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Effects of Filling Pressure, Outflow Resistance, Heart Rate and Coronary Perfusion on Ventricular Compliance.* (31167)

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In relating the Starling law of the heart to cardiac performance the end diastolic pressure is often used in place of the diastolic volume of the ventricle. The assumption is made that the pressure-volume relationship of the ventricle remains constant, despite experimental manipulation, so that a given filling pressure will induce the same amount of stretch of the myocardial fibers in each situation examined. This assumption has been questioned in the past and cases in which end diastolic pressure and diastolic volume varied independently from each other have been presented(1,2). Changes in diastolic compliance have been described during post-extrasystolic potentiation in the isolated isovolumic right ventricle(3). Moreover, a change in stroke volume may take place at a constant filling pressure(4). Such a change in cardiac performance could be due to changes in cardiac contractility(5) or to an altered metabolic state(6). Another explanation could be found however in a change of the distensibility or compliance of the ventricle, such that a different diastolic volume would occur at the same end diastolic pressure.

The experiments to be reported were designed to determine whether the pressure-volume relationship of the heart is indeed constant over a physiological range of conditions, and to study in some detail some of the parameters which influence it.

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Methods. Mongrel dogs (20-30 kg) are anesthetized with Nembutal (30 mg/kg i.v.). The procedure for the isolation and metabolical support of the heart has been previously described in detail(6). Briefly, the aorta is cannulated and the coronary arteries are perfused with whole blood, under conditions of either constant pressure or constant flow. The coronary venous blood and the left ventricular thebesian flow drain in a gravimetric flowmeter. After the heart is isolated and put on a tray, complete heart block is induced by ligating the His bundle through a small right atrial incision. The ventricular rate is then controlled by a stimulator.

The left atrium is widely opened and a latex balloon inserted into the left ventricle and secured in place by suturing the mitral valve around an attached plastic collar.

The balloon is filled with saline solution to achieve any desired ventricular volume, and is connected *via* a valve system to a specially designed plethysmograph. The instrument consists of a vertical lucite tube (A) (I.D. 6 cm) which is half filled with saline (Fig. 1). Two stainless steel wires are immersed into the solution and connected to the variable arm of a Wheatstone bridge (B). The pumping action of the heart on the fluid filled balloon will alternately increase and decrease the level of the solution in the tube, thus changing the resistance between the wires and unbalancing the bridge. This change

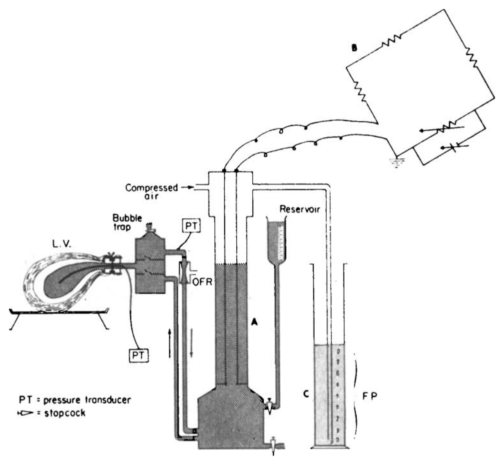

FIG. 1. Heart plethysmograph. (For explanations see text).

of resistance is linear with the change in height of the solution, so that systolic, diastolic and stroke volume can be measured. Changes in diastolic volume of the heart are reflected in a shift of the record baseline. Compressed air is continuously blown into the tube and allowed to escape through a water column (C), whose height determines the pressure inside A, fixing the filling pressure of the heart (FP). The outflow resistance (OFR) is regulated by a Starling resistor located on the outflow line.

Calculation of the left ventricular diastolic compliance. From a fast speed record (50-100 mm/sec) of the ventricular volume curve the point at the end of diastole is identified where the heart is neither filling nor ejecting. The intraventricular pressure is measured at the same instant. The compliance of the ventricle is calculated as the ratio ventricular volume/ventricular pressure at that point (ml/mm Hg).

