New Technique for Determining Instantaneous Myocardial Force-Velocity Relations in the Intact Heart

By William Grossman, Harold Brooks, Steven Meister, Herbert Sherman and Lewis Dexter

ABSTRACT

A new technique is described for the instantaneous determination of myocardial force-velocity relationships. The method employs electronic differentiation of the logarithm of intraventricular pressure, which yields a continuous on-line record of \((dP/dt)^{-1}\) (the ratio of the rate of rise of ventricular pressure \((dP/dt)\) to the simultaneous ventricular pressure \(P\)). A further technique is described for the automatic projection of force-velocity vector loops, displaying \((dP/dt)^{-1}\) on the ordinate against ventricular pressure on the abscissa in a beat-to-beat fashion. An excellent correlation \((r = 0.982)\) was demonstrated between \((dP/dt)^{-1}\) determined by conventional methods and that derived electronically by use of the logarithmic amplifier circuit. Experimental studies are described which document the responsiveness of \((dP/dt)^{-1}\) determined by the present method to interventions known to affect myocardial contractility. An increase in \((dP/dt)^{-1}\) was observed following infusions of \(CaCl_2\), norepinephrine, and glucagon, and a decrease following pentobarbital. Insofar as \((dP/dt)^{-1}\) is a valid index of myocardial contractility, the present method permits on-line, beat-to-beat evaluation of changes in ventricular function under a variety of circumstances.

KEY WORDS
myocardial contractility
(dP/dt)^{-1}
logarithmic amplifier
dog heart
force-velocity relations

In recent years there has been an increasing interest in the application of concepts derived from studies of muscle mechanics to the problems of cardiac physiology. The fundamental relationships between force and velocity in striated muscle as elaborated by A. V. Hill (1) have been extended to cardiac muscle by the work of Sonnenblick (2, 3) and others (4-6). Although developed tension and velocity of shortening may be directly measured in the isolated muscle preparation, these parameters can be determined only indirectly in the intact heart. Consequently, several elaborate techniques have been devised whereby angiographic and hemodynamic data may be transformed by use of the appropriate formulæ into force-velocity relations (7-10). Specifically, it has been shown (7, 11, 12) that the ratio of the rate of rise of ventricular pressure \((dP/dt)\) to the simultaneous ventricular pressure \(P\) approximates, under certain assumptions, the contractile element velocity \((V_{cc})\) during isovolumic systole. Furthermore, graphic plots of this ratio \((dP/dt)^{-1}\) on the ordinate, against ventricular wall stress (a function of ventricular geometry and \(P\)) on the abscissa, gives an equivalent of the force-velocity relation as obtained from isolated heart muscle.

A disadvantage of this method is that \((dP/dt)^{-1}\) must be computed from experi-

\(^1\)Two of the more important assumptions here are that (1) studies are done at low resting tensions, so that the parallel elastic component may be ignored and analysis performed on a two-component model; and (2) the series elasticity (\(K\)) remains relatively constant from moment to moment and from heart to heart.

From the Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts 02115. Supported in part by U. S. Public Health Service Grant ST01-HE-05324-12. Received October 5, 1970. Accepted for publication December 7, 1970.

Circulation Research, Vol. XXVIII, February 1971
mental data and force-velocity plots determined by rather laborious effort only at the completion of an experimental study. It seemed desirable, therefore, to develop a method which would make available both \((dP/dt)^2\) and corresponding force-velocity plots instantaneously, thereby allowing the on-line study of changes in contractility in a beat-to-beat fashion. The present study reports the development of such a method, utilizing a simple logarithmic amplifier circuit.

**Methods**

Studies were conducted in four healthy open-chest mongrel dogs, using chloralose anesthesia (80 mg/kg), atrial pacing (SDSA Grass Stimulator), and controlled respirations with 40% oxygen delivered through an endotracheal tube connected to a Harvard respiratory pump set at 12 to 16 respirations per minute. Left ventricular (LV) pressure was measured through a short (4-inch), 14-T gauge, semirigid Teflon needle inserted into the LV apex and connected directly to a Statham P23Db pressure transducer without intervening tubing. Aortic pressure was measured at the arch of the aorta through a 13-gauge Teflon cannula inserted into the right carotid artery. All recordings were made on an Electronics for Medicine DR-8 photographic recorder.

