Original Contributions

Cardiac Cycle Length Modulates Cardiovascular Regulation That Is Dependent on Previous Beat Contraction History

Bryan K. Slinker

Previous studies of the beat-to-beat regulation of left ventricular performance in the intact cardiovascular system have shown that the performance of the left ventricle on any one beat is influenced by the mechanical events of the previous beat, so-called previous beat contraction history. The general hypothesis investigated in this study is that previous beat contraction history occurs because of the perturbation of one or more biochemical processes with time courses that are long relative to one cardiac cycle. If this is true, then previous beat contraction history should depend on the interval between beats and, therefore, should extend beyond the previous beat to two, or even three, previous beats as heart rate is increased. Hemodynamic responses to random preload and afterload changes were measured in 11 anesthetized open-chest dogs on right heart bypass at three paced heart rates. Multiple linear regression was used to analyze these hemodynamic sequences and identify variables from the previous one, two, or three beats that were important in the mechanical history dependence of left ventricular function. The results of this analysis showed that under baseline conditions, all 11 hearts showed one beat of history dependence, with only two of 11 hearts showing a dependence on the previous two or three beats. At the highest heart rate, all 11 hearts still showed one beat of history dependence, but 10 of 11 hearts showed two beats of history dependence, and four of 11 showed three beats of history dependence \( (p<0.05) \). A general framework for the mechanism underlying these findings, which relates previous beat contraction history to the interval-dependent mechanical restitution phenomenon, is proposed and discussed. \( \textit{Circulation Research} \ 1991;69:2-11 \)

In previous studies of the beat-to-beat regulation of left ventricular performance in the intact cardiovascular system, we have shown that the performance of the left ventricle on any one beat is influenced by the mechanical events of the previous beat.\(^1,2\) We have called this phenomenon previous beat contraction history to distinguish it from other short-term (within-beat)\(^3,4\) and long-term (many-beat)\(^5,6\) contraction history or “memory” phenomena that have been described in both isolated cardiac muscle and the whole heart. A similar phenomenon also has been demonstrated in several studies of isolated cardiac muscle.\(^7-10\)

Previous beat contraction history is probably important in the small beat-to-beat adaptations the left ventricle makes in response to continuously changing demands and loading conditions. Under normal conditions in the open-chest anesthetized dog, previous beat contraction history is required to accurately model and predict the beat-to-beat changes in left ventricular performance that occur with transient changes in preload and afterload.\(^1,2\) Under certain conditions, most notably mechanical alternans, it is impossible to model or predict beat-to-beat left ventricular performance during the adaptation to transient loading changes without the inclusion of previous beat contraction history.\(^1\) Thus, one general model structure, which includes previous beat contraction history, accounts for widely different hemodynamic states, including mechanical alternans.

The mechanism underlying previous beat contraction has not been determined. However, we have speculated that the underlying mechanism has its basis in one or more biochemical processes that have long time courses relative to one cardiac cycle.\(^2\) In a general sense, I hypothesize that previous beat contraction history results from the presence, and interaction, of two events. The first event requires the influence of the mechanical event of cardiac contrac-
tion on one or more biochemical processes, and the second event is a delay whereby the perturbed biochemical process is not completely restored to its nominal steady state before the next contraction.

There is strong evidence from isolated cardiac muscle that loading conditions and shortening, in particular, influence action potential duration\textsuperscript{6,11} and free calcium in the myoplasm.\textsuperscript{12,15} As a result of the action of this first event, one or more biochemical processes is perturbed, thus moving it away from its nominal steady state. For example, one extensively studied delay is the hypothesized transfer of calcium between functionally distinct uptake and release compartments in the sarcoplasmic reticulum, which is thought to underlie the phenomenon of mechanical restitution.\textsuperscript{14-16} If the time course of this transfer is long relative to cardiac cycle length, the stage is set for perturbation of calcium uptake by the sarcoplasmic reticulum (or some other process), which then might lead to different amounts of calcium transferred to the release store between beats, thus allowing a mechanical event on one beat to influence activation and contraction on the next beat.\textsuperscript{17} A similar process also has been proposed to explain mechanical alternans.\textsuperscript{9,18}

