The Influence of Left Ventricular Filling on Postextrasystolic Potentiation in the Dog Heart

Edward L. Yellin, Arthur Kennish, Chaim Yoran, Shlomo Laniado,
Nancy M. Buckley, and Robert W.M. Frater

SUMMARY We studied the role of left ventricular filling on postextrasystolic potentiation (PESP) in the intact dog heart by calculating changes in end-systolic and end-diastolic volumes on a beat-to-beat basis from electromagnetic measurements of phasic mitral inflow and aortic outflow. In all, 161 extrasystolic sequences with compensatory pauses in 13 dogs were analyzed. The first postextrasystolic cycle showed an increased end-diastolic volume (EDV) in 94%, a decreased end-systolic volume (ESV) in 50%, and an estimated increased ejection fraction in 85% of the sequences. In the 91 sequences with a coupling index £0.7, despite a 76% increase in filling time, there was during the compensatory pause only a 6% increase in filling volume when compared to control. The net filling volume, stroke volume, and diastolic filling period for the sum of the extra- and postextrasystolic cycles were, respectively, 78%, 80%, and 116% of the sum of two control cycles. This retarded filling rate is attributed to a lower left atrial pressure, a reduced left ventricular relaxation rate, and a relaxation to a higher pressure minimum, all of which decrease the amplitude of the atrioventricular pressure gradient. Nevertheless, in 98% of the postextrasystolic cycles, stroke volume was augmented when compared to control (ratio, 1.49 ± 0.26; mean ± SD), due in part to intrinsic mechanisms, to increased preload (EDV), and to decreased afterload. As a first approximation, the effects of increases in preload were separated from intrinsic increases in contractility following an extrasystole by defining potentiation in terms of decreased ESV and/or increased ejection fraction. With the former criterion, 50% of the sequences showed PESP; with the latter, PESP occurred in 85% of the sequences. Circ Res 44: 712-722, 1979

STUDIES IN isolated muscle preparations (Cranefield, 1965) and isovolumic ventricles (Cranefield, 1965; Hoffman et al., 1965) with controlled preload have shown that extrasystoles give rise to increases in the magnitude of developed tension and in the rate of development of tension in subsequent contractions. Postextrasystolic potentiation (PESP) is clearly an intrinsic property of cardiac muscle and is independent of afterload and preload.

In the intact, ejecting heart, postextrasystolic increases in peak left ventricular pressure (PLVP), maximum dp/dt, and stroke volume (SV) also have been demonstrated clearly. (Cranefield, 1965; Hoffman, et al., 1965; Takada et al., 1970; Anderson et al., 1976). However, the influence of ventricular filling on PESP in the intact heart has never been
clarified, because no studies have been reported which accurately measure changes in ventricular volume during the extra- and postextrasystolic cycles.

This study was designed to investigate the role of ventricular filling on PESP in the intact, ejecting heart, beating at its intrinsic rhythm, so that the extrasystole is followed by a contraction whose timing is determined by the relative excitability of the ventricle to the next sinoatrial node discharge. This investigation differs from all previous reports in that instantaneous changes in left ventricular volume were calculated on a beat-to-beat basis from measurements of phasic inflow and outflow. Our goal was to elucidate the hemodynamics of PESP during the sequence of control, extrasystolic, and postextrasystolic cycles by calculating the changes in ESV and EDV, and by analyzing the factors that influence ventricular filling. This was accomplished by quantitatively and qualitatively studying the mitral flow waveform, the duration of filling, and the time variation of the left atrial and ventricular pressure curves.

Methods

Dog Preparation

Thirteen adult mongrel dogs weighing 20–30 kg were anesthetized with pentobarbital (30 mg/kg, iv) and placed on artificial respiration, as described previously (Laniado et al., 1973). The chest was opened via a midsternotomy and thoracotomy at the 4th left intercostal space. Catheter-tip manometers (Millar PC-350 and PC-460) were introduced into the left ventricle and left atrium via apical puncture and the pulmonary vein, respectively. During cardiopulmonary bypass, an electromagnetic flow transducer was sutured above the mitral annulus, and the wires were brought out through the atrial appendage; a second flow probe was placed on the ascending aorta.

Phasic mitral and aortic flows were measured with a two-channel square-wave flowmeter (Carolina Medical Electronics, model 501). Aortic pressure was measured with a Statham transducer (P23De) attached to a 30-cm catheter in the right carotid artery. All three pressure transducers were adjusted to equal sensitivity and common zero. These parameters, as well as left ventricular dp/dt (by an RC coupled differentiator) and the ECG, were recorded on an oscillographic recorder (Electronics for Medicine, DR-12) at paper speeds of 50 and 100 mm/sec.

