End-Systolic Pressure As a Balance Between Opposing Effects of Ejection

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Ejection has previously been thought to exert only negative effects on end-systolic left ventricular pressure, via mechanisms like shortening deactivation and the force-velocity relation. Whether ejection also exerted a positive influence on pressure generation was tested by comparing two successive beats: 1) the last beat of steady-state ejection versus 2) a totally isovolumic contraction at the end-systolic volume. In 12 isolated, blood-perfused canine hearts loaded with a simulated arterial system, ejecting end-systolic pressure exceeded isovolumic pressure by approximately 10 mm Hg when ejection fraction was 0.3. With both higher and lower ejection fractions, the excess of ejecting end-systolic pressure was smaller; beyond an ejection fraction of roughly 0.5, the trend reversed so that ejecting end-systolic pressure fell below isovolumic pressure. The maximum excess in ejecting end-systolic pressure was quite variable (1–17 mm Hg), but the pattern of its variation with ejection fraction was consistent. A correlate of the positive effect of ejection on ventricular pressure was found in the timing of end systole. For an ejection fraction of 0.4, the systolic duration of ejecting beats was approximately 45% longer than in isovolumic beats (range, 23–67%). Potentially, a positive effect of ejection might be due to a residual influence of the stronger activation of cardiac myofilaments early in ejecting systole during which the sarcomeres were at longer lengths than in the isovolumic beat at end-systolic volume (length-dependent activation). A hypothetical model based on this mechanism reproduced both of the positive effects of ejection that were observed: excess end-systolic pressure and prolonged duration of systole. Thus, the approximate load independence of end-systolic pressure could result from the counter balance between opposing influences of ejection. (Circulation Research 1989;64:265–275)

The essence of the pressure-volume ratio to describe ventricular contraction is the concept that the instant-by-instant value of ventricular pressure depends principally on the simultaneous value of ventricular volume.1-2 Later work3-13 showed that this concept is an idealization and that there are at least two additional factors to be considered: 1) instantaneous flow velocity4-12 and 2) the deactivating or uncoupling effect of muscle shortening during ejection.3-8,13 Both these additional factors act negatively to reduce ventricular pressure during ejection or at the end of systole. Hence, one would predict that the maximal end-systolic pressure (ESP) at any volume would occur when there was no ejection (i.e., a totally isovolumic contraction).

Counter to this expectation, however, flow-pulse studies4-8 produced a paradoxical finding. When a small flow pulse was ejected after the ventricle had built up considerable pressure isovolumically, the resulting ESP was consistently greater than the peak pressure the same ventricle could develop in a totally isovolumic contraction at the end-systolic volume (ESV). The original pressure-volume ratio concept would have predicted no difference in ESPs, and the additional influence of shortening deactivation would have predicted less pressure following ejection. In this unexpected observation, ejection seemed to act on pressure in a positive rather than a negative sense. Additional evidence, showing that the duration of systole in ejecting beats is substantially longer than in isovolumic beats,14 provided another suggestion for a positive effect of ejection that could not be explained by the concept of a unique time course for the ventricular pressure-volume ratio.

The present study tested whether such a positive effect could also be seen when the amount and timing of ejection more closely simulated what occurs in vivo rather than following the small and narrow arbitrary
flow pulses used originally. Using an isolated canine heart preparation, ESP in contractions simulating normal ejection was compared to ESP in an isovolumic beat having the same volume as that reached at end systole. The results indeed demonstrated both positive and negative effects of ejection on ESP.

Materials and Methods

Preparation

The surgical preparation of an isolated canine ventricle has been described elsewhere. Briefly, each experiment used a pair of mongrel dogs (20–22 kg), anesthetized with sodium pentobarbital (30–40 mg/kg i.v.). The chest of the heart donor was opened under artificial ventilation, and the subclavian artery and right atrium were cannulated and connected to the femoral arteries and veins, respectively, of a support dog. After ligation of the azygous vein, superior and inferior venae cavae, brachiocephalic artery, descending aorta, and pulmonary hili, the heart was removed from the chest. The pericardium was removed, the left and right ventricles were vented, and the chordae tendinae were cut. A thin balloon mounted on a brass adaptor was placed in the left ventricle, and the adaptor was sewn into the mitral valve anulus. The balloon adaptor then was connected to a ventricular volume control servopump system. A constant volume of distilled water filled the pump and balloon. Therefore, absolute volume changes in the balloon were precisely controlled and measured by the volume servopump. Coronary arterial pressure was measured by a catheter placed via the brachiocephalic trunk into the aortic root. A servo-controlled perfusion pump (model 1215, Harvard Apparatus, South Natick, Massachusetts) maintained mean coronary arterial pressure at 100 mm Hg throughout the experiment. Coronary arterial blood temperature was maintained at approximately 37°C with a heat exchanger. The left ventricular pressure was measured in the balloon with a catheter tip micromanometer (model PC-380, Millar, Houston, Texas). Ventricular pressure-volume loops were monitored on-line on an X-Y storage oscilloscope. Ventricular pressure and volume were also digitized (200 Hz sampling rate, 12 bit A/D converter) for later computer analysis (PDP 11/23).