If this general framework is true, then the expression of previous beat contraction history should depend on the interval between beats. Therefore, the purpose of this study was to test the hypothesis that previous beat contraction history extends beyond the previous beat to two, or even three, previous beats as heart rate is increased above baseline. Accordingly, experiments analogous to those reported by Slinker and Glantz\textsuperscript{2} were performed at three levels of heart rate. In addition, the specific bradycardic drug UL-FS 49 was given to decrease heart rate below baseline. If the resultant cardiac cycle length is longer than the time for full restoration of the biochemical process that is hypothesized to be perturbed by the mechanical events of the previous beat, then previous beat contraction history should be diminished or absent at slow heart rates.

Materials and Methods

Experimental Preparation

Data were collected in 14 open-chest anesthetized random-source dogs of either sex (25.5±4.5 kg [mean±SD]; range, 21–37 kg). General anesthesia was induced by intravenous \(\alpha\)-chloralose (100 mg/kg) and intramuscular morphine (2 mg/kg). The dogs were intubated, and surgical anesthesia was maintained with supplemental \(\alpha\)-chloralose and morphine given as necessary at one half the initial doses. Respiratory rate and tidal volume were adjusted, and intravenous sodium bicarbonate was given as necessary to maintain \(\text{PCO}_2\) at 35–45 mm Hg, \(\text{HCO}_3^-\) at 20–28 mmol/l, and pH at 7.3–7.4. Arterial \(\text{PO}_2\) always exceeded 80 mm Hg.

After the chest was opened with a median sternotomy, widely incising the pericardium, and the heart was suspended in a pericardial cradle, the dog was placed on right heart bypass. The azygos vein was ligated and large-bore (10 mm i.d.) cannulas were placed into both cavae via incisions in the right atrium. A 30F cannula was placed into the pulmonary artery via an incision in the right ventricular outflow track. A 20F vent with multiple side holes was placed in the right ventricle via an incision in the free wall. These cannulas were connected to a bypass circuit, and cardiac output was controlled to keep peak left ventricular pressure at 100–110 mm Hg.

An umbilical tape snare was placed around the proximal descending thoracic aorta, and after blunt dissection between the aortic root and main pulmonary artery, an electromagnetic flow probe (Carolina Medical Electronics, King, N.C.) was placed on the aortic root.

Left ventricular volume was measured using the conductance catheter system described by Baan et al\textsuperscript{19} (Leycom, Leiden, The Netherlands) connected to a 7F catheter with an array of eight ring electrodes equally spaced over 7 or 8 cm at the catheter tip (Webster Laboratories, Baldwin Park, Calif.). This catheter was inserted into the left ventricle via a stab incision in the apex and was positioned so that its tip could be felt in the region of the aortic sinuses; the last electrode was approximately 1 cm into the left ventricle as measured from the epicardium of the apex. The catheter was connected to the supporting electronics with a cable that inverted the leads to account for the reversal of the electrode array from the retrograde placement assumed by the device. Conductance of the blood was determined at the beginning of data collection.

Left ventricular pressure was measured with a 7F catheter-tip micromanometer (Millar Instrument Co., Houston) inserted via a femoral artery. This catheter was calibrated in 37°C saline immediately before placement. Periodically throughout the experiment, zero drift was corrected by matching diastolic pressures with a pressure measured from the fluid-filled catheter lumen and zeroed to a mid-chest reference.

To block the autonomic nervous system, the vagosympathetic nerves were cut in the neck, the ansa subclavia was cut, and the first four thoracic chain sympathetic ganglia were removed. Pacing leads were attached to the right atrium, and pacing at a few beats per minute above capture was begun. All recordings were made without the pericardium and on right heart bypass to minimize the effect of direct ventricular interaction and artifacts in measuring left ventricular volume due to changes in the right ventricular volume contribution to the parallel conductance sensed by the conductance catheter.

Protocol

The experimental approach was similar to that previously described by Slinker and Glantz.\textsuperscript{2} Random perturbations in cardiovascular system function, designed to produce a broad range of hemodynamic
transients within the normal physiological range, were introduced by varying the speed of the bypass pump and occluding the aortic snare. These data then were analyzed using multiple linear regression.