**LOGARITHM OF LV PRESSURE**

The output of the carrier preamplifier receiving the LV pressure signal was fed into the input of a logarithmic amplifier channel. The log amplifier channel was then balanced (according to the directions provided by the manufacturer's operating manual) and the output of the log amplifier, now the \(\ln\) of LV pressure, was differentiated electronically by an RC circuit with a time constant of 0.5 msec and an output linear of 75 mm/sec with 0.004-sec time lines and including the pressure transducer back on pressure but with \(\ln P/dt\) on baseline (by pulling out the jack that connected \(\ln P\) to the differentiating circuit) to obtain a horizontal axis. Next, the force-velocity curves were superimposed on horizontal and vertical axes for ease of measurement.

**RECORDING OF \(dlnP/dt\)**

The linear output jack of the log amplifier channel was also connected through an RC-differentiating circuit to a second d-c amplifier channel. Thus the multitrace monitor of the DR-8 recorder now displayed LV pressure, \(\ln P\) pressure, first derivative of \(\ln P\) pressure (\(dlnP/dt\)), and first derivative of LV pressure (\(dP/dt\)).

**CALIBRATION**

\(dP/dt\) was calibrated in the usual manner by introducing a signal of constant slope into the RC-differentiating circuit at the completion of each experiment and noting the amplitude response of the RC circuit. Calibration of \(dlnP/dt\) was obtained as follows: On a section of experimental record (Fig. 1) taken at 200 mm/sec with 0.004-sec time lines and including LV pressure, \(dP/dt\), and \(dlnP/dt\), vertical lines were drawn for determination of simultaneous LV pressure (mm Hg), \(dP/dt\) (mm Hg/sec), and \(dlnP/dt\) (mm deflection). \(dP/dt\) (mm deflection) equals \((dP/dt)^2\) which is equal to \(dP/dt\) (mm Hg/sec) divided by simultaneous LV pressure (mm Hg). If at a given instant during

The basis of the above circuitry is as follows. It will be recalled that a rule of differential calculus is \(d/dy)lnx=(dx/dy)x^{-1}\) (13). Accordingly, \((d/dt)lnP=(dP/dt)x^{-1}\). The differentiated output of the log amplifier circuit described above therefore gives a continuous readout of \((dP/dt)^2\).
ventricular systole (see Fig. 1) the logarithmic circuit (dlnP/dt) registers a response of amplitude x (mm deflection), and at the same instant the value for dP/dt is a mm Hg/sec and that for LV pressure is b mm Hg, then it follows that each mm of recorded deflection of the logarithmic circuit (dlnP/dt) represents an input of (a/b)x-1 sec-1, which is the calibration factor for dlnP/dt. Ten determinations of this calibration factor were made for any given experiment and then averaged. In general, calibration factors taken from the early downslope (prior to 50% decline from its peak value) of dlnP/dt seem to have been most constant and accurate. Following determination of the dlnP/dt calibration factor, 10 to 15 points were taken from different parts of the experimental record for a given day and dP/dt (mm Hg/sec) divided by LV pressure (mm Hg) was determined along with the simultaneous value of dlnP/dt, using the calibration factor just determined. The resultant data were plotted on a scatter graph for all experiments (Fig. 2).

FIGURE 1
Section of experimental record taken at 200 mm/sec, including logarithm of LV pressure (lnP), derivative of the logarithm of LV pressure (dlnP/dt), aortic pressure (AO), derivative of LV pressure (dP/dt), and LV (LV) pressure. See text for details of calibration method.

EXPERIMENTAL STUDIES
A series of experiments was performed to determine if this method is truly responsive to changes in myocardial contractility. Positive inotropic interventions included intravenous CaCl2, glucagon, and norepinephrine. A negative inotropic intervention was intravenous pentobarbital. Recordings of dlnP/dt, dP/dt, LV pressure, and aortic pressure were taken before and after each intervention.

RESULTS
VALIDATION OF THE METHOD
A scatter graph of (dP/dt)(P-1 on the ordinate against dlnP/dt on the abscissa summarizing data from four experiments is plotted in Figure 2. A close correlation between the two parameters was obtained with a correlation coefficient of r = 0.962 and a slope of 0.965 for the regression line.