Arterial blood gases and pH were controlled by regulating the air/oxygen mixture and by administering bicarbonate iv. Occasionally a 50-mg dose of lidocaine was given iv to suppress arrhythmias. No attempt was made to study systematically the effect on PESP of various states of cardiac function, but since the consequences of the surgery frequently required the use of blood volume to correct for hypovolemia and the use of norepinephrine to improve the state of the heart, the control data include a wide range of cardiac function.

Procedure

One hundred extrasystoles occurred spontaneously in 10 dogs. Since these extrasystoles tended to occur late in the cycle, we induced electrically an additional 61 extrasystoles in five dogs to get a wider range of coupling interval. (In two of the dogs there were both spontaneous and induced extrasystoles.) Electrical stimuli were applied to the right ventricle from a bipolar electrode sewn on the epicardium, excited by a stimulator and isolation unit (Grass S-88 and SIU-5), and driven by an R wave-coupled trigger. Stimulus duration was 3 msec, with an intensity adequate to produce an extrasystole at the selected time in the cycle. Recordings were taken during periods of stable ventricular function, and only sequences with fully compensated (defined as RR2 + RRp = 2RRc; see Glossary) postextrasystolic cycles in normal sinus rhythm were analyzed. Spontaneous and induced extrasystoles showed no significant differences when compared at comparable coupling intervals.

The test sequences were randomly selected for analysis, except when it was necessary to ensure that they included an adequate range of heart rates, cardiac function, and coupling interval. The random selection with respect to time in the respiratory cycle and the large number of sequences analyzed served to minimize any respiratory influence on the results. The RR interval was measured from the onset of the QRS complex. Although it was often difficult to define clearly this point on the extrasystolic R wave, this approach was used rather than the stimulus artifact or the peak of the R wave. This was done because the foot more closely approximated the onset of the mechanical event, since the latency period from the stimulus artifact to depolarization was quite variable, and the extrasystolic R wave was frequently very broad (Figs. 1 and 2).

Data Reduction and Analysis

The test sequence of three cardiac cycles to be analyzed (control, extrasystole, and postextrasystole) is defined in Figure 1, which is a typical oscillographic record from an experiment. Each cycle begins and ends with the onset of mitral flow. Three cycles preceding the extrasystole were averaged to provide a control value. SV and filling volume (FV) were calculated by digitizing the flow curves with a sonic digitizer (Science Accessories Corp. GP-2) coupled to a programmable calculator (Hewlett-Packard 9820A) or to a digital computer (PDP-11/34). The average of from three to five traces per curve was used in the calculations.

The accuracy of the method was verified by digitizing small and large areas placed at different locations on the tablet. For example, 10 measure-
**Glossary**

**Abbreviations**

RR  | Time between two R waves on the ECG (sec)
FV  | Filling volume (ml)
SV  | Stroke volume (ml)
PLVP | Peak left ventricular pressure (mm Hg)
DFP | Diastolic filling period, determined from the mitral flow curve (sec)
LVEDP | Left ventricular end-diastolic pressure (mm Hg)
dp/dt | Maximum rate of change of left ventricular pressure (mm Hg/sec)
EDAoP | End-diastolic aortic pressure, at time of aortic valve opening (mm Hg)
ESV | End-systolic volume
EDV | End-diastolic volume
EF | Ejection fraction = SV/EDV

**Subscripts**

C  | Control cycle
ES | Extrasystolic cycle
P | First postextrasystolic cycle

**Derived Indices**

CI  | Coupling index = RR_{ES}/RR_{C}
CR  | Compensation ratio = (RR_{ES} + RR_{P})/2RR_{C}
ΔESVI | Index of change in ESV (C–P)*
= (FV_{ES} + FV_{P})/(SV_{ES} + SV_{P})
ΔEDVI | Index of change in EDV (C–P)†
= (FV_{ES} + FV_{P})/(SV_{C} + SV_{ES})
ΔESV/FV_{C} | Change in ESV (C–P) as a fraction of control filling volume
ΔEDV/FV_{C} | Change in EDV (C–P) as a fraction of control filling volume
EF_{P/C (0.5)} | Ratio of EF_{P}/EF_{C} (based on an assumed value of EF_{C} = 0.5) = 2SV_{P}/(FV_{ES} + FV_{P} + SV_{C} - SV_{ES})

* Based on: ESV_{C} + FV_{ES} - SV_{ES} + FV_{P} - SV_{P} = ESV_{P}. Thus, a value of ΔESVI < 1.0 indicates a decrease in ESV_{P} and conversely.
† Based on: EDV_{C} - SV_{C} + FV_{ES} - SV_{ES} + FV_{P} = EDV_{P}. Thus, a value of ΔEDVI > 1.0 indicates an increase in EDV_{P} and conversely.