Each data set consisted of the record of hemodynamic events caused by a random sequence of aortic constrictions and pump speed changes (these interventions were random to the extent that their timing, duration, and order were not predetermined, followed no fixed sequence, and varied between experimental runs). All data were collected with the respirator off at end expiration. To obtain good estimates of the parameters in the regression equations, perturbations were designed to cover as wide a range of left ventricular volume and pressure as possible. However, to avoid confounding our study with changes in myocardial metabolism, data collection was limited to 30–45 seconds with the respirator off, and an effort was made to keep peak left ventricular pressure above 60 mm Hg. After each sequence of hemodynamic changes, a 2-minute wait was allowed for hemodynamic variables to return to baseline before the next random sequence was recorded.

Two or three such random sequences were recorded at each heart rate. Three levels of paced heart rate were studied under normal conditions: baseline, approximately 1.3 times baseline, and approximately 1.6 times baseline. Data were obtained at all three heart rates in 11 dogs. In six dogs (three of the 11 and three additional), heart rate was slowed with the specific bradycardic drug UL-FS 4921-24 given intravenously (1 mg/kg). Pacing was continued after UL-FS 49 administration at a few beats per minute above capture.

**Data Analysis**

**Data selection.** All data were digitized on-line with a 500-Hz sampling rate. Using data analysis software developed in our laboratory, left ventricular pressure and ventricular volume were determined at end diastole (time at which left ventricular dP/dt exceeded 10% of peak positive dP/dt on that beat) and end systole (10 msec before minimum left ventricular dP/dt, to correct for the fact that the time of minimum dP/dt tends to overestimate ejection time at higher heart rates). Because only beat-to-beat changes in stroke volume within a dog were needed and because of the errors involved in attempting to determine parallel conductance, volume was uncorrected for parallel conductance. Furthermore, the effects of parallel conductance were reduced in this preparation by placing the dog on right heart bypass and venting the right ventricle. The monoeponential time constant of left ventricular pressure decay was computed from the regression of the natural logarithm of pressure versus time from the end of systole to the time when left ventricular pressure was 5 mm Hg higher than the next end-diastolic pressure. After zero flow was set to the average diastolic flow for the 60 msec before end diastole of each beat, stroke volume for each beat was computed as the integral of aortic flow (when present, pacing spikes recorded in the flow signal were removed by linear interpolation across the base of the spike).

Each beat-to-beat time series of these hemodynamic variables was stored for multiple linear regression analysis. At each heart rate, sequences free of extrasystoles were selected for analysis. When more than one data set was appropriate, the one chosen for analysis was selected randomly.

**Regression equations.** Data analysis followed the general approach outlined by Slinker and Glantz. Briefly, the observed beat-to-beat changes in left ventricular performance, quantified as stroke volume, ΔV, were fit to a model incorporating preload, afterload, and heart rate (R). Heart rate was included rarely (it was needed occasionally for small escapes from pacing), and thus we concentrated on preload and afterload as the primary traditional determinants of ventricular function, as expressed in the equation

\[
\Delta V(k) = b_0 + b_{ved} V_{cd}(k) + b_{pes} P_{es}(k)
\]

where \(b_0\) is the regression intercept and \(b_{ved}\) and \(b_{pes}\) are regression coefficients quantifying the effect of left ventricular end-diastolic volume \(V_{cd}(k)\) and end-systolic pressure \(P_{es}(k)\), of any beat, \(k\), on left ventricular stroke volume \(\Delta V(k)\) on that beat.

