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DT Yue, D Burkhoff, MR Franz, WC Hunter and K Sagawa

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# Postextrasystolic Potentiation of the Isolated Canine Left Ventricle

## Relationship to Mechanical Restitution

David T. Yue, Daniel Burkhoff, Michael R. Franz, William C. Hunter, and Kiichi Sagawa

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

**SUMMARY.** We established, for the isolated, isovolumically beating canine left ventricle, a comprehensive description of postextrasystolic contractile strength ( $dP/dt_{max}$ ) as a function of extrasystolic and postextrasystolic stimulus intervals. In contrast to previous studies of postextrasystolic beats in in situ hearts, these isolated ventricles contracted isovolumically so that  $dP/dt_{max}$  was not affected by fluctuations in preload and afterload and was therefore considered to be a reliable index of intrinsic contractility. With the interval preceding extrasystoles constant, postextrasystolic contractile strength increased monoexponentially to a plateau as the interval preceding postextrasystoles lengthened, with a mean time constant ( $\pm$ SD) of  $182 \pm 44$  msec ( $n = 53$ ). The onset of this increase in postextrasystolic contractile strength coincided with repolarization of the extrasystolic action potential. With the interval preceding postextrasystoles held constant and long (1200 msec), postextrasystolic contractile strength decreased according to a monoexponential function as the interval preceding extrasystoles lengthened [mean time constant ( $\pm$ SD) of  $176 \pm 18$  msec ( $n = 10$ )]. These phenomena could be quantitatively summarized by a single equation description of postextrasystolic contractile strength which involved monoexponential functions with one time constant. The mathematical form of this description led us to a simple interpretation of these phenomena in terms of currently proposed excitation-contraction coupling models of the heart. (*Circ Res* 56: 340-350, 1985)

THE MARKED INFLUENCE of changes in stimulation pattern upon the contractile strength of extrasystoles and postextrasystoles has long fascinated both the physiologist and the physician (Cranefield, 1965). For the physiologist, these phenomena appear to be fundamental manifestations of the beat-to-beat kinetics of activator calcium (Morad and Goldman, 1973), whereas, for the physician, they represent relationships which may prove to be sensitive indicators of contractility and disease state (Reichel et al., 1974; Anderson et al., 1979).

Despite such long-standing interest in these phenomena, their quantitative characterization at the ventricular level has remained incomplete. Information regarding the dependence of extrasystolic and postextrasystolic contractile strength upon preceding stimulus intervals has been primarily derived from superfused, isolated muscle (Johnson, 1979). Far less is known at the ventricular level mainly because of the uncertainty in determining whether changes in observed pressure reflect alterations in stimulation pattern or the associated fluctuations in preload and afterload (Anderson et al., 1976; Burkhoff et al., 1984a).

These difficulties were recently surmounted by the use of an isolated, perfused canine ventricle in our study of the force-interval relationship of extrasystoles (Burkhoff et al., 1984a). In this preparation, preload and afterload could be held constant by

making the isolated ventricle contract isovolumically, thereby rendering contractile strength a direct function of preceding stimulus intervals. In addition, the atria could be removed, thus facilitating the ability to pace the ventricle as desired over a broad range of intervals. We demonstrated for the isovolumically beating ventricle that extrasystoles exhibited the phenomenon known from isolated muscle studies as mechanical restitution (Braveny and Kruta, 1958). Specifically, extrasystolic ventricular contractile strength rose with a monoexponentially increasing time course as the interval preceding extrasystoles was gradually lengthened.

The purpose of the present study was to extend our previous work with extrasystoles and establish, in the isolated heart, a comprehensive description of postextrasystolic contractile strength. The strength of postextrasystoles was a function of both the interval preceding extrasystoles (ESI) and the interval preceding postextrasystoles (PESI). With ESI constant, postextrasystolic strength increased as PESI was lengthened (postextrasystolic mechanical restitution), and, with PESI fixed, postextrasystolic strength increased as ESI was shortened (postextrasystolic potentiation). These phenomena could be quantitatively summarized by a single equation which describes postextrasystolic contractile strength. The simplicity of the description led us to a novel interpretation of these phenomena in terms

of currently proposed excitation-contraction (e-c) coupling models of the heart.

## Methods

### Surgical Preparation

A total of 14 isolated, perfused canine hearts were studied. The procedures used to isolate and support a canine heart were similar to those described by Suga and Sagawa (1974). A pair of mongrel dogs was anesthetized with sodium pentobarbital (30 mg/kg, iv). The femoral arteries and veins of one dog (support dog) were cannulated and connected to a perfusion system that was used to supply oxygenated blood to the isolated heart. The chest of the second dog (donor dog) was opened under artificial respiration. The left subclavian artery was cannulated with the arterial line of the perfusion system. The brachiocephalic artery was cannulated to monitor the coronary perfusion pressure. The azygous vein, superior and inferior vena cavae, descending aorta, and lung hili

were ligated. The heart was then removed from the donor dog. Left and right atria were completely excised to eliminate spontaneous supraventricular rhythms and thereby facilitate the exploration of a wide range of stimulated pacing intervals. All chordae tendinae were freed from the mitral valve leaflets. A metal adapter that held isolated heart to the ventricular-volume servo-pump system was sutured to the mitral ring. When the surgical preparation was complete, the isolated heart was positioned such that a water-filled, latex balloon was inside the left ventricular cavity. Accumulation of blood in the space between the balloon and ventricular wall was avoided by venting.

The ventricles were made to contract isovolumically throughout a given protocol by holding balloon volume, and therefore left ventricular volume, constant at a single level set between 15 and 35 ml. In all experiments, the coronary perfusion pressure was maintained constant at a selected level between 80 and 100 mm Hg by a servo-controlled perfusion pump (Harvard Apparatus, model 1215). The temperature of the perfusate was maintained between 35° and 37°C. Since the atria had been excised

TABLE 1  
Definition of Experimental Variables

Variable		
Type	Name	Definition
Pacing intervals	SSI	Steady state cycle length: interval between steady state stimuli
	ESI	Extrasystolic stimulus interval: interval between extrasystolic and last steady state stimuli
	PESI	Postextrasystolic stimulus interval: interval between extrasystolic and postextrasystolic stimuli
Measured quantities	$dP/dt_{max}$ (SS)	Steady state beats Extrasystolic beats Postextrasystolic beats } Maximum rate of rise of pressure
	$dP/dt_{max}$ (ES)	
	$dP/dt_{max}$ (PES)	
	MAPD <sub>90</sub>	Duration of monophasic action potentials, measured at 90% repolarization
Force-interval relations	MRC <sub>es</sub>	Extrasystolic mechanical restitution curve: normalized $dP/dt_{max}$ of extrasystoles plotted vs. ESI
	MRC <sub>pes</sub>	Postextrasystolic mechanical restitution curve: normalized $dP/dt_{max}$ of postextrasystoles plotted vs. PESI, with ESI held constant
	PESPC	Postextrasystolic potentiation curve: normalized $dP/dt_{max}$ of fully restituted postextrasystoles plotted vs. ESI
Parameters characterizing force-interval relations	<i>Extrasystolic Mechanical Restitution Curve (MRC<sub>es</sub>)</i>	
	CR <sub>max,es</sub>	Maximum extrasystolic contractile response: plateau value
	T <sub>trc,es</sub>	Time constant
	t <sub>0,es</sub>	ESI-axis intercept value
	<i>Postextrasystolic Mechanical Restitution Curve (MRC<sub>pes</sub>)</i>	
	CR <sub>max,pes</sub>	Maximum postextrasystolic contractile response: plateau value
	T <sub>trc,pes</sub>	Time constant
	t <sub>0,pes</sub>	PESI-axis intercept value
	<i>Postextrasystolic Potentiation Curve (PESPC)</i>	
	A	Amplitude
B	Plateau value	
T <sub>pespc</sub>	Time constant	

and, therefore, could not be used as a pacing site, the hearts were stimulated, instead, with one bipolar electrode placed near the AV node, and the other at the apex. This electrode placement was chosen in an attempt to activate the ventricle through the His-Purkinje system.

