Influence of Acute Changes in Preload, Afterload, Contractile State and Heart Rate on Ejection and Isovolumic Indices of Myocardial Contractility in Man

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SUMMARY To determine the sensitivity of several isovolumic and ejection phase indices of myocardial contractility to loading, inotropic stimulation and heart rate in man, 14 patients (pts) were studied during cardiac catheterization with simultaneous recordings of left ventricular (LV) pressures and ultrasound dimensions. Measurements were made of instantaneous and mean circumferential fiber shortening velocity (V_CFR), maximal (max) rate of LV pressure rise (dP/dt), dP/dt divided by end-diastolic circumference [(dP/dt)/C], (dP/dt)/C divided by aortic valve opening pressure [(dP/dt)/CP], peak contractile element velocity (V_CE) using total LV pressure, V_CFR extrapolated to zero total pressure (V_max), V_CE at a developed pressure of 10 mm Hg (V_CE,DP_10) and dP/dt at a common isovolumic-developed pressure of 40 mm Hg [(dP/dt)/DFP_40]. Results are expressed in per cent change of the mean for the group. Acute preload increase (8.6% increase in end-diastolic circumference) with constant heart rate at 7 pts produced insignificant changes in V_CE, an 8.3% increase in max dP/dt, no change in (dP/dt)/C, a variable response in (dP/dt)/CP, 18% reduction in peak V_CE, 16% reduction in V_max, 14% increase in V_CE,DP_10, and a 10% increase in (dP/dt)/DFP_40. An acute increase in afterload produced by angiotensin in 8 pts (44% increase in peak stress) led to a 38% decrease in V_CE, a 2.5% increase in max dP/dt, no significant change in (dP/dt)/C, a 26% reduction in (dP/dt)/CP, variable responses in peak V_CE and V_max, an 11% increase in V_CE,DP_10 and minor changes in (dP/dt)/DFP_40. All of the contractility indices were augmented significantly by isoproterenol and atrial pacing.

In a given patient, max dP/dt appears to be useful in the assessment of acute changes in inotropic state since the magnitude of its response to abrupt changes in preload is small and to afterload-insensitive. Normalizing max dP/dt for end-diastolic circumference assures better stability during loading with good sensitivity to inotropic stimulation. V_CE may be used whenever changes in afterload are minimal. The isovolumic measurements of V_CE (regardless of whether total or developed pressure is used) lack sufficient stability during acute changes in loading conditions to warrant their use in the quantitative assessment of acute changes in inotropic state.

THE ANALYSIS OF MYOCARDIAL PERFORMANCE in terms of force-velocity-length relations led to the development of several isovolumic and ejection phase indices of myocardial contractility. The sensitivity of these indices to acute changes in preload, afterload, and contractile state have been evaluated in isolated muscle preparations and in the intact animal heart, but data in humans are very limited. The time course of left ventricular (LV) circumferential wall stress and fiber shortening velocity (V_CFR) was recently determined in this laboratory by simultaneous recordings of LV pressure (micromanometer) with echocardiographic LV dimensions. Using this methodology, the effects of acute changes in preload, afterload, and contractility on V_CFR were evaluated in patients with varying hemodynamic states. V_CE was found to be relatively insensitive to changes in preload, inversely related to acute changes in afterload, and directly sensitive to inotropic stimulation.

The purpose of the present study was to compare a variety of isovolumic indices to V_CE in man as regards their responses to acutely altered loading conditions, changes in contractility, and variation in heart rate.

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Dr. Quinones was supported by a research fellowship award from the American Heart Association and the Texas Affiliate of the American Heart Association.

Presented at the 47th Scientific Sessions of the American Heart Association, Dallas, Texas, November 1974.

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Received August 6, 1975; revision accepted for publication September 10, 1975.