Results. The diastolic compliance was calculated under the following conditions: a) changes of outflow resistance (OFR); b) changes of filling pressure (FP); c) changes of heart rate (HR); d) changes of coronary perfusion pressure (PP). Each one of these parameters was changed independently while the others were kept constant. Fig. 2 shows the results of the 2 typical experiments and the pooled data are presented in Table I.

Effect of increasing OFR. The OFR was increased in successive steps in 24 experiments. In 17 cases there was a decrease in diastolic compliance. However, in 4 instances a diphasic pattern (increase followed by a decrease when OFR was further increased) was observed. No change was observed in 2 cases while the compliance increased in one experiment.

Effect of increasing FP. An increase of FP induced a decrease of compliance in 17 cases

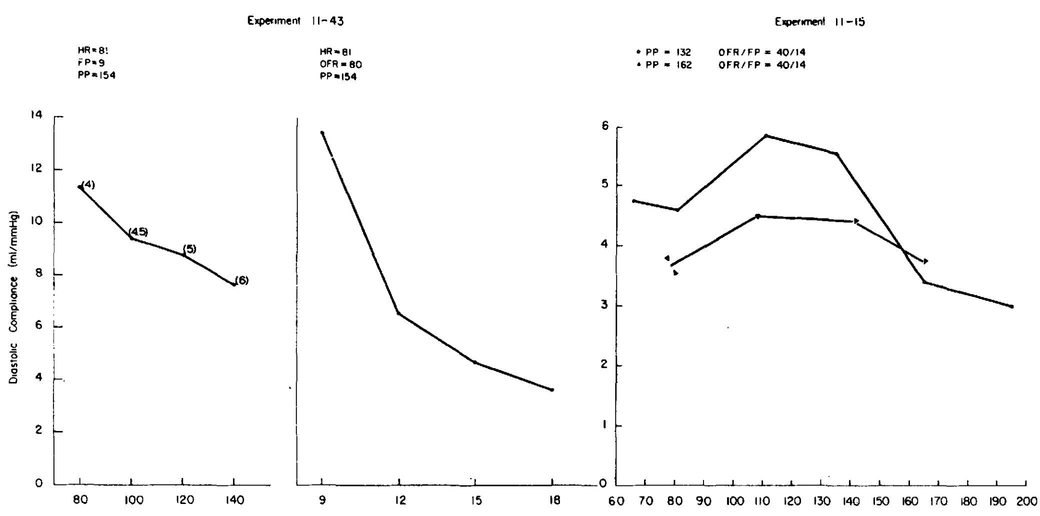

FIG. 2. Effect of increasing OFR, FP, HR, and coronary PP on diastolic compliance. Numbers in brackets represent values of left ventricular end diastolic pressure.

TABLE I.

Experimental changes	No. of exp.	Changes of compliance: Decrease	Increase	Diphasic pattern	No change
Increase of OFR	24	17	1	4	2
" " FP	23	17	5		1
" " HR	12		7	5	
" " PP	8	5	2		1

and an increase in 5. No change was observed in one instance.

Effect of changing HR. The diastolic compliance was measured in 12 runs while the heart rate was increased. In 7 cases there was a clear increase and in 5 instances a diphasic pattern was observed. In the latter cases the compliance increased in the different hearts up to a heart rate of 120-150 and then decreased when the HR was increased further. It should be noted, however, that in those cases in which only an increase of compliance was observed the heart rate had not been increased above 150 beats/min, so that it cannot be excluded that even in these hearts a decrease of compliance could have been observed at higher rates.

Effect of increasing coronary PP. When the PP was increased in 8 instances the diastolic compliance decreased slightly in 5 cases, increased in 2 and did not change in one.

Discussion. The study of the possible changes of ventricular compliance under different physiological conditions has been difficult in the past because the cardiometers used recorded the sum of the volumes of the 2 ventricles and did not allow measurement of absolute volumes but only detection of volume changes. An improvement was achieved in the experiments where one ventricular circumference or diameter was measured(2,7). These techniques, however, offer only a partial view of the parameter under examination, namely, the volume of the ventricle. The advantage presented by the plethysmograph used in the present experiments is that one is able to measure the volume of the left ventricular cavity alone in absolute values, and to control the coronary perfusion independently from the work demands imposed on the heart.

