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The Influence of Preload Measured as Diastolic Mural Force on Myocardial Contractility Indices[1,2] (38478)

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There have been reports in the recent literature citing the influence of ventricular preload on indices of myocardial contractility. Most of these reports used left ventricular end-diastolic pressure (LVEDP) as an indicator of preload (1–6), but few have used an indicator which incorporated a geometry factor. Since ventricular radius contributes to the force in the ventricular wall and, therefore to the load on the myocardial fiber, directly measured mural force ($MF = P\pi R^2$) should provide a more accurate indication of preload changes than pressure alone. Therefore, the purpose of this investigation was to examine the influence of preload changes as measured by either MF or LVEDP on five simultaneously recorded indices of contractility. These indices were peak rate of pressure rise of left ventricular pressure (dP/dt) (1, 2), maximum physiological velocity of the contractile elements (Vpm) (3–6), time from onset of contraction to VPM ($t\text{-}Vpm$) (3, 4), the ratio of dP/dt to instantaneous pressure at 5 mmHg developed pressure [$(dP/dt)/K\cdot 5$] (7), and the ratio of dP/dt to common peak isovolumic developed pressure [(dP/dt)/CPIP] (1, 4).

Method. Eighteen mongrel dogs weighing from 18 to 31 kg (mean = 21.4 kg) were anesthetized with 20 mg/kg pentobarbital sodium. After institution of positive pressure respiration with room air, each animal received a supplemental dose of barbital sodium (150 mg/kg) intraperitoneally to maintain a steady state of anesthesia. Polyethylene catheters were inserted in a femoral vein and artery. The tip of the arterial catheter was positioned in the ascending aorta for the measurement of aortic blood pressure with a Statham P23Dd pressure transducer. Through a ventral midline incision in the neck, both vagii were isolated and severed. A left lateral thoracotomy was performed and the pericardium widely incised. A short (15 cm), rigid, plastic cannula was inserted into the left ventricle through the apex for measurement of left ventricular pressure (LVP) with a Statham P23Dd pressure transducer. The first derivative of LVP (dP/dt) was determined using a Hewlett–Packard 8805B Carrier Amplifier, Option 7 Differentiator. All measured parameters were recorded on a Hewlett–Packard 7878A Physiological Monitoring System. Additionally, the LVP and dP/dt were recorded and stored on magnetic tape (Hewlett–Packard 3955 Magnetic Recording System).

A divide circuit (MC 1594/1494 Monolithic Four-Quadrant Multiplier; Motorola Semiconductor Products) was used to calculate the instantaneous quotient (dP/dt)/LVP. From this recording, Vpm and $t\text{-}Vpm$ were determined using the Voigt model for cardiac muscle so that the quotient would not tend toward infinity at low pressures. The LVP, dP/dt and $(dP/dt)/K\cdot 5$ were then calculated directly from this trace using developed pressure rather than total pressure. The value for CPIP was determined to be 30 mmHg, and this too was multiplied by K to convert the quotient to muscle lengths per second (ML/sec). Henceforth, (dP/dt)/CPIP will be referred to as $(dP/dt)/K\cdot 30$.

Each animal was pretreated with 0.5 mg/kg propranolol (Inderal) to prevent reflex variations in contractility, and control measurements were taken after all measured parameters had stabilized. Each animal then received three intravenous infusions of dextran (Macrodex), each equal to 1% of

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its body wt (BW). Each increment of fluid was allowed to drip from an IV apparatus over a period of approximately seven minutes. Measurements were made immediately after each infusion and again after a 5-min stabilization period. Following the third stabilization period, the animals were then bled back to near control levels of LVEDP, allowed to stabilize, and another recording taken.