METHODS

Fourteen patients were studied during diagnostic right and left heart catheterization in the postabsorptive state following premedication with 10 mg of intramuscular diazepam. Informed consent was obtained from each patient. The hemodynamic diagnoses are listed in table 1. All except two patients (#10 and #11) had normal angiographic measurements of systolic ejection fraction and mean V_CE performed using previously described methods, and all patients had normal coronary arteries. Echograms from the interventricular septum and left ventricular (LV) posterior wall were recorded simultaneously with high-fidelity LV pressure and its first derivative in an Electronics for Medicine DR-8 multichannel photographic recorder. The ultrasound recordings were obtained with a Smith-Kline ultrasonoscope interfaced to the multichannel recorder, using a 2.25 MHz, 0.5 inch transducer focused at 5 cm, with a repetition rate of 1000 impulses/sec. The technique utilized in this laboratory for adequate visualization of the interventricular septum, fragments of the mitral valve, posterior LV wall endocardium and epicardium has been previously described. Left ventricular pressure was measured with a Millar Instruments 8 F catheter-tip micromanometer; the signal from the micromanometer was calibrated by matching it with a simultaneous lumen pressure using a Statham P23 Db transducer with reference to a zero level 5 cm below the angle of Lewis. The catheter was positioned in the left ventricle so that LV pressure (micromanometer) and central aortic pressure (lumen) could be recorded simultaneously. Recordings of pressures and echograms were taken simultaneously at a paper speed of 100 mm/sec. In addition, central aortic pressure, LV
pressure and its first derivative (dP/dt) were recorded at a paper speed of 200 mm/sec.

Measurements and Calculations

The LV internal diameter (D) was measured in cm from the posterior wall endocardium to the interventricular septum (fig. 1). Measurements of D and of LV pressure were obtained every 20 msec from the time of the LV end-diastolic pressure (EDP) to end systole (time when the LV pressure descent crosses the level of the incisura in the central aortic pressure) utilizing an X-Y digitizer and programmed calculator.* Posterior wall thickness (h) at end diastole and at end systole was measured as the distance from pericardial to endocardial echoes; intermediate points between end diastole and end systole were calculated every 20 msec assuming a linear change in h from end diastole to end systole. The time course of endocardial VCF was determined as:

\[ V_{CF} \text{ (circ/sec)} = \frac{(D1 - D2)/(t \times D1)} {X} \]

(1)

where D1 and D2 represent sequential measurements of D and t = the time between the two measurements (20 msec). In order to attenuate the random motion associated with the manual planimetry, the posterior wall endocardial and the interventricular septal echoes from a single beat were digitized five times; each D represented the average of five measurements. Mean VCF was calculated as:

\[ \text{Mean } V_{CF} \text{ (circ/sec)} = \frac{Dd - Ds}{\text{LVET} \times Dd} \]

(2)

where Dd and Ds represent measurements of D at end diastole and end systole respectively, and LVET = the LV ejection time measured from the time when the LV pressure crosses the level of the diastolic central aortic pressure to end systole; in the patient with mitral regurgitation LVET was measured from end diastole to end systole.

The time course of circumferential LV wall stress was calculated assuming a thin wall ellipsoidal model using the Timoshenko and Winowsky-Krieger’s Equation.12

\[ \text{LV stress (gm/cm}^2\text{)} = P \times \tau \left[ 1 - (2r^2/L^2) \right] / h \]

(3)

where P = intracavitary pressure in gm/cm²; \( \tau \) = intracavitary radius (D/2) in cm, L = long axis of the LV which was assumed in this study to be twice the minor diameter (D) in all instances, and h = posterior wall thickness in cm.