### Variables

To describe accurately the force-interval relation of extra- and postextrasystoles, we found it necessary to use a number of variables. Although these will be carefully defined in the text, they are also compiled and described briefly in Table 1.

### Measurements

The left ventricular pressure was measured by a catheter-tip pressure transducer (Millar 300) placed inside the latex balloon within the left ventricle. The left ventricular pressure was electronically differentiated (Gould model 13-4615-71, corner frequency 30 Hz). The maximum rate of rise of left ventricular pressure ( $dp/dt_{max}$ ) was used to quantify contractile strength.

A cardiac surface electrogram was recorded by placing one electrode at the base of the right ventricle and another at the base of the left ventricle. By examining the shape of this signal, we could identify ventricular escape and aberrantly conducted beats which were then excluded from analysis.

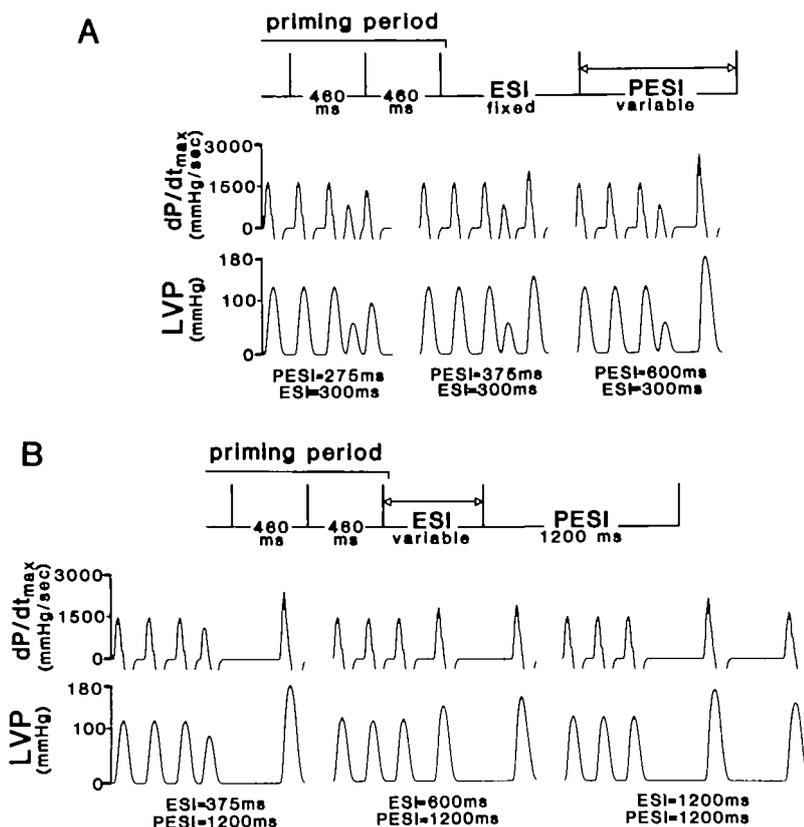
To measure the durations of local myocardial depolarization, we recorded monophasic action potentials (MAP) from the epicardial surface of the left ventricle using a new contact-electrode recording technique (Franz et al., 1983). The recording device consisted of two electrodes (sintered Ag-AgCl) mounted on the distal end of an

L-shaped cantilever. One electrode, placed at the tip of the cantilever, was pressed against the epicardium by a spring-loading mechanism. The other electrode was positioned 5 mm proximal to the tip. Electrical contact between the proximal electrode and the heart was made through a small saline-soaked piece of foam rubber. The voltage across the two electrodes was differentially amplified to obtain the MAP signal. The time duration from the upstroke of the MAP to 90% repolarization will be referred to as the  $MAPD_{90}$ .

### Protocols and Representation of Data

A digital computer (Intel, model iSBC 86/12A) controlled a pacer which supplied current to the electrodes. The computer was programmed to produce two types of pacing paradigms.

The first type of pacing pattern is shown by the set of schematized pacing spikes at the top of Figure 1A. During the "priming period," ventricles were paced by a series of 15–20 regularly timed stimuli delivered at a rate of 130 beats/min (equivalent to a steady state cycle length of 460 msec). The priming period was long enough so that the mechanical and electrical responses to stimulation had been at a steady state for at least 8 beats before an altered stimulus interval was imposed. If an escape or aberrantly conducted beat occurred during this time, such that a steady state was not observed for at least the last 5 beats of the priming period, another set of regularly timed stimuli was delivered before proceeding further. An extrasystolic stimulus followed the last regularly timed stimulus of the priming period by an interval called the extrasystolic interval(s) (ESI). A postextrasystolic stimulus was then delivered which followed the extrasystolic stimulus by an



**FIGURE 1.** Original records from a single, isovolumically beating isolated heart. Each frame shows three steady state responses, an extrasystolic response, and a postextrasystolic response for various stimulus intervals. Left ventricular volume was 23 ml. Panel A: top; schematized pacing spikes illustrating the stimulation protocol used to determine postextrasystolic mechanical restitution curves (see text for details). The extrasystolic interval (ESI) is the interval between the last stimulus in the priming period and the extrasystolic stimulus. The postextrasystolic interval (PESI) is the interval between extrasystolic and postextrasystolic stimuli. Bottom: ventricular responses illustrating recovery of postextrasystolic contractile strength as PESI was increased with ESI constant at 300 msec. LVP is left ventricular pressure. Panel B: top; schematized pacing spikes illustrating the stimulation protocol used to determine postextrasystolic potentiation curves and extrasystolic mechanical restitution curves simultaneously (see text for details). Bottom: ventricular responses illustrating simultaneous decline of postextrasystolic contractile strength and recovery of extrasystolic contractile strength with lengthening ESI.

interval called the postextrasystolic interval(s) (PESI). This sequence was repeated with ESI held constant while PESI was changed with each repetition. The longest PESI was either 1200 msec, or, if this was not possible, that interval which was determined by the timing of ventricular escape beats. The shortest PESI was that which elicited a postextrasystolic contraction just after complete relaxation of the extrasystolic contraction. If PESI were shortened beyond this point, postextrasystolic beats became fused to extrasystoles so that the contractile strength of postextrasystoles, independent of the contribution from incompletely relaxed extrasystoles, could not be determined. By not allowing PESI to be this short, we excluded such fused beats from analysis.