The procedure used in these experiments to calculate the left ventricular compliance deserves comment. In the measurement of the intraventricular pressure the values obtained represent a parameter which is continuously changing not only in time but also in the different sections of the ventricular cavity, so long as fluid is moving, being accelerated and changing direction in the cavity itself. For this reason, in order to obtain values which can be compared in different dynamic situations, the compliance is calculated at the instant when there is zero flow. The data so obtained represent the static pressure-volume relationship of the ventricular cavity, since the influences of the movement and acceleration of the fluid and/or of the ventricle as a whole are eliminated.

From the data presented in Table I it is evident that the ventricular diastolic compliance varies in the great majority of cases under the imposed changes in experimental conditions. Thus when either OFR or FP are increased there is in most experiments a clear decrease of the diastolic compliance, which means that the end diastolic pressure increases disproportionately more than the diastolic volume. That this is the case when FP is increased could have been expected from the non-rectilinear shape of the classical diastolic pressure-volume curve. The same direction of change is seen when the resistance to ejection (OFR) is increased while FP is maintained constant.

The decrease of compliance observed when coronary PP is elevated is in all cases small and may be related either to the stiffening of the intramyocardial vessels under the effect of the increased pressure or to an altered metabolic state influencing the myocardium itself.

The increased compliance observed in 5 cases when the heart rate was increased agrees with observations on the frog heart(8). It was found that the dilatation of the frog ventricle induced by an increase of OFR, at constant FP, was greater at higher heart rates, which would imply an increase of diastolic compliance. An inverse relation can usually be found between diastolic compliance and volume with most of the changed conditions experimentally imposed on these hearts. If the ventricle behaves according to the Laplace equation ($PR = 2T$), an increase of its radius (and of its volume) should bring about an increase of the wall tension. This could explain the diminished compliance observed when the ventricular volume is increased under the effect of an elevation of either FP or OFR. This inverse relation does not appear to hold when a change in ventricular volume is brought about by a change in heart rate, at constant FP or OFR. This observation suggests that some factor other than a mechanical effect influences the ventricular compliance in these circumstances. Alterations in elastic modulus due to chemical metabolic changes appear to occur.

Summary. The compliance of the isolated working heart is not constant but varies when physiological parameters are changed. The obvious corollary of this observation is that end diastolic pressure values are not always reliable indices of the diastolic ventricular volume, because the amount of stretch induced by a given filling pressure may be widely different in different conditions of performance. This fact should be kept in mind whenever one is to interpret ventricular function curves.

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Effect of Concomitant Treatment by Cortisone and N-Ethylisatin β-Thiosemicarbazone on Neurovaccinia Virus Infected Mice. (31168)

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N-ethylisatin β-thiosemicarbazone (NEITC) was reported as the most active of a series of related compounds which protected mice against a lethal neurovaccinia virus infection(1). Although NEITC was shown to markedly reduce the formation of elementary or inclusion bodies in mouse brain infected with vaccinia virus, the drug did not suppress the inflammatory response in the meninges(2). In this connection, certain forms of herpetic keratitis were reported to respond to the administration of pyrimidine nucleosides and corticosteroids(3-6). Therefore it was of interest to study the effect of concomitant therapy of NEITC and an anti-inflammatory steroid, cortisone, in vaccinial meningoencephalitis. The results of a preliminary study(7), are presented here.

Materials and methods. Viruses. The passage history of the WR strain of vaccinia virus and vesicular stomatitis virus (VSV) has been described(2). Vaccinia virus was used as the eighth to tenth passage on the chorioallantoic membrane (CAM) of 12-day-old chick embryos to produce 10% stock pools having an LD_{50} mouse brain titer between $10^{6.5}$ to $10^{7.5}$/0.03 ml. VSV was used as the fifth or sixth passage in chick fibroblast tissue cultures to produce stock pools having a plaque-forming unit (PFU) titer of