All measurements were processed by the programmed calculator and time plots of endocardial VCF and LV hoop stress were constructed (fig. 1). A 5th order polynomial equation was fitted to the VCF curve. From these graphs the following data were determined: maximal (max) VCF, peak LV stress, and VCF at peak stress. The advantages and limitations of this combined ultrasound-pressure recording method in determining VCF and hoop stress have been discussed previously.10

The following measurements were taken from the isovolumic period of left ventricular pressure: (1) maximum rate of pressure rise (max dP/dt); max dP/dt divided by the LV end-diastolic circumference (C = Dd \( \times \) \( \pi \)), (2) max dP/dt divided by C and by central aortic diastolic pressure ([dP/dt]/CP), and (3) contractile element velocity (VCE), calculated every 10 msec as the ratio of dP/dt to its instantaneous isovolumic pressure (total as well as developed pressure) assuming a fixed series elastic constant of 24.13 Peak VCE was measured directly and VCE at zero load (VCE\(_{\text{max}}\)) was linearly extrapolated from the total pressure-VCE curve. VCE at a developed pressure of 10 mm Hg was taken from the developed pressure-velocity curve as an approximation of VCE\(_{\text{max}}\) since VCE at zero developed pressure is infinite. In addition, the ratio of dP/dt to a common isovolumic developed pressure of 40 mm Hg was measured. All of the isovolumic indices represent the average of five beats recorded at paper speed of 200 mm/sec. Plots of VCE versus pressure (total as well as developed pressure) may be seen in figure 2.

Experimental Protocol

All the experimental data were collected before angiography. Measurements were taken prior to and during the following interventions:

(A) Acute preload increase: In 7 patients with normal LV function, 250–400 cc of Dextran (6 patients) or physiologic saline (1 patient) was infused during a 10–15 minute period to achieve an increase in LVEDP from normal to 15 mm Hg or more. Heart rate was kept constant by atrial pacing in all 7 patients.

(B) Acute change in afterload: In 8 patients (6 with normal LV function, 1 volume overload, 1 myocardial disease) angiotensin (1 \( \mu \)g/cc) was infused at a rate sufficient to produce a distinct pressor response. Heart rate was held constant by atrial pacing in 6 of the 8 patients. In one patient afterload was reduced acutely by amyl nitrite inhalation.

(C) Changes in inotropic state: Isoproterenol was infused in 3 patients with normal LV function (chronotropic response to 120 beats/min). Heart rate was also increased by atrial pacing in 6 patients. Statistical analysis of the data was done using a paired t-test.

Results

Results are summarized in table 1 and figures 2 to 8. The volume expansion produced by the infusion of Dextran or saline resulted in a distinct increase in preload as measured by a significant increase in LVEDP (from 7.9 \( \pm \) 1 to 17.4 \( \pm \) 0.8 mm Hg), and by an 8.6% increase in end-diastolic circumference (from 13.14 \( \pm \) 0.57 to 14.29 \( \pm \) 0.74). This amount of preloading was associated with a small (12.8%) increase in peak stress or afterload. In contrast, angiotensin infusion and its resulting hypertension produced a marked increase in afterload (44.4% increase in peak stress) with a small increase in preload (3.7% increase in end-diastolic circumference). Significant reductions in end-diastolic circumference and in peak stress were observed during isoproterenol infusion and during atrial pacing.

*Hewlett Packard Model 9100B.
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**V<sub>CF</sub>**

Figure 3 summarizes the response of V<sub>CF</sub> to loading and contractility. Increasing preload was associated with small changes in max V<sub>CF</sub> (2% increase, NS), V<sub>CF</sub> at peak stress (5.9% decrease, P < 0.02), and mean V<sub>CF</sub> (1.3% decrease, NS). In contrast, increasing afterload with angiotensin produced significant (P < 0.01) reduction in all three velocities: max V<sub>CF</sub> fell by an average of 34.2%, V<sub>CF</sub> at peak stress fell by 42.4%, and mean V<sub>CF</sub> fell by 37.8%. V<sub>CF</sub> was augmented significantly (P < 0.01) by isoproterenol and by atrial pacing; max V<sub>CF</sub> increased by 92% with isoproterenol, and by 45% with atrial pacing; V<sub>CF</sub> at peak stress increased by 51% with isoproterenol and by 44% with atrial pacing, and mean V<sub>CF</sub> increased by 58% and 46% with isoproterenol and atrial pacing, respectively.