Loading System to Simulate Normal Ejection

This study used a modified version of the impedance loading system for the isolated canine ventricle, similar to the one previously reported from this laboratory. The basic characteristics and performance were essentially the same as those of the previous one. Briefly, the arterial afterload system was simulated with a three-element Windkessel model, and the preload system was simulated with a simple dc pressure source having a filling resistance in series. In the original impedance-loading system, these simulation models were set up on an analog computer that calculated the instantaneous flow out of or into the ventricle that should occur in response to the instantaneous ventricular pressure measured in the isolated heart. In the new impedance-loading system, the instantaneous flow was calculated digitally every 2 msec with a high-performance 16-bit microprocessor (8086/8087, Intel, Santa Clara, California) by feeding digitized instantaneous ventricular pressure to programs that implemented the equations describing the preload and afterload system models. The calculated instantaneous flow was then numerically integrated with respect to time, and the integral was used as the command signal to the volume servo-pump through a 12-bit digital to analog converter. With this loading system, the ejection pattern and stroke volume of a given left ventricle depended on its interaction with the afterload system parameters (Rc, Rp, and C) set in the arterial model.

Experimental Protocol

First, a steady state of ejection was established. Then, at the end of one contraction, the ventricular volume servo system was switched to hold volume constant—either at the volume reached at end-ejection or after some variable degree of filling had occurred. Figure 1A shows original chart recordings from an example of this protocol in which a small amount of filling occurred before volume was clamped. Only data from the last ejecting beat and the first isovolumic beat were analyzed in the present study so that physiologic processes involved in beat-to-beat transients could be excluded. Several beats later (not shown) the volume clamp was released, and the initial steady ejecting state was restored.

The switch from ejecting to isovolumic contraction modes was repeated with volume clamped at another volume near end ejection. The aim was to have two volumes bracketing the volume at the end-systolic point in the ejecting contraction (see Figure 1C). Note that the ESV (see solid square in Figure 1C) was often slightly larger than the volume at end ejection. Occasionally, filling was allowed to proceed closer to end-diastolic volume (EDV) before clamping (see the two isovolumic contractions at higher volumes in Figure 1C), but data from such larger-volume isovolumic contractions were used for purposes other than comparing ESPs.

After completing a set of switches to isovolumic as in Figure 1C, the parameters of the arterial model were altered, primarily by changing peripheral resistance, so that the stroke volume was substantially different. The protocol was then repeated at the new steady state of ejection. Peripheral resistance values were chosen to obtain a suitably wide range of ejection fractions; they ranged from 0.6 to 14 mm Hg/ml/sec, depending on heart rate (90–130 beats/min) and the intrinsic size and contractility of the left ventricle. On average, the minimum peripheral resistance was 1.4 mm Hg/ml/sec and the maximum was
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7. To form a complete data set, three or four (average, 3.5) levels of peripheral resistance were tested. The order of applying large versus small stroke volumes differed randomly among preparations.

Data Analysis

End systole was defined as that point during ejection where the pressure-volume ratio was maximum. In calculating this ratio, "volume" refers to the stressed volume, that is, volume exceeding $V_o$, the volume axis intercept of the end-systolic pressure-volume (ESPVR) relationship. For this limited purpose, $V_o$ was estimated from the peak pressures of the set of isovolumic contractions. When calculating the time to end systole, the peak of the epicardial electrogram indicated the start of systole.