In 12 of the animals, a strain gauge arch of the type described by Hefner *et al.* (9) was used for on-line determinations of mural force (MF), or load. This arch was sutured to the left ventricle with deeply penetrating sutures, and the muscle between the feet of the arch and the anchoring sutures was cut to assure that no fibers remained which would tend to hold the feet of the arch together. Measurements of MF with this arch have been shown to correlate well with the product of directly recorded LVP and the square of ventricular radius (9–11). Changes in diastolic mural force (DMF) were considered to be representative of changes in preload. Figure 1 is a representative tracing of the recorded parameters

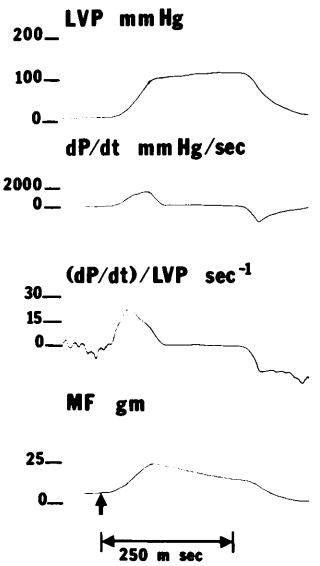

FIG. 1. Representative sample of recorded and derived parameters. LVP = left ventricular pressure; *dP/dt* = rate of rise of LVP; *(dP/dt)*/LVP = quotient derived from divide circuit; MF = tracing from mural force gauge. Arrow indicates point of measurement of diastolic mural force (preload).

(excluding aortic pressure) illustrating the recording fidelity and temporal relationships of the various parameters.

Statistical analyses were performed with a Wang 700 Series Computer.

Results. The results of the volume loading are summarized in Table I. The aortic systolic (SYS) and diastolic (AoD) pressures did not show any significant change. However, the LVEDP and DMF were significantly increased in direct relation to the volume change, thus indicating an increase in preload.

The *dP/dt* and $(dP/dt)/K \cdot 30$ increased in a manner which was dependent upon the increase in preload, while $(dP/dt)/K \cdot 5$ and *t-Vpm* failed to show any statistically significant change from control. The *Vpm* index, using total pressure, demonstrated an inverse relation to the preload and was significantly decreased at the 3% BW level. That $(dP/dt)/K \cdot 30$ was influenced by an increase in preload more than *Vpm* was surprising, since *Vpm* has been considered to be more dependent upon preload than $(dP/dt)/K \cdot 30$ (2–4, 10).

When the data from all dogs were pooled and each of the contractility indices were correlated with either LVEDP or ΔDMF, all the regression coefficients were nonsignificant. This lack of significance was most likely due to variations among the individual dogs for the following reason. Selecting $(dP/dt)/K \cdot 30$ as a representative index, Table II illustrates that this index was significantly correlated with LVEDP in 12 of the 18 dogs and with DMF in 10 of 12 dogs. However, the slopes of the correlations varied over a 15-fold range for LVEDP and over an 80-fold range for DMF.

Discussion. Regarding the use of the Hefner type strain gauge arch, changes in preload were considered to have occurred when there were changes in diastolic mural force (DMF). The LaPlace relation defines force in a hollow body as the product of pressure and radius squared, and has been used by numerous investigators to determine the tension in the ventricular wall (13–19). Hefner *et al.* demonstrated that this arch measured this product of pressure and radius squared, and subsequent studies by Newman and Walton (10, 20, 21) have demonstrated

TABLE I. INFLUENCE OF INCREASING BLOOD VOLUME ON VELOCITY MEASUREMENTS.[a]