**dP/dt**

The responses to loading and contractility of max dP/dt, max dP/dt corrected for preload [(dP/dt)/C], and max dP/dt corrected for preload and aortic valve opening pressure [(dP/dt)/CP] are shown in figure 4. Preloading was associated with an 8.3% mean increase in max dP/dt (range 2–12%, P < 0.01), with no significant change in (dP/dt)/C (120 ± 5.3 to 120 ± 5.8 mm Hg/sec/cm) and with a variable response in (dP/dt)/CP (1–22% reduction in five patients, 2% increase in two). Increasing afterload was ac-
Table 1. Data During Acute Changes in Preload, Afterload, and Contractility

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age/Sex/BSA</th>
<th>HR (beats/min)</th>
<th>LV (mm Hg)</th>
<th>Max dP/dt (mm Hg/sec)</th>
<th>Cd (cm)</th>
<th>Peak stress (gm/cm²)</th>
<th>Diagnosis</th>
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<tr>
<td>4</td>
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<td>94</td>
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Mean: 1579 ± 1710; 13.14 ± 14.29; 258 ± 291

SEM: ± 103 = ± 126 = ± 0.57 = ± 0.74 = ± 31 = ± 30

Abbreviations: BSA = body surface area; F = female; M = male; HR = heart rate; LV = left ventricular pressure; Max dP/dt = maximum rate of isovolumic pressure rise; Cd = end-diastolic circumference; C = control; AL = afterload; ISO = isoproterenol; AP = atrial pacing; AS = aortic stenosis (peak gradient < 20 mm Hg); Cong. card. = congestive cardiomyopathy; AI = aortic insufficiency; MR = mitral regurgitation; SEM = standard error of the mean.

Companioned by a 0 to 5% increase in max dP/dt (2.5% mean, P < 0.05), by insignificant changes in (dP/dt)/C (from 102 ± 11 to 100 ± 11 mm Hg/sec/cm) and by a 26% reduction in (dP/dt)/CP (P < 0.01). Isoproterenol and atrial pacing produced significant (P < 0.01) increases in max dP/dt (101% and 25%, respectively), (dP/dt)/C (128% and 39%, respectively) and (dP/dt)/CP (156% and 34%, respectively).

Figure 5 shows an example of the LV pressure and dP/dt response to loading in patient 2. In the control state, max dP/dt occurred about 10 msec prior to aortic valve opening pressure. An interval between max dP/dt and aortic valve opening pressure ranging from 8 to 15 msec was observed at rest in all 14 patients. During the angiotensin-induced hypertension, max dP/dt occurred as early as 20 msec prior to aortic valve opening pressure. The magnitude of max dP/dt was not altered by increasing afterload; in contrast an 8.6% increase in max dP/dt was observed during Dextran infusion (preload). Figure 6 is taken from patient 15 to whom an amyl nitrite inhalation was given in order to acutely reduce afterload; heart rate was kept constant by atrial pacing. In contrast to control, during the amyl nitrite-induced hypotension max dP/dt occurred at the time of aortic valve opening and it was of lesser magnitude (1080 mm Hg/sec) than control (1350 mm Hg/sec). (dP/dt)/C also fell during amyl nitrite (95.5 to 76.4 mm Hg/sec/cm) while (dP/dt)/CP rose (1.22 to 1.86 sec/cm³). Stress VCx plots during control and amyl nitrite are also shown in figure 6. The increase in VCx produced by reducing afterload is readily apparent.

Vcx

Figure 7 shows the responses of Vmax and peak VCx (total pressure) to loading and contractility. Increasing preload produced a 7 to 32% reduction in Vmax (15.8% mean, P < 0.01) and an 11 to 38% reduction in peak VCx (17.6% mean, P < 0.01). The response of these two indices to afterload was variable; decreases were observed predominantly in those cases in which afterloading was accompanied...
by secondary increases in LV filling pressures. Both indices were augmented significantly ($P < 0.01$) by isoproterenol (88% and 75% increase in $V_{\text{max}}$ and peak $V_{CE}$, respectively), and by atrial pacing (41% and 50% increase in $V_{\text{max}}$ and peak $V_{CE}$, respectively).

