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

SUMMARY. We established, for the isolated, isovolumically beating canine left ventricle, a comprehensive description of postextrasystolic contractile strength \(dP/dt_{\text{max}}\) as a function of extrasystolic and postextrasystolic stimulus intervals. In contrast to previous studies of postextrasystolic beats in situ hearts, these isolated ventricles contracted isovolumically so that \(dP/dt_{\text{max}}\) 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 (±SD) of 182 ± 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 (±SD) of 176 ± 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 contractile strength increased as PESI was lengthened (postextrasystolic potentiation), and, with PESI fixed, postextrasystolic strength increased as ESI was shortened (postextrasystolic mechanical restitution). 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 hilus 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 servocommanded perfusion pump (Harvard Apparatus, model 1215). The temperature of the perfusate was maintained between 35° and 37°C. Since the atria had been excised

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**Extrasystolic Mechanical Restitution Curve (MRC<sub>max</sub>)**

- $CR_{max}$: Maximum extrasystolic contractile response: plateau value
- $T_{max}$: Time constant
- $t_{max}$: ESI-axis intercept value

**Postextrasystolic Mechanical Restitution Curve (MRC<sub>max,PESI</sub>)**

- $CR_{max,PESI}$: Maximum postextrasystolic contractile response: plateau value
- $T_{max,p}$: Time constant
- $t_{max,p}$: PESI-axis intercept value

**Postextrasystolic Potentiation Curve (PESPC)**

- A: Amplitude
- B: Plateau value
- $T_{max,P}$: 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\text{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 up-stroke of the MAP to 90% repolarization will be referred to as the MAPD\text{90}.

Protocols and Representation of Data

A digital computer (Intel, model iSBC 86/12A) controlled a pacemaker 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](https://example.com/figure1.png)
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\text{max} and left ventricular pressure (LVP) were small (leftmost frame of Figure 1A with PESI = 300 msec). PESI was lengthened, postextrasystolic dP/dt\text{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_p) which were constructed by plotting postextrasystolic dP/dt\text{max} (normalized by the last preceding steady state dP/dt\text{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) by the Taylor series method of nonlinear least-squares 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 monoeponential 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_p) 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_p 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](http://circres.ahajournals.org/)

**Figure 2.** Top: stimulation protocol used to determine postextrasystolic mechanical restitution curves (MRC_p). Bottom: four MRC_p measured from a single ventricle. dP/dt\text{max}(PES) and dP/dt\text{max}(SS) are the extrasystolic and steady state dP/dt\text{max}. 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 monoeponential 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 mono-exponential rise to a plateau level, termed the "maximum postextrasystolic contractile response (CRmax,pes)." The solid curves in Figure 2 are mono-exponential functions of the form:

\[
\frac{dP}{dt^{\text{max}(\text{PES})}} = \frac{dP}{dt^{\text{max}(\text{SS})}} CR_{\text{max,pes}}[1-\exp\left(-\frac{(\text{PESI}-t_{\text{pe},\text{pes}})}{T_{\text{mrc,pe}}}\right)],
\]

where \(dP/dt^{\text{max}(\text{PES})}\) and \(dP/dt^{\text{max}(\text{SS})}\) are defined in Table 1; \(t_{\text{pe},\text{pes}}\) is the PESI-axis intercept of the fitted curve; and \(T_{\text{mrc,pe}}\) is the time constant of postextrasystolic mechanical restitution. For each curve, \(CR_{\text{max,pe}}\), \(t_{\text{pe},\text{pes}}\), and \(T_{\text{mrc,pe}}\) were chosen to provide the best least-squares fit to the data. The quality of the fit for the four MRCpes 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 MRCpes obtained from all 11 ventricles in this series and the mean RMSNE (±SD) was 2.00 ± 0.63%, indicating that MRCpes were well-fitted by the monoexponential form.

Second, \(T_{\text{mrc,pe}}\) 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 MRCpes within 9 of 12 sequentially determined sets of curves (from 11 ventricles). In the other three sets of curves, there was only one MRCpe whose time constant differed significantly (\(P < 0.05\)) from those of the other curves in each set. Furthermore, the variation of \(T_{\text{mrc,pe}}\) with changes in ESI was small in all 12 sets of curves. This is demonstrated by normalizing the \(T_{\text{mrc,pe}}\) of each set of curves with the \(T_{\text{mrc,pe}}\) corresponding to an ESI of 460 msec, and noting that the mean normalized time constant (±SD) was 101 ± 63% for each of the sets of curves. If a reduction of \(t_{\text{pe},\text{pes}}\) is taken as a quantitative indicator of the amount of leftward shift, then a correlation between \(t_{\text{pe},\text{pes}}\) and \(T_{\text{mrc,pe}}\) would suggest that the leftward shift and the shortening of extrasystolic action potentials were interrelated.

Finally, the fully-restituted plateau value of the MRCpes (CRmax,pes) increased as ESI was reduced in all 12 sets of curves. In Figure 2, for example, CRmax,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.