Other definitions can be found in legend to Figure 1.

The zero level for aortic flow was determined at end-diastole; that for mitral flow was determined during systole. The latter also was checked during cardiac fibrillation before coming off bypass, and at the termination of the experiment with potassium-induced cardiac arrest.

Although the flow probes were calibrated, the following additional procedure was adopted to attain the accurate measurement of SV and FV that is crucial to the interpretation of the data. For each test sequence to be analyzed, the average of control FV during three cycles was divided by the average of a similar number of control SV. The ratio defined a correction factor (K) which sometimes differed from 1.0, and which was then used to adjust each measured SV during the test sequence. The FV was chosen as the standard because the mitral flow probe is in direct contact with the blood and therefore is inherently more accurate than the cuff-type aortic probe. The use of the factor K minimizes the effects of nonrandom errors such as possible operator bias during digitizing, improper selection of baselines, neglect of coronary flow during systole, and flowmeter drift. The calculated FV and SV were within 10% of the values obtained using only the flowmeter calibration. For example, the standard deviation of K within the results of one experiment was an average of 10.2% of the mean. Results based on the average value of K for any one complete experiment were not statistically different from those obtained by using a value based on each sequence of cycles. Nonrandom calibration errors do not affect the results, since, as described below, most of the parameters are analyzed on the basis of changes in ratios.

Abbreviations, definitions, and derivations of indices to be used and analyzed in this study are presented in the Glossary. Because the absolute volume of the ventricle at the time of each extrasystole was not measured, the parameters of cardiac function used in the derived indices are related to changes in ventricular volume that occur during the extra- and postextrasystolic cycles. For example, the two indices related to changes in ESV and EDV (Δ ESVI and Δ EDVI, Glossary) are both derived solely from measurements of inflow and outflow and require no knowledge of initial volume (see footnotes to Glossary). The ejection fraction (EF) ratio, however, requires an assumption for the control EF. The rationale for its use is discussed below.

Extra- and postextrasystolic hemodynamic results, as well as the sums of the two, are presented...
as ratios with their control values and with twice control values, respectively; thus, the data all are normalized to control.

**Coupling Index (CI) and Δ ESVI**

A preliminary analysis of the data revealed that the results were not unique to any one dog. For example, in each of nine of the 13 dogs, the mean Δ ESVI did not differ significantly from the mean of the population of the 161 extrasystolic sequences studied. Since the results did not seem to be related to any intrinsic state of the individual dog, we chose to examine the ensemble of test sequences on the basis of the timing of the extrasystole and the functional state of the heart at the time of the extrasystole. The results first will be presented by organizing the individual test sequences into two groups: those with CI ≤ 0.7 and those with CI > 0.7. It has been shown (Takada et al., 1970) that the hemodynamic response to extrasystoles is minimal when the CI is greater than 0.8, and that the magnitude of the changes increases as the CI decreases. To delineate the influence of the time, we have chosen to group the data above and below a value of 0.7.

The first group, the early extrasystoles, will then be subdivided into two groups based on the value of Δ ESVI. The rationale for this subdivision is complex. (1) Since all postextrasystolic contractions occur in the presence of a decreased EDAoP, SVp augmentation is due in part to the decreased afterload; in addition, PLVPp and dp/dt increase may not have reached their potential maximums due to the early opening of the aortic valve. Thus, these pressure indices of contractility may not be appropriate for the characterization of PESP. (2) An increased EDVP (Δ EDVI = 1.34 ± 0.23) occurred in 94% of all sequences. This increased preload must influence the developed pressure and SV of the postextrasystolic cycle. (3) Δ ESVI had a nearly normal frequency distribution, with a mean of 0.978 and a standard deviation of 0.083 (range: 0.53-1.32). The median value was 1.0. Thus, half of the postextrasystolic contractions ejected to a decreased, and half to an increased, ESV. This result was independent of preload as shown by a linear regression analysis between the two parameters (r = 0.20). As a consequence of these three points, and in an effort to understand the hemodynamics of PESP in the intact heart, we decided as a first approximation to characterize the postextrasystolic response as potentiated (P) if the ESVp decreased, and as not potentiated (NP) if the ESVp increased.

**Statistical Analysis**

Statistical significance of calculated changes is based on the standard t-test for grouped data, with differences accepted at the $P < 0.05$ level. Data are presented below as means ± SD. The number of sequences (n) is not the same for every variable, since with very early extrasystoles extrasystolic left ventricular pressure (LVPp) fuses with LVP and DFPp fuses with DFP. Furthermore, aortic pres-
Results

Qualitative Description

Original oscillographic records of two test sequences with $CI \leq 0.7$ and $CI > 0.7$ are shown in Figures 1 and 2, respectively. The pressure-volume loops derived from these two records are shown in Figure 3. These data are typical of most of the test sequences. A qualitative description is given below before the quantitative results which elucidate the hemodynamic changes are presented.