The data for $V_{CE}$ using developed pressure are illustrated in figure 8. $V_{CE}$ at a developed pressure of 10 mm Hg ($V_{CE}DP_{10}$) was augmented significantly ($P < 0.01$) by increasing preload (14.4% mean) as well as by afterloading (11.3% mean). $dP/dt$ divided by a common isovolumic developed pressure of 40 mm Hg ([dP/dt]/$DP_{40}$) also increased significantly ($P < 0.02$) during preloading (10% mean), but remained statistically unchanged during increasing afterload ($32.5 \pm 2.1$ to $33.4 \pm 2.5$ sec$^{-1}$). Both indices were augmented significantly ($P < 0.01$) by isoproterenol (67% and 64% for $V_{CE}DP_{10}$ and $dP/dt)/DP_{40}$, respectively) and by atrial pacing (21% and 22% for $V_{CE}DP_{10}$ and [dP/dt]/DP$_{40}$, respectively). An example of the effect of preload on the pressure-$V_{CE}$ curve using total as well as developed LV pressure is shown in figure 2.

**Discussion**

The systolic ejection fraction and circumferential fiber shortening velocity ($V_{CF}$) are two commonly used indices of LV function. We have previously shown that ejection fraction varies directly with preloading and inversely with afterloading, while $V_{CF}$ remains stable during changes in preload but responds inversely to afterload. Both indices are sensitive to inotropic stimulation with isoproterenol and digitalis. In addition to these findings, the present study shows that $V_{CF}$ is also sensitive to heart rate augmentation by atrial pacing. This may be interpreted as indicating that the Treppe effect operates in man and that $V_{CF}$ is capable of detecting it. However, since atrial pacing led to a reduction in afterload (peak stress fell from 291 to 189 gm/cm$^2$), which will contribute to improving $V_{CF}$, the magnitude of the Treppe effect, if any, is not well defined by $V_{CF}$. The isovolumic indices may be helpful in resolving this question (see below).

The maximum rate of isovolumic pressure rise (max $dP/dt$) was proposed as an early isovolumic index of myocardial contractility. Studies in the opened chest dog have shown that $dP/dt$ is sensitive to changes in preload. Our data indicate definite, but quantitatively small (8.3%), increases in max $dP/dt$ induced by preloading, the percent change in $dP/dt$ being similar to the percent increase in end-diastolic circumference (8.6%). Thus, $dP/dt$ normalized for end-diastolic circumference remained stable during the augmented preload. Studies in closed chest dogs (anesthetized as well as conscious preparations) have also indicated that the changes in max $dP/dt$ induced by altering preload are smaller than those observed in the opened chest experiments. As shown in figure 6, max $dP/dt$ did not occur at the time of aortic valve opening but slightly before (10 msec). Increasing blood pressure with angiotensin prolonged the interval between max $dP/dt$ and aortic valve opening without altering the magnitude of max $dP/dt$. In contrast, rapid blood pressure reduction with amyl nitrite led to a fall in max $dP/dt$ (as well as in [$dP/dt)/C$) which did occur at the time of aortic valve opening. These results indicate that aortic valve opening pressure does not usually affect max $dP/dt$ unless it is low enough to limit its full development. Similar conclusions can be derived from previous animal work. Therefore, max $dP/dt$ does not need to be corrected for afterload within physiological levels of blood pressure. In fact, when max $dP/dt$ was normalized for

![Figure 3](http://circ.ahajournals.org/...
end-diastolic circumference and aortic valve opening pressure (as proposed by Frank and Levinson), it failed to remain stable during an acute increase in afterload.