For calculating ESP difference between ejecting and isovolumic contractions, comparison between the two modes of contraction was carried out in the pressure-volume plane, which ignored differences in the time to end systole. Calculation of the pressure difference required an estimate of the peak isovolumic pressure that would have occurred if the ventricle had contracted at precisely the same volume as at the end-systolic point in the ejecting beat. This was obtained by interpolating linearly between the points observed at the peaks of the two closest bracketing isovolumic contractions. Interpolation was required only to extend over a small interval: The volume of the isovolumic beat that was the closest one to the ejecting end-systolic volume averaged only 0.5 ml less than the ejecting ESV. To test the reproducibility of the ESP difference, in 40 cases the measurement was repeated 2 or 3 times for the same ejecting state but not with the same two isovolumic volumes. The standard deviation of $\Delta ESP$ was ±0.56 mm Hg over this set of repeated measurements.

Results

Panels A and B in Figure 1 present a clear example of the sort of "positive" effect of ejection on ESP that was observed. On suddenly switching from a steady-state ejecting mode to an isovolumic mode of contraction, ESP in the isovolumic beat fell 13 mm Hg below ESP in the ejecting beat, despite the isovolumic beat having a slightly higher volume.

The effect of varying stroke volume (with nearly constant EDV) is portrayed in Figure 2, which shows three different steady-state ejecting pressure-volume loops and an associated isovolumic beat at the end-ejection volume. The dashed line connects the points of peak isovolumic pressure. Even with the smallest stroke volume (loop 1), there was a substantial excess of ESP (10.2 mm Hg) compared with that expected from the isovolumic contraction. As stroke volume increased (loop 2), this excess in ESP became even greater (12.7 mm Hg). However, for a very large stroke volume (loop 3), the trend reversed, and ESP was then only slightly larger (2.6 mm Hg) in the ejecting contraction. (Note that the dashed line in Figure 2 was drawn only for illustrative purposes; the numerical differences in ESP were obtained as described in "Materials and Methods," using a second isovolumic contraction, not shown, associated with each ejecting state.)

$\Delta ESP$ between ejecting and isovolumic contractions was plotted as a function of ejection fraction in Figure 3. Panel A presents the data from Figure 2 (points labeled 1–3) combined with other runs from the same heart at a fixed inotropic state. A quadratic regression (constrained to have $\Delta ESP$ equal 0 when ejection fraction equals 0) was then fit to these data.
FIGURE 2. Three pairs of ventricular pressure-volume trajectories with different ejection fractions. Shown in each pair is last beat of steady ejecting state and succeeding isovolumic beat at end-ejection volume. To help visualize isovolumic beats, a dashed line was drawn connecting their peak pressures. The end-systolic point is marked (+) on each ejecting pressure-volume loop. Note that excess of ejecting end-systolic pressure was function of ejection fraction. The three beats numbered here correspond to labeled points in Figure 3A.

The parabolic regression curve was drawn over only the range of ejection fractions for which there was data. The scatter about the regression line in this example had a standard error of estimation (SEE) of ±2.2 mm Hg. This was typical but slightly greater than the global average, which had a mean SEE of ±1.8 mm Hg.

Panel B summarizes the difference in ESPs between ejecting and isovolumic contractions. Shown are the quadratic regression curves (determined as shown in panel A) for a total of 15 conditions in the 12 hearts studied. The trend for small-to-moderate ejections to have an excess of pressure compared to isovolumic contractions is clear, as well as the observation that this trend reverses when ejection fraction is large. Notice, however, that the regression curves varied considerably among different hearts. The maximum ΔESP in the regression curves ranged from 1.4 to 16.5 mm Hg, and the crossover point from positive to negative ΔESP ranged from an ejection fraction of 0.30 to 0.67. With some consistency, a larger maximum ΔESP was correlated (r=0.84) with a larger ejection fraction at cross-over.

Some of the variability in ΔESP may have been due to differences in contractile state. For instance, panel C shows three sets of data from the same heart under different contractile states. The central curve was the control state; the highest curve occurred during a continuous infusion of dobutamine into the coronary perfusion, and the lowest curve was observed after a bolus of propranolol. This effect of contractility was not pursued systematically, however.

Another measure indicating the positive influence that ejection exerts on pressure development is the time (relative to the start of a contraction) at which the ESP is reached. For example, panel A in Figure 4 shows the time course of left ventricular pressure for three superimposed beats: an ejecting beat (center trace) and isovolumic contractions at both EDV and ESV. The time to end systole in the isovolumic beat at ESV (see dotted vertical line at the ×) was 120 msec after the peak of the R wave of the ECG (whose time is indicated by the arrow on the abscissa). Compared to this, the time to ejecting end systole (see the dashed line at the solid squares) was 190 msec—an increase in duration of 58%. The isovolumic contraction at EDV had a slightly longer duration than at ESV (135 msec), but this was an increase of only 12%.

