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The Influence of Drug-Induced Alterations in the Pressor-Inotropic State on Left Ventricular Dynamics (39132)[1]

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The dynamic performance of the intact ventricle is regulated on a beat to beat basis by at least three major factors (1). Three factors must be considered when attempting to assess the total influence of drug administration or other interventions on ventricular performance: (i) load, which is a function of pressure and ventricular size; (ii) contractile state; and (iii) heart rate.

Isolated muscle preparations lend themselves to accurate control and measurement of these variables. Load can be set precisely by adding known weights to the muscle and then dividing this weight by the cross-sectional area of the muscle to provide some estimate of stress on the individual fiber (2). Likewise, the contractile state can be evaluated with tension and displacement transducers while holding the load constant (3). Frequency of contraction is governed rather easily with a stimulator. On the other hand, while determining rate in the intact heart is simple, the determination of loading conditions and the inotropic state, especially on a beat-to-beat basis, becomes more complex. Load in the intact ventricle is the hydraulic force acting against the contractile forces. This hydraulic force is determined by the pressure within the ventricle and the area over which this pressure acts (4). A cross section of the left ventricle through the long axis describes a nearly circular area. Therefore, the load on the ventricle can be estimated as a function of the product of the ventricular pressure and the square of the radius (5). Evaluation of ventricular loading conditions, then, requires simultaneous measurement of pressure and radius or direct measurement of force in the ventricular wall throughout the cardiac cycle.

Ventricular loading conditions are matched by developed tension. Acute changes in contractile tension developed in the ventricular wall are a function of two components: (i) a fiber length-dependent phenomenon (Frank–Starling effect) and (ii) the inotropic state of the muscle, a length-independent phenomenon. Tension developed, by either or both of these two mechanisms, must match and momentarily exceed the load placed on the ventricle in order for ejection to take place.

The inotropic state of the intact ventricle is most frequently evaluated either with some contractile element velocity index, usually derived from pressure measurements such as (dP/dT/kP (6)), or with some tension index such as the Walton–Brodie strain gauge arch (7). Both of these indices of the contractile state are thought to be relatively free from the influence of loading conditions.

In most reported investigations of the cardiovascular action of drugs, the inotropic, chronotropic, and pressor effects of the drug are usually examined. How these effects alter the relationship between load on the heart and the contractile state is seldom considered. Therefore, the purpose of this present investigation is to examine the influence of commonly used sympathomimetic drugs on the relationship between ventricular load and developed tension.

Methods. Thirty-two mongrel dogs weighing 10–31 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg). The animals were ventilated with room air delivered by a positive pressure respirator with a stroke volume of 20/ml/kg and a rate of 12–16 breaths/min. Aortic pressure (AP) was measured with a Statham P23dB transducer connected to a catheter passed from the femoral artery to a level near the apex of the heart. The femoral vein was cannulated

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for drug infusions. The chest was entered through the fifth intercostal space and the pericardium was opened and sutured to the chest wall. Left ventricular pressure (LVP) was measured with a Statham 23dB pressure transducer connected to a stiff nylon cannula passed through the apical dimple. Bilateral vagotomy was performed through an incision in the neck.

Three strain gauge arches were sutured to the left ventricle to measure changes in inotropism, ventricular load (mural force), and heart size: (i) Contractile force (CF), an index of inotropism, was measured with a Walton–Brodie arch. (ii) Mural force (MF) was measured with a Hefner arch (5). This arch provides a measure of the hydraulic forces acting against the ventricular wall and this measurement is independent of the shape of the ventricular cavity, thickness of the ventricular wall, the distribution of forces exerted by the individual muscle fibers, the orientation of muscle bundles, or the presence of shearing forces. This force is determined only by the pressure and the cross-sectional area of the cavity, and has been shown to correlate with the product of pressure (LVP) and the square of the cross-sectional radius of the cavity. (iii) Changes in length of an epicardial muscle segment (MSL) were determined with an isotonic strain gauge arch and used as an index of ventricular size changes (8).