In the intact heart it is impossible to completely separate preload from afterload. Augmenting afterload with angiotensin produced a small (3.7%) increase in end-diastolic circumference which probably accounted for some of the small increases observed in max dP/dt. Max dP/dt

![Figure 4](image)

**Figure 4** Effects of acute increases in preload (PL), afterload (AL) and contractility on maximal (max) dP/dt. dP/dt divided by end-diastolic circumference [(dP/dt)/C] and dP/dt divided by end-diastolic circumference and aortic valve opening pressure [(dP/dt)/CP]. Max dP/dt was augmented by preloading but remained stable during afterloading; (dP/dt)/C remained stable during both preload and afterload increases; (dP/dt)/CP was reduced significantly by increasing afterload. All three indices were augmented by isoproterenol (ISO) and atrial pacing. C = control.

![Figure 5](image)

**Figure 5** Example of a pressure curve from a normal left ventricle (LV) during increases in afterload (angiotensin) and preload (Dextran). Note that max dP/dt does not occur at the time of aortic (AO) diastolic pressure but slightly before (10 msec and 20 msec prior to AO diastolic pressure during control and angiotensin, respectively). Max dP/dt was not affected by afterloading but increased by 9% with preloading.
FIGURE 6 Simultaneous left ventricular (LV) echogram, pressure and aortic (AO) blood pressure recorded before (control) and during acute afterload reduction with amyl nitrite inhalation (constant heart rate). In contrast to control, max dP/dt during the acute hypotension occurs at the time of aortic valve opening and it is of a lesser magnitude than control. The panel on the right shows the relation between V_cT and stress for the two afterload states. An inverse relation between V_cT and afterload is readily apparent.

FIGURE 7 Response of V_max and peak contractile element velocity (V_CE), calculated using total pressure, to acute increases in preload (PL), afterload (AI) and contractility. Increasing preload produced significant reduction in V_max and peak V_CE. The response to afterloading was variable; a decrease was observed in both indices in the cases in which afterloading led to secondary increases in left ventricular filling pressures. Both indices responded to isoproterenol (ISO) and atrial pacing. C = control.
corrected for end-diastolic circumference \( \frac{[dP/dt]}{C} \) remained essentially unchanged during afterloading (except during the amyl nitrite-induced reduction in aortic valve opening pressure). Both max \( dP/dt \) as well as \( (dP/dt)/C \) were significantly augmented by isoproterenol and by atrial pacing (confirming the positive inotropic influence of heart rate in man, as suggested by \( V_{CE} \) above). Thus, max \( (dP/dt)/C \) seems to be an index of myocardial contractility which remains stable during acute changes in loading and responds sensitively to inotropic stimulation.

Knowledge of myocardial mechanics provides some physiologic rationale for the use of max \( dP/dt \) normalized for end-diastolic circumference. During the isovolumic phase of contraction (isometric in isolated muscle preparations), the activated contractile element (CE) shortens and stretches a series elastic element (SE). The rate of force development during this contraction \((dF/dt)\) is dependent on both the shortening velocity \((dL/dt)\) of the CE (which is equal to the lengthening velocity of the SE) and the instantaneous stress-strain relation of the SE. Thus: \( dF/dt = (dL/dt)_{SE} \times (dF/dL)_{SE}. \) At a given afterload both \( dL/dt \) and \( dF/dt \) are increased by increasing resting muscle fiber length or by augmenting contractility. \( V_{CE} \) in the intact heart, measurements of contractile element velocity \( V_{CE} \) have been attempted using the ratio of \( dP/dt \) to \( K \) where \( P = \) intracavitary pressure and \( K = \) a normalized modulus of series elasticity, assumed to be similar in all types of hearts. Because of controversy regarding the use of total versus developed LV pressure in these calculations (a controversy based on different models of CE in alignment with SE and parallel elastic, as well as in experimental observations of responses to loading), we decided to evaluate the commonly used measurements of \( V_{CE} \), applying both measurements of pressures. Peak \( V_{CE} \) and extrapolated \( V_{max} \), calculated using total pressure, were both found to vary inversely with preloading (16% and 18% reduction, respectively). The responses to changes in afterload were more variable; inverse changes were observed predominantly in the cases with afterload-induced elevations in LV filling pressures. Opposite results were observed when developed pressure was utilized. Thus, \( V_{CE} \) at a developed pressure of 10 mm Hg \( (V_{CE}DP_{w}) \) and \( dP/dt \) divided by a common isovolumic developed pressure of 40 mm Hg \([dP/dt]/DP_{w}\) were both augmented significantly (14% and 10%, respectively) by preloading. Increasing afterload produced also an increase in \( V_{CE}DP_{w}(11\%) \) but no signifi-
indices of contractility in man/quinones, gaasch, alexander

