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# Quantitative Comparison of the Force-Interval Relationships of the Canine Right and Left Ventricles

Daniel Burkhoff, David T. Yue, Michael R. Franz, William C. Hunter,  
Kenji Sunagawa, W. Lowell Maughan, and Kiichi Sagawa

*From the Department of Biomedical Engineering, The Johns Hopkins University, School of Medicine, Baltimore, Maryland*

**SUMMARY.** We quantitatively compared the extrasystolic and postextrasystolic responses of the right ventricle and left ventricle of the same heart, which have vastly different geometries, architectures, and muscle masses. We studied nine isolated, supported canine hearts whose right and left ventricles were made to contract isovolumically with balloons placed in both chambers. The ventricles were paced with the following pattern: 20 regularly timed priming stimulations, followed by a test stimulation at a variable test pulse interval, and, finally, by a second test stimulation which was always delivered 1200 msec after the first test pulse. In each heart, approximately 15 different test pulse intervals between 300 and 1200 msec were investigated. Both the maximum developed pressure and maximum rate of pressure development, expressed as a percentage of their steady state values during the priming period were used to quantify the extra- and postextrasystolic responses. For each extrasystolic and postextrasystolic test beat, the normalized response of the right ventricle was plotted vs. that of the left ventricle. The regression line and correlation coefficient between the two were determined. The average result from nine hearts gave a slope of  $0.96 \pm 0.05$ , an intercept of  $4.52 \pm 4.05\%$  and a correlation coefficient of  $0.995 \pm 0.004$ . This analysis indicated that, despite the differences in right and left ventricular geometry, architecture, and mass, their force-interval behaviors were nearly identical. (*Circ Res* 54: 468-473, 1984)

THE force-interval relationship of cardiac muscle is believed to reflect cellular processes involved in the regulation of contractile performance, and has, therefore, been applied to assess myocardial function in the intact ventricle (Johnson, 1979). However, because ventricular geometry, architecture, and other structural factors influence the transduction of myocardial fiber force to intracavitary pressure, it is not obvious how the globally measured force-interval relationship of the entire ventricle quantitatively relates to that of its constituent fibers. Although qualitative similarities between the force-interval relationships of isolated cardiac muscle and the left ventricle are apparent in the literature, a direct quantitative comparison has never been made, and appears impossible with existing methodologies, for at least two reasons. First, isolation of cardiac muscle and maintenance of its viability by superfusion may alter its properties (Reichel, 1976), thus precluding a direct quantitative comparison to in situ blood-perfused myocardium. Second, comparison of the properties of the entire ventricle with those of a small region of its wall is not possible, because techniques for precisely quantifying regional myocardial contractility are not available. Thus, indirect approaches must be employed to assess the influences of structural factors on the ventricular force-interval relationship.

There are marked differences in geometry, archi-

ture, and muscle mass between the right and left ventricles. In this investigation, we took advantage of these differences to determine if such structural factors influence the ventricular force-interval relationship. The force-interval relationship was systematically characterized by measuring the responses of the right and left ventricles of the same isolated, supported, canine heart to programmed extra- and postextrasystolic stimulations over a wide range of stimulus intervals. The responses of the right and left ventricles were quantitatively compared. So that we could quantify ventricular responses independent of loading conditions, both ventricles contracted isovolumically.

We show that the normalized force-interval relations of the right and left ventricles are nearly identical. Based on this result, a mathematical model was formulated which related ventricular to average myocardial fiber properties and incorporated the concept that chamber geometry, architecture, and muscle mass do not influence the ventricular force-interval relationship.

