Long-term Versus Intrabeat History of Ejection As Determinants of Canine Ventricular End-Systolic Pressure

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We studied the effect of ejection on end-systolic pressure in isolated heart preparations. Ejecting beats were compared with isovolumic beats having the same volume as at end systole. While holding end-systolic volume constant, various stroke volumes, including negative stroke volumes (volume injected during systole), were imposed using a predetermined volume command. After switching contraction mode between ejecting and isovolumic, we measured the immediate and steady changes in end-systolic pressure. In the first isovolumic beat after switching from steady-state ejecting beats, the change in end-systolic pressure was variable, depending on the stroke volume. The end-systolic pressure of the ejecting beat exceeded that of the isovolumic beat on average by up to 18 mm Hg with small stroke volume, but the ejecting end-systolic pressure became lower than isovolumic with either large stroke volume (stroke volume/end-systolic volume <0.96) or with negative stroke volume. During the transient phase following a switch from ejecting to isovolumic, the end-systolic pressure gradually decreased to a steady state. Consequently, even in steady state, ejecting end-systolic pressure exceeded isovolumic pressure over a significant range of stroke volume (stroke volume/end-systolic volume <1.18).

After returning contraction mode from isovolumic back to ejecting, we observed responses that were a mirror image. These results indicated that in addition to negative uncoupling effect, ejection exerts positive effects on ventricular end-systolic pressure that are manifest both quickly and gradually. We hypothesized that the mechanism responsible for the positive effect is length-dependent activation via the larger volume (both at the initiation of contraction and averaged over a cardiac cycle) of a beat that ejects compared to one held isovolumic at end-systolic volume. The results with volume injection were consonant with this concept. (Circulation Research 1989;64:255–264)

In addition to the currently prevalent thought that ejection exerts an inhibitory effect on ventricular end-systolic pressure, recent studies using small volume reductions during systole\(^1,\(^2\) or by indirect comparison\(^3\) suggest that there may be a positive effect of ejection under certain conditions. In this laboratory, too, Hunter et al\(^4\) showed, in more physiologically afterloaded ventricles, that the end-systolic pressure in the first isovolumic beat after switching contraction mode was lower than that of the preceding steady-state beats ejecting to the same volume when ejection fraction was less than 49%, suggesting a facilitatory effect of ejection. This study, however, was confined to the very first beat after switching the mode. Therefore, it remains ambiguous how this facilitatory effect of ejection relates itself to the earlier findings on the negative effect of ejection concluded from comparison between steady-state end-systolic pressure of ejecting and isovolumic contractions.\(^5,\(^6\)\)

The transient change in end-systolic force or shortening after switching the contraction mode has been studied by several investigators in heart muscle.\(^10,\(^11\) The results indicated the presence of short- and long-term memory of loading condition. Parmley et al\(^10\) and then Jewell and Rovell\(^11\) identified a positive effect of shortening on force generation in terms of the transient decline of peak isometric force observed after switching contraction mode from steady isotonic beats to steady isometric beats at the same initial length. However, Donald et al\(^10\) showed this effect of shortening to be either positive or negative, depending on multiple factors such as frequency of stimulation and muscle bath temperature.
In all of these studies, transient changes in contractile strength were observed when the mode of contraction was switched between shortening and isometric at the end-diastolic length. When cardiac muscle was held isometric at end-systolic length, however, Suga and Sagawa showed that the direction of the transient change reversed compared to a change at end-diastolic length. This study used a blood-perfused, in situ papillary muscle preparation and suggested that the direction of the transient force changes depended on the relative magnitudes of force when switching between isometric and isotonic contractions. In a similar preparation, Nwasokwa et al noted that peak systolic force of auxotonic contraction was greater than that of isometric contraction at the same length when the shortening extent was relatively small. Obviously, there are multiple determinants of muscle force development in isometric and shortening contractions.