The early extrasystole shown in Figure 1 and in Figure 3, panel A, interrupts the filling process and produces a ventricular contraction incapable of opening the aortic valve. In particular, note (1) the slow rate of increase and the small amplitude of early inflow following the extrasystole compared to control; (2) the decreased $EDA_{OP}$ at the first postextrasystolic contraction, and (3) the augmented SV and LVP during the contraction. The mitral inflow record during the compensatory pause shows a decrease in both rate and amplitude of early filling, but an increase in filling period. $LVEDP_p$ is greater than control, reflecting the increased $EDV_p$.

$PLVP_p$ increases, suggesting potentiation; $SV_p$ is augmented, suggesting either potentiation or a response to the decreased $EDA_{OP}$. On the other hand, the increased $E SV_p$ may indicate an unchanged or a decreased contractility.

The later extrasystole shown in Figure 2 and in Figure 3, panel B, exhibits some of the above characteristics with three notable exceptions: the extrasystolic contraction produces a small SV, $PLVP_p$ is not augmented, and $ESV_p$ is less than control. Potentiation of force of contraction is not evident, but ejection to an ESV smaller than control implies an increase in contractility.

These two examples illustrate all the possible changes in hemodynamic function that may occur during extrasystoles. However, this does not imply a relation unique to each of the pressure-volume loops shown in Figure 3, for example between increased $PLVP_p$ and no $SV_{ES}$ in panel A; the changes can occur in various combinations. Note that both sequences show an increased $EDV$ preceding the first postextrasystolic contraction and an increased SV during that contraction. Panel A, however, shows an increased SV and panel B a decreased ESV relative to control following that contraction.

Control Hemodynamic Data

Table 1 presents the control hemodynamic data for test sequences subdivided according to timing of the extrasystoles (columns 1 and 2) and the changes in ESV (columns 3 and 4). These data indicate that we have studied a wide range of cardiac function (assessed from preload, afterload, and inotropic state), heart rate, and values of CI. There was no evidence of abnormal physiological function.
TABLE 1  Control Hemodynamic Data*

<table>
<thead>
<tr>
<th></th>
<th>CI ≤ 0.7</th>
<th>CI &gt; 0.7</th>
<th>Potentiated</th>
<th>Nonpotentiated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>124 ± 32 (91)</td>
<td>112 ± 25 (70)</td>
<td>124 ± 28 (43)</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>0.624 ± 0.073 (91)</td>
<td>0.794 ± 0.044 (70)</td>
<td>0.623 ± 0.070 (43)</td>
</tr>
<tr>
<td></td>
<td>CO (liters/min)</td>
<td>2.53 ± 0.79 (91)</td>
<td>1.93 ± 0.65 (70)</td>
<td>2.18 ± 0.59 (43)</td>
</tr>
<tr>
<td>PLVPC (mm Hg)</td>
<td>98 ± 19 (91)</td>
<td>103 ± 21 (70)</td>
<td>91 ± 19 (43)</td>
<td>103 ± 20 (48)</td>
</tr>
<tr>
<td>LVEDPC (mm Hg)</td>
<td>6.8 ± 3.3 (91)</td>
<td>6.4 ± 3.4 (70)</td>
<td>7.0 ± 3.9 (43)</td>
<td>6.6 ± 2.6 (48)</td>
</tr>
<tr>
<td>EDAoPC (mm Hg)</td>
<td>52 ± 15 (52)</td>
<td>57 ± 16 (32)</td>
<td>58 ± 14 (18)</td>
<td>49 ± 13 (34)</td>
</tr>
</tbody>
</table>

* Refers to the condition immediately preceding the test sequence. Abbreviations defined in the Glossary. Data are presented as mean ± SD; numbers in parentheses indicate number of sequences.

\[ \text{PLVPC} = \text{PLVP} + \text{EDAoP} \]

Since control heart rate and cardiac output are independent of CI, no test of significance for these data was performed.

Although the differences in PLVPC and EDAoPC between the P and NP groups are statistically significant, there is no evidence that they are physiologically significant in this study. With linear regression, these two parameters did not appear to influence the indices used. No significant correlations were found between the indices of volume change (Δ ESVI or Δ EDVI) and control values of preload (LVEDPC), afterload (EDAoPC), and contractility (dp/dtc and PLVPC).

When the data of column 2 (Table 1, CI > 0.7) were divided into P and NP, there was no significant difference between any of the six pairs of results. These control data indicate that analyses based on CI and ESV are independent of any nonrandom control parameter.