## Methods

### Preparation

Experiments were performed on nine isolated canine hearts. The surgical procedures used to isolate and support the canine heart were identical to those previously reported by Burkhoff et al. (1984). Briefly, two dogs were

anesthetized with sodium pentobarbital (30 mg/kg, iv). Arterial blood from the support dog perfused the coronary arteries of a heart isolated from the second donor dog. Coronary venous blood from the isolated heart was returned to the venous system of the support dog. The coronary perfusion pressure was maintained at 80 mm Hg by a servo-controlled finger pump (Harvard Apparatus model 1245) that regulated the flow of arterial blood from the support dog. The blood temperature was maintained at 37°C by a heat exchanger. The right and left atria of the isolated heart were opened and the chordae tendinae were freed from both mitral and tricuspid valve leaflets. A metal adapter was sutured to each valvular annulus, and served to hold a water-filled balloon inside each ventricle. The volume of each balloon was maintained at a constant known value by a servo-system described in detail by Suga and Sagawa (1977). A micromanometer (Millar 380) placed inside each balloon was used to measure intraventricular pressure. The pressure signals were electronically differentiated and filtered (Gould model 13-4615-71, corner frequency 30 Hz). The  $dP/dt$  signals were not calibrated because we only considered relative changes in  $dP/dt_{max}$ . In order to reduce the spontaneous heart rate so that a wide range of stimulus intervals could be attained, both right and left atria were excised as completely as possible. An epicardial electrogram was used to distinguish paced beats from spontaneous ventricular beats, which were excluded from analysis. All signals were recorded on an eight-channel pen recorder (Gould 2800).

#### Experimental Protocol

The hearts were paced with bipolar pacing leads; one electrode was placed at the left ventricular apex and the other at the base of the right ventricle. A computer-controlled stimulator (Sunagawa et al., 1982) was used to produce the stimulation sequence depicted in Figure 1. A "priming period" consisted of 20 regularly timed stimuli at a rate called the priming frequency. This was followed by two test stimulations, the first at a variable test pulse interval (TPI), and the second at a fixed interval of 1200 msec after the first. Several values of the TPI between 300 and 1200 msec were tested. In all hearts, a priming frequency of 130 beats/min was used. In three hearts, priming frequencies of 100 and 160 beats/min were also investigated.

#### Effect of Ventricular Volume

In three hearts, we tested whether the choice of ventricular volumes affected the relationship between right and left ventricular force-interval behaviors. The force-interval relationships of the right and left ventricles were measured under four combinations of high and low volumes ranging from 15 to 45 ml in each chamber. We show that, within this range, volume did not influence this

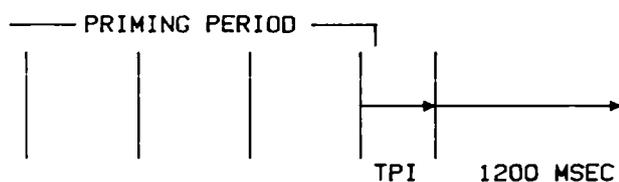


FIGURE 1. Pacing protocol. The last of a series of 20 priming stimuli is followed by two test stimulations, an extrasystole introduced at a variable test pulse interval (TPI), followed by a postextrasystole at a fixed interval of 1200 msec

relationship (see Results). Therefore, in the remaining hearts measurements were made at a single volume setting of approximately 25 ml in each chamber.

#### Data Analysis

The test responses of the right and left ventricles were quantified by two parameters: the maximum developed pressure,  $P_{max}$  (peak systolic pressure minus end-diastolic pressure) and the maximal rate of pressure development,  $dP/dt_{max}$ . For comparison between right and left ventricles, each test response was normalized to the steady state  $P_{max}$  or  $dP/dt_{max}$  of the respective ventricle during the priming period. The relationship between right and left ventricular force interval behaviors was quantified by plotting the normalized left ventricular responses vs. the normalized right ventricular responses for each extrasystolic and postextrasystolic contraction and determining the line of regression and correlation coefficient between them. Test beats introduced at very short TPIs, whose pressure waveforms were fused with that of the last priming beat, were excluded from analysis.