The ventricular responses to the first type of stimulation protocol, illustrated by the original records in Figure 1A, were used to determine postextrasystolic mechanical restitution curves (defined below). When PESI was short, postextrasystolic  $dP/dt_{max}$  and left ventricular pressure (LVP) were small (leftmost frame of Figure 1A with PESI = 275 msec). As PESI was lengthened, postextrasystolic  $dP/dt_{max}$  and pressure increased monotonically (middle and rightmost frames of Figure 1A with PESI equal to 375 and 600 msec, respectively). The recovery of postextrasystolic contractile strength with lengthening PESI was graphically represented by postextrasystolic mechanical restitution curves ( $MRC_{pes}$ ) which were constructed by plotting postextrasystolic  $dP/dt_{max}$  (normalized by the last preceding steady state  $dP/dt_{max}$  and expressed in %) as a function of PESI. Note that since ESI was fixed (ESI = 300 msec in the particular example shown in Figure 1A), extrasystolic  $dP/dt_{max}$  did not change with each repetition of the stimulation sequence.

The second type of pacing pattern (top of Fig. 1B) was similar to the first, except that, with each repetition of the sequence, ESI was varied while PESI was held constant at an interval of 1200 msec. The shortest ESI was that which elicited an extrasystolic contraction just after complete relaxation of the last steady state contraction, thereby excluding from analysis those extrasystoles which were "fused" to steady state beats. The longest ESI was 1200 msec.

The mechanical responses to the second type of stimulation pattern, illustrated by the original records in Figure 1B, were used to simultaneously determine extrasystolic mechanical restitution curves and postextrasystolic potentiation curves (both defined below). When ESI was short, the  $dP/dt_{max}$  and pressure of extrasystoles were small, whereas those indices for postextrasystoles were large (leftmost frame of Figure 1B with ESI = 375 msec). As ESI was lengthened, the contractile strength of extrasystoles increased while that of postextrasystoles decreased (middle and rightmost frames of Figure 1B with ESI equal to 600 and 1200 msec, respectively). The recovery of extrasystolic contractile strength with lengthening ESI was represented by extrasystolic mechanical restitution curves ( $MRC_{es}$ ) which were constructed by plotting extrasystolic  $dP/dt_{max}$  (normalized by the last steady state  $dP/dt_{max}$  and expressed in %) as a function of ESI. The simultaneous decline of postextrasystolic contractile strength with lengthening ESI was graphically represented by postextrasystolic potentiation curves (PESPC). PESPC were constructed by plotting the  $dP/dt_{max}$  of postextrasystoles following long PESI equal to 1200 msec (normalized by the last steady state  $dP/dt_{max}$  and expressed in %) as a function of ESI.

## Analysis

Monoexponential functions were fitted to the three types of curves discussed above ( $MRC_{pes}$ ,  $MRC_{es}$ , and PESPC) by the Taylor series method of nonlinear least-squared error estimation (Draper and Smith, 1981).

The quality of the fit was estimated by the root mean squared error normalized by the magnitude of the exponential (RMSNE) and expressed in percent.

Ninety-five percent confidence intervals were determined for the time constants associated with the fitted monoexponential functions by using a linearized estimate of the variance-covariance matrix (Draper and Smith, 1981). Differences between two time constants were considered statistically significant ( $P < 0.05$ ) when their 95% confidence intervals did not overlap.

## Results

### Effect of Different Extrasystolic Intervals on Postextrasystolic Mechanical Restitution

To establish a comprehensive description of postextrasystolic contractile strength as a function of both ESI and PESI, we determined a number of postextrasystolic mechanical restitution curves ( $MRC_{pes}$ ) corresponding to a wide range of different ESI. Four major properties of postextrasystolic mechanical restitution were demonstrated by all 11 ventricles studied in this series. These properties are illustrated by the  $MRC_{pes}$  in Figure 2, which were measured from a single, representative ventricle. The four curves were obtained in a sequential manner over a period of 20–30 minutes and correspond to ESI values of 300, 350, 460, and 1200 msec. The

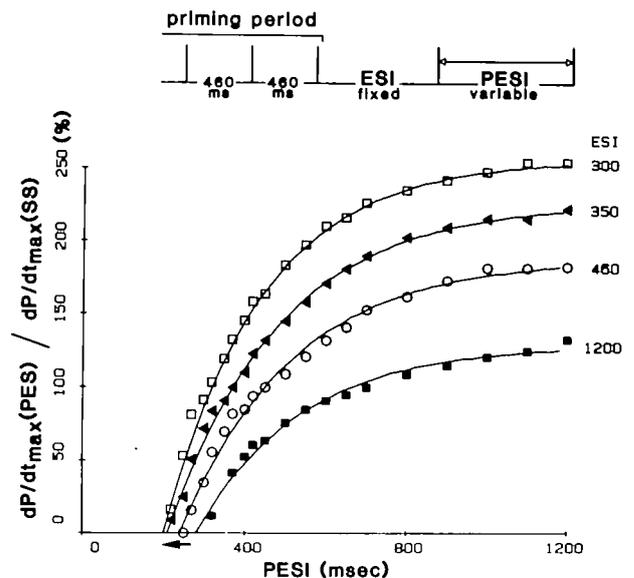


FIGURE 2. Top: stimulation protocol used to determine postextrasystolic mechanical restitution curves ( $MRC_{pes}$ ). Bottom: four  $MRC_{pes}$  measured from a single ventricle.  $dP/dt_{max}(PES)$  and  $dP/dt_{max}(SS)$  are the extrasystolic and steady state  $dP/dt_{max}$ s. The four curves were obtained with ESI set equal to 300 (open square), 350 (filled triangle), 460 (open circle), and 1200 (filled square) msec. Solid curves are least-squares fitted monoexponential functions.

stimulation pattern ("first type") used to obtain these curves is reproduced at the top of Figure 2.

First, the curves were well-described by a monoexponential rise to a plateau level, termed the "maximum postextrasystolic contractile response ( $CR_{\max, \text{pes}}$ ). The solid curves in Figure 2 are monoexponential functions of the form:

$$\frac{dP/dt_{\max}(\text{PES})}{dP/dt_{\max}(\text{SS})} = CR_{\max, \text{pes}} \{1 - \exp[-(\text{PESI} - t_{0, \text{pes}})/T_{\text{mrc, pes}}]\}, \quad (1)$$

where  $dP/dt_{\max}(\text{PES})$  and  $dP/dt_{\max}(\text{SS})$  are defined in Table 1;  $t_{0, \text{pes}}$  is the PESI-axis intercept of the fitted curve; and  $T_{\text{mrc, pes}}$  is the time constant of postextrasystolic mechanical restitution. For each curve,  $CR_{\max, \text{pes}}$ ,  $t_{0, \text{pes}}$  and  $T_{\text{mrc, pes}}$  were chosen to provide the best least-squares fit to the data. The quality of the fit for the four  $MRC_{\text{pes}}$  in Figure 2 was quantified by root-mean-squared normalized errors (RMSNE) which were 1.54, 1.47, 2.60, and 3.10%, corresponding to ESI values of 300, 350, 460, and 1200 msec, respectively. Monoexponentials were fitted to the 53  $MRC_{\text{pes}}$  obtained from all 11 ventricles in this series and the mean RMSNE ( $\pm$ SD) was  $2.00 \pm 0.63\%$ , indicating that  $MRC_{\text{pes}}$  were well-fitted by the monoexponential form.

