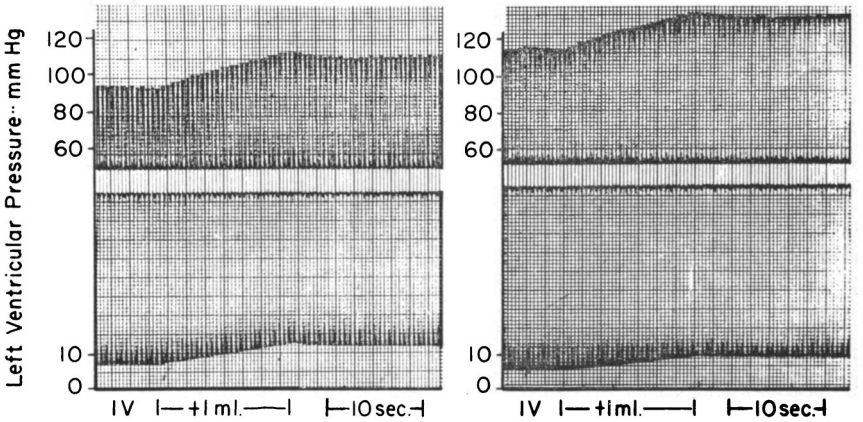

FIG. 2. Pressure–volume relations of beating heart before (left panel); and after (right panel) administration of ouabain (0.125 mg) directly into the aortic cannula. Initial volumes (IV) identical. Rise in pressure in each case produced by addition of 1 ml of fluid to balloon in left ventricle. Following ouabain administration, systolic pressure was consistently higher and diastolic pressure was lower; (upper channel) systolic pressure; (lower channel) diastolic pressure. Paper speed, 2.5 mm/sec.

ships illustrated in Figs. 3 and 4 were each approximated with a linear regression equation determined by the method of least squares. Using a modified analysis of covariance, an F test fror parallelism of the regression equation slopes was made. Results of this analysis and the tests for each experiment (Table I) show no significant difference in the slopes of the regression equations within an experiment, indicating that the inotropic agents used did not alter distensibility.

To further clarify the statistical procedures, the following explanation is offered. The hypothesis that no differences exist between the slopes within an experiment was tested. This hypothesis is equivalent to parallelism of the slopes within an experiment. The variance ratio of F test was used to test the hypothesis. The probability of an F statistic as large or larger than the observed F is given immediately below each observed F in Table I. When this probability is small (less than 0.01), the null hypothesis of no differences should be rejected and differences between the slopes assumed. When this probability is large (greater than 0.05), it is unlikely that the null hypothesis should be rejected. In Table I, all probabilities were

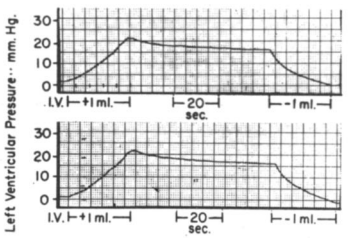

FIG. 3. Pressure–volume relationships of arrested heart without (upper panel); and with (lower panel) epinephrine in perfusion fluid: Epinephrine administered at rate of 0.5 μg/min. Initial volume identical. Recording shows increase in presssure caused by addition of 1 ml of fluid to balloon, stress relaxation at constant volume, and decrease in pressure with removal of fluid. There is no apparent difference in the curves. Paper speed, 1 mm/sec.

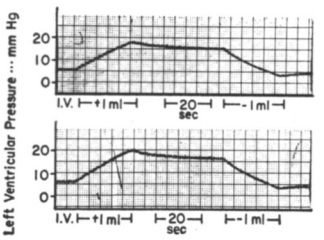

FIG. 4. Pressure–volume relationships of fibrillating heart without (upper panel); and with (lower panel) epinephrine in perfusion fluid: Epinephrine administered at a rate of 0.5 μg/min. As in Fig. 3, recording shows increase in pressure caused by addition of 1 ml of fluid to balloon, stress relaxation at constant volume, and decrease in pressure with removal of fluid. No apparent difference in curves. Paper speed, 1 mm/sec.

TABLE I. Pressure–Volume Slopes (mm Hg/ml) with Tests for Homogeneity.[a]