Drugs were selected to produce varied alterations in inotropism and/or pressure and thereby produce alterations in the relationship between the contractile state of the ventricle and the load on the ventricle. Drugs were infused at a constant rate and all measurements were made during the steady state of the drug response. Drugs administered and infusion rates were as follows: phenylepherine (Phe), 10 μg/kg/min; norepinephrine (NE), 1 μg/kg/min; isoproterenol (ISO), 1 μg/kg/min. Additionally, the NE administration was repeated following α-adrenergic blockade with phentolamine (0.5 mg/kg).

Results. Figures 1–4 show typical responses to the drugs infused. Table I summarizes the steady-state responses of the recorded parameters to the infused drugs.

As shown in Fig. 1 and Table I, Phe, a classic vasopressor drug, produced a significant increase in diastolic AP, LVP, and MSL. These changes were reflected by a significant increase in MF, which was not

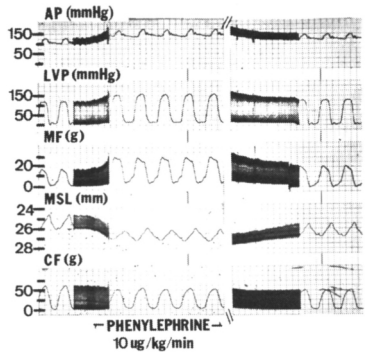

FIG. 1. Typical response of the recorded parameters to the infusion of phenylepherine (10 μg/kg/min). AP, aortic pressure; LVP, left ventricular pressure; MF, mural force; MSL, muscle segment length; CF, contractile force.

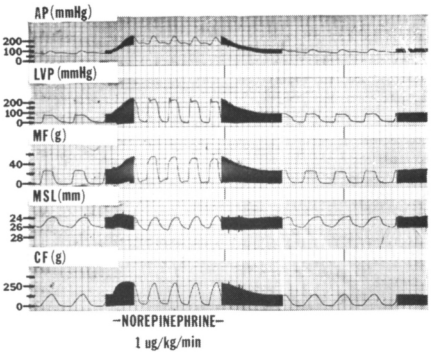

FIG. 2. Response to norepinephrine infusion (1 μg/kg/min). Abbreviations same as Fig. 1.

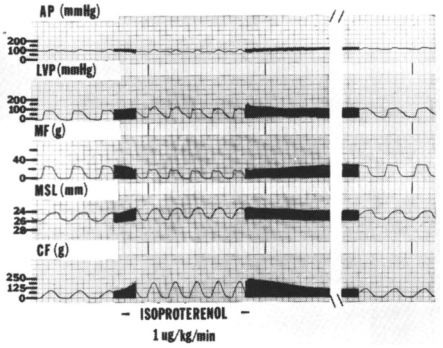

FIG. 3. Response to isoproterenol infusion (1 μg/kg/min). Abbreviations same as Fig. 1.

accompanied by an increase in CF. The vasopressor component of NE activity produced similar changes in AP, LVP, and MSL, which resulted in an increase in MF; however, this increase in ventricular load was matched by a positive inotropic effect, i.e., significantly increased CF (Fig. 2, Table I).

Isoproterenol infusion produced a decrease in diastolic AP and MSL that resulted in a decrease in MF accompanied by an increase in CF (Fig. 3, Table I). A pattern similar to this response was seen when NE was infused following α-adrenergic blockade with phentolamine, i.e., decreased MF accompanied by increased CF (Fig. 4, Table I). The effect of these drug infusions on the relationship between ventricular contractile state and load are summarized in Fig. 5.