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

To determine whether the leftward shift of MRCpes with decrease in ESI was associated with the shortening of the extrasystolic action potential, we simultaneously determined the PESI-axis intercepts (\(t_{\text{pe},\text{pes}}\)) of MRCpes and the duration of monophasic action potentials of extrasystoles in three ventricles. If a reduction of \(t_{\text{pe},\text{pes}}\) is taken as a quantitative indicator of the amount of leftward shift, then a correlation between \(t_{\text{pe},\text{pes}}\) 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, \(\Delta t_{\text{pe},\text{pes}}\) (defined as the difference of a given \(t_{\text{pe},\text{pes}}\) from the \(t_{\text{pe},\text{pes}}\) when ESI = 460 msec), measured in this series, \(t_{\text{pe},\text{pes}}\) declined every time ESI decreased.

FIGURE 3. Time-axis intercept of MRCpes (\(t_{\text{pe},\text{pes}}\)) plotted as a function of ESI. The relationship demonstrates the "leftward shift" of MRCpes along the PESI axis as ESI is shortened. Each symbol type corresponds to curves comprising a sequentially determined set of MRCpes measured from within a single ventricle. Data from 12 sets of curves are shown.
was plotted vs. \( \Delta \text{MAPD}_{90} \) (defined as the difference of an extrasystolic MAPD_{90} from the steady state MAPD_{90}) (Fig. 4). The line of regression between \( \Delta t_{\text{pe}} \) 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 MRC_{pe} shifted leftward by a comparable amount. Furthermore, the absolute values of steady state MAPD_{90} and \( t_{\text{pe}} \) when ESI was 460 msec were similar; their respective mean values (±SD) were 227 ± 21 and 246 ± 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 CR_{max,pe} upon ESI: Relationship to Extrasystolic Mechanical Restitution

To ascertain directly the variation of the maximum postextrasystolic contractile response of MRC_{pe} (CR_{max,pe}) 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 (MRC_{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 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 CR_{max,pe}.

![Figure 5](http://circres.ahajournals.org/)
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:

\[
\text{CR}_{\text{max,pe}} = B + A \left( \exp\left[ -\frac{(\text{ESI}-\text{to,es})}{\text{T}_{\text{pe,pc}}} \right] \right),
\]

where \( B \) is the plateau level and \( A \) expresses the amplitude of the PESPC; \( \text{to,es} \) is the ESI-axis intercept for the simultaneously determined MRC\( \text{es} \) and \( \text{T}_{\text{pe,pc}} \) 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 \( \text{T}_{\text{pe,pc}} \) chosen to provide the best least-squares fits to the data. In this ventricle, \( A = 171\% \), \( B = 108\% \), and \( \text{T}_{\text{pe,pc}} = 199\text{ msec} \), 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 (±SD) was 2.59 ± 0.87%, demonstrating that all PESPC were essentially monoexponential in shape. The mean value for the time constant of the PESPC (\( \text{T}_{\text{pe,pc}} \) (±SD)) was 176 ± 18 msec. The mean value (±SD) for \( A \) was 168 ± 32%, and for \( B \) was 105 ± 13%.

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

\[
\frac{d\text{P}/d\text{t}_{\text{max},(\text{ES})}}{d\text{P}/d\text{t}_{\text{max},(\text{SS})}} = \text{CR}_{\text{max,es}} \left[ 1 - \exp\left( -\frac{\text{ESI}-\text{to,es}}{\text{T}_{\text{mrc,es}}} \right) \right],
\]

where \( d\text{P}/d\text{t}_{\text{max},(\text{ES})} \) and \( d\text{P}/d\text{t}_{\text{max},(\text{SS})} \) are defined in Table 1; \( \text{CR}_{\text{max,es}} \) is the plateau level of the curve; \( \text{to,es} \) is the ESI-axis intercept for the fitted curve; and \( \text{T}_{\text{mrc,es}} \) 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 \( \text{CR}_{\text{max,es}} \), \( \text{to,es} \), and \( \text{T}_{\text{mrc,es}} \) chosen to provide the best least-squares fit to the data. In this case, \( \text{CR}_{\text{max,es}} = 173\% \), \( \text{to,es} = 276\text{ msec} \), and \( \text{T}_{\text{mrc,es}} = 216\text{ msec} \). The root-mean-squared normalized error (RMSNE) for this curve was 1.80%. Monoexponentials of the form in Equation 3 were fitted to all 10 MRC\( \text{es} \) obtained from the 10 ventricles in this series and the mean RMSNE (±SD) was 1.93 ± 0.40%. The mean parameter values (±SD) were: \( \text{T}_{\text{mrc,es}} = 189 ± 30\text{ msec} \), \( \text{CR}_{\text{max,es}} = 166 ± 23\% \), and \( \text{to,es} = 284 ± 32\text{ msec} \).