Expt.:	1 (VF)	2 (AA)	3 (VF)	4 (VF)	5 (AA)	6 (VF)	7 (AA)	8 (VF)	9 (VF)
	C 35.6	C 26.6	C 19.4	C 44.9	C 27.4	E 14.3	C 13.1	E 12.7	NE 10.5
	C 35.2	C 26.0	C 19.1	C 43.7	C 29.3	E 13.9	C 13.1	E 12.4	NE 10.8
	C 41.3	E 29.4	C 17.6	C 40.0	C 29.8	C 13.1	E 14.3	C 13.1	C 10.0
	C 37.7	E 28.4	E 17.4	C 35.0	E 29.6	C 13.1	E 15.0	C 13.1	C 10.2
	E 38.5	C 24.6	E 19.3	C 39.1	E 28.5			E 13.1	NE 10.8
	E 36.6	C 27.6	C 19.3	E 43.4	E 29.5				
	E 37.6			E 43.0	C 29.7				
	E 35.8			E 45.1	C 27.5				
				C 45.3					
				C 46.4					
Observed	F 2.57	2.29	2.59	1.14	2.50	1.01	2.14	0.561	0.466
Prob. of larger	F 0.034	0.082	0.056	0.36	0.05	0.42	0.14	0.70	0.76

[a] C = control solution; E = epinephrine (0.5–1 μg/min); NE = norepinephrine (0.5–1 μg/min); VF = ventricular fibrillation; and AA = anoxic arrest.

greater than 0.05 except for Expt. 1. We therefore conclude that the regression slopes are parallel within experiments.

Discussion. The present data confirm previous observations that in the contracting isovolumetric heart administration of inotropic agents results in lowered end-diastolic pressure, as well as increased contractile force (1, 2).

In the arrested or fibrillating heart, similar inotropic intervention had no significant effect on pressure–volume relationships. Although arrested and fibrillating hearts are "unphysiologic preparations," they exhibited pressure–volume and stress–relaxation curves similar in appearance to diastolic pressure–volume curves of the contracting heart. Thus, it is thought that if inotropic agents had a specific effect on myocardial distensibility, it would be apparent in this preparation.

The relationship between diastolic filling and contractile force of the heart determined by Starling (6) has been studied by many investigators (7–10). While it is agreed that the heart responds to increased filling pressure by increased stroke work, it has been shown that in the intact organism the interplay of neural and humoral factors may mask or override the Starling effect.

Studies of ventricular relaxation have established that it is not entirely a passive process and that filling pressure and filling time are not the only determinants of diastolic volume. The evidence for a "diastolic suction" effect has been reviewed by Brecher (11); and Rushmer *et al.* (12) suggested that the potential energy stored as interfascicular tension during systole is released during diastole to facilitate ventricular filling. Wiggers (13) suggested that diastolic volume could be increased by increasing initial pressure, thus overcoming the tendency of the ventricles to resist stretch, or by reducing the power of the ventricle to resist stretch. The latter effect would indicate a decrease in cardiac tone or increased distensibility. He presented evidence that epinephrine increased the speed of ventricular contraction and relaxation, the latter effect resulting in more complete diastolic relaxation with a greater volume in the presence of lower initial tension.

Sarnoff and Berglund (8) and Mitchell *et al.* (14) plotted mean atrial pressure against stroke work of the homolateral ventricle under various conditions such as sympathetic stimulation, severe anemia, and reduced coronary flow. They demonstrated a series of Starling or ventricular function curves showing that, for any given circulatory state, there is a consistent relationship between atrial pressure and ventricular stroke work. However, they were unable to demonstrate changes in ventricular distensibility.

Rushmer (7), recording simultaneous cardiac pressure–circumference relationships in dogs, found that during epinephrine stimulation increased diastolic circumference was associated with a fall in diastolic pressure. He attributed this to a change in myocardial distensibility.

Thus, it would seem that diastolic filling might be affected by changes in rate of relaxation and altered distensibility. Since the distensibility behavior of biological tissues is related to visco-elastic and plastic characteristics (15), alteration in these characteristics could influence ventricular filling in the time available for diastole.

Changes in ventricular distensibility associated with chronic disease have been noted. Decreased distensibility of the left ventricle has been observed in severe obesity, aortic stenosis, and obstructive cardiomyopathy (16–18). This has been attributed to increased stiffness due to marked ventricular hypertrophy.

Other patients with left ventricular disease and left ventricular enlargement have been found to have normal resting pulmonary arterial and wedge pressures, suggesting increased distensibility due to a change in elastic properties of the ventricle (19).

Whether physiologic changes in myocardial compliance occur remains open to question. If such were the case, it would influence cardiac function. Changes in diastolic compliance would alter diastolic filling at any given filling pressure, and if such changes were related to alteration in length of the contractile element, would also affect contractile force and stroke output.

Although the exact mechanism of alteration of end-diastolic pressure in the contracting isovolumetric heart remains to be clarified, these studies support the premise that such alterations are related to change in contractile force.

Summary. Pressure–volume studies of the effect of inotropic agents on distensibility of the isolated cat heart are reported. In the beating heart, increased systolic pressure produced by these agents was associated with lowering of the end-diastolic pressure.

In the nonbeating heart, administration of inotropic agents did not result in any change in pressure–volume relationships. These results suggest that the changes in end-diastolic pressure noted in the beating heart were related to increased contractile force.

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