Discussion. Since Woods' (9) classic study, the applicability of some form of La Place's law to determine the load on the intact heart has been proven acceptable by numerous investigations. This load, reflected by forces in the wall of the ventricle, plays a significant role in determining the dynamic performance of the ventricle. The significance of loading conditions is most easily illustrated in the isolated cardiac muscle. When a given gram mass is suspended from a papillary muscle held at a fixed length, the muscle will contract isometrically until the contractile tension equals the load. At this point, the muscle shortens isotonically and moves the load. Sufficient mass can be added to the muscle so that no isotonic contraction occurs and a pure isometric contraction is produced (10). These events in isolated muscle are directly transferable to the intact ventricle. Normally, the intact ventricle contracts isovolumicly until developed tension matches the load imposed by the pressure and ventricular size at aortic valve opening and then an auxotonic contraction takes place during ejection of the stroke volume. Additionally,

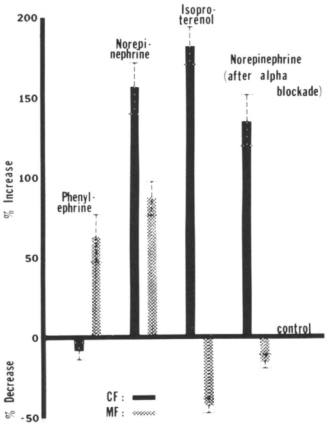

FIG. 5. Alterations in ventricular mural force (MF) and contractility (CF) produced by drug infusions. Bars are mean values ± SE for eight animals in each drug group.

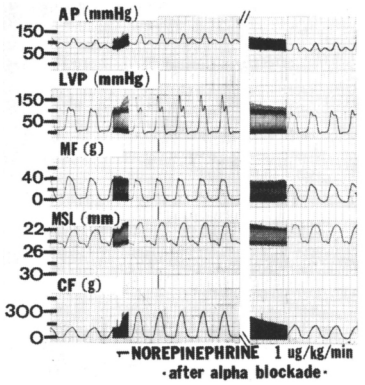

FIG. 4. Norepinephrine infusion (1 μg/kg/min) following pretreatment with 5 mg/kg phentolamine. Abbreviations same as Fig. 1.

TABLE I. STEADY-STATE EFFECTS OF DRUG INFUSIONS OF VENTRICULAR DYNAMICS[a]

Drugs	Max Δ Diastolic AP	Max Δ LVP	Max Δ MF	Max Δ MSL	Max Δ CF	Max Δ HR
Phe, 10 μg/kg/min	+60.3 ± 13.9	+72.8 ± 16.0	+69.0 ± 15.4	+2.7 ± 0.4	−8.3 ± 6.0*	−2.5 ± 1.5*
NE, 1 μg/kg/min	+85.7 ± 12.3	+91.9 ± 14	+87.9 ± 11.5	+2.1 ± 0.4	+157.4 ± 17.6	+21.1 ± 4
Iso, 1 μg/kg/min	−19.6 ± 5.4	+28.2 ± 7.0	−43.7 ± 4.2	−3.4 ± 0.5	+181.2 ± 13.7	+38.9 ± 10.1
NE + αBlk, 5 mg/kg phentolamine NE, 1 μg/kg/min	+18.5 ± 5.9	+40.0 ± 9.0	−16.5 ± 4.6	−1.5 ± 0.4	+134.9 ± 16.7	+20.1 ± 1.8

[a] Values are mean ± SE in percent change from control obtained in eight animals per drug treatment. Diastolic AP, aortic diastolic pressure; LVP, left ventricular pressure; MF, mural force; MSL, muscle segment length; CF, contractile force; HR, heart rate. All values are significantly different from control ($P < 0.05$) except as indicated by *.

as in isolated muscle preparations, load may be increased to such an extent the ventricle undergoes a total isovolumic contraction and does not eject (11). Thus, loading conditions alone influence significantly the dynamic performance of the ventricle.