Hemodynamic Parameters during Test Sequence with CI ≤ 0.7 and CI > 0.7

**Extrasystole**

The hemodynamic parameters during the extrasystole are presented in Figure 4, panel A. For values of CI ≤ 0.7, 49% of the control FV enters the ventricle before the extrasystolic contraction, the ejected SV is 12% of its control value, and the PLVP is 47% of control. The ratio $\frac{SV_{ES}}{FV_{ES}}$ (not shown in Figure 4) is 0.25 ± 0.34. As the CI increases, these values also increase with a proportionately greater increase in the SV compared to the FV and PLVP. The ratio $\frac{SV_{ES}}{FV_{ES}}$ also increases (to 0.56 ± 0.34), with the individual data points showing a large scatter and a poor linear correlation with CI.

**Postextrasystole**

The hemodynamic parameters during the postextrasystolic cycle are shown in Figure 4, panel B. When the CI is ≤0.7, the FV is only 6% greater than control despite the 76% increase in DFP, and augmentation is indicated by the increases in SV, PLVP, and dp/dt of 49%, 13%, and 21%, respectively. The increased SV may have been influenced by the 17% decrease in EDAoP; the 55% increase in LVEDP indicates an increased EDV, which will be shown below.

With the increase in CI and subsequent shortening of the interval preceding the first postextrasystolic contraction, all the parameters show the same trends but at a lower ratio to control.

**Extra + Postextrasystole**

To test the effects of the compensatory pause, Figure 4, panel C, presents the ratio of total inflow,
outflow, and filling period during the extrasystole plus postextrasystole to twice the value of their counterparts during control. This 2-fold base represents the predicted sum of two normal cycles. With a CI \( \leq 0.7 \), the total FV is 79% of twice control, the total SV is 80% of twice control, and the summed DFP is 116% of twice control. When the CI increases, the DFP approaches 1.0 and the values of filling and ejection increase slightly.

Except for FV/C, all the parameters in Figure 4 differ significantly from an assumed population mean of 1.0; i.e., they exhibit a significant change from control.

Panels B and C of Figure 4 indicate that, although there are statistical differences based on the timing of the extrasystole, there are no profound physiological differences in the hemodynamic parameters as a consequence of that timing. The results indicate that increases in FV are minor compared to increases in DFP, and that potentiation, as defined by SV and PLVP, occurs frequently. The possibility of defining potentiation as a change in contractility leading to decreased ESV was next assessed by examining the hemodynamic data from test sequences of early extrasystoles.

Hemodynamic Parameters during Test Sequences with CI \( \leq 0.7 \), Subdivided into Potentiated and Nonpotentiated Postextrasystolic Responses

**Extrasystole**

During the extrasystole (Fig. 5, panel A) comparing both groups to control, filling decreased (46% and 52%), ejection decreased (9% and 14%, so that \( \text{SVr}_{\text{ES}}/\text{FVr}_{\text{ES}} = 0.20 \) and 0.30), and developed pressure decreased (41% and 52%). The last parameter is the only one of the three that shows a weak but statistical difference between P and NP. Thus, the factor that determines the postextrasystolic response is not unmasked by analysis of the hemodynamics during the extrasystole.

**Postextrasystole**

The hemodynamic parameters normalized to control during the postextrasystolic cycle are shown in Figure 5, panel B. Particularly noteworthy is the significantly greater SV of the P compared to the NP contractions (1.63 vs. 1.36), despite the fact that the FV of the P cycles is less than that of the NP cycles (1.0 vs. 1.11). Thus augmentation as measured by SV is consistent with potentiation as measured by ESV. This consistency is also manifested in the greater values for PLVP (1.17 vs. 1.08) and \( \text{dp}/\text{dt} \) (1.28 vs. 1.13) ratios. Note also that there is no significant difference between the P and NP groups with respect to the LVEDP and ED AoP ratios.

**Extra + Postextrasystole**

The normalized values for the total inflow and outflow (Fig. 5, panel C) are similar to those of Figure 4, panel C. Although statistically significant, the differences between P and NP are small for the FV and SV parameters. The differences in DFP are not statistically significant. These data indicate again that total FV is not commensurate with total DFP.

With the sole exception of FV/C for the P group, all the parameters differ significantly from an assumed population mean of 1.0. Note that if the averages of the results in both Figures 4 and 5 (filled circles) are compared, it can be seen that there are no profound physiological differences among these groups of test sequences. Factors related to timing of the extrasystole, such as FV and DFP, change in predictable ways. These results suggest that we focus next on indices related to changes in volume.