The purpose of this study is twofold: 1) to further analyze the previously found, ejection-fraction-dependent facilitatory effect of ejection on end-systolic pressure development by switching the contraction mode in both directions in one ventricle and 2) to clarify the relation between the immediate and steady-state responses following the switch of contraction mode so that we can gain insight into the mechanism of the facilitatory effect of ejection. We switched the contraction from ejecting to isovolumic mode and back to ejecting mode always at the same end-systolic volume and determined the immediate and steady-state responses of end-systolic pressure after the switch. We also studied the effect of negative ejection (i.e., increasing ventricular pressure during systole) on end-systolic pressure by comparison with isovolumic end-systolic pressure at the same end-systolic volume.

Materials and Methods

Surgical Preparation

The surgical preparation for the supported isolated canine heart used in this study has been described previously. Briefly, in each experiment a pair of mongrel dogs (20–25 kg) were used. Both dogs were anesthetized with sodium pentobarbital (25–30 mg/kg i.v.). After opening the chest of the smaller dog (heart donor), the subclavian artery and right atrium were cannulated and connected to the femoral arteries and veins, respectively, of the larger dog (support dog). The heart was removed after ligation of the azygous vein, superior and inferior venae cavae, brachiocephalic artery, descending aorta, and pulmonary hilus. After establishing perfusion of the coronary artery with arterial blood from the other dog, the left atrium was opened and the chordae tendineae were cut. A ring adapter was sewn to the mitral anulus, and a thin balloon connected to a ventricular volume control servo-pump system was placed in the left ventricle via mediation of the adapter. Coronary arterial pressure was measured by a catheter placed via the brachiocephalic trunk into the aortic root. Coronary arterial blood temperature was maintained at approximately 37°C with a heat exchanger. Left ventricular pressure was measured in the balloon with a catheter tip micromanometer (model PC 380, Millar, Houston, Texas).

End-Diastolic Versus End-Systolic Volume Clamp

Since our interest was to investigate the effect of contraction history on end-systolic pressure at identical end-systolic volume, we commanded our volume servo-pump to clamp the end-systolic volume precisely at a predetermined value. While there were several sources of inaccuracy that could have caused slight deviations in actual ventricular volume from what we measured (e.g., compliance of the rolling diaphragms sealing the pump piston to the cylinder was 0.6 ml/200 mm Hg), we estimated that the maximum difference in actual end-systolic volume between 'isovolumic' and ejecting contractions could have been no more than 0.5 ml. In our experiment, several potential sources of error in control of ventricular volume were minimized because the error mechanisms were pressure dependent (e.g., the compliance mentioned above), and the differences in pressure compared in this study amounted to no more than 30 mm Hg. The direction of the difference also varied with conditions.

To let the ventricle eject from a given end-diastolic volume exactly to a predetermined end-systolic volume, we generated by a computer an appropriately shaped volume command for the ventricular volume-control servo-pump. The time courses of ventricular outflow and inflow were approximated by triangular waveforms; the heart was paced from electrodes at the apex of the left ventricle at a rate either 110/min or 120/min; and the onset and end of ejection and filling were properly timed so that the pressure-volume loop would appear physiologic in shape, and the end of systole would occur at a prescribed end-systolic volume. The onset of ejection thus controlled ranged from 20 to 156 msec after the onset of contraction (identified by a measurable rise in ventricular pressure), and the peak velocity of ejection ranged from 63 to 500 ml/sec.

With this computer software we could also inject a known volume into the ventricle while the ventricle was contracting. This type of contraction will be called injected contraction hereafter; it was accompanied by the onset of injection at 0–92 msec after the onset of rise in ventricular pressure and the peak injection velocity of 48–283 ml/sec. Figure 1 shows pressure and volume tracings for two types of contraction mode. As reported in earlier studies, the end of systole of the ejecting contraction occurred later than that of isovolumic contraction (panel A), whereas it occurred earlier in injected contraction (panel B).
Protocols

A total of 17 hearts were studied. In six of them the effect of ejection on end-systolic pressure at the same end-systolic volume was examined with a wide range of stroke volumes (stroke volume protocol). Another five hearts were used to study the effect of inotropic interventions (inotropic intervention protocol). A third group of six hearts were used to test a hypothesis that the slow component of the positive effect of ejection on end-systolic pressure derives from the length-dependent activation that operates through the greater average volumes of the ejecting beats than the isovolumic beat (average volume protocol).