Second,  $T_{\text{mrc, pes}}$  varied little with alterations in ESI, as illustrated by the four sequentially determined curves in Figure 2. Their time constants were 243, 278, 276, and 255 msec, corresponding to ESI of 300, 350, 460, and 1200 msec, respectively. More generally, there was no statistical significance ( $P > 0.05$ ) to the differences in time constant among the  $MRC_{\text{pes}}$  within 9 of 12 sequentially determined sets of curves (from 11 ventricles). In the other three sets of curves, there was only one  $MRC_{\text{pes}}$  whose time constant differed significantly ( $P < 0.05$ ) from those of the other curves in each set. Furthermore, the variation of  $T_{\text{mrc, pes}}$  with changes in ESI was small in all 12 sets of curves. This is demonstrated by normalizing the  $T_{\text{mrc, pes}}$  of each set of curves with the  $T_{\text{mrc, pes}}$  corresponding to an ESI of 460 msec, and noting that the mean normalized time constant ( $\pm$ SD) was  $101 \pm 12\%$  ( $n = 41$ ) (time constants of curves with ESI = 460 msec not included in the mean). Finally, there was no significant trend to the minor variations of normalized time constant that did exist. For each set of curves, the line of regression between normalized  $T_{\text{mrc, pes}}$  and ESI was determined, and the average slope of this regression ( $\pm$ SD) was  $-0.02 \pm 0.07\%/msec$  ( $n = 12$ ). The mean  $T_{\text{mrc, pes}}$  ( $\pm$ SD) corresponding to an ESI of 460 msec was  $181 \pm 41$  msec ( $n = 12$ ).

The third general property was a leftward shift of the  $MRC_{\text{pes}}$  as ESI was reduced, as denoted by the arrow drawn in Figure 2. To quantify the amount of shift as a function of ESI, we plotted the PESI-axis intercept ( $t_{0, \text{pes}}$ ) vs. ESI for each of the 12 sets of curves in this series (Fig. 3). For 52 of 53 curves

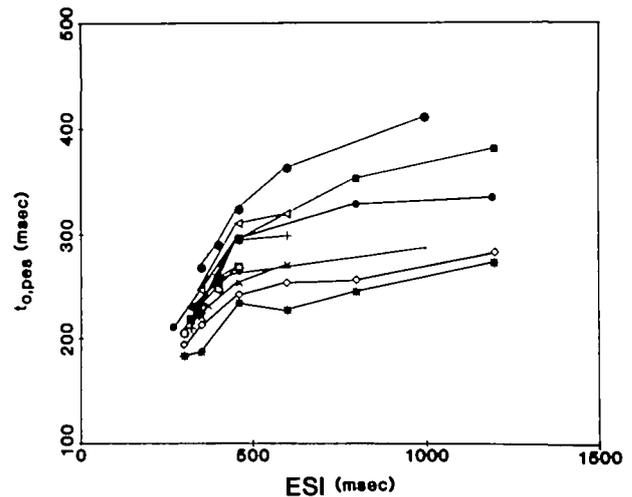


FIGURE 3. Time-axis intercept of  $MRC_{\text{pes}}$  ( $t_{0, \text{pes}}$ ) plotted as a function of ESI. The relationship demonstrates the "leftward shift" of  $MRC_{\text{pes}}$  along the PESI axis as ESI is shortened. Each symbol type corresponds to curves comprising a sequentially determined set of  $MRC_{\text{pes}}$  measured from within a single ventricle. Data from 12 sets of curves are shown.

measured in this series,  $t_{0, \text{pes}}$  declined every time ESI decreased.

Finally, the fully-restituted plateau value of the  $MRC_{\text{pes}}$  ( $CR_{\max, \text{pes}}$ ) increased as ESI was reduced in all 12 sets of curves. In Figure 2, for example,  $CR_{\max, \text{pes}}$  was 258, 228, 189, and 129% corresponding to ESI levels of 300, 350, 460, and 1200 msec. The details of this property will be deferred to the last section of the Results.

With regard to extrasystolic mechanical restitution, the  $MRC_{\text{es}}$  (defined in Methods in connection with the "second type" of pacing protocol) is equivalent to an  $MRC_{\text{pes}}$  with ESI set equal to the steady state cycle length, SSI (460 msec in this study). Then, from the first and second properties discussed above, we know that the  $MRC_{\text{es}}$  will rise monoexponentially with a time constant virtually equal to that of any  $MRC_{\text{pes}}$ .

#### Relationship between PESI-Axis Intercept and Action Potential Duration of Extrasystoles

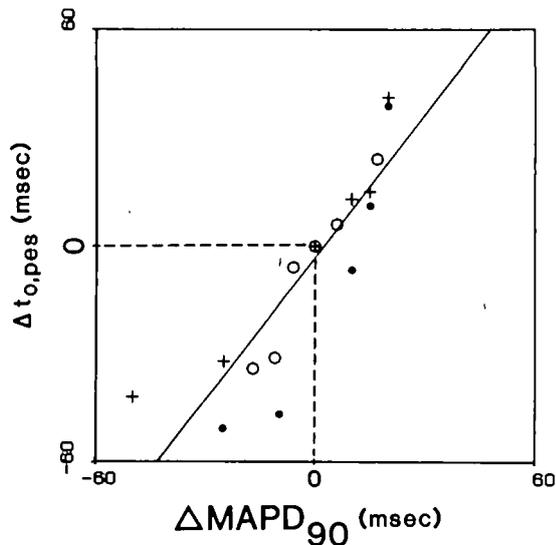
To determine whether the leftward shift of  $MRC_{\text{pes}}$  with decrease in ESI was associated with the shortening of the extrasystolic action potential, we simultaneously determined the PESI-axis intercepts ( $t_{0, \text{pes}}$ ) of  $MRC_{\text{pes}}$  and the duration of monophasic action potentials of extrasystoles in three ventricles. If a reduction of  $t_{0, \text{pes}}$  is taken as a quantitative indicator of the amount of leftward shift, then a correlation between  $t_{0, \text{pes}}$  and the duration of extrasystolic monophasic action potentials would suggest that the leftward shift and the shortening of extrasystolic action potentials were interrelated.

For each ventricle,  $\Delta t_{0, \text{pes}}$  (defined as the difference of a given  $t_{0, \text{pes}}$  from the  $t_{0, \text{pes}}$  when ESI = 460 msec)