If Equation 1 proved to be inadequate (model acceptance criteria are discussed below), the next step was to fit a model incorporating previous beat contraction history of one-beat duration; that is, variables quantifying mechanical events of the previous beat, \(k-1\), were incorporated into the model. Following the notation used by Slinker and Glantz, let \(g_{AV}(k-1)\) be a linear function of \(\Delta V, P_{es},\) end-systolic volume \(V_{es}\), and time constant of relaxation (\(\tau\)) on the previous beat:

\[
g_{AV}(k-1) = b_{AV1} \Delta V(k-1) + b_{pes1} P_{es}(k-1) + b_{Ves1} V_{es}(k-1)
\]

and

\[
g_{AV}(k-2) = b_{AV2} \Delta V(k-2) + b_{pes2} P_{es}(k-2) + b_{Ves2} V_{es}(k-2)
\]

where \(b_{AV1}, b_{pes1}, b_{Ves1},\) and \(b_{AV2}, b_{pes2}, b_{Ves2}\) are regression coefficients relating the respective previous beat variables to \(\Delta V(k)\). The regression model describing history dependence for one beat can be expressed in general terms by combining Equations 1 and 2:

\[
\Delta V(k) = b_0 + b_{ved} V_{cd}(k) + b_{pes} P_{es}(k) + g_{AV}(k-1)
\]

Analogous previous beat functions can be added to the model to account for history extending to two or three previous beats. Specifically, the functions

\[
g_{AV}(k-2) = b_{AV3} \Delta V(k-3) + b_{pes3} P_{es}(k-3) + b_{Ves3} V_{es}(k-3)
\]

and

\[
g_{AV}(k-3) = b_{AV4} \Delta V(k-4) + b_{pes4} P_{es}(k-4) + b_{Ves4} V_{es}(k-4)
\]
can be added to Equation 3 to obtain the most general model examined

\[ \Delta V(k) = b_0 + b_{Ved} V_{ed}(k) + b_{Ped} P_{ed}(k) + g_{AV}(k-1) + g_{AV}(k-2) + g_{AV}(k-3) \]

(6)

In the limiting case in which no predictor variables from the previous beats are required, all coefficients in \( g_{AV}(k-1) \), \( g_{AV}(k-2) \), and \( g_{AV}(k-3) \) would be zero, and Equation 6 would reduce to Equation 1. The specific forms of the functions \( g_{AV}(k-1) \), \( g_{AV}(k-2) \), and \( g_{AV}(k-3) \) were determined for each dog separately at each heart rate.

**Statistical procedures.** All statistical analyses were done using MINITAB. Multiple linear regression model-building techniques were used to select the “best” model description of the observed stroke volume response at each heart rate. The general strategy was to fit, in stages, increasingly complex models, starting with Equation 1, to a random hemodynamic data sequence at each heart rate until model acceptance criteria were met. Model acceptance criteria were 1) maximal \( R^2 \) subject to the constraint that the change in \( R^2 \) due to adding a variable was greater than 0.02 and 2) lack of autocorrelation among the residual errors in fit, indicating that the assumption of no systematic errors was met (for details, refer to Slinker and Glantz). The goal was to have \( R^2 \) exceed 0.70. The goal for using autocorrelation to help determine model structure was to have insignificant first-order autocorrelation, which was judged by the Durbin-Watson statistic. At each stage, the model fit to the data was evaluated against these acceptance criteria. If both criteria were met, the model building stopped. If not, model building proceeded to the next stage.

At the first stage, ordinary multiple linear regression was used to fit Equation 1 to each data set. The three possible additional stages used stepwise multiple regression to select previous beat variables and thus determine the form of Equation 2, then Equation 4, and finally, Equation 5. If a variable was determined to be statistically significant \( (p<0.05) \) using stepwise regression, it was generally added only if the improvement in \( R^2 (\Delta R^2) \) was greater than 0.02. However, statistically significant predictor variables with \( \Delta R^2 \) less than 0.02 were included if doing so led to satisfying the residual error autocorrelation criterion. For each stage, the results of any previous stages were retained (i.e., forced) in the model. Model building never proceeded beyond the model given by Equation 6.

**Results**

Average (±SD) heart rates for the three pacing levels in 11 dogs in the absence of UL-FS 49 were 131±13, 173±9, and 207±9 beats/min. After UL-FS 49 was given to six dogs, the average heart rate was 84±10 beats/min.