Force-velocity vector loops, with dlnP/dt on the ordinate and LV pressure on the abscissa, were recorded for every experiment in the control state and following each intervention. Equivalent force-velocity curves were plotted out on graph paper, with (dP/dt)(P-1 on the ordinate against LV pressure on the abscissa, and excellent agreement in the shape and dimensions of the curve was obtained between these curves ((dP/dt)(P-1 vs. P) and those obtained with the log amplifier circuit (dlnP/dt vs. P) for all four experiments. An example of this agreement is shown in Figure 3. Valve opening occurred at approximately 80 mm Hg, as determined from simultaneous records of phasic aortic pressure.

EXPERIMENTAL STUDIES
The effects of administration by intravenous bolus of calcium chloride, glucagon, norepinephrine, and pentobarbital are tabulated in Table 1. CaCl2 administration in four experiments resulted at 30 seconds in a marked increase in dP/dt (+108%), dlnP/dt (+23%), a fall in LV end-diastolic pressure (—93%), and an increase in aortic mean pressure (+14%) (Fig. 4). Intravenous norepinephrine (50-μg bolus) in two experiments produced an increase at 20 seconds in dP/dt (+200%), dlnP/dt (+127%), aortic mean pressure (+38%), and a decrease in LV end-diastolic pressure (—88%) (Fig. 5). Glucagon (1-mg bolus) in one experiment was followed by
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FIGURE 2

Scatter graph of multiple values of \( \frac{d\ln P}{dt} \) on the ordinate against simultaneous \( \frac{dP}{dt} \) divided by LV pressure on the abscissa. Values represent 40 measurements taken at random from four different experiments. A high degree of correlation was obtained, with \( r = 0.982 \) and the slope of the regression line \( m = 0.965 \).

TABLE 1

Effects of Known Inotropic Interventions

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>LVEDP (mm Hg)</th>
<th>( \frac{dP}{dt} ) (mm Hg/sec)</th>
<th>Aortic mean pressure (mm Hg)</th>
<th>( \frac{dP}{d\ln P} ) (mm Hg/mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.0 ± 1.4</td>
<td>1860 ± 190</td>
<td>130 ± 7</td>
<td>46 = 7</td>
</tr>
<tr>
<td>30°</td>
<td>1.5 ± 1.3</td>
<td>3870 ± 180</td>
<td>143 ± 13</td>
<td>56 = 4</td>
</tr>
<tr>
<td>60°</td>
<td>0 ± 0.1</td>
<td>2240 ± 50</td>
<td>141 ± 11</td>
<td>65 ± 9</td>
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<tr>
<td>CaCl₂ (0.5 g iv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (50 µg iv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>12</td>
<td>2540</td>
<td>114</td>
<td>30</td>
</tr>
<tr>
<td>20°</td>
<td>2</td>
<td>7630</td>
<td>157</td>
<td>68</td>
</tr>
<tr>
<td>30°</td>
<td>5</td>
<td>4910</td>
<td>116</td>
<td>56</td>
</tr>
<tr>
<td>45°</td>
<td>8</td>
<td>4430</td>
<td>146</td>
<td>44</td>
</tr>
<tr>
<td>60°</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon (1 mg iv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>8.5</td>
<td>2480</td>
<td>174</td>
<td>31</td>
</tr>
<tr>
<td>30°</td>
<td>8.5</td>
<td>2750</td>
<td>170</td>
<td>32</td>
</tr>
<tr>
<td>60°</td>
<td>0.5</td>
<td>5530</td>
<td>188</td>
<td>60</td>
</tr>
<tr>
<td>Pentobarbital (5 mg iv)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15</td>
<td>3220</td>
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<td>2580</td>
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<tr>
<td>45°</td>
<td>24</td>
<td>1360</td>
<td>77</td>
<td>18</td>
</tr>
</tbody>
</table>

Values are means ± SE. LVEDP = left ventricular end-diastolic pressure.
FIGURE 3

A force-velocity vector loop with $\frac{d\ln P}{dt}$ on the ordinate and LV pressure ($P$, mm Hg) on the abscissa is displayed in the lower frame. An equivalent force-velocity curve, determined from data recorded immediately following the photographic recording of the vector loop, is shown in the upper frame. This force-velocity curve was obtained by plotting $\frac{dP}{dt}$ divided by simultaneous LV pressure ($\frac{dP}{dt}|P-1$ sec$^{-1}$) on the ordinate against LV pressure ($P$, mm Hg) on the abscissa. Valve opening occurred at approximately 80 mm Hg. There is good agreement in shape and dimensions between the curves resulting from the two methods, particularly in the portion of the curve before valve opening.