In six hearts, we studied the effect of ejection volume on the transient and steady-state differences in end-systolic pressure (ESP) between ejecting and isovolumic beat (ejection series). We also injected variable amounts of water into the ventricular balloon in systole by the servo pump and studied the effects on ESP in comparison with isovolumic ESP at the same ESV (injection series).

At the beginning of each experimental ejection series end-systolic volume (ESV) was set at 20 or 25 ml, at which a peak isovolumic pressure between 60 and 120 mm Hg was developed. This ESV was maintained throughout the ejecting series. End-diastolic volume (EDV) was set so that stroke volume (SV) would range from 5 to 35 ml and the ratio SV/ESV from 0.2 to 1.5. After a steady-state end-systolic pressure (ESP) was observed in the ejecting condition, contraction was switched to isovolumic mode at a volume identical to ESV of the preceding ejecting beats and the transient response in peak systolic pressure was observed until a steady state was achieved (the peak isovolumic pressure is also referred to as ESP). It took about 3 minutes (range, 2–4 minutes) for ESP to reach the steady state. Then contraction was switched back to ejecting mode from the same end-diastolic volume as before and the transient response of ESP was followed for a few minutes until the steady state was observed. Only when this final steady-state ESP was within ±10% of the initial steady-state ESP were the data accepted for analysis.

In the injection series, ESV was set at 40 ml so that we could inject a range of volume (IV) between 5 and 17 ml in systole. As in the ejection series, contraction mode was switched from injected contraction to isovolumic contraction, and then back to injected contraction while the ESP response was observed.

The effect of inotropic intervention on the difference in ESP was studied by intracoronary infusion of calcium chloride (30 mg/l at a rate of 0.5–1.0 ml/min) in four hearts and verapamil (100 μg/ml at a rate of 0.5–1.0 ml/min) in five hearts. To facilitate the analysis, EDV was set so as to make the ratio of stroke volume to end-systolic volume (SV/ESV) at 0.5, 1.0, and 1.5. The responses of ESP to switching contraction mode at the three SV/ESV ratio were compared before and during infusion of those drugs.

In the above protocols, the ventricular volume (or wall muscle length) averaged over the cardiac cycle is greater in the ejecting beats than the isovolumic beats at the ESV. We hypothesized that this history of greater average volume (or muscle length) is responsible for a slowly developed facilitation of ESP observed in ejecting contractions and for the slow inhibition of ESP observed when we switched to isovolumic contractions. To test this hypothesis, we changed (in each of 6 hearts) the volume at which the ventricle was made to contract isovolumically after steady-state ejecting contraction to three different volumes: 1) same as the ESV, 2) same as the average volume, and 3) same as the EDV of the preceding ejecting volume.

Statistical Analysis

Data are shown as mean±standard error of the mean (SEM) unless otherwise indicated. Comparison of matched pairs was made by paired t test, and the differences were considered significant if p<0.05.18

Results

Effect of Stroke Volume

Under isovolumic conditions, the basal slope of the end-systolic pressure-volume relation for the six
hearts studied in the stroke volume protocol averaged 4.0 mm Hg/ml (range, 3.3–5.3 mm Hg/ml).

Ejecting versus isovolumic contractions. The ESP response to switching contraction mode varied with stroke volume and time after the switch in contraction mode. Panel A of Figure 2 shows a representative example of responses at a small SV (12 ml). Immediately after the switch from steady-state ejecting beat to isovolumic beat, the first isovolumic ESP was lower than that of the preceding ejecting beat. Over the following 2 to 3 minutes, the isovolumic ESP further decreased to a level much lower than that of the steady-state ejecting contraction. When the contraction was switched back to ejecting mode, the ESP immediately after the switch was higher than the preceding steady isovolumic ESP. Thereafter, ESP kept increasing monotonically to the same level as the ESP seen during the previous steady ejecting contractions.