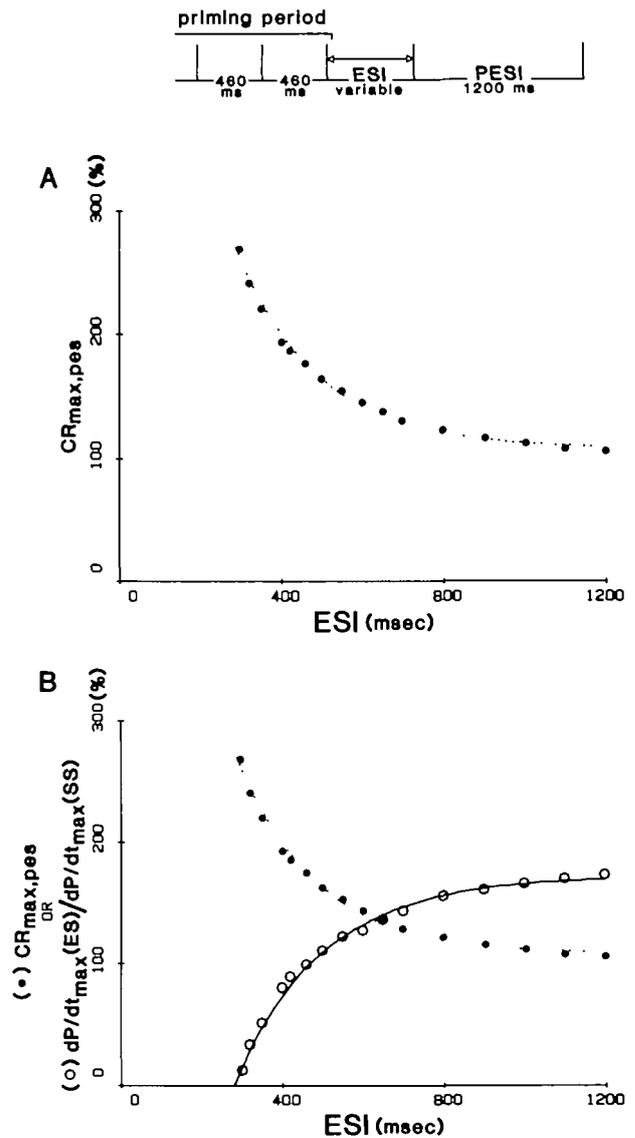
was plotted vs.  $\Delta\text{MAPD}_{90}$  (defined as the difference of an extrasystolic  $\text{MAPD}_{90}$  from the steady state  $\text{MAPD}_{90}$ ) (Fig. 4). The line of regression between  $\Delta t_{0,\text{pes}}$  and  $\Delta\text{MAPD}_{90}$  was determined for the pooled data from the three ventricles (slope = 1.32; y-axis intercept = -3.34 msec;  $r = 0.88$ ;  $n = 18$ ), and the results indicate that, as the extrasystolic action potential shortened, the  $\text{MRC}_{\text{pes}}$  shifted leftward by a comparable amount. Furthermore, the absolute values of steady state  $\text{MAPD}_{90}$  and  $t_{0,\text{pes}}$  when ESI was 460 msec were similar; their respective mean values ( $\pm\text{SD}$ ) were  $227 \pm 21$  and  $246 \pm 15$  msec ( $n = 3$ ). Hence, our results are consistent with the hypothesis that the onset of postextrasystolic mechanical restitution coincided with and may have been causally linked to repolarization of the extrasystolic action potential.

**Dependence of  $\text{CR}_{\text{max,pes}}$  upon ESI: Relationship to Extrasystolic Mechanical Restitution**

To ascertain directly the variation of the maximum postextrasystolic contractile response of  $\text{MRC}_{\text{pes}}$  ( $\text{CR}_{\text{max,pes}}$ ) as a function of ESI and determine whether this function was related to the mechanical restitution curve of extrasystoles, we simultaneously determined postextrasystolic potentiation curves (PESPC) and extrasystolic mechanical restitution curves ( $\text{MRC}_{\text{es}}$ ) in this series of 10 ventricles. The stimulation protocol used to determine these curves ("second type") is reproduced at the top of Figure 5. Notice, with reference to the results shown in Figure 2, that all postextrasystoles arising from the long



**FIGURE 4.** Relation between changes in the minimum required PESI for  $dP/dt_{\text{max}}(\text{PES})$  to reach zero ( $\Delta t_{0,\text{pes}}$ ) and changes in the duration of the extrasystolic monophasic action potential ( $\Delta\text{MAPD}_{90}$ ).  $\Delta t_{0,\text{pes}}$  is equal to the difference of the PESI-axis intercept of a given  $\text{MRC}_{\text{pes}}$  from that of an  $\text{MRC}_{\text{pes}}$  determined with ESI = 460 msec. Each symbol type corresponds to curves comprising a sequentially determined set of  $\text{MRC}_{\text{pes}}$  measured from within a single ventricle. Data from three ventricles are shown.



**FIGURE 5.** Top: stimulation protocol used to obtain a postextrasystolic potentiation curve and extrasystolic mechanical restitution curve, simultaneously. Panel A: postextrasystolic potentiation curve (PESPC) demonstrating tendency for decline in postextrasystolic contractile strength with lengthening ESI.  $\text{CR}_{\text{max,pes}}$  is the fully restituted postextrasystolic  $dP/dt_{\text{max}}$  normalized by  $dP/dt_{\text{max}}(\text{SS})$  and expressed in percent. The dotted curve is a least-squares fitted monoexponential function. Panel B: simultaneously determined extrasystolic mechanical restitution curve ( $\text{MRC}_{\text{es}}$ ) (open circles and solid curve) and PESPC replotted from panel A (filled circles and dotted curve), illustrating that the time course of postextrasystolic potentiation and of mechanical restitution are governed by similar time constants.  $dP/dt_{\text{max}}(\text{ES})$  is the  $dP/dt_{\text{max}}$  of extrasystoles. The solid curve is a least-squares fitted monoexponential function.

PESI in this protocol (1200 msec) would manifest almost fully-restituted plateau levels of contractile strength. Therefore, postextrasystolic contractile strength was nearly equivalent, after normalization by the steady state response and expressed in percent, to  $\text{CR}_{\text{max,pes}}$ .

The PESPC (Fig. 5A) and the  $\text{MRC}_{\text{es}}$  (open circles,

Fig. 5B), which were simultaneously obtained from a single, representative ventricle, illustrate three major results.

First, postextrasystolic potentiation curves decreased monoexponentially to a plateau level as described by a function of the form:

$$CR_{\max, \text{pes}} = B + A (\exp[-(\text{ESI}-t_{0, \text{es}})/T_{\text{pespc}}]), \quad (2)$$

where B is the plateau level and A expresses the amplitude of the PESPC;  $t_{0, \text{es}}$  is the ESI-axis intercept for the simultaneously determined  $MRC_{\text{es}}$ ; and  $T_{\text{pespc}}$  is the time constant of the PESPC. The dotted curve fitted to the PESPC in Figure 5A is derived from Equation 2 with A, B, and  $T_{\text{pespc}}$  chosen to provide the best least-squares fit to the data. In this ventricle,  $A = 171\%$ ,  $B = 108\%$ , and  $T_{\text{pespc}} = 199$  msec, with a root-mean-squared normalized error (RMSNE) of 2.59%. Monoexponentials of the form in Equation 2 were fitted to all 10 PESPC obtained from the 10 ventricles in this series and the mean RMSNE ( $\pm$ SD) was  $2.59 \pm 0.87\%$ , demonstrating that all PESPC were essentially monoexponential in shape. The mean value for the time constant of the PESPC ( $T_{\text{pespc}}$ ) ( $\pm$ SD) was  $176 \pm 18$  msec. The mean value ( $\pm$ SD) for A was  $168 \pm 32\%$ , and for B was  $105 \pm 13\%$ .