Panel B shows the effect that such a difference in timing would have in the pressure-volume analysis. If pressures were compared isochronally (instead of ignoring time as in Figure 2), the excess of ejecting ESP over isovolumic ESP would become much greater. The dashed line connects the points in the isovolumic contractions that are synchronous with end systole in the ejecting beat (all indicated by solid squares). In this case, ejecting ESP would be approximately 50 mm Hg greater than in an isovolumic contraction at the same time and volume.

Figure 5 compares the increase in the duration of systole (ejecting versus isovolumic at ESV) for different ejection fractions. Panel A collects all the data points from the same contractile state of the same heart as shown in the example of Figure 4. A quadratic regression (constrained to have ΔT equal 0 when ejection fraction equals 0) was then fit to these data. The parabolic regression curve was drawn over only the range of ejection fractions for which there was data. The scatter about the regression line in this example (SEE=±3.6%) was typical but slightly less than the global average (SEE=±4.4%).

Panel B summarizes the increase in systolic duration of ejecting versus isovolumic contractions (at ESV). Shown are the quadratic regression curves (determined as in panel A) for a total of 15 conditions in the 12 hearts studied. The trend indicated strongly increasing duration of ejection up to EFs of 0.3 or 0.4. With even more ejection, there was a more variable response: Duration became somewhat shorter, remained nearly unchanged, or even continued to increase.
Figure 3. Excess end-systolic pressure in ejecting (versus isovolumic) beats as function of ejection fraction. Panel A: Each point represents one of many ejecting steady states (from one heart in one contractile state); three labeled points correspond to cases shown in Figure 2. Solid line depicts quadratic regression fit to points shown (with additional constraint that regression must have zero pressure difference at zero ejection fraction). Panel B: Regression lines for all hearts and all conditions studied. Each line was derived as in panel A, and each was drawn only over range of ejection fractions for which there was data. Panel C: Effect of catecholamine stimulation and blockade. Center regression line (■), control conditions; upper line (diamonds), during dobutamine infusion; bottom line (▲), after propranolol.

Panel C compares the time to end systole (peak pressure) in isovolumic contractions as a function of volume. For comparison with panel B, the data are presented in an analogous way. In this case, "ejection fraction" meant \((V_{\text{large}} - V_{\text{small}}) / V_{\text{large}}\) or \(V_{\text{small}}\) corresponded to a volume near end-ejection of a preceding ejecting beat, and \(V_{\text{large}}\) would have been an arbitrary larger volume (up to EDV), as shown in Figure 1C. There was a consistent and (at fixed contractility) relatively monotonic increase of systolic duration with volume, but this increase was much smaller than the increase in systolic duration for an ejecting beat operating between the same volumes.

Discussion

This study provides clear evidence for the existence of mechanism(s) by which ejection exerts a positive influence on left ventricular pressure that is manifest within the same beat that ejection occurs. For small-to-moderate ejection fractions, the net effect of ejection led to greater pressure at end systole than in an isovolumic contraction at end-systolic volume. As ejection fraction grew above roughly 50%, the net effect of ejection became negative. Thus, the net effect of ejection on ESP appears to be governed by an approximate balance between at least two opposing factors.

Previously, ejection has been generally thought to exert only negative influences on the ability of the ventricle to generate pressure. Ejection-related deactivation or uncoupling phenomena were noted in early German studies on ventricular pressure-volume relations, and were specifically studied by Suga and colleagues. Previous work by Hunter et al suggested explicit time courses for a deactivating effect during systole. Similar deactivation phenomena at the level of cardiac muscle have also long been recognized.

That there might be a positive effect of ejection on ESP is a more recent development and has been less thoroughly documented. The first systematic ventricular evidence appeared as unexpectedly high ESP following small volume reductions in middle or late systole. This observation was phenomenologically ascribed to a "volume influence factor" that reduced the effect of volume changes occurring later in systole. A "super activated" state following small ejections was also noted by Vaartjes and Boom. Campbell et al, working with in situ hearts, have also recently noted a "paradoxically high" ESP following ejection.