#### Results

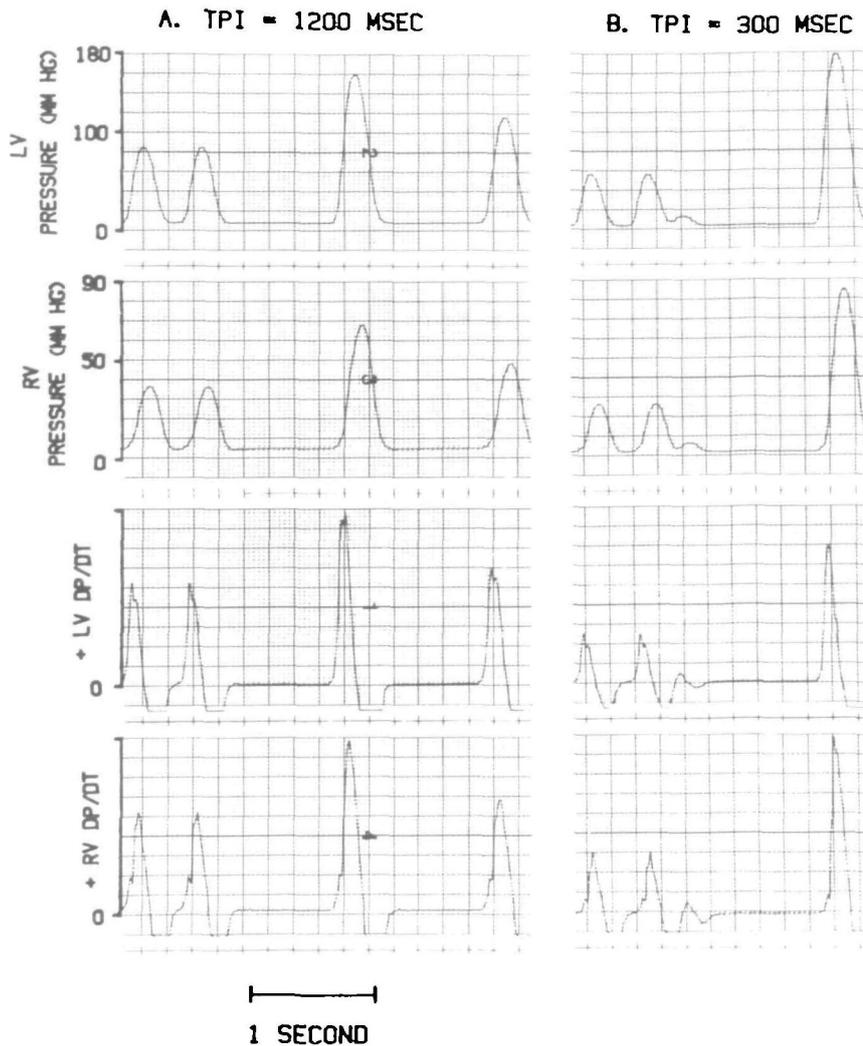
In the original recordings in Figure 2, the general features of the myocardial force-interval relationship are illustrated. Extrasystoles introduced after long pauses were stronger than steady state contractions, and were followed by relatively weaker postextrasystoles (left panel). In contrast, extrasystoles introduced after short TPIs were weaker than steady state contractions, and were followed by relatively strong postextrasystoles (right panel). This behavior was observed in both right and left ventricles.

The results of a representative experiment with a priming frequency of 130 beats/min are illustrated in Figure 3. The responses of the RV (x) and LV (o) on the first test beat, as quantified by normalized  $P_{max}$ , are plotted as a function of the TPI in Figure 3A. The contractile response of the test beats varied between 25% and 200% that of a steady state beat. In both ventricles, as the TPI was increased, the contractile response rose in a monotonic manner to a plateau level. The responses of both ventricles were nearly identical to each other. The results obtained when  $dP/dt_{max}$  was used as the contractile index were identical.

The postextrasystolic responses of the right and left ventricles are shown in Figure 3B. In both ventricles, as the TPI was increased, the normalized  $P_{max}$  of the postextrasystole decreased from a maximum of 260% to a minimum level of 140% that of steady state in a monotonic manner. The normalized responses of both ventricles were very similar to each other over the entire range of test intervals investigated.