Panel B of Figure 2 shows the ESP responses when SV was relatively large (20 ml). Immediately after switching the contraction mode from ejecting to isovolumic contraction, the ESP was higher than the steady ejecting ESP. The isovolumic ESP then decreased to a steady level. When the contraction mode was switched from isovolumic to ejecting contraction, the ESP immediately decreased but increased thereafter to the same level as before.

Although not clearly visible in Figure 2, we sometimes observed a small transient of short duration (5–10 seconds) following the immediate response. As illustrated in Figure 3, this component will be referred to as the rapid transient in this paper. The rapid transient was usually a mild increase after the ejection-to-isovolumic switch, and a mild decrease after the isovolumic-to-ejection switch. These rapid transients were usually small and variable. Therefore, we can describe only their qualitative features, without quantitative analysis.

Injected versus isovolumic contractions. An example of responses following the mode switch between injected and isovolumic contractions are shown in Figure 4. In panel A, ventricular volume was driven from 30 to 40 ml during systole (IV = 10 ml; IV/ESV ratio = 0.25). In panel B, while attaining the same end-systolic volume (40 ml) EDV was smaller so that a larger volume (17 ml) could be injected (IV/ESV ratio = 0.425). Regardless of the IV/ESV ratio, the first isovolumic ESP after the switch from injected to isovolumic contractions was always higher than the preceding injected ESP. This was followed by a biphasic transient response of ESP, first rapid and mild decline and then a slow increase to a steady-state level that was always higher than that of injected beats. On returning from isovolumic to injected contractions, we observed mirror-image responses just as was the case with the ejection series.

In Figure 5 the immediate responses after switching the contraction mode, ΔP_in, are plotted on the ordinate as a function of normalized stroke volume (SV/ESV) plotted on the abscissa. We normalized the stroke volume by ESV instead of EDV because, in this study, ESV was fixed whereas EDV had to be changed to alter SV. The IV was considered negative stroke volume, and the data from the injection series were thus plotted over the negative region of SV/ESV. As shown in Figure 3, ΔP_in was defined as follows:
FIGURE 4. Ventricular pressure and volume tracing of injection series protocol. Contraction mode was switched between injected and isovolumic at same end-systolic volume. Panel A: An experimental run with a small injection volume (ESV=40 ml and EDV=30 ml). Panel B: An experimental run with a large injection volume (ESV=40 ml and EDV=23 ml). In both panels ESP increased immediately after the switch from injected to isovolumic mode, then it increased gradually to a higher level.

\[ \Delta P_{\text{inst}} = [\text{ESP of the preceding steady-state beat}] - [\text{ESP of the 1st beat after the switch}] \]

Plotted in panel A of Figure 5 are \( \Delta P_{\text{inst}} \) after switching from ejecting to isovolumic contraction (to the right of the origin) and after switching from injected to isovolumic contraction (to the left of the origin). All the data were measured in one heart. A quadratic regression was fit to these data with a constraint that \( \Delta P_{\text{inst}} = 0 \) when SV/ESV=0. The results suggest a negative effect of both large amounts of ejection (SV/ESV>0.8) and any amount of injection on ESP. In this ventricle, the average scatter about the regression curve was ±4.0 mm Hg.

Shown in panel B are six quadratic regression curves fitted to the data from all six hearts in this protocol. The average scatter was ±4.8 mm Hg. The maximum \( \Delta P_{\text{inst}} \) for these regression curves ranged from 2.9 to 16.1 mm Hg among the hearts with a mean ± SEM value of 8.1 ± 4.8 mm Hg. The SV/ESV value for the crossover point from positive to negative \( \Delta P_{\text{inst}} \) (referred to as zero crossing point hereafter) represents the normalized SV at which there is no difference in ESP immediately after switching the contraction mode between ejecting and isovolumic contraction. The ratio ranged from 0.77 to 1.17 with a mean and SEM of 0.96 ± 0.15. This SV/ESV ratio corresponds to an ejection fraction of slightly less than 50%.