A constant time to end systole has been thought to be an adequate approximation for isolated canine hearts, based on a previous report which found the time to end systole to increase only 10% from isovolumic to ejecting beats. Counter to this expectation, however, the time to end systole was significantly prolonged for ejecting beats in the present study of isolated canine hearts, in agreement with previous studies using other preparations. The original observation goes back to Otto Frank, who reported in his classic work on frog ventricles that "the maximum of the isotonic curve occurs later than that of the isometric curve." More recently, Elzinga and Westerhof found an increase in systolic duration of up to 55% for ejecting compared to isometric contractions in both cat trabeculae and...
isolated cat hearts. The pattern of changes in systolic duration with varying degrees of ejection that they observed (their Figure 6) clearly resembles that found in the present study (Figure 5). Even the in situ canine heart appears to display significant variation in time to end systole, as individual anecdotes demonstrate: For example, Taylor et al.23 cited a case showing 60% increase in duration, and Igarashi and Suga24 reported 26-32% longer times to end systole in ejecting versus isovolumic contractions.

**Potential Mechanisms**

The positive effect of ejection on ESP may not be entirely related to the process of ejection itself, rather to the different initial conditions that necessarily precede ejection. This potential mechanism could result from the combination of two recently discovered phenomena: 1) The Frank-Starling law of the heart appears to be caused primarily by length-dependent activation23 (i.e., at longer sarcomere lengths the relationship between developed force and cytoplasmic free-calcium concentration becomes more sensitive to calcium). 2) There is considerable delay in the development of peak isometric force following the appearance of the peak concentration of activating calcium in the cytoplasm very early in a contraction.26-28 Furthermore, even in tonically activated cardiac muscle, there is considerable delay between a sudden change in length and the slow approach of force to its corresponding level.29,30

Thus, in an ejecting contraction, sarcomeres are at a longer length initially and could therefore develop more force for the same level of cytoplasmic calcium than in the isovolumic contraction originating from a shorter end-systolic length. Because of the delay between cytoplasmic calcium and force generation, the greater potential for force production (initially established during the isovolumic contraction phase in the ejecting beat) might not disappear immediately as sarcomeres shortened during ejection. Thus, it is plausible that there could be a residual positive effect on end-systolic force resulting from the initially greater degree of activation at the longer lengths present earlier in an ejecting contraction.

To give a more concrete example of this "memory" mechanism, a simplified system that obeys the principles outlined above was investigated (see "Appendix"). Figure 6A shows the normalized time courses of "activating calcium" and "isometric force," which are separated by a large delay consistent with the literature.26-28 Traces 1 and 4 (panel B) depict the force developed in fully isometric contractions at two different lengths. However, when shortening between these two lengths occurs during the contraction (traces 2 and 3), the systolic force seen after reaching the lower length is greater than expected from the isometric contraction originating at the lower length (trace 4). The later the change in length occurs, the more dominant is the influence of the longer initial length and the greater the disparity between the systolic force "expected" for the lower length (from the fully isometric contraction) and that observed following shortening. This trend is consistent with the results of previous ventricular experiments.4,8 which examined the differential effects of altering the time when changes in volume occurred (similar to the changes in length in Figure 6B). In those studies, this effect was characterized by a "volume influence factor,"
and the mechanism presented here would explain this phenomenon.

While the "memory" mechanism outlined above for the "positive" effect of ejection is plausible, it cannot explain all of the observations reported in the literature where ejection seemed to promote pressure development. For instance, in cardiac muscle, a small amount of isotonic shortening against a high afterload can sometimes (early in relaxation) produce a force transiently exceeding the isometric contraction recorded at the diastolic length at the same moment of time. Similar observations for pressure development by rat ventricles were also recently noted in a few preparations by Campbell et al. The above mechanism for the positive effect of ejection also could not reproduce a second phenomenon, namely, that terminating ejection prematurely near the end of systole leads eventually to earlier relaxation of pressure. Brutsaert and colleagues have shown similar behavior in cardiac muscle: Increased loads applied late in systole (and the consequent reduction or termination of shortening) abbreviates the duration of contraction. In all these cases, it seems that the process of ejection itself is the source of a positive effect on pressure or on the duration of systole, but what the potential mechanism could be for a direct positive effect of ejection is presently unclear.