Discussion

An excellent correlation was demonstrated in the present study between $(dP/dt)P^{-1}$ determined by conventional methods and $d\ln P/dt$ derived by electronically differentiating the logarithm of the left ventricular pressure. This correlation was predicted on theoretical grounds from the formula for the derivative of a logarithmic function (13), and its experimental verification provides a simple method for the on-line measurement of $(dP/dt)P^{-1}$.

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the validity of \((dP/dt)^{-1}\) either as a good approximation of \(V_{ce}\) or as a precise measure of myocardial contractility. Unresolved problems at this time are the constancy of series elasticity \((K)\) from individual to individual or even in the same individual from moment to moment. A recent study by Brutsaert et al. (14) has helped clarify this problem in the cat papillary preparation, but there is very little information currently available about \(K\) in the intact heart of animals or man. Since \((dP/dt)^{-1} = K \cdot V_{ce}\) during isometric systole, measurement of \((dP/dt)^{-1}\) is a composite of changes in \(K\) and \(V_{ce}\), and therefore depends upon the properties of both the contractile and series elastic components. The extrapolation of \((dP/dt)^{-1}\) to zero pressure (unloaded muscle) in order to obtain theoretical maximum contractile element velocity (or \(V_{max}\)) has been criticized by Mirsky (15, 18) and is known to be fraught with error on technical grounds, owing to the small number of points obtainable experimentally on the initial downslope of the force-velocity curve. Furthermore, the validity of \(V_{max}\) as a representation of the maximum contractile element velocity has recently been criticized on theoretical grounds (17). Mirsky and others have suggested that the peak value of \((dP/dt)^{-1}\) may be a useful contractility index (15, 16, 18, 19), and this value is directly obtainable using the logarithmic amplifier.

The present study also reports the development of a method for the recording of force-velocity vector loops, and documents close correlation between the resultant curves and force-velocity curves calculated by previous methods. It should be pointed out that the representation of \((dP/dt)^{-1}\) on the ordinate against \(P\) on the abscissa can only be
FIGURE 5
Experimental record of the effects of a 50-mg intravenous bolus of norepinephrine on left ventricular performance in a thoracotomized dog. Increases in dlnP/dt, LV systolic pressure, dP/dt, and aortic mean pressure, and a decrease in LV end-diastolic pressure followed within 15 seconds of the injection. A rise in LV systolic pressure preceded the increase in dlnP/dt, as opposed to the response to intravenous calcium.

considered equivalent to the ventricular force-velocity relationship during isovolumic systole. Only during this period is myocardial wall tension a linear function of ventricular pressure, as dictated by the law of Laplace (7, 11). The significance, therefore, of that portion of the vector loops beyond the valve opening (Fig. 3) is unclear and bears further investigation. It should be clear that $V_{\text{max}}$ could easily be extrapolated from data provided by the vector loop force-velocity curve; we have not done this in our experiments because of the criticisms of $V_{\text{max}}$ alluded to above.

The responsiveness of $(dP/dt)P^{-1}$ determined by the present method to various interventions affecting the inotropic state was demonstrated in experimental studies. Intravenous infusions of CaCl$_2$, norepinephrine, and glucagon have previously been shown to augment myocardial contractility as determined by a variety of techniques (20-22). In our studies $(dP/dt)P^{-1}$ determined by the present logarithmic method increased promptly following administration of each of these agents; the increase was associated with a fall of LV end-diastolic pressure. Pentobarbital, on the other hand, has been shown to have a depressant effect on myocardial contractility, and this was reflected by the early drop in $(dP/dt)P^{-1}$ which preceded a fall in LV end-diastolic pressure.

Acknowledgment
We wish to express our grateful appreciation to Mr. Burton Cutting and Mrs. Marcia Handin for their valuable technical assistance. In addition, we gratefully acknowledge the secretarial assistance of Miss Susan Jubelirer and Mrs. Brenda Johnson.

References
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doi: 10.1161/01.RES.28.2.290

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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