**Indices of Ventricular Volume Change during Test Sequences with CI \( \leq 0.7 \) Subdivided into Potentiated and Nonpotentiated Postextrasystolic Responses**

The indices that describe the changes in ventricular volume for those sequences with early extra-
systoles are compared in Figure 6. \( \Delta ESVI \) has been described above; it represents the basis for the division into P and NP. \( ESV/FV_c \) represents the change in ESV (control to postextrasystole) as a fraction of the control TV. The results show that the P group has a decreased ESV equal to 26% of its \( FV_c \), and the NP group has an increased ESV equal to 14% of its \( FV_c \). This separation unmasks the possible occurrence of large changes in ESV. The index reflecting the change in EDV (\( \Delta EDVI \)) is statistically greater in the NP group, but there is no supporting evidence that this reflects a physiologically significant difference. Expressed as a fraction of control TV, the EDV in the P and NP groups increased by 37% and 50%, respectively.

These large increases in EDV\(_P\), along with the large increases in SV\(_P\), indicate that changes in EF might provide a meaningful insight into PESP. Since the absolute volume of the ventricle was not measured in this study, we have estimated the fractional change in volume by assuming control EF values of 0.4, 0.5, and 0.6. These values cover the range normally found for the anesthetized, open-chest dog. The results for \( EF_c = 0.5 \) shown in Figure 6 then can be translated into a decrease in ESV of 26% for the P group, and an increase in ESV of 14% for the NP group. The assumed EF also leads to calculated increases in EDV for both the P and NP groups of 18% and 25%, respectively.

We have also calculated the EF for the postextrasystolic beat, normalized to control, by assuming a control EF of 0.4, 0.5, and 0.6. The ratio \( \left[ EF_{P/C, 0.5} \right] \) for the P and NP groups is plotted in Figure 6. The values for the P and NP sequences are 37% and 9%, respectively. Similar trends were found with assumed control EF of 0.4 or 0.6. Thus, in the normal range of EF for the anesthetized dog, the normalized \( EF_p \) for the P group is statistically and apparently physiologically greater than for the NP group. When the volume indices with \( CI > 0.7 \) are divided into P and NP, the results are comparable to those of Figure 6, but with values closer to control.

**Correlation of Changes in ESV with Other Parameters and Indices**

CI, SV\(_{ES}/FV_{ES} \), LVEDP\(_P\), LVEDP\(_C\), EDAoP\(_P\), PLVP\(_P\), PLVP\(_C\), heart rate \( \Delta EDVI \) were all plotted as functions of \( \Delta ESVI \). Linear regression analysis applied to these data, based on either the ensemble of sequences or on treating the average of each dog as one data point, showed poor correlations. In two dogs with 13 and 12 extrasystolic sequences and constant heart rate (160 and 156 beats/min, respectively), no correlation could be found between \( \Delta ESVI \) and CI.

To test the hypothesis that there was a relation between \( \Delta ESVI \) and \( \Delta EDVI \) unique to the particular properties of each individual dog, linear regression between the two parameters was tried for each dog. There is considerable variation within each dog as well as between dogs (mean \( r = 0.34 \pm 0.51 \), range: \(-0.68 \) to 0.88, \( n = 13 \)).

**Discussion**

In contrast to the isolated muscle preparation and isovolumic ventricle with their precise control of preload, afterload, and inotropic state, the intact ejecting heart offers less opportunity for control. On the other hand, the intact ejecting heart offers a greater opportunity for the evaluation of the interrelation of the many factors involved in PESP. This study represents the first approach to the direct investigation of the role of filling in PESP and provides an overview of the many hemodynamic parameters that influence the ventricular response to extrasystoles. This overview is provided by studying the cardiac response to a single premature contraction which occurs at varying intervals from the normal sinus beat and is followed by a fully compensatory pause, and which occurs during varying conditions of cardiac function. Furthermore, pressures in the left atrium and aorta are determined by the normal physiological processes. With this approach and with the measurement of mitral inflow to the left ventricle, we have developed several new interpretations of the dynamics of PESP in the intact heart.

As a consequence of this approach we are faced with the problem of defining an index of contractility that is based on ejection parameters and is independent of preload and afterload. This is clearly not possible. If preload and afterload were controlled, however, the ESV would be a suitable index. Since in this study all the postextrasystolic cycles contracted against a decreased afterload, and since change in ESV was not correlated with the change...
in EDV, the use of Δ ESVI as an index of potentiation providing a first approach toward analyzing the data is not unreasonable. Nevertheless, although we conclude that this study provides new and useful information, we are unable to determine why some cycles exhibit potentiation based on an ejection index and some do not. Thus the major thrust of the following discussion will be toward analyzing the hemodynamic determinants of left ventricular filling.