Second, as noted earlier in the Results, extrasystolic mechanical restitution curves ( $MRC_{\text{es}}$ ) are a subset of  $MRC_{\text{pes}}$ , so that  $MRC_{\text{es}}$  could be described by a function of the form:

$$\frac{dP/dt_{\max}(\text{ES})}{dP/dt_{\max}(\text{SS})} = CR_{\max, \text{es}} \{1 - \exp[-(\text{ESI}-t_{0, \text{es}})/T_{\text{mrc, es}}]\}, \quad (3)$$

where  $dP/dt_{\max}(\text{ES})$  and  $dP/dt_{\max}(\text{SS})$  are defined in Table 1;  $CR_{\max, \text{es}}$  is the plateau level of the curve;  $t_{0, \text{es}}$  is the ESI-axis intercept for the fitted curve; and  $T_{\text{mrc, es}}$  is the time constant of extrasystolic mechanical restitution. The solid curve fitted to the  $MRC_{\text{es}}$  in Figure 5B (open circles) represents Equation 3 with  $CR_{\max, \text{es}}$ ,  $t_{0, \text{es}}$ , and  $T_{\text{mrc, es}}$  chosen to provide the best least-squares fit to the data. In this case,  $CR_{\max, \text{es}} = 173\%$ ,  $t_{0, \text{es}} = 276$  msec, and  $T_{\text{mrc, es}} = 216$  msec. The root-mean-squared normalized error (RMSNE) for this curve was 1.80%. Monoexponentials of the form in Equation 3 were fitted to the 10  $MRC_{\text{es}}$  obtained from the 10 ventricles in this series and the mean RMSNE ( $\pm$ SD) was  $1.93 \pm 0.40\%$ . The mean parameter values ( $\pm$ SD) were:  $T_{\text{mrc, es}} = 189 \pm 30$  msec,  $CR_{\max, \text{es}} = 166 \pm 23\%$ ,  $t_{0, \text{es}} = 284 \pm 32$  msec.

Third, PESPC and  $MRC_{\text{es}}$  were closely interrelated in that the time constants of curves obtained from the same ventricle were nearly identical. This interrelationship is visually emphasized in Figure 5B which displays on the same set of axes the PESPC (filled circles and dotted curve replotted from Fig. 5A) and the simultaneously measured  $MRC_{\text{es}}$  (open circles and solid curve). In Figure 5B, the time constant of the  $MRC_{\text{es}}$  ( $T_{\text{mrc, es}}$ ) was 216 msec, whereas that for the PESPC ( $T_{\text{pespc}}$ ) was 199 msec. The mean difference between the two time constants ( $\pm$ SD) for

pairs of curves measured in the same ventricle ( $T_{\text{mrc, es}} - T_{\text{pespc}}$ ) was only  $-13 \pm 23$  msec ( $n = 10$ ). The small difference in time constant between simultaneously obtained  $MRC_{\text{es}}$  and PESPC was not statistically significant ( $P > 0.05$ ) in 9 of the 10 ventricles studied.

## Discussion

We showed, for the isolated canine ventricle, that the dependence of postextrasystolic contractile strength upon preceding stimulus intervals was determined by four quantitative properties:

1. Postextrasystolic mechanical restitution follows a monoexponential rise to a plateau (Eq. 1, Fig. 2).
2. The time constant of postextrasystolic mechanical restitution ( $T_{\text{mrc, pes}}$ ) was invariant with changes in ESI, and was virtually the same as the time constant of restitution following steady state beats ( $T_{\text{mrc, es}}$ ).
3. The time to the onset of postextrasystolic mechanical restitution ( $t_{0, \text{pes}}$ ) decreased as extrasystoles became more premature (Fig. 3). This decrease was correlated with the shortening of extrasystolic action potentials (Fig. 4).
4. The maximum postextrasystolic contractile response ( $CR_{\max, \text{pes}}$ ) is a decreasing monoexponential function of ESI (Eq. 2, Fig. 5A), and the time constant of this decrease ( $T_{\text{pespc}}$ ) was approximately equal to the time constant of extrasystolic mechanical restitution ( $T_{\text{mrc, es}}$ ).

We will focus upon three aspects of these results: first, the synthesis of the above properties into a single equation which describes postextrasystolic potentiation; second, the relationship of our results to past work, both at the muscle and ventricular levels; and third, the interpretation of our results in terms of currently proposed e-c coupling models.

### Single-Equation Description of Postextrasystolic Contractile Strength

The properties listed above can be condensed into a single equation which provides a comprehensive description of postextrasystolic contractile strength following pacing at a given steady rate (130 beats/min, in our study). Based upon the second and fourth properties outlined above, we can make the approximation that all the time constants ( $T_{\text{mrc, pes}}$ ,  $T_{\text{mrc, es}}$  and  $T_{\text{pespc}}$ ) are equal, so that, henceforth, we will refer to only one time constant designated T. Then, upon combining Equations 1 and 2, we have the following simple expression which describes the normalized contractile strength of any postextrasystolic beat preceded by intervals within the ranges explored in this study:

$$\frac{dP/dt_{\max}(\text{PES})}{dP/dt_{\max}(\text{SS})} = \{ A (\exp[-(\text{ESI}-t_{0, \text{es}})/T]) + B \} \times \{ 1 - \exp[-(\text{PESI}-t_{0, \text{pes}})/T] \}, \quad (4)$$

where  $t_{0, \text{pes}}$  varies in parallel with the  $\text{MAPD}_{90}$  of extrasystolic beats (Fig. 4), and  $t_{0, \text{es}}$  has been shown

to correlate closely with  $\text{MAPD}_{90}$  of steady state beats (Burkhoff et al., 1984a). This equation describes a provocative phenomenon: interval-dependent postextrasystolic contractile behavior dominated by essentially one time constant.

Since it has been shown in the isolated canine heart (Burkhoff et al., 1984a) and in isolated muscle (Rumberger and Reichel, 1972) that the time constant of extrasystolic mechanical restitution is independent of the steady state stimulation rate, we believe that our description for postextrasystoles (Eq. 4) will hold for priming period rates other than 130 beats/min. Only the particular values for A, B, and  $t_{0,es}$  would differ for different priming period rates.

### Relationship to Past Work

Our results are very similar to phenomena which have been observed, at least in part, in isolated mammalian cardiac muscle. Unfortunately, a full comparison is not possible because either some of the protocols required for our description have not been pursued, or comparable quantitative analysis of the data has not been performed.

Postextrasystolic mechanical restitution curves,  $\text{MRC}_{pes}$ , have been measured in isolated papillary muscles or ventricular trabeculae of the cat (Hoffman et al., 1956), rabbit (Johnson et al., 1964; Wohlfart, 1979), and dog (Anderson et al., 1976). Qualitatively, these  $\text{MRC}_{pes}$  appear as if they could have been described by a monoexponential time course whose time constant was insensitive to changes in ESI; however, explicit analysis to determine these properties was not performed. Johnson and coworkers (1964) did quantify their data by fitting functions to their  $\text{MRC}_{pes}$ . However, since they used nested exponential functions to describe their curves, it is difficult to determine whether monoexponential functions with a single time constant would have fit their data as well.

Postextrasystolic potentiation curves (PESPC) and extrasystolic mechanical restitution curves ( $\text{MRC}_{es}$ ) were simultaneously determined in isolated papillary muscles of the cat (Bass, 1975) and rabbit (Wohlfart, 1979). PESPC declined with a time course approximately equal to that of the rise of  $\text{MRC}_{es}$  with lengthening ESI, but there was no quantitative analysis to determine whether this was actually the case. In earlier work, Hoffman et al. (1956) and Braveny and Kruta (1958) measured curves that were similar to our PESPC, except that the PESI was varied with changing ESI such that  $\text{ESI} + \text{PESI} = 2 \times \text{SSI}$ . Their "pseudo PESPC" appeared to decline in a fashion reciprocal to the rise of  $\text{MRC}_{es}$ .