Balance Between Positive and Negative Effects of Ejection

While the "memory" mechanism—working unopposed—would have the potential to create large differences in ESP, the net differences in ESP that were
FIGURE 7. Panel A: Pressure-volume trajectories for model ventricle showing the balancing of "positive" against "negative" effects of ejection. "Positive" effect of ejection was based on delayed-force "memory" phenomenon (as in Figure 6). The "negative" effects of ejection were both deactivation and internal resistance. See "Appendix" for details. Cases 1–4 present combinations of phenomena (indicated by the table) that were included in model (×) or excluded from it (−). The dashed line shows end-systolic pressure-volume relationship for isovolumic contractions; this was the same for all cases. Panel B: Pressure-volume ratios and timing of end systole for model cases presented in panel A. As in experimental data, end systole was defined as time of peak pressure-volume ratio, which was plotted here on ordinate (scale at right). Isovolumic contractions followed same time course as Case 3. In all other cases, time to end systole was prolonged (as indicated by arrows a and b, for example). For reference, the activation signal in model (from Figure 6A) is shown as A(t), using scale at left.

actually observed in the present study were often rather modest. It seems that the negative influences of ejection (internal resistance, deactivation) could have counterbalanced much of the positive influence that the "memory" mechanism would provide. This approximate balance of opposing influences could serve to make the relationship between ESP and volume less sensitive to changes in loading.

To illustrate the concept of balance between "positive" and "negative" effects of ejection, a hypothetical ventricle was constructed (see "Appendix") that included both 1) the "memory" property and 2) the instantaneous and the persistent "negative" effects of flow (i.e., ventricular internal resistance and deactivation, respectively). The model ventricle was connected to a Windkessel arterial load just as in the actual experiments. Figure 7A shows the pressure-volume loops generated when the "positive" and "negative" effects of ejection were present or absent in the model. The dashed line in Panel A represents the ESPVR for isovolumic contractions.

When both "positive" and "negative" effects of ejection were eliminated (leaving the pure E(t) model), the pressure-volume loop (3) was just tangent to the isovolumic ESPVR, as expected. However, when both "positive" and "negative" effects were included (loop 2), ejection continued beyond the isovolumic ESPVR, and the ejecting ESP exceeded the corresponding isovolumic ESP by 10.3 mm Hg, similar to the excess in ESP found experimentally. If either one or the other of the "positive" or "negative" effects of ejection were present by itself—without the counteracting influence of the other—then the ejecting pressure-volume loops fell far away from the isovolumic ESPVR (loops 1 and 4). Thus, the individual "positive" and "negative" mechanisms may have the potential to exert inherently potent effects should their "balance" be disturbed in some cardiac state.

At present, however, it is uncertain whether the counteracting effects are actually as large as suggested by Figure 7A or are a balance between smaller factors, since only the net resultant of the balance was measured in this study. In fact, the model presented here should not be regarded as an attempt to precisely and quantitatively describe a comprehensive picture of ventricular dynamics. Instead, its aims were 1) to foster a qualitative understanding of some of the various effects that might be operative, and 2) to check whether the proposed factors would even be consistent with the observations.

Mechanism Prolonging Systole During Ejection

Figure 7B presents the time course of contraction (as judged by the pressure-volume ratio) for the cases simulated in panel A. No matter what model case was being simulated, the time course of isovolumic contraction was always the same. This is shown as trace 3, which is also the time course of an ejecting beat for the pure E(t) model. As trace 1 shows, adding just the "positive" ("memory") effect increased the time to end systole during ejection, but only by 11% (arrow a). Including the "negative" as well as the "positive" effects (trace 2) dramatically increased the time to end systole by 42% (arrow b) for ejecting versus isovolumic con-
tractions. Even without the "positive" ("memory") effect, including internal resistance still prolonged the duration of systole (trace 4 versus trace 3), but the presence of "memory" greatly enhanced this tendency (trace 2 versus trace 4).

Thus, in the ventricular model, the primary factor responsible for the increased duration of an ejecting systole appeared to be the limit imposed on the velocity of ventricular ejection by the internal resistance effect. In cardiac muscle mechanics, a similar increased duration has been observed for shortening contractions compared to isometric ones. Here, too, the suggested mechanism was the intrinsic limit on the velocity of muscle shortening as expressed by the force-velocity relation.