cant change in \( \frac{dP}{dt}/DP_{ae} \). All of the indices were augmented by isoproterenol and atrial pacing. Mahler and associates, working in chronically instrumented conscious dogs, have recently reported results similar to ours with max dP/dt, peak \( V_{CF} \) (total pressure) and \( dP/dt/DP_{ae} \).

The concept of \( V_{max} \) as an important contractility index has been supported by studies in isolated papillary muscles in which increasing initial resting fiber length has led to a rightward shift of the force-velocity curve without a change in the extrapolated \( V_{max} \), while a positive inotropic intervention has produced an upward shift of the curve and of the extrapolated \( V_{max}\). Grossman and co-workers have presented data in intact animals and in man suggesting that \( V_{max} \), extrapolated from developed pressure, is independent of acute alterations in preload while \( V_{max} \) derived from total pressure responds inversely (similar to our data) to preload. The authors concluded that use of developed pressure was preferred to the use of total pressure in constructing force-velocity curves during the isovolumic period in man. However, the concept that \( V_{max} \) (even in the isolated cardiac muscle) is independent of resting muscle length is by no means universally accepted. The theoretical analysis by Pollack as well as the experimental studies by Forman et al. support the opposite concept: that \( V_{max} \) is directly dependent on preload. In the present study we have observed a preload-induced upward shift of the developed pressure-velocity curve (fig. 2). Even though we did not attempt to extrapolate this curve to \( V_{max} \), visual inspection of the curves in figure 2 might support the concept that \( V_{max} \) is indeed preload dependent.

The results from this study, therefore, suggest that max dP/dt may be used to evaluate acute changes in contractility in man, since its response to loading is small (within physiologic ranges of blood pressure). Normalizing max dP/dt for end-diastolic circumference assures an even better stability during loading, and an equal sensitivity to inotropic stimulation. The isovolumic measurements of \( V_{CF} \) (regardless of whether total or developed LV pressure is used) lack sufficient stability during changes in loading to warrant their use in assessing acute changes in inotropic state (with the exception of \( dP/dt/DP_{ae} \) which may be useful in situations of predominant afterload change). The problems of these measurements in separating normal from abnormal LV function in man have also been well established.

In the absence of variable afterload, \( V_{CF} \) is a reliable index to identify acute alterations in myocardial contractility. The sensitivity of all of these indices to heart rate demonstrates the importance of maintaining this physiologic parameter constant when assessing acute alterations in contractile state, particularly during pharmacologic interventions.

The above results, however, are not entirely applicable to the evaluation of contractile state among different patients. That is, even though \( dP/dt/C \) was the most stable index during alterations in loading, it should not be expected to be the most accurate in separating patients with normal from those with reduced myocardial contractility. Since dP/dt reflects changes in \( V_{CF} \) (dL/dt) as well as in the stiffness of the series elastic during contraction \( (dF/dL) \), alterations in the stress-strain relation of the SE produced by heart disease (a theoretical consideration which has been proven for myocardial infarction) would be expected to affect the total magnitude of max dP/dt. In addition, chronic left ventricular dilatation is not due entirely to sarcomere stretch, but is brought about to a considerable extent by "slippage" or "re-arrangement" of muscle fibers. Thus, in chronic LV dilatation end-diastolic circumference is not a true index of muscle fiber stretch, and therefore \( dP/dt/C \) is not an accurate normalization of dL/dt for initial resting fiber length. Comparison among different hearts is therefore precluded.