The leftward shifts of  $\text{MRC}_{pes}$  that we observed in the ventricle with shortening of ESI were probably observed in isolated cardiac muscle by Johnson et al. (1964) and Anderson et al. (1976), but they did not specifically demonstrate this phenomenon. Even so, the ventricular behavior might have been anticipated on the basis of previous electrophysiological studies on isolated muscle. Voltage clamp studies with sheep Purkinje fibers (Gibbons and Fozzard,

1971; Lipsius et al., 1982) and with cat ventricular tissue (Tritthart et al., 1973; Trautwein et al., 1975) suggested that the processes of mechanical restitution are voltage dependent and proceed at appreciable rates only after the membrane has repolarized beyond a certain potential range ( $\sim -35$  to  $-60$  mV). Then, shortening of extrasystolic action potentials with increased prematurity (Boyett and Jewell, 1978) would allow mechanical restitution to begin sooner and thereby cause a leftward shift of  $\text{MRC}_{pes}$ . In our previous studies with isolated canine ventricles (Burkhoff et al., 1984a) and in humans (Franz et al., 1983), we were able to verify a similar prediction that the leftward shifts of extrasystolic mechanical restitution curves ( $\text{MRC}_{es}$ ) correlated with the shortening of steady state action potentials when the heart rate used in the priming period was increased. That  $\Delta t_{0,pes}$  and  $\Delta \text{MAPD}_{90}$  were not exactly equal may relate to the fact that  $\Delta t_{0,pes}$  is a global, ventricular property, whereas  $\Delta \text{MAPD}_{90}$  is a local epicardial property. Then, with slight regional variations of action potential duration and time of activation (Watanabe et al., 1983),  $\Delta t_{0,pes}$  might differ somewhat from  $\Delta \text{MAPD}_{90}$ .

Our description of postextrasystolic potentiation also appears to be in general agreement with the results obtained from in situ canine ventricular preparations. Anderson et al. (1976) measured  $\text{MRC}_{pes}$  which rise monotonically to a plateau. Elzinga et al. (1981) measured PESPC which decline monotonically to a plateau. However, in either case, no quantitative analysis was directed at determining whether the curves were monoexponential.

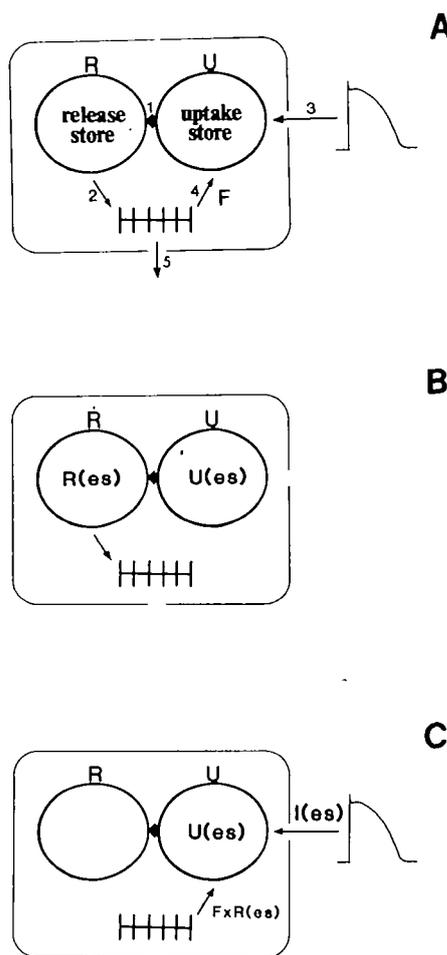
Even if more extensive protocols and analysis had been performed in these in situ studies, the quantitative comparison of in situ ventricular data to our results would remain problematic. Those in situ ventricles were ejecting and filling, not isovolumically contracting, so that measured contractile strength (usually  $dP/dt_{max}$ ) was not only a function of stimulus interval, but also of changing preload (Starling mechanism) and afterload (variable severity of  $dP/dt_{max}$  attenuation by ejection) (Burkoff et al., 1984a). In situ force-interval relations using a preload and afterload insensitive index of contractile strength, such as  $E_{es}$  (Sagawa, 1981), will have to be determined before a direct quantitative comparison of our results to the in situ ventricle can be made.

### Interpretation of Results

The simplicity of our phenomenological results—that the functions which describe extra- and postextrasystolic contractile strength ( $\text{MRC}_{es}$ ,  $\text{MRC}_{pes}$ , and PESPC) are all monoexponential with the same time constant—suggested that it might be relatively simple to understand the mechanism underlying these phenomena. Yet, it was not at all clear whether currently proposed models of e-c coupling (Wood et al., 1969; Beeler and Reuter, 1970; Gibbons and Fozzard, 1971; Morad and Goldman, 1973; Edman and Johannsson, 1976; Wohlfart, 1979) could provide a straightforward explanation for our findings.

This was because these hypotheses were proposed as a set of qualitative descriptions of individual e-c coupling events, while prediction of the PESPC and its relationship to the  $MRC_{es}$  or  $MRC_{pes}$  would require quantitative integration of the results of many individual steps occurring over two cardiac cycles. We therefore developed the following quantitative formulation of an e-c coupling model which makes it possible to visualize clearly how the monoexponential nature (with identical time constants) of our descriptive functions ( $MRC_{es}$ ,  $MRC_{pes}$ , PESPC) could, in fact, represent the net, ensemble behavior of the individual steps which comprise those currently proposed e-c coupling hypotheses.

Figure 6A depicts a model cardiac cell whose e-c



**FIGURE 6.** Hypothesized e-c coupling events within a single cardiac cell. Panel A: calcium fluxes during a single cardiac cycle. The internal store is functionally divided into an uptake store (U) and release store (R) between which sequestered calcium gradually "moves" during the repolarized interval between beats. The myofilaments are represented by the cross-hatched line. F is the recirculation fraction. Panel B: intracellular events which relate most directly to the determination of extrasystolic contractile strength.  $R(es)$  is the amount of calcium released to the myoplasm during an extrasystole.  $U(es)$  is the amount of calcium left in the internal store at the time of the extrasystolic stimulus. Panel C: intracellular events which contribute most directly to the determination of postextrasystolic contractile strength.  $I(es)$  is the amount of calcium which enters the cell to be sequestered by the uptake store during an extrasystole.

coupling properties are a representative composite of those currently proposed in the literature. The general attributes of such a model are developed below.

A common feature of the models cited above which is crucial for the prediction of our results is that the internal store of calcium, presumably the sarcoplasmic reticulum, has the property that sequestered calcium gradually becomes more releasable in the interim between beats. In the present formulation, this is functionally represented by splitting the internal store into an "uptake store" (labeled U) and "release store" (labeled R). Calcium sequestered by the internal store first enters the U store, and then "moves" slowly to the R store with a monoexponential time course characterized by an invariant time constant T (Fig. 6A, 1). The two compartments and the movement of calcium between them need not be interpreted in an anatomical sense; they could just as well be considered a convenient representation for the recovery of releasability from a single internal store compartment [one example of which might be the recovery of sensitivity to  $Ca^{++}$ -induced  $Ca^{++}$  release from sarcoplasmic reticulum (Fabiato, 1983)].