Panel C shows the regression curves for the responses after the switch from isovolumic to ejecting (or injected) contraction. The regression curves have a shape that is the mirror image of those in panel B. The crossover points ranged from 0.77 to 1.16 with a mean and SEM of 0.89 ± 0.13.

FIGURE 5. Graphs showing immediate responses \( (\Delta P_{\text{inst}}) \) after switch in contraction mode. Panel A: Data from 1 heart are plotted as a function of normalized stroke volume (SV/ESV). Solid curved line indicates the parabolic regression with a constraint at the origin. Panel B: Parabolic regression curves from the 6 hearts are shown for the switch from ejecting (or injected) to isovolumic mode (E to I). Panel C: Parabolic regression curves for the switch from isovolumic to ejecting (or injected) mode (I to E). Small a and b in panels B and C indicate regression curves for corresponding hearts.

The transient responses of ESP \( (\Delta P_{\text{slow}}) \) from six hearts are plotted in Figure 6 again as a function of SV/ESV. We defined the \( \Delta P_{\text{slow}} \) by the following equation

\[ \Delta P_{\text{slow}} = [\text{ESP in the eventual steady state}] - [\text{ESP after rapid transient}] \]

where ESP at the end of the rapid transient has the meaning indicated in Figure 3.

In panel A of Figure 6, data from the same heart as in Figure 5A are plotted as a function of normalized stroke volume. Following the switch from ejection to isovolumic modes, \( \Delta \text{ESP}_{\text{slow}} \) was always negative for ejecting contractions (positive range of SV/ESV), whereas \( \Delta \text{ESP}_{\text{slow}} \) was always positive for injected contractions (negative range of SV/ESV). The solid line indicates a linear regression constrained at the origin. A significant negative correlation was observed within the range studied \( (r = -0.964, p < 0.001) \). In panels B and C, linear regression lines from all the hearts are shown for the responses after the ejection(or injection)-to-isovolumic switch and the isovolumic-to-ejection(or injection) switch, respectively. All the
correlation coefficient values were significant and exceeded 0.80 in magnitude. In four of the six hearts, the absolute value of the slope was larger for the isovolumic-to-ejection (or injection) switch.

Finally, the steady-state difference between the ejecting and isovolumic contractions \( \Delta P_{es} \) are shown in Figure 7. We defined \( \Delta P_{es} \) as follows

\[
\Delta P_{es} = [\text{ejection ESP in steady state}] - [\text{isovolumic ESP in steady state}]
\]

In panel A, \( \Delta P_{es} \) data from the same heart as in Figures 5A and 6A are plotted as a function of normalized SV. As with the immediate responses data, a quadratic curve fitted well. Since the rapid transients were small in magnitude, this curve is close to the sum of the immediate response curve and the slow response line. Data from all the hearts are summarized in panel B. The zero crossing points (SV/ESV value at which there was steady-state difference in ESP between ejecting and isovolumic beats) ranged from 0.97 to 1.30 with the mean and SEM of 1.18±0.12. This mean ratio corresponds to an ejection fraction of 54%, a value at the lower end of the physiologic range of ejection fractions.

**Effect of Inotropic Intervention**

The responses before and during the infusion of inotropic agents are summarized in Figure 8. With the infusion of verapamil (left side panels), both immediate (panel A) and slow response (panel B) significantly decreased their magnitude. The zero crossing point of steady-state difference \( \Delta P_{es} \) (panel C) shifted slightly to the left. Those changes with verapamil were all statistically significant. With calcium chloride infusion (right-side panels in Figure 8), changes into the opposite direction were observed but they were not statistically significant.