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\( \text{es} \) (\( \text{T}_{\text{mrc,es}} \)) was 216\text{ msec}, whereas that for the PESPC (\( \text{T}_{\text{pe,pc}} \)) was 199\text{ msec}. The mean difference between the two time constants (±SD) for pairs of curves measured in the same ventricle (\( \text{T}_{\text{mrc,es}} - \text{T}_{\text{pe,pc}} \)) was only −13 ± 23\text{ 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 (\( \text{T}_{\text{mrc,pe}} \)) was invariant with changes in ESI, and was virtually the same as the time constant of restitution following steady state beats (\( \text{T}_{\text{mrc,es}} \)).

3. The time to the onset of postextrasystolic mechanical restitution (\( \text{to,pe} \)) 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 (\( \text{CR}_{\text{max,pe}} \)) is a decreasing monoexponential function of ESI (Eq. 2, Fig. 5A), and the time constant of this decrease (\( \text{T}_{\text{pe,pc}} \)) was approximately equal to the time constant of extrasystolic mechanical restitution (\( \text{T}_{\text{mrc,es}} \)).

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 (\( \text{T}_{\text{mrc,pe}}, \text{T}_{\text{mrc,es}}, \text{T}_{\text{pe,pc}} \)) 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:

\[
\frac{d\text{P}/d\text{t}_{\text{max},(\text{PES})}}{d\text{P}/d\text{t}_{\text{max},(\text{SS})}} = \left[ A \left( \exp\left[ -\frac{\text{ESI}-\text{to,es}}{T} \right] \right) + B \right] \times \left[ 1 - \exp\left( -\frac{\text{ESI}-\text{to,pe}}{T} \right) \right],
\]

where \( \text{to,pe} \) varies in parallel with the MAPD\(_{90}\) of extrasystolic beats (Fig. 4), and \( \text{to,es} \) has been shown...
to correlate closely with 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 $t_0$, 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, 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 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 MRC$_{pes}$, but 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 (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 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 ESI + PESI = 2 × SSI. Their "pseudo PESPc" appeared to decline in a fashion reciprocal to the rise of MRC$_{es}$.

The leftward shifts of 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 (Trithart 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 (~ −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 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 (MRC$_{es}$) correlated with the shortening of steady state action potentials when the heart rate used in the priming period was increased.

That $\Delta t_{pes}$ and $\Delta$MAPD$_{90}$ were not exactly equal may relate to the fact that $\Delta t_{pes}$ is a global, ventricular property, whereas $\Delta$MAPD$_{90}$ is a local epicardial property. Then, with slight regional variations of action potential duration and time of activation (Watanabe et al., 1983), $\Delta t_{pes}$ might differ somewhat from $\Delta$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 MRC$_{pes}$, which rise monotonically to a plateau. Elzenga 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) (Burkhoff 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 (MRC$_{es}$, 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 Johansson, 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 or MRCpes 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 monoeponential nature (with identical time constants) of our descriptive functions (MRCCT, MRCpes, 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 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 monoeponential 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 releaseability 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/dW and estimated peak 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 + (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-
the amount of calcium released on the extrasystolic beat ($R(es)$) is therefore equal to $R_{\text{max}}(ss)$ multiplied by an exponential factor:

$$R(es) = R_{\text{max}}(ss) \left[1 - \exp\left[-\frac{(ESI - t_{0,es})}{T}\right]\right]. \quad (5a)$$

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 $ESI - t_{0,es}$, where $t_{0,es}$ 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 $R_{\text{max}}(ss)$ and $R(es)$ (Eq. 5b):

$$U(es) = R_{\text{max}}(ss) \left[1 - \exp\left[-\frac{(ESI - t_{0,es})}{T}\right]\right]. \quad (5b)$$

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 ($MRC_{es}$):

$$\frac{dP/dt_{\text{max}}(ES)}{dP/dt_{\text{max}}(SS)} = \frac{R_{\text{max}}(ss)}{R(ss)} \times \left[1 - \exp\left[-\frac{(ESI - t_{0,es})}{T_{\text{MRC}_{es}}}\right]\right]. \quad (5c)$$

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 which recirculated back to the U store, $F \times R(es)$.

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

where $I_{\text{max}}$ 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 ($PESPC$):

$$CR_{\text{max, PES}} = \frac{R_{\text{max}}(ss)}{R(ss)} \left[\frac{R_{\text{max}}(ss)}{R(ss)} \left(F - h + \frac{I_{\text{max}}}{R_{\text{max}}(ss)}\right) \left(1 - \exp\left[-\frac{(ESI - t_{0,es})}{T}\right]\right)\right] \quad (8)$$

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 function which increases from zero to unity as a function of the repolarized interval (approximated by $PESI - t_{0, pes}$):

$$\frac{dP/dt_{\text{max}}(PES)}{dP/dt_{\text{max}}(SS)} = \left[\frac{A\exp\left[-\frac{(ESI - t_{0,es})}{T}\right]}{A\exp\left[-\frac{(ESI - t_{0,es})}{T}\right]} + B\right] \times \left[1 - \exp\left[-\frac{(PESI - t_{0,pes})}{T}\right]\right], \quad (9)$$

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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