Variable	Control	1% BW	5 min	2% BW	5 min	3% BW	5 min	−bld
SYS mmHg	113.8	124.2	121.5	124.4	122.4	125.2	123.9	116.3
	±3.8	±3.4	±3.4	±3.2	±3.4	±3.3	±3.6	±3.5
AoD mmHg	89.0	93.8	91.2	91.5	89.4	91.4	90.8	87.7
	±2.7	±2.5	±2.5	±2.5	±2.6	±2.7	±2.9	±3.1
LVEDP mmHg	3.4	8.3***	7.7***	12.7***	12.0***	17.6***	15.3***	5.2**
	±0.4	±0.7	±0.8	±1.1	±1.1	±1.3	±1.3	±0.5
ΔDMF gm	0.0	5.5***	5.4***	9.5***	9.2***	12.1***	11.7***	3.9***
	±0.0	±0.9	±0.9	±1.3	±1.3	±1.5	±1.6	±0.8
dP/dt mmHg/sec	1598.0	1826.1*	1904.2*	2031.1**	2060.0**	2130.3***	2180.3***	2085.3**
	±76.2	±93.4	±98.3	±103.1	±105.1	±10.42	±96.5	±116.3
$(dP/dt)/K \cdot 5$ ml/sec	2.05	2.35	22.7	2.40	2.43	2.46	2.45	2.36
	±0.12	±0.10	±0.10	±0.12	±0.12	±0.15	±0.13	±0.12
$(dP/dt)/K \cdot 30$ ml/sec	1.23	1.38	1.44*	1.55**	1.54***	1.64***	1.65***	1.49**
	±0.05	±0.07	±0.08	±0.08	±0.07	±0.07	±0.07	±0.08
Vpm ml/sec	1.86	1.74	1.81	1.67	1.73	1.61*	1.67	2.01
	±0.09	±0.07	±0.08	±0.07	±0.07	±0.06	±0.06	±0.09
t-Vpm msec	28.7	26.3	26.6	26.2	26.8	27.3	27.3	26.9
	±1.1	±1.0	±1.1	±1.0	±1.3	±1.1	±1.0	±0.8
HR beats/min	167.5	164.0	165.4	167.2	169.3	172.2	174.1	169.9
	±4.0	±3.9	±4.1	±4.3	±4.4	±4.7	±4.9	±4.2

[a] Abbreviations: SYS = systolic pressure; AoD = aortic diastolic pressure; LVEDP = left ventricular enddiastolic pressure; ΔDMF = change in diastolic mural force; *dP/dt* = maximum rate of rise of ventricular pressure; $(dP/dt)/K \cdot 5$ = ratio of *dP/dt* to instantaneous pressure at 5 mmHg developed pressure; $(dP/dt)/K \cdot 30$ = ratio of (dP/dt) to instantaneous pressure at 30 mmHg developed pressure (CPIP); *Vpm* = maximum physiological velocity of contractile elements; *t-Vpm* = time from onset of contraction to *Vpm*; HR = heart rate; % BW's = percent body wt fluid infused; 5 min − 5 min after previous intervention; −bld = removal of blood; * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$.

TABLE II. LINEAR REGRESSION CORRELATIONS FOR $(dP/dt)/K \cdot 30$ VERSUS PRELOAD IN EACH ANIMAL.[a]

	$(dP/dt)/K \cdot 30$ vs LVEDP			$(dP/dt)/K \cdot 30$ vs ΔDMF		
Dog. No.	*Slope*	*r*	*P*	*Slope*	*r*	*P*
1.	0.076·	0.321	NS	0.054	0.842	1%
2.	0.066	0.743	5%	0.028	0.271	NS
3.	0.061	0.810	5%	0.087	0.904	1%
4.	0.022	0.587	NS	0.025	0.712	5%
5.	0.015	0.650	NS	0.047	0.854	1%
6.	0.028	0.922	1%	0.028	0.917	1%
7.	0.016	0.865	1%	0.032	0.930	1%
8.	0.011	0.570	NS	0.022	0.652	NS
9.	0.022	0.912	1%	0.040	0.939	1%
10.	0.007·	0.709	5%	0.006	0.723	5%
11.	0.025	0.890	1%	0.50	0.898	1%
12.	0.005·	0.515	NS	0.007	0.783	5%
13.	0.034	0.883	1%			
14.	0.027	0.811	5%			
15.	0.029	0.509	NS			
16.	0.022	0.710	5%			
17.	0.024	0.866	1%			
18.	0.017	0.766	5%			

[a] Slope = change in $(dP/dt)/K \cdot 30$ per unit change in LVEDP or ΔDMF; r = linear regression coefficient; P = probability.

that values obtained with this arch corresponded with calculated values of wall force, being influenced by changes in ventricular size and/or pressure. When the resultant curves of calculated wall stress (15, 16, 22) are compared with curves derived from the MF gauge (10, 20 and Fig. 1) it can be seen that there is little difference between their contour and time relationships.