**Importance of Average Volume History**

A representative result of average volume protocol is shown in Figure 9. The average volume over the cardiac cycle of the preceding ejecting contractions is shown by the arrow at the right end of the LVV channel in each panel of the figure. When the mode was switched to isovolumic contraction, the volume was set at ESV in panel A, at an intermediate volume in panel B, and at EDV in panel C. With these changes in the isovolumic beat volume, the direction of the slow change after switching the mode reversed itself from decrease to indifference, and to increase (after a rapid transient decrease). In four ventricles we observed similar results, whereas in two the slow response was almost flat even at the end-diastolic volume.

**Discussion**

**Immediate Versus Slow Responses**

In this study, we examined both the immediate and long-term effect of switching contraction mode on end-systolic pressure when end-systolic volume was held constant. We switched contraction mode not only from ejecting to isovolumic but also from isovolumic back to ejecting; and we identified imme-
Immediate and slow responses in both sequences of switch. The results are summarized diagrammatically in Figure 10, in which the immediate and slow ESP responses are shown as a hysteresis loop. Panel A presents the case for small stroke volume and panel B for large stroke volume. In both panels, the upper right corner of the loop (a) represents the steady-state ejecting ESP, the upper left corner (b) the first isovolumic ESP after a switch, the lower left corner (c) the steady-state isovolumic ESP, and the lower right corner (d) the first ejecting ESP after a switch. Since both a and b are preceded by almost the same number of steady-state ejecting beats, the change observed between a and b (broken arrow) reflects the effect of ejection that disappears within one beat (intrabeat effect). The change seen between b and c (open arrow) reflects the effect of ejection that fades away gradually over many beats (long-term effect). Similar conjectures can be applied consistently to the changes after the second switch: The path from c to d represents the intrabeat effect, and the path from d to a the slowly developed long-term effect of ejection.

As Hunter et al showed previously, the direction of the immediate response to switching from ejecting to isovolumic contraction (a to b in Figure 10) was dependent on stroke volume, being downward for a small stroke volume (panel A) and upward for a large stroke volume (panel B). The value of SV/ESV at which the response changed its direction was 0.96, which corresponds to an ejection fraction of 49% (Figure 5). This is also in agreement with the previously observed crossover ejection fraction of 49%.

In contrast to the dichotomy of immediate response, however, we found the subsequent slow response to be always a decrease after switching the mode from ejecting to isovolumic contraction (b to c in Figure 10) and always an increase after switching the mode in the opposite direction (d to a in Figure 10), regardless of stroke volume. The absolute magnitude of the slow response was positively correlated with stroke volume (Figure 6).

Consequently, the steady-state ejecting ESP with a small stroke volume (a in Figure 10A) was higher than the steady-state isovolumic ESP (c in Figure 10A) even to a greater extent than the immediate ejecting ESP. When stroke volume was large, however, the steady-state ejecting ESP could be less than, equal to, or greater than the steady-state isovolumic ESP, depending on whether the SV/ESV ratio was greater than, equal to, or less than 1.18, respectively.
These findings are quite different from earlier studies that unanimously reported that ejection ESP was more or less smaller than isovolumic ESP with any stroke volume. Very recently, however, Igarashi et al. reported that steady-state ejecting ESPs with small ejection fraction were located above the steady-state isovolumic end-systolic pressure-volume relation line. Although the values for the pressure difference estimated from their Figure 2 are smaller than the ΔPn values reported here, their observation clearly corroborates our findings. Their data also suggest that, with positive inotropic interventions, the equilibrium point at which the ejecting and isovolumic ESPs are equal shifted to the larger ejection side and with negative inotropic interventions, shifted to the smaller side. These data are also consonant with our findings (Figure 8), although we could find a statistically significant difference only for the negative inotropic intervention.