In Figure 3C, the normalized responses of the right ventricle were plotted vs. those of the left ventricle for each pair of points in Figure 3A and 3B. The experimental points fell very close to the line of identity (dotted line).

The combined results obtained from the same ventricle when priming frequencies of 100, 130, and



**FIGURE 2.** Recordings from a single isolated heart paced with a priming frequency of 130 beats/min and beating isovolumically. Left and right ventricular pressure tracings and their positive derivative tracings (+LV  $dP/dt$  and +RV  $dP/dt$ , respectively) from the last two priming beats, and both test beats are shown. In panel A, LV volume was 35 ml, RV volume was 25 ml, and the test pulse interval (TPI) was 1200 msec. In panel B, LV volume was 25 ml, RV volume was 20 ml, and the TPI was 300 msec.

160 beats/min were investigated are shown in Figure 4. Linear regression analysis was performed on these data, and the regression slope, intercept, and correlation coefficient ( $r^2$ ) were 0.94, 7.5%, and 0.994, respectively, when  $dP/dt_{max}$  was used as the contractile index (Fig. 4A) and 0.97, 5.10% and 0.998, respectively, when  $P_{max}$  was used (Fig. 4B).

All of the paired RV and LV normalized test responses from a given heart were pooled to obtain a single regression equation. This was also done for the three hearts in which different priming frequencies were investigated. The average results ( $n = 9$ ), summarized in Table 1, indicate that the force-interval behaviors of the right and left ventricles, as quantified by the normalized indices, were nearly identical.

#### Effect of Volume

The effect of ventricular volume was studied in three hearts. In Table 2, the results of a representative experiment where the right and left ventricular force-interval relationships were compared under different preloading conditions are summarized. The

volume in each ventricle was varied over more than a 2-fold range. The regression lines clustered around the line of identity with high correlation coefficients, regardless of whether the left ventricular volume was greater or less than the right ventricular volume. Thus, preload did not significantly affect the relation between right and left ventricular force-interval behavior within the range tested.

#### Discussion

This study demonstrated that the force-interval relationships of the right and left ventricles were nearly identical (Table 1) under the defined experimental conditions. This identity was demonstrated for a wide range of pacing intervals which produced test beats of contractile strengths between 20% and 300% that of steady state beats. Furthermore, this identity was not affected by changes in volume in either left or right ventricles (Table 2). This result held for both contractile indices measured ( $P_{max}$  and  $dP/dt_{max}$ ).

Whereas the force-interval behavior of the left ventricle has been studied in some detail (Johnson,