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Regional Myocardial Function in the Conscious Dog During Acute Coronary Occlusion and Responses to Morphine, Propranolol, Nitroglycerin, and Lidocaine

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SUMMARY Regional myocardial function following occlusions of the circumflex coronary artery was studied in unanesthetized dogs using miniature ultrasonic crystal pairs implanted subendocardially within the left ventricle for measurement of control, marginal, and ischemic lengths. As early as five beats after coronary occlusion, reduced function was apparent in ischemic zones, and an increase in heart rate occurred (78 to 115 beats/min) at an average of 25 sec. In the control zones, shortening initially increased from a constant end-diastolic length, but later end-diastolic length also increased by 7.5%. Shortening in the marginal zones was reduced by 50% at 90 sec as holosystolic expansion developed in the ischemic zones. On reperfusion, systolic function returned to normal within a few minutes while protodiastolic abnormalities persisted for up to 45 min. With coronary occlusions longer than two minutes most dogs exhibited arousal and further tachycardia; this reaction was prevented by morphine. During two minute occlusions morphine also decreased the heart rate increase by 37%, and marginal segment shortening was improved by 40%. Prior administration of propranolol also decreased heart rate during coronary occlusion and produced similar improvement in marginal segment function; however, in contrast to morphine, there was depression of contraction in the control segments. Nitroglycerin given during coronary occlusion caused decreases in end-diastolic length of all segments and increased shortening in the marginal segment by 28%. Lidocaine administered during coronary occlusion produced a mild depression of myocardial function in all regions of the heart.

THE REGIONAL NATURE of the contractile responses of the myocardium after experimental coronary occlusion has been recognized since the work of Tennant and Wiggers.1 However, the dynamic shortening and lengthening characteristics of various regions of the left ventricle and the responses to various forms of treatment have not been defined in the conscious animal. An understanding of these characteristics could have considerable importance in assessing therapy designed to improve myocardial performance during ischemic episodes, or to reduce ischemic damage after acute coronary occlusion in man. The present study extends our previous observations in the anesthetized, open-chest dog2 to an analysis of regional myocardial function during acute coronary occlusion in the unanesthetized animal. Our primary purposes were to define acute hemodynamic changes in relation to the dynamic alterations in function of the normal myocardium and the marginal and central ischemic zones, as well as the reproducibility of these responses with a second coronary occlusion. In addition, the studies were designed to study the responses to several therapeutic agents commonly used in the management of myocardial ischemia (nitroglycerin, propranolol) and acute myocardial infarction (morphine, lidocaine), with a particular view to assessing differences in the responses of normal and ischemic regions of the left ventricle to these drugs.

Methods
Dogs were prepared for study at surgery under general anesthesia. Following left thoracotomy and pericardiotomy, a high fidelity pressure micromanometer (Konigsberg, P-22) and a silastic fluid-filled catheter of 0.5 mm inner diameter were inserted into the left ventricular chamber through the ventricular apex and secured in position with intramyocardial sutures. The circumflex coronary artery was dissected free near its origin and a hydraulic cuff placed around it. Three pairs of small ultrasonic crystals were then implanted in the left ventricular wall in a circumferential plane close to the endocardium and as near the left ventricular

From the Department of Medicine, University of California, San Diego, and Scripps Clinic and Research Foundation, La Jolla, California. Supported by NIH Research Grant No. HL 12373 and by Myocardial Infarction Research Unit Contract Award N01-HV-81332, awarded by the National Heart and Lung Institute. Address for reprints: John Ross, Jr., M.D., Director, Cardiovascular Division, M-013, University of California, San Diego, La Jolla, California 92093. Received May 12, 1975; revision accepted for publication September 3, 1975.
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_Circulation_. 1976;53:293-302
doi: 10.1161/01.CIR.53.2.293
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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