Practical Implications

The systematic differences observed in ESP for different ejection fractions imply that different ESPVRs will be obtained by protocols that change ejection fraction in different ways. For example, if one slowly reduces the preload to the left ventricle while holding afterload impedance constant, then ejection fraction is roughly the same for all beats. Extrapolating from the present study, one would expect the resultant ESPVR to be approximately parallel to the isovolumic ESPVR but displaced up or down by an amount dependent on the ejection fraction. If a different afterload impedance is used (e.g., changing total peripheral resistance), a shift in the ESPVR would be expected; and indeed, such a change has been observed.

On the other hand, if the protocol produces a set of beats with widely varying ejection fractions, then based on this study, one would expect a different ESPVR compared to a set of beats with relatively constant ejection fractions. Such a difference has been noted by Baan's group. For instance, when the protocol involves a sudden increase of arterial impedance, stroke volume declines even though EDV may increase. Consequently, at each increment to the next higher pressure-volume point, the ejection fraction becomes successively smaller. Because of the consistent change in ejection fraction within such a set of beats, one would predict that the resulting ESPVR would be steeper than that obtained from a protocol that did not change ejection fraction, if the experimental range of ejection fractions corresponds to the region where ESP increases as EF decreases. Indeed this predicted change in ESPVR is in the direction of the discrepancy noted by Baan.

However, there is also a range of small ejection fractions over which the positive effect of ejection dominates, and ESP increases as ejection fraction increases. If the left ventricle were working in this range, increasing ejection (by reducing peripheral resistance) could lead to an augmented ESP and consequently a shift up (and to the left) of the ESPVR. Indeed, there is a report of such a trend, although the reported magnitude exceeds what would be expected from the results presented here.

Immediate Versus Steady State

This study purposely focused on peak isovolumic pressure only for the first beat after switching modes. Both the first isovolumic beat and the last ejecting beat had identical systolic histories; namely, preceding beats were in the steady-state ejecting condition. Thus, the differences we found should be due to effects of ejection that act within the same contraction, rather than effects that carry over from one contraction to another. Such beat-to-beat influences are well documented in muscle mechanics and also appear at the ventricular level, but we aimed to eliminate them in this study to focus on mechanisms operating within the time span of a single systole.

Appendix

This appendix provides mathematical details for the hypothetical model of ventricular pumping dynamics that was used to illustrate (in Figures 6 and 7) the mechanism suggested in the text for a "positive" effect of ejection on ESP. Each factor included in the model corresponds to one of the ventricular mechanical properties found experimentally.

Representation of the "Memory" Phenomenon

To implement the suggested mechanism, which involved a significant delay between activation and force development, the conceptual picture embodied in the time-varying pressure-volume ratio, E(t), had to be revised. According to the E(t) concept, the current instantaneous value of volume is the primary determinant of ventricular pressure at each instant of contraction. The delay factor, on the other hand, introduces a dependence on the history of contraction up to the current time. The simplest framework to conceptually represent this "memory" phenomenon can be outlined as a two-step process: 1) Instantaneous values of ventricular volume and "activation" combine to produce the "potential" for pressure development. However, this "potential" is not instantaneously realized. 2) Only after a considerable delay is pressure actually developed. The delay property is most simply represented by a first-order process, which has the effect of low-pass filtering the "potential" for pressure. In mathematical terms

$$\frac{dP}{dt} = \frac{[A(t) V(t) - P_0(t)]}{\tau}$$

Step 1 is represented by the product A(t) V(t). A(t) represents an activaton function that is multiplied by the instantaneous ventricular volume [V(t)] to produce the potential pressure that could be achieved if there were enough time to reach equilibrium. P_0(t) represents the isovolumically developed pressure, and the differential equation governing the change of P_0(t) embodies the first-order "memory" process (step 2). \(\tau\) represents the time constant of the memory, which was chosen to be 0.15 second. A(t) was chosen to be a simple mathematical function.
that produced reasonable values for peak pressure and time-to-peak in isovolumic contractions. The function was \( A(t) = 130[\exp(-t/0.04) - \exp(-t/0.05)] \), and it is sketched in Figures 6A and 7B.