Because the hemodynamic perturbations were done randomly, the sequences of hemodynamic perturbations in the data sets selected for analysis varied widely from experiment to experiment. This was an advantage, because consistency of results produced from a variety of interventions strengthens data interpretation. Although the sequences varied in terms of timing of interventions, the range over which the hemodynamic variables varied was similar across all heart rates (Table 1), except for the expected effects of alternans at the highest heart rate. Figure 1 shows examples of random sequences of hemodynamic variables. These three sequences were obtained at different heart rates, as noted on the figure. Of particular interest is the response observed at the highest heart rate, at which there was a mechanical alternans that waxed and waned in amplitude as the preload and afterload changed. This was a frequent observation at the fastest heart rate. In no cases was heart rate fast enough so that sustained mechanical alternans was present in the absence of preload and afterload changes.

**Effect of Increasing Heart Rate**

Figure 2 shows an example of the fit of the data shown in the upper panel of Figure 1. Table 2 shows the values for the 11 experiments of overall model \( R^2 \) and Durbin-Watson statistic, \( D \), for the first stage of model building, in which multiple linear regression was used to fit data from each random sequence to Equation 1. In general, one or both model acceptance criteria were not met for all data. Although \( R^2 \) was greater than 0.70 for the fits to many of the sequences, in only one sequence (experiment 229, highest heart rate) were both criteria met. Overall, Equation 1 does poorly, as expected from the previous report of Slinker and Glantz in the model building process.

Figure 3 summarizes the results of fitting Equation 6 to each sequence of data during subsequent stages of model building. In this figure, each dot (●) represents statistical significance \( (p<0.05) \) of regression coefficients associated with the functions of previous beat variables given by Equations 2, 4, and 5. The top panel shows the results for the lowest heart rate in each of the 11 dogs. All dogs required one additional stage of model building; that is, the fitting of \( g_{AV}(k-1) \) was necessary to satisfy both model acceptance criteria. Only two of 11 dogs required additional stages: in one dog, the function \( g_{AV}(k-2) \) was needed, and in another dog, the function \( g_{AV}(k-3) \) was needed. The middle panel of Figure 3 shows the results for the next higher heart rate in these 11 dogs. At this higher heart rate, all 11 dogs continued to exhibit previous beat contraction history at least one beat back in time. In addition, seven dogs showed more than one beat of contraction history: six with two-beat and one with three-beat history dependence. The bottom panel of Figure 3 shows the results for the highest heart rate in these 11 dogs. At this highest heart rate, all 11 dogs still showed at least one beat of contraction history.
Now, however, 10 dogs showed more than one beat of contraction history: six with two-beat and four with three-beat history dependence.

Thus, at basal heart rates, previous beat contraction history predominantly involves only one previous beat. However, as heart rate increases, previous beat contraction history extends first to two, then three previous beats. Figure 4 summarizes the extent of previous beat contraction history as a function of heart rate and shows the statistically significant pattern of previous beat contraction history extending to two and three beats back in time as heart rate increases ($p<0.05$ by Friedman's test). Table 3 shows the $R^2$ and Durbin-Watson D statistics from the final model selected for each sequence. In contrast to the results shown in Table 2 for the fits to Equation 1, the final fits to Equation 6 resulted in almost all sequences meeting both model acceptance criteria. In no case did a fit fail both criteria. For the three sequences in which $R^2$ was less than 0.70 and the
seven sequences in which the autocorrelation criterion was not met, an additional stage of model fitting was attempted by examining the fourth previous beat. In no case did this additional stage improve the model fits. There were no obvious reasons for the low $R^2$ at low and middle heart rates in dog 230 and middle heart rate in dog 228.

**Effect of Decreasing Heart Rate**

The results obtained from analyzing the random sequences recorded after UL-FS 49 was given to lower heart rate below basal were indistinguishable from the results obtained under basal heart rate conditions without UL-FS 49. These results are shown in Figure 5, which shows the pattern of significant regression coefficients in a format like that of Figure 3. All six dogs required at least one beat of contraction history for adequate model fit to the data. In addition, one dog required two beats of contraction history, and another required three beats.