**Rapid Transient Response**

In earlier studies on the effect of shortening history in excised muscle preparations, the authors switched contraction mode between isotonic and isometric twitch at the same initial length and identified a positive effect of shortening by a beat-to-beat reduction in isometric force or increase in the extent of shortening that occurred over several beats immediately after the switch. However, the effect of shortening history revealed in these previous studies does not appear to us to be based on the same mechanism that controlled the long-term effect of ejection in our study. The major difference is the time interval over which the effects develop: several beats in excised muscle versus 1–2 minutes in our study. There often was a rapid initial transient phase that we observed, which had a time course similar to the transients observed in muscle. However, this rapid transient phase was often opposite in direction (see Figure 3) to that reported for excised muscle. Perhaps this difference in direction could be due to our clamping isovolumic contractions at end-systolic volume, whereas the muscle isometric twitches were clamped at end-diastolic length, as suggested by Suga’s work with in situ papillary muscle. For example, panel C of Figure 9 shows a case where we did clamp isovolumic volume to its end-diastolic value, and the rapid transient (compare the first and second beats after the switch to isovolumic mode) was now in the direction expected from excised muscle studies. Hunter et al. also reported a partially similar combination of rapid and slow transient changes in end-systolic pressure in response to a step increase in volume of isovolumic conditions. We sometimes observed even more complex triphasic responses of ventricular pressure. Its difference from the simpler transient response of heart muscle is intriguing, but the present study did not provide the immediate explanation for that.

Probably the most important feature of the present study lies in the protocol that ESP was compared at the same end-systolic volume between isovolumic contraction and ejecting contraction, thus from different end-diastolic volumes. We consider the immediate and slow positive effects of ejection to be caused by the history of larger ventricular volume in the ejecting contractions in our experiment. This will be discussed next.

**Ejection As a Positive Factor**

Ejection has long been considered to have solely a negative effect on ventricular pressure development. Also, in heart muscle, the deactivating (or uncoupling) effect of shortening has been well documented. The magnitude of this effect is
known to depend on peak velocity of ejection (shortening) and the amount of ejection (shortening).1,5-7 The negative effect is observed on sudden stretch as well as shortening of muscle.21,22 It is therefore fair to ascribe the negative effect of ejection to displacement between the myosin and actin filaments.

How can we explain the positive effect of ejection? We ascribe this to two effects of muscle length on myocardial cardiac handling: 1) change in Ca\textsuperscript{2+} affinity of myofilaments and 2) change in Ca\textsuperscript{2+} availability to myofilaments.

Length-dependent change in Ca\textsuperscript{2+} affinity of myofilaments is based on the finding in skinned muscle that the tension-pCa curve shifted to the left at longer sarcomere length.23 The study using aequorin luminescence suggested that this affinity change probably occurs even when the length is changed within one beat (intrabeat effect—immediate response).

The change in Ca\textsuperscript{2+} availability has been shown as the gradual increase/decrease in aequorin luminescence following muscle stretch/release that paralleled the slow change in developed force (long-term effect—slow response). Those investigators who studied the gradual change in developed force after a step change in muscle length also discussed the implication of Ca\textsuperscript{2+} availability.25-27 Gradual change has been shown to exist also in a ventricular preparation.19,28 Although these studies were done in isometric or isovolumic condition, a recent study by Nichols provides strong support for applying the concept of length-dependent activation to ejecting ventricle, in that he changed the muscle length only during diastole and observed a similar slow change in developed force.

For an ejecting ventricle in the present experiment to come to the same end-systolic volume as that of isovolumic beat, the ventricle naturally must have a larger volume at the beginning of systole and during most of one cardiac cycle than in the isovolumic beat at the same end-systolic volume. In view of the above-mentioned intrabeat and long-term effect of the length-dependent activation in heart muscle, the history of larger volume in the ejecting contraction in our experiment has potentials to influence ventricular pressure development both immediately (intrabeat effect) and over many subsequent beats (long-term effect).