Interest in the phenomenon of PESP has shifted from its application to paired pacing (Cranefield, 1965; Hoffman et al., 1965) to its use as a measure of myocardial contractility (Takada et al., 1970; Anderson et al., 1976) and as an indicator of myocardial viability in diseased hearts. The latter approach relies on the measurement of segmental contractile patterns during the postextrasystolic beat (Dyke et al., 1974; Banka et al., 1976; Popio et al., 1977) and/or on the hemodynamic responses to extrasystoles, e.g., EF, PLVP, dp/dt, and estimated V max (Popio et al., 1977; Hamby et al., 1975; Cohn et al., 1975; Van der Werf et al., 1976). With one exception (Van der Werf et al., 1976), these clinical studies have used only those extrasystoles with a fully compensatory pause.

Although PESP is an intrinsic property of cardiac muscle, in the intact ejecting heart the postextrasystolic response to an extrasystole is determined by (1) the timing of the extrasystole (a transient rate change), (2) the timing of the postextrasystolic cycle (duration of the compensatory pause), and (3) the net filling of the ventricle (preload). Two recent studies on dogs have sought to clarify these influences.

Anderson et al. (1976) measured end-diastolic dimensions with sonomicrometers and controlled the atrial pacing rate to keep EDGeometry P = EDGeometry C. They used as an index of potentiation the ratio (dp/dt P)/(dp/dt C). No other hemodynamic parameters were reported in the study. Here, too, there was no fully compensatory pause.

The second study, by Takada et al. (1970), is the most comprehensive study to date, and offers the best opportunity for comparison with our results. Using dogs with reservoir-controlled aortic and left atrial pressure, a constant pacing rate of 135 beats/min, and a coupling interval that varied from 260-425 msec (CI: 0.60–1.0), they measured aortic, left ventricular, and left atrial pressures, SV, dp/dt, and myocardial tension. They reported the following:

- SVES/SVC = 0.20, SV P/SVC = 1.60, (SV ES + SV P)/2 SVC = 0.80, PLVP ES/PLVP C = 0.80, PLVP P/PLVP C = 1.10, and EDAoP P/EDAoP C = 0.85. (Note that these figures are approximate since we have extrapolated them from graphs with considerable scatter.) These values are comparable to the means of data from all the extrasystoles used in our experiments: 0.24, 1.43, 0.83, 0.58, 1.10, and 0.84, respectively. In spite of the fact that we used cardiopulmonary bypass and a mitral flow probe, our data are comparable.

Determinants of Changes in Left Ventricular Volume

The finding that the rate of left ventricular filling during the compensatory pause (i.e., the volume inflow per unit of filling time) is significantly lower than during the control cycle is an important observation, and suggests a need to consider the factors that influence filling and hence EDV. We have shown (Yellin et al., 1976) that the pressure-flow relations across the normal mitral valve are governed by inertial and resistive forces. The rate of volume inflow is determined by the magnitude of the atrioventricular pressure difference and the rate at which this difference is developed. Thus the rate of fall of ventricular pressure, the value to which it falls, and the atrial reservoir pressure combine to create the driving force for inflow. In addition, EDV is influenced by the time for filling and by the ESV following the previous ejection. These factors will now be discussed for each of the cycles in the extrasystolic sequence.

Filling Prior to the Extrasystolic Contraction

The direct measurement of phasic mitral flow has shown that approximately 25% of the filling volume enters the ventricle before the minimum left ventricular pressure is reached (Yellin et al., 1976). As a consequence, some filling will always occur unless the coupling interval approaches a value short enough for fusion of cycles, and in general there is a significant inflow before the extrasystolic contraction (58% of control in this study).

In addition, the development of pressure by the left ventricle is slow during the extrasystolic contraction. This allows more time for filling before reversal of the atrioventricular pressure gradient and retards the rate of inflow deceleration from its rapid early phase (Laniado et al., 1973).

Ejection during the Extrasystole

The observation that stroke volume is smaller relative to both control (SV ES/SV C = 0.58) and preload (SV ES/FV ES = 0.38) can be explained by a combination of intrinsic depression and asynchronous contraction. These effects were separated in another report in which we analyzed spontaneous supraventricular premature contractions from the same dogs used in this study. In 78 cases of atrial extrasystoles followed by normal QRS complexes, the FV ES was consistently greater than the SV ES (15 ± 6 vs. 12 ± 7 ml, P < 0.01) (Yellin et al., 1978). Thus, although asynchrony of contraction plays a role in the depression of left ventricular function during idioventricular extrasystoles, it cannot account completely for the smaller SV observed, and
we may conclude that the extrasystolic ejection is depressed by virtue of an intrinsic response to a change in rate, thereby increasing ESV.