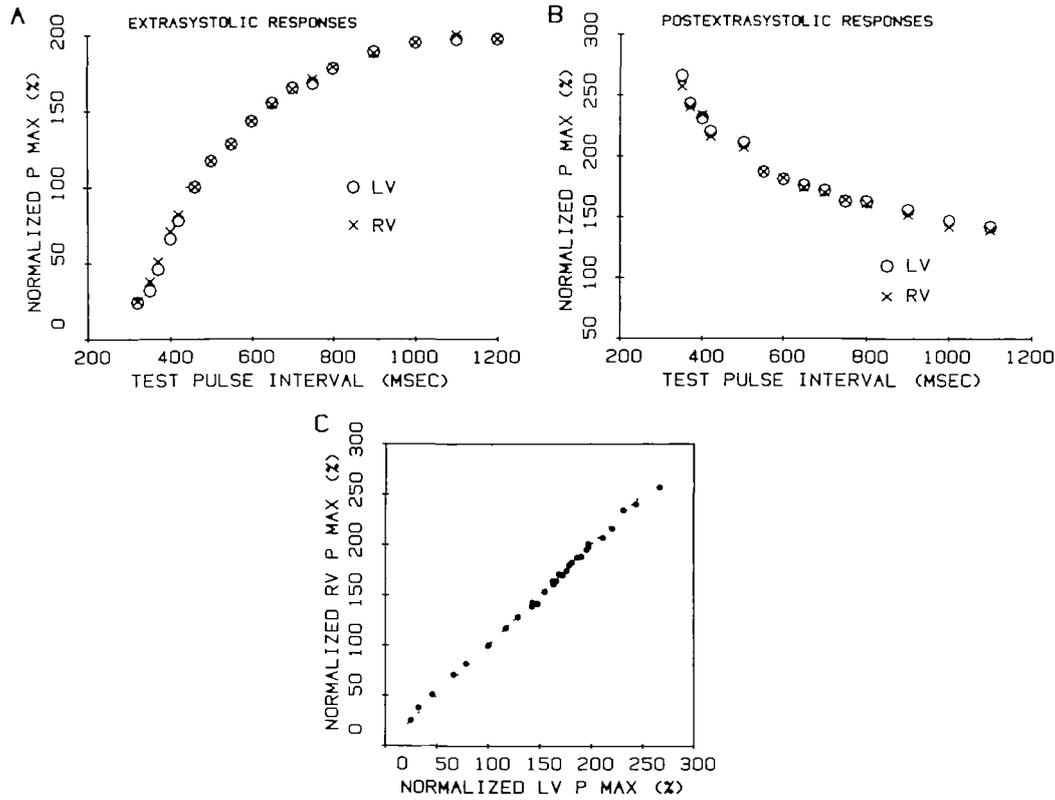


FIGURE 3. Representative results from a single ventricle. Panel A. normalized responses of both the left (○) and the right (×) ventricles on the first test beat as measured by normalized  $P_{max}$  are plotted as a function of the test pulse interval. Panel B: left and right ventricular responses on the second test beats are plotted as a function of the test pulse interval. Note that the y-axis scales are different in panels A and B, but that the 100% levels (dotted lines) represent the same steady state contractile response. Panel C: right and left ventricular responses on each test beat shown in panels A and B are plotted vs. each other. The line of identity (dotted line) was drawn to emphasize the observation that the right and left ventricular responses were nearly identical on all test beats:  $RV = 0.97 LV + 5.10\%$  ( $r^2 = 0.998$ ).