The results indicated that dP/dt was dependent upon preload and this finding was in agreement with other studies which have demonstrated its dependence upon load (1, 2, 10).

The ratio $(dP/dt)/K \cdot 5$ has recently been introduced into the literature by Parmley *et al.* (7). When developed pressure is used to calculate VCE from the equation $(dP/dt)/DP$, the quotient tends toward infinity at low developed pressures. In order to circumvent this problem, yet still obtain a value representative of *Vmax*, it was considered that $(dP/dt)/K \cdot 5$ would be appropriate. Little mention was made concerning the influence of load changes on this index; therefore, its relation to preload changes was examined in this study. From the data in Table II there appears to be no significant change in this index with changes in preload. However, there is a great deal of variation in the values obtained with the smallest standard error being 0.10 ml/sec and two standard errors (0.20 ml/sec) have a magnitude of approximately 10% of the mean value. Thus, this index may have little clinical significance in assessing normal myocardial function. This does not take into account that the normal values fell in a range between 1.25 and 3.75 ml/sec, also indicating a wide variation in measurement of this variable.

The maximum physiological velocity (*Vpm*) of the contractile elements as an index of contractility gained favor among cardiologists because it could be measured directly without the possibility of an error in extrapolation (3, 4). However, this concept has become subject to criticism since it is usually determined by the use of total pressure (Voigt model for cardiac muscle) and thus dependent upon preload (12, 13). Results from this study support the claim of preload dependence, with *Vpm* decreasing as preload increases. One of the major reasons for the use of total pressure in determining *Vpm* is that this method is more easily used when divide circuits are employed to calculate the quotient online. If the use of developed pressure is attempted in determining *Vpm* with a divide circuit, there are

obvious difficulties encountered when the denominator (pressure) approaches zero. Thus, most investigators have used the Voigt model when determining *Vpm* in the intact heart. Notwithstanding, recent investigations by Parmley *et al.* (12) have demonstrated that isolated cardiac muscle determinations of *Vpm* are also dependent upon preload even when developed tension is employed in the equation $(dT/dt)/KT + C$. Therefore, it appears that the *Vpm* index is dependent upon preload regardless of which method is used for its determination.

This dependence of *Vpm* on preload when total pressure was used prompted Mehmel *et al.* (4) to suggest that the time from the onset of contraction to *Vpm* (*t-Vpm*) may be acceptable index of contractility. In intact ventricles they found no statistical difference in *t-Vpm* during volume and pressure loading of the ventricle. However, there was a relatively large standard deviation reported in their data. In the control state after propranolol administration, their *t-Vpm* was reported to be 23 ± 4 msec. Here again one standard deviation (standard error not reported) accounts for a variation of approximately 16% of the mean value. In this present study the value reported in Table I, obtained under vagotomy and beta-blockade with propranolol, shows a mean of 28.7 msec with a standard error of 1.1 msec. Although not reported in the table, the standard deviation for this parameter was 4.8 msec.

The index (dP/dt)/CPIP, or as in this study $(dP/dt)K \cdot 30$, has been considered to be the most reliable index for measuring contractility (2, 12); therefore, the effects of an increased preload due to increasing blood volume were examined in all dogs using LVEDP as an index of preload as well as ΔDMF in the 12 dogs in which this was determined. The results of this examination are summarized in Table II. These data indicate that the ratio $(dP/dt)K \cdot 30$ was indeed influenced by changes in preload, and the use of DMF as an index of preload indicates that this ratio may be more dependent upon preload than the use of LVEDP would indicate. In ten of the 12 animals, the correlation coefficient using DMF was greater than when LVEDP was used, and the p statistic was more significant in five of these ten.

In conclusion, the results of this study demonstrate some of the problems which may be encountered when attempts are made to examine changes in myocardial contractility in the face of simultaneous changes in preload. Due to wide variations in the control state, difficulties may arise when comparing myocardial contractility among patients. Many of these indices have proved useful determinants of changes in contractility when the myocardium is challenged with positive inotropic agents. However, if relatively small changes are observed, erroneous interpretations of drug action may result if changes in preload are not accounted for.

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