**Filling during the Compensatory Pause**

"Compensatory pause" is a term first used by Woodworth (1903), who concluded that the increased RR interval exactly compensated for the shortness of the extrasystole. Further, other studies on isolated muscle (Cranefield, 1965) and intact heart (Anderson et al., 1976) suggest that shortening the postextrasystolic RR interval increases contractility as measured by developed tension and dp/dt. Although SV was not determined under those conditions, the commonly held assumption has been that increasing the filling period during the "compensatory pause" provides a concomitant increase in FV (Takada et al., 1970; Beck et al., 1971; Cohn et al., 1977). However, the net SV and stroke work of the extrasystolic plus first postextrasystolic cycles is only approximately 90% of that provided by two normal beats.

Our observation (Fig. 4, CI < 0.7) that the postextrasystolic FV is only 6% greater than control despite an increase in filling period of 76% requires further discussion of the factors that determine the atrioventricular pressure difference. In all the test sequences analyzed for this study, the driving pressure difference for mitral inflow during the compensatory pause is diminished for the following reasons:

1. The left atrial v wave is lower than control, indicating that at the time of mitral valve opening the upstream reservoir pressure is lower than control (Fig. 2). This may be due to a decreased pulmonary venous flow resulting from poor right ventricular contraction during the extrasystole and/or the effects of an atrial contraction (during the extrasytolic extrasystole) which transiently drives the venous return upstream.

2. The rate of fall of ventricular pressure following the extrasystolic contraction is always slower than in control cycles, thereby reducing the rate at which the driving pressure is developed and retarding early filling (Figs. 1 and 2).

3. The minimum pressure to which the ventricle relaxes following the extrasystole is nearly always higher than in the control, thereby reducing the ventricular contribution to the magnitude of the pressure gradient, and hence the rate of early inflow (Figs. 1 and 2).

**Ejection during the Postextrasystolic Cycle**

In this study the average increase in the postextrasystolic SV was 43% (greater at low CI, Figure 5), with only three of 161 responses showing a decrease in SV. This augmentation of SV can be related to an intrinsic property of cardiac muscle, the increased EDV (only six of 161 postextrasystolic responses showed a decrease in EDV), and the decreased EDAoP. The quantification of each of these influences should be the subject of future studies.

**Starling's Law and PESP**

Patterson et al. (1914) studied the relationship between EDV and SV (measured by cardiometry) by observing the steady state response to a change in venous return resulting from a change in total blood volume. They noted that, when free of neural influence, EDV, ESV, and SV all increased with an increase in FV, and that several beats were required before equilibration of SV and FV in response to a sustained change in FV. Thus it appears that EF tends to stay constant. A constant EF would, over the course of a few beats, either achieve equilibrium between inflow and outflow at a new EDV, or return to the control EDV if the change in venous return were only transient. This reasoning is confirmed by studies on isolated muscle subjected to a sudden change in preload, which show that the developed tension following a sudden stretch is less than the steady state value for the new preload. (Parmley and Chuck, 1973; Lakatta and Jewell, 1977). It is reasonable to speculate that, since the first postextrasystolic contraction occurs before there is any feedback from the neural control system, we may conclude that the ventricular SV response to the transiently increased EDV is augmented less than Starling's law would predict. That is, the transient response is less than the steady state response.

If we follow the same reasoning, we can argue that an increase in the postextrasystolic EF implies an augmentation beyond that predicted by Starling's law. Since we have not measured EF, we have avoided defining potentiation on the basis of EF and have chosen instead to use a directly measured index of volume change (Δ ESVI) to characterize potentiation in the intact heart. It is interesting to note, however, that if we assume an EF as large as 0.6 for the control cycle, then 85% (137 of 161) of the postextrasystolic cycles have an EF greater than or equal to control. This is a conservative estimate, since the percent would increase if we assumed a lower and more physiological control EF. On the other hand, only 47% (75 of 161) of the postextrasystolic cycles showed a decrease in ESV relative to control. Control data in Table 1 indicate that left ventricular function was in the normal
range, and thus our data on PESP support the finding that normal hearts exhibit this property (Takada et al., 1970; Van der Werf et al., 1976) and are in contrast to reports that suggest that only failing hearts show significant PESP (Hoffman et al., 1965; Beck et al., 1971; Kvasnicka et al., 1975).

Finally, it can be argued that the anesthetized, open-chest dog that has just undergone cardiopulmonary bypass is a poor model for the study of PESP. The magnitudes of many of the hemodynamic responses to extrasystoles will undoubtedly differ in a more physiological preparation. Nevertheless, given the insight provided by the direct measurement of mitral flow, we expect the general trends described in this study, particularly the factors related to filling, to be observed in the unanesthetized dog.

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