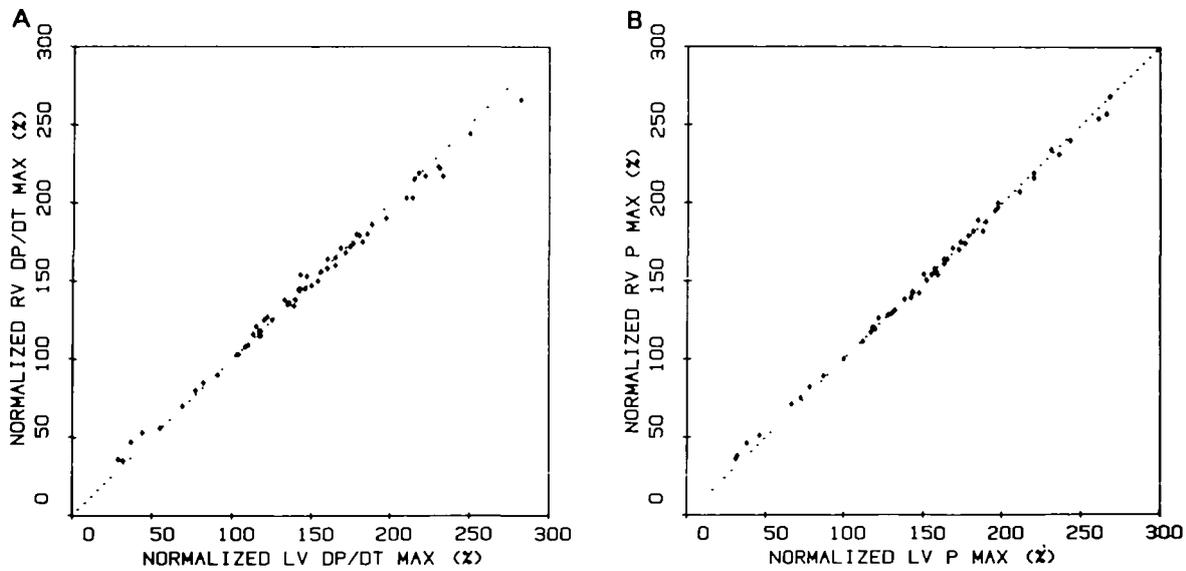


FIGURE 4. Combined results from a single ventricle when priming frequencies of 100, 130, and 160 beats/min were used. This figure illustrates that the right and left ventricular force-interval relationships were nearly identical over a wide range of contractile states, independent of the choice of contractile index. Panel A. for  $dP/dt_{max}$ ,  $RV = 0.94 LV + 8.8\%$  ( $r^2 = 0.994$ ). Panel B: for  $P_{max}$ ,  $RV = 0.97 LV + 5.20\%$  ( $r^2 = 0.998$ ). The dotted lines are lines of identity.

TABLE 1  
Relation between Right and Left Ventricular Force-Interval Relationships

Contractile index	Slope	Intercept	$r^2$
$P_{\max}$	$0.96 \pm 0.05$	$4.24 \pm 4.31\%$	$0.995 \pm 0.004$
$dP/dt_{\max}$ ( $n = 9$ )	$0.96 \pm 0.05$	$4.79 \pm 3.79\%$	$0.994 \pm 0.004$

Results expressed as mean  $\pm$  sd.

1979), the right ventricular force-interval relationship has been examined relatively little (Siebens et al., 1959; Millar et al., 1966; Hammon et al., 1975). The results of those studies indicated that the right ventricle behaved qualitatively like the left ventricle. However, no previous study quantitatively compared the right and left ventricular force-interval relations in detail while the mechanical loading conditions of both ventricles were controlled.

That ventricular volumes did not influence the similarity between the right and left ventricular force-interval behaviors is consistent with previous results. For both isolated cardiac muscle and intact left ventricles, the normalized force-interval relationship is independent of preload (Anderson et al., 1976; Burkhoff et al., 1984). It seems reasonable to assume that the same is true for the right ventricle. Therefore, the choice of ventricular volumes should not have affected the results.

Several investigators have developed quantitative models which relate the pressure generated in a ventricular chamber to the force generated by its constituent muscle fibers (Falsetti et al., 1970; Anderson et al., 1974; also see Yin, 1981, for a recent review). Most of them can be expressed in the following form:

$$P_{v,\max}(\text{Vol}) = nG(\text{Vol})e_{\max}, \quad (1)$$

where  $P_{v,\max}(\text{Vol})$  is the maximum ventricular pressure as a function of volume (Vol),  $n$  is a proportionality factor reflecting the number of cells in the chamber and wall thickness,  $G(\text{Vol})$  is a geometrical factor which relates the size, shape, and architecture of the ventricle to the effective length of a hypothetical "average" muscle fiber, and  $e_{\max}$  is a factor that describes the contractile state of this "average" muscle fiber at peak activation.

One factor not considered in Equation 1 is the possibility that the geometric factor  $G$  is not only a

TABLE 2  
Effect of Volumes on the Relation between Right and Left Ventricular Force-Interval Behaviors

Volume		Regression data		
LV	RV	Slope	Intercept	$r^2$
35	45	0.99	-0.07%	0.994
35	20	0.96	-1.22%	0.986
20	25	0.96	3.92%	0.997
15	40	0.97	-3.34%	0.971

function of volume, but also of regional contractility. If different regions of the heart interact in a nonlinear fashion to produce the overall chamber pressure, then proportionate changes in regional contractility might result in a disproportionate change in pressure. However, the studies of Olsen et al. (1981) suggest that ventricular geometry is independent of contractility in the *steady state*. In the theoretical development to follow, we will assume that  $G$  is independent of contractility under both steady state and *transient* conditions.