Alterations in load—phenylephrine. In these experiments, the influence of an increase in load alone is best demonstrated by the Phe infusions. The elevation of aortic pressure and dilation of the ventricle produced by Phe imposed a 69% increase in load on the ventricle. This increase in load was not matched by a simultaneous increase in the inotropic state measured as CF. Since developed tension must match and momentarily exceed the load in order for the ventricle to continue to eject, the increased load was matched by a shift up the Frank–Starling curve producing more developed tension. This is evident in these experiments by the increased MSL. Since the Frank–Starling function is limited, there can be only limited compensation to increased load by this mechanism and it is possible to shift the ventricle to the descending portion of the Frank–Starling curve resulting in acute heart failure. This disparity between load and inotropism produced by Phe is probably in part responsible for the decline in use of pure vasopressor agents in cardiogenic shock.

Simultaneous alterations in load and contractile state—norepinephrine and isoproterenol. When a drug has simultaneous effects on vascular resistance, heart rate, heart size, and myocardial contractility, the relationship between load and developed tension becomes a complex function of at least these four variables. In the present study, NE (+ chronotropic, + inotropic, and vasopressor) and ISO (+ chronotropic, + inotropic, and vasodilator) were selected to illustrate this point. Infusions of NE, at the dose selected, produced an increased load (MF) on the ventricle, as seen with Phe. The two determinants of load, pressure and ventricular size, were both increased, as evident by measurement of AP, LVP, and MSL. However, as opposed to Phe infusions, NE produced a significant increase in CF which exceeded the increased load. Therefore, although an increased load was imposed on the ventricle, an inotropic effect was manifested at a longer fiber length both producing increased developed tension to match or exceed the load.

This response with NE is contrasted to that seen with ISO. Infusions of ISO, at the dose selected, resulted in decreased MF and increased CF. It is interesting to point out that this decrease in ventricular load occurred in the presence of increased LVP. The reduction in load was due to a reduction in ventricular size as evidenced by decreased MSL and serves to emphasize the contribution of radius as a determinant of ventricular load. Although not precisely analyzed in these experiments, the increased heart rate produced by ISO and the resulting decreased diastolic intervals probably contributed to the reduction in ventricular size. The contribution of pressure is shown when the relationship between load and CF was reversed when NE was given following α-adrenergic blockade. Implicit in these findings is the fact that ventricular loading conditions cannot be determined by measurement of LVP alone but must be either directly measured as MF or determined from measurements of LVP and ventricular radius.

These findings are summarized in a diagram (Fig. 6) showing the influence of these agents on the interrelation between developed tension and ventricular load. The CF-length curves in Fig. 6 were not directly measured in these experiments but represent atypical typical curves obtained with a Walton–Brodie arch with adjustable feet in

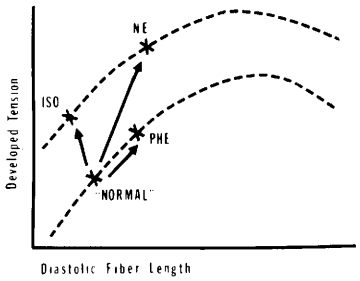

FIG. 6. Alterations in developed tension produced by different pressor-inotropic states in response to drugs.

response to the administration of a positive inotropic agent (12, 13). The lower curve represents the control state, while the upper curve represents the response to positive inotropic intervention. Additionally, symmetrical alterations in the CF-length relationship produced by positive and negative inotropic interventions have been demonstrated by Reeves and Hefner (12). Also, the exact position of the point labelled "normal" on the CF-length curve is unknown; however, the ventricle of the open-chest dog responds to increased aortic pressure with increased stroke work (14). This type of response indicates that length-dependent increases in CF are operative in the open-chest dog and the "normal" point may be assumed to be on the ascending limb. Except for the precise location of the "normal" point, data obtained in the present experiments support the alterations in ventricular dynamics described in Fig. 6.

Summary. These experiments present new data, obtained by direct measurement, describing the influence of Phe, NE, and ISO on ventricular MF or load. Measurement of MF along with measurements of ventricular pressure, size, and inotropic state allows for a more complete and meaningful characterization of the response of the intact ventricle to pharmacological interventions.

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