Upon stimulation, the calcium in the R store is completely released into the myoplasmic space (Fig. 6A, 2), and an action potential is elicited which gives rise to calcium entry into the cell (Fig. 6A, 3). Most of this entry calcium is thought to enter the U store directly, while contractile strength in that beat is assumed to reflect primarily the amount of internally released calcium (Fozzard, 1977). Accordingly, in this formulation, contractile strength and the amount of released calcium are related by a constant of proportionality. The assumption of linearity is supported by the finding in aequorin-injected canine Purkinje fibers that the relation between  $dF/dt_{max}$  and estimated peak intracellular  $[Ca^{++}]$ -resting intracellular  $[Ca^{++}]$  is approximately linear for variably restituted contractions (Yue et al., 1984), and the approximation that ventricular pressure relates linearly to muscle stress (see Discussion in Burkhoff et al., 1984b).

Calcium bound to the myofilaments and in the myoplasm is removed through two pathways. A "recirculation fraction" (F) of the released calcium "recirculates" back to the U store (Fig. 6A, 4) (Morad and Goldman, 1973). The remainder of the released calcium is extruded from the cell (Fig. 6A, 5). Finally, it is postulated that there is no movement of calcium from U to R stores until the membrane is repolarized beyond a certain range. This idea is based upon our leftward shift results and the voltage clamp data discussed in connection with these phenomena.

Having discussed the general features of the model, we now specify the particular form of the events associated with the determination of extrasystolic contractile strength (Fig. 6B). Let  $R_{max}(ss)$  be the amount of calcium in the U store just before any calcium moves from U to R stores following the steady state contraction which precedes an extrasys-

tole. The amount of calcium released on the extra-systolic beat ( $R(es)$ ) is therefore equal to  $R_{max}(ss)$  multiplied by an exponential factor:

$$R(es) = R_{max}(ss) \{1 - \exp[-(ESI - t_{o,es})/T]\}. \quad (5a)$$

Since calcium is assumed to move from uptake to release stores only after the membrane has repolarized, the numerator of the argument of the exponential is proportional to  $ESI - t_{o,es}$ , where  $t_{o,es}$  approximates the action potential duration in the preceding steady state beat (Burkhoff, 1984a). The amount of calcium left in the uptake compartment at the time of the extrasystolic stimulus [ $U(es)$ ] must be the difference between  $R_{max}(ss)$  and  $R(es)$  (Eq. 5b):

$$U(es) = R_{max}(ss) \{\exp[-(ESI - t_{o,es})/T]\}. \quad (5b)$$

Recalling that we have assumed that contractile strength and amount of released calcium are linearly related, and defining  $R(ss)$  as the amount of calcium released on a steady state beat, we obtain Equation 5c as the model's expression for an extrasystolic mechanical restitution curve ( $MRC_{es}$ ):

$$\frac{dP/dt_{max}(ES)}{dP/dt_{max}(SS)} = \frac{R_{max}(ss)}{R(ss)} \times \{1 - \exp[-(ESI - t_{o,es})/T_{mrc,es}]\}. \quad (5c)$$

Having described the state of the internal store when the extrasystole occurs, we next explore the details of events which contribute most directly to postextrasystolic contractile strength. There are three sources of calcium for postextrasystoles (Fig. 6C). Consider first the amount of calcium [ $I(es)$ ] which enters the cell via the extrasystolic action potential to be sequestered by the U store. A number of investigators have provided evidence suggesting that the magnitude of the slow inward  $Ca^{++}$  current is inversely related to the amount of calcium released (Edmands et al., 1968; Hiraoka and Sano, 1976; Simurda et al., 1976; Tsien and Marban, 1982). To account for this,  $I(es)$  is assumed to vary inversely with  $R(es)$  such that:

$$I(es) = I_{max} - hR(es), \quad (6)$$

where  $I_{max}$  is a positive constant equal to the maximum possible value of  $I(es)$  and  $h$  is a positive constant equal to the intensity of the inverse relation. The second calcium source which contributes to the postextrasystole is the amount of calcium which recirculated back to the U store,  $F \times R(es)$ . Finally, there is the amount of calcium which was left in the U store at the time of the extrasystolic stimulus [ $U(es)$  in Eq. 5b]. If we consider only fully restituted postextrasystolic responses, there is sufficient time for all the calcium in the internal store—the calcium which came into the U store through the membrane, the recirculated calcium, and the calcium that was in the U store at the time of the extrasystolic stimulus—to move to the R store by the time of the postextrasystolic stimulus. Thus, the

amount of calcium released on fully restituted postextrasystoles would be simply:

$$F R(es) + U(es) + I(es). \quad (7)$$

Substituting into Equation 7 for  $R(es)$ ,  $U(es)$ , and  $I(es)$  from Equations 5a, 5b, and 6, respectively, and normalizing the result by  $R(ss)$ , we have the following model prediction for a postextrasystolic potentiation curve (PESPC):

$$CR_{max,pes} = \underbrace{\left[ \frac{R_{max}(ss)}{R(ss)} (F - h) + \frac{I_{max}}{R(ss)} \right]}_B + \underbrace{\left[ \frac{R_{max}(ss)}{R(ss)} (1 - F + h) \right]}_A \left( \exp \left[ \frac{-(ESI - t_{o,es})}{T} \right] \right). \quad (8)$$

After integrating the events of the past two cardiac cycles, we see in Equation 8 that the e-c coupling model of Figure 6 predicts exactly the experimentally determined PESPC form (Eq. 2), with the indicated model interpretations for the constants B and A. The important predictions of the model (contained in Eqs. 5c and 8) are: (1) not only should the  $MRC_{es}$  follow a monoexponential time course, but also the PESPC, and (2) the time constants characterizing the  $MRC_{es}$  and PESPC should be the same.

Furthermore, it is simple to show from Equation 8, that the model accurately predicts the experimentally derived form of the  $MRC_{pes}$ . Calcium movement from U to R stores during the repolarized period preceding postextrasystoles is also postulated to follow a monoexponential time course with time constant T. Then, the model prediction for a  $MRC_{pes}$  is simply Equation 8 multiplied by an exponential time function which increases from zero to unity as a function of the repolarized interval (approximated by  $PESI - t_{o,pes}$ ):

$$\frac{dP/dt_{max}(PES)}{dP/dt_{max}(SS)} = \{A(\exp[-(ESI - t_{o,es})/T]) + B\} \times \{1 - \exp[-(PESI - t_{o,pes})/T]\}, \quad (9)$$

where the model predictions for A and B are given in Equation 8. Equation 9 agrees with the experimentally derived form for the  $MRC_{pes}$  (Eq. 4).

In summary, interval dependence of extrasystolic and postextrasystolic contractile strength that is described by essentially a single time constant (Eq. 4) can be quantitatively explained by an e-c coupling model in which calcium releaseability from an internal store increases with a monoexponential time course, provided that other processes involved in determining contractile strength (e.g., Eq. 6) relate linearly to the amount of calcium released. If such an interpretation is correct, then mechanical restitution and postextrasystolic potentiation curves represent macroscopic phenomena which bear a direct and interpretable relation to events on a much smaller scale. As such, these curves may provide

valuable insights into the intracellular events of the heart in both health and disease.

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*Address for reprints: David T. Yue, Traylor Building, Room 223, Department of Biomedical Engineering, The Johns Hopkins University, School of Medicine, 720 Rutland Avenue, Baltimore, Maryland 21205.*

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INDEX TERMS: Cardiac force-interval relationship • Postextrasystolic potentiation • Mechanical restitution • Excitation-contraction coupling • Isolated ventricle