If all other factors are maintained constant, the contractile state of the muscle on a given beat is dependent on the history of the pacing sequence prior to that beat. Such pacing-dependent contractile state variations can be accounted for by modifying Equation 1 as follows:

$$P_{v,\max}(\text{Vol}, H) = nG(\text{Vol})e_{\max}(H), \quad (2)$$

where  $H$  denotes the history of the pacing sequence prior to the contraction. We can express the *normalized* ventricular response on a test stimulation such as an extrasystole or a postextrasystole using Equation 2 as:

$$\frac{P_{v,\max}(\text{Vol}, T)}{P_{v,\max}(\text{Vol}, SS)} = \frac{nG(\text{Vol})e_{\max}(T)}{nG(\text{Vol})e_{\max}(SS)}, \quad (3)$$

where  $H = T$  denotes a test stimulation and  $H = SS$  denotes steady state pacing. Since we consider only isovolumic contractions,  $G(\text{Vol})$  is the same on both steady state and test beats. Also, the mass,  $n$ , of the ventricle remains constant. Equation 3 simplifies to:

$$\frac{P_{v,\max}(T)}{P_{v,\max}(SS)} = \frac{e_{\max}(T)}{e_{\max}(SS)}. \quad (4)$$

Our finding of equivalent right and left ventricular force-interval behaviors can be expressed using Equation 4 as:

$$\frac{e_{\max,R}(T)}{e_{\max,R}(SS)} = \frac{e_{\max,L}(T)}{e_{\max,L}(SS)}, \quad (5)$$

where the subscripts R and L denote right and left ventricular properties, respectively. Equation 5 must be interpreted with caution. First, because Equation 5 expresses the equivalence of ratios between steady state and test conditions, our analysis does not reveal information about the relation between the absolute functioning of the average right and left ventricular fibers. Second, only under the condition of relatively homogeneous force-interval properties throughout each ventricle would relations concerning average muscle properties have much to do with the behavior of the large majority of individual muscle fibers.

In summary, the equivalence between normalized right and left ventricular behaviors could result from two possible situations. It could be that the force-interval properties of all the myocardial cells are fairly uniform throughout both ventricles and that, as expressed in the theoretical formulation, ventric-

ular structure does not influence the global expression of those properties. Alternatively, the force-interval properties could be nonuniformly distributed, while ventricular geometry compensates in such a way that the right and left ventricles exhibit the same normalized global behaviors. Our results cannot be used to distinguish between these two possibilities. We favor the concept that the force-interval properties are fairly homogeneous over the heart, because it seems unlikely that regional variations could have been exactly compensated by geometric factors so that the right and left ventricular force-interval behaviors would always be so consistently similar.

If our viewpoint is correct, then the measurement of the force-interval relationship appears to be an attractive approach for evaluating muscle performance in the whole ventricle, since, as expressed in Equation 4, information about fiber functioning may be retrievable independent of ventricular structure. It has previously been proposed that a ratio similar to that expressed in Equations 3 and 4 be used as an index of contractility, since this ratio varies in a predictable way with inotropic interventions (Anderson et al., 1976). Based on the above analysis and on recent interpretations of the myocardial force-interval relationship (Wohlfart, 1979), such an index would provide information complementary to other, commonly referenced ventricular contractile indices [such as  $dP/dt_{\max}$  or  $E_{\max}$  (Sagawa, 1974)] which do depend on ventricular size and geometry, as well as the functional state of the muscle.

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Address for reprints: Daniel Burkhoff, Department of Biomedical Engineering, The Johns Hopkins University, School of Medicine, 720 Rutland Avenue, Traylor Building, Room 223, Baltimore, Maryland 21205

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INDEX TERMS: Force-interval relationship • Postextrasystolic potentiation • Right ventricle • Left ventricle