**Discussion**

This study demonstrates that the expression of previous beat contraction history-dependent left ventricular performance depends on cardiac cycle length. Under baseline conditions, the performance of the left ventricle on any beat, $k$, depends on mechanical events associated with the contraction of the previous beat, $k-1$. Only two of the 11 hearts studied showed evidence of a dependence on the mechanical events of beats $k-2$ or $k-3$. This result confirms our previous reports of this phenomenon$^{1,2}$

---

**Figure 1.** Representative random sequences from one experiment showing the beat-to-beat changes in aortic flow, left ventricular volume, left ventricular $dP/dt$, and left ventricular pressure during preload and afterload changes. Heart rate (HR) for each sequence is indicated on the right of the figure. Data are from experiment 237.

**Figure 2.** Beat-to-beat changes in measured stroke volume (○) shown together with fits to Equation 1 (-----) and Equation 3 (-----). Fit using Equation 3 is much closer to the data than is the fit using Equation 1. These data are the same as shown in the top panel of Figure 1.
using different anesthesia, a different preparation (right heart bypass) to simplify the hemodynamic transients and remove other potential confounding variables, and different methods to introduce the hemodynamic transients.

As heart rate increased above baseline, however, the performance of the left ventricle on beat k began to depend not only on mechanical events of beat k−1, but also on the events of beat k−2. At the highest heart rate, 10 of 11 hearts showed such a dependence, with four of these hearts also showing a dependence on the mechanical events of beat k−3. On the other hand, decreasing heart rate neither diminished nor abolished previous beat contraction history. (Although the possibility of a direct cardiac effect of UL-FS 49 exists, it is unlikely that this significantly altered these results, because this drug has, at most, minimal other inotropic or hemodynamic effects,21-24 with small positive inotropic effects being observed only at low stimulus frequencies or very high concentrations of the drug.24) Thus, the specific hypothesis tested in this study is confirmed for increased heart rate, but not for decreased heart rate.

Given these different results, depending on the direction of change in heart rate, what can be concluded about the general hypothesis that previous beat contraction history has, at least in part, a mechanism requiring a biochemical process of restoration or transfer that has a long time constant relative to cardiac cycle length?

One of the best described restoration processes is the hypothesized transfer of calcium between functionally distinct uptake and release compartments, probably within the sarcoplasmic reticulum.17 This process is postulated to be involved in mechanical alternans9,18 and the phenomenon of mechanical restitution.14-16,32 Studies of mechanical restitution have yielded quantitative descriptions of this transfer that can be used to interpret the disparate results of increased and decreased heart rate in the present experiment. From the results of mechanical restitution experiments, the time constant of the transfer of calcium from the uptake to the release compartment has been estimated to be on the order of 200 msec in the isolated dog heart14,16 and approximately 750 msec in isolated ferret papillary muscle.32 Examination of full restitution curves presented in these studies shows a plateau, thought to represent the maximum accumulation of calcium in the release store, that occurs only after approximately 1,000 msec14,16 or even as long as 2,000 msec, consistent with the four or five time constants necessary to reach saturation of a monoexponential process.

The average heart rate with UL-FS 49 was 84 beats/min, corresponding to a cardiac cycle length of 715 msec (the slowest individual heart rate was 72 beats/min, corresponding to a cardiac cycle length of 830 msec). The average heart rate at the highest rate without UL-FS 49 was 207 beats/min, corresponding to a cardiac cycle length of 290 msec. Therefore, the observed range of average cardiac cycle intervals in this study was 290–715 msec, and even the slowest heart rates observed in the present study have cycle intervals shorter than the time necessary for saturation of calcium in the release store. Thus, to abolish previous beat contraction history, heart rate would have to be slowed at least to the range of 50–60 beats/min, corresponding to cycle lengths of 1,000–1,200 msec, if not slower. Viewed in this framework, the lack of effect of slowing heart rate on the expression of previous beat contraction history does not invalidate the hypothesis.

The general framework proposed to underlie the phenomenon of previous beat contraction history is presented schematically in Figure 6. Although obvi-
Figure 3. Pattern of entry of previous beat hemodynamic variables into previous beat functions \( g_{k-1}(\cdot) \), \( g_{k-2}(\cdot) \), and \( g_{k-3}(\cdot) \), as given by Equations 2, 4, and 5, at each of the three heart rates studied for experiments (Expt.) in 11 dogs. Each dot (●) represents the presence of a statistically significant (p<0.05) regression coefficient for the indicated variable. Top panel: sequences recorded at baseline heart rate (H.R.); middle panel: sequences recorded at approximately 1.3 times baseline; bottom panel: sequences recorded at approximately 1.6 times baseline. As heart rate increases, more dots appear in the \( g_{k-2}(\cdot) \) and \( g_{k-3}(\cdot) \) columns, indicating extension of previous beat contraction history to two, then three, previous beats as heart rate increases. ESV, end-systolic volume; ESP, end-systolic pressure; SV, stroke volume; \( \tau \), time constant of relaxation.