A model having a form identical to Equation 1, but substituting force for pressure and length for volume, was the basis for the simulations presented in Figure 6B. This described the idealized behavior expected from the model if no negative factors (e.g., internal resistance or deactivation) acted. As this figure shows, the "memory" phenomenon may be a source of the "volume influence factor" observed in flow-pulse experiments.\(^6\)

The motivation behind Equation 1 was to represent the "memory" phenomenon in as simple a way as possible. Naturally, this does not accurately reflect all aspects of observed behavior. For example, it cannot predict the change in systolic duration of isovolumic contractions at different volumes (Figure 5C), and the relaxation of ventricular pressure appears to occur more slowly in the model (Figures 6 and 7B) than in vivo.

**Representation of Negative Effects of Ejection**

From studies of ventricular dynamics,\(^3\)-\(^13\) two types of negative effects of ejection are expected: 1) a resistive-type loss and 2) a persistent loss that remains even after flow has ceased (deactivation). Internal resistance \( [R(t)] \) expresses the property that flow out of the ventricle \( [Q(t)] \) reduces the measured left ventricular pressure \( (LVP) \):

\[
LVP(t) = P_0(t) - R(t) \cdot Q(t)
\]

Here, \( P_0(t) \) represents the ventricular pressure that would be present if there were no ejection at the current instant of time. Observations\(^8\),\(^10\),\(^12\) indicate that ventricular resistance increases in proportion to \( P_0 \) [i.e., \( R(t) = k \cdot P_0(t) \)] with \( k = 0.0015/(\text{ml/sec}) \) for a typical isolated canine heart. Another way of expressing the resistance phenomenon is in terms of the maximum flow rate \( (Q_{\text{max}}) \), where \( k = 1/Q_{\text{max}} \).

Using this, the expression above can be rearranged:

\[
LVP(t) = P_0(t) \left[ 1 - \frac{Q(t)}{Q_{\text{max}}} \right]
\]

Mathematical descriptions of the second negative effect of flow (deactivation) have received less attention in the literature.\(^6\),\(^8\) In the present model, deactivation was coupled to the differential equation governing \( P_0 \), so that the effect would persist even after flow had ended.

\[
dP_0/dt = [A(t) \cdot V(t) - P_0(t)]/\tau - K_a \cdot P_0(t) \cdot Q(t)
\]

The form of the added term was suggested empirically by the following: 1) To provide more deactivation later in systole,\(^8\) the rate of loss was set proportional to the current \( P_0(t) \). 2) Since the rate of pressure loss is proportional to the rate of volume change, integrating shows that the amount of pressure loss will be proportional to the amount of ejected volume, as suggested experimentally.\(^6\) \( K_a \) is a constant coefficient governing the magnitude of this effect. It was assigned the value 0.01/ml, corresponding to 1% loss of pressure for each milliliter ejected.

This model ventricle was loaded with the same Windkessel arterial model as loaded the actual ventricle during the experiments. For the case shown in Figure 7, the parameters were \( R_s = 0.1, R_p = 1.5 \) [both in mm Hg/(ml×sec)], and \( C_a = 0.4 \) ml/mm Hg.

To examine the relative roles of the various mechanical properties, four cases were studied containing the "positive" and "negative" influences of ejection in various combinations. Case 2 contained all the properties and thus was governed by Equations 2 and 3. In Case 1, all the "negative" influences were eliminated so that the "positive" effect of ejection operated unopposed. This was achieved by setting \( K_a \) to zero and \( Q_{\text{max}} \) to infinity in Equations 2 and 3. In Case 3, neither the "positive" nor "negative" factors were present, and the model therefore reduced to the \( E(t) \) description as originally proposed by Suga\(^1\):

\[
LVP(t) = E(t) \cdot V(t)
\]

The time course of \( E(t) \) was chosen so that the time course of isovolumic LVP would be the same in all cases. Finally, in Case 4, there was no "positive" effect of ejection. This was achieved by replacing Equation 3 with the following modified set of equations:

\[
dD/dt = K_p Q
\]

\[
P_0(t) = E(t) V(t) - D(t)
\]

where \( D(t) \) represents the amount of pressure loss caused by deactivation. Equation 2 was still used to relate LVP to \( P_0 \). In all of these cases, \( V(t) \) represented the stressed volume, that is, the volume in excess of the dead volume, \( V_o \).

The general form of the model described here matches (as a ventricular analog) a model proposed previously\(^44\),\(^45\) to describe influences of shortening on cardiac muscle. This muscle model was based on simplified equations similar to Huxley's original proposal\(^46\) to describe myofilament dynamics. The model is also consistent with the observed mechanical behavior of tonically activated cardiac muscle.\(^29\)

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