In the first ejecting beat after the switch from isovolumic mode, calcium availability may not change, but the initial larger volume of the ejecting beat allows contractile protein to bind more calcium than in preceding isovolumic beats. Since the calcium transient is known to precede force generation, reaching its peak very early in a contraction,30 the muscle length in the early phase of systole can be a determinant of force generation. We consider that the pressure difference we observed in the first beat after switching contraction mode (Figure 5) is the net effect of two opposing factors, that is, the positive effect of the larger initial volume of an ejecting beat and the negative uncoupling pressure effect of ejection. The positive effect predominates with small ejection, but as the ejection becomes larger, the negative uncoupling effect outweighs so that the net effect is negative.

In the subsequent period, the calcium availability gradually increases because of the larger volume of ejecting beats that leads to a gradual increase in ESP. Regarding the subcellular event that leads to an intracellular calcium accumulation, many hypotheses have been submitted reflecting the complex nature of intracellular calcium regulation. These are 1) enhanced transsarcolemmal calcium influx,26 2) reduced calcium efflux,24 and 3) alteration in calcium handling by sarcoplasmic reticulum,30 all of which are believed to be length dependent.

**Importance of Average Volume History for the Slow Transient**

We tested a hypothesis that the ventricular volume history is the determinant of the long-term inhibitory effect invariably noted after switching the mode to isovolumic contractions. The results indicated that the relative magnitude of the volume of isovolumic beats to the average volume of the preceding ejecting beats could predict the course of the long-term change in subsequent ESP (Figure 9). This finding lends support to the importance of average ventricular volume as a determinant of the long-term effect of ejection. Following the observations of Nichols, however, a further refinement would be to test whether mean diastolic volume might be better than average volume over the entire cycle as a predictor of the slow transient changes in ESP.

Tucci et al.39 studied the slow response after switching the contraction mode from ejecting beat to isovolumic beat at the same end-diastolic volume. They, too, observed a slow increase in ESP, though it was very small. This is at least in qualitative accordance with our concept.

**Significance of Injected Contraction Experiment**

Throughout the present study, we considered two mechanisms as the major determinants of the effect of ejection on ESP, that is, intermyofilamental displacement and history of ventricular volume. Our study of injected contractions was also designed along this line of reasoning. We considered that ESP during an injected beat would also be controlled by these two factors. One of them (the displacement factor) should have a negative effect as in an ejecting beat, but the other factor (the ventricular volume history) should also have a negative effect unlike the ejecting beat because the injected beat has both smaller initial and time-averaged volumes than an isovolumic beat with the same end-systolic volume. We expected that these two negative factors would sum to effect large decrease in ESP, both immediately and gradually after switching to injected contraction. This expec-
Ejection Fraction As a Controller of End-Systolic Pressure

We normalized the stroke volume by end-systolic volume because end-systolic volume was fixed in this study. On the other hand, in the previous study, Hunter et al. identified the immediate effect as a function of ejection fraction because they fixed the end-diastolic volume and changed ejection fraction by varying end-systolic volume. Interestingly, however, our results for the immediate effect, after being converted into ejection fraction, showed a very good agreement with theirs (crossing points were exactly the same in both studies). This fact suggests the physiological importance of ejection fraction as a controller of end-systolic pressure regardless of the way one changes ejection fraction.

Summary

We studied the effect of ejection on ventricular end-systolic pressure at the same end-systolic volume by switching contraction mode between ejective and isovolumetric contraction. We confirmed the previously identified positive and negative effects. Of the positive effect, we identified two components: One manifested itself immediately (intrabeat effect) while the other appeared gradually over dozens of beats (long-term effect). These two positive components are combined with the negative uncoupling effect of ejection and exert a variable net effect on ventricular end-systolic pressure after a sudden switch in contraction mode. We discussed the importance of the larger initial and average volumes of an ejecting beat as a cause for this positive effect, probably through two length-dependent calcium handling mechanisms in cardiac muscle.

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References


Key Words • stroke volume • length-dependent activation • end-systolic pressure • injected contraction
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