Regardless of the effect of the first beat on the underlying biochemical process, it has been completely restored before the next beat. That is, if the mechanical events of the first beat move the restoration process from the solid curve to the dashed curve in the upper panel of Figure 6, the contraction of the next beat will not be influenced, because this process has been fully restored.

However, at a normal heart rate, as illustrated in the panel next to the lower panel of Figure 6, the effect of the first beat on the underlying biochemical process has not been restored completely before the next beat. At any time before full restoration, the perturbation caused by the first beat (i.e., moving from the solid to dashed curve in the upper panel of Figure 6) causes the restoration to reach a different point at the time of the second beat. Thus, the mechanical events that perturb the first beat will influence the contraction of the next beat. Continuing this schematic outline, at a fast heart rate (HR=200 in Figure 6), the interval between beats is short enough so that the perturbation in restoration caused by the mechanical events of the first beat has not reached its saturation level even by the third beat. Thus, the mechanical events of the first beat can influence the contraction of two subsequent beats.

This general framework is supported by the results of the present study. Nonetheless, the specific biochemical process proposed need not be the only one involved, nor need not necessarily be involved at all. However, by linking previous beat contraction history to the interval-dependent phenomenon of mechanical restitution, we gain a persuasive parsimony of underlying mechanisms. Furthermore, the proposal that mechanical alternans shares at least some of these same interval-dependent
processes strengthens these links. Mechanical alternans as observed, for example, in the lower panel of Figure 1 clearly is linked to previous beat contraction history. In fact, mechanical alternans has been modeled successfully starting from theoretical systems analysis considerations that led to a difference equation model incorporating what I have called previous beat contraction history, that is, the dependence of the function of one beat, beat k, on the mechanical events of the previous beat, beat k - 1. Mechanical alternans also has been speculated to share, at least in part, the mechanism underlying mechanical restitution and interval dependence.9,18

Thus, the proposed framework, which is supported in its general form by the results of this study, parsimoniously ties together the various phenomena of mechanical alternans, mechanical restitution, and previous beat contraction history. This study confirms our prior observation that previous beat contraction history is an important determinant of the beat-to-beat fine tuning of contraction required for the left ventricle to adapt to continually changing demands and loading conditions. As such, it is important for our understanding of the regulation of left ventricu-

![Figure 6](https://example.com/f6.png)

**Figure 6.** Schematic representation of the general framework proposed to explain previous beat contraction history. Upper panel represents the time course of restoration of a biochemical process in the myocardium. Lower three panels represent different heart rates (HR), with vertical lines representing beats occurring at regular intervals on the same time scale as the restoration of the biochemical process. See text for detailed discussion of this scheme.
lar performance. Moreover, if the mechanism outlined above proves to be substantially correct in its specific form, then previous beat contraction history reveals an important system-level regulatory role for the functionally distinct uptake and release compartments involved in calcium cycling during cardiac muscle activation and deactivation.

Acknowledgments

The author thanks Stephen Bell and David Robbins for excellent technical assistance, Nancy Perrine for typing the manuscript, Trish Warshaw for preparing the illustrations, Chuck Richardson for supplying the data acquisition software, and Martin LeWinter for helpful advice and encouragement. The UL-FS 49 was kindly supplied by Bohreriger-Ingelheim, Ridgefield, Conn.

References


KEY WORDS • cardiac mechanics • dogs • hemodynamics • systolic function • ventricular function
Cardiac cycle length modulates cardiovascular regulation that is dependent on previous beat contraction history.

B K Slinker

Circ Res. 1991;69:2-11

doi: 10.1161/01.RES.69.1.2

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/69/1/2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/