End-Systolic Pressure Determines Stroke Volume from Fixed End-Diastolic Volume in the Isolated Canine Left Ventricle under a Constant Contractile State

Hiroyuki Suga, Akira Kitabatake, and Kiichi Sagawa

SUMMARY We studied the effect of systolic pressure and volume changes on the end-systolic pressure at a fixed end-systolic volume in the left ventricle of excised, cross-circulated canine hearts. Instantaneous ventricular volume was controlled and both end-diastolic and end-systolic volumes were clamped, as preprogrammed by a volume servo pump system. Ventricular ejection was completed at the end of natural systole. When the onset and velocity of ejection were widely varied during contractions with a given set of end-diastolic and end-systolic volumes, the end-systolic pressure was little affected by the changes in the systolic pressure and volume under a stable contractile state. When the end-diastolic volume was increased from the isovolumic condition, the end-systolic pressure at the same end-systolic volume decreased (P < 0.05) from the peak isovolumic pressure by 5-14%, for an ejection fraction of 40-70%. When the end-systolic volume was decreased while the end-diastolic volume was fixed, the end-systolic pressure decreased in proportion to end-systolic volume. These results were interpreted to indicate that, when ejection ends at the end of systole, stroke volume of the ventricle with a given end-diastolic volume is determined predominantly by the end-systolic pressure rather than by the entire systolic courses of the pressure and volume.

AFTERLOAD, preload, and contractility are major determinants of the stroke volume of the ventricle (Bishop et al., 1976; Parmley et al., 1977) and the amount of shortening of cardiac muscle (Braunwald et al., 1976). In most experiments on cardiac muscle, afterload is an isotonic force rather than a time-varying force, and the constant after load force determines instantaneous shortening velocity and the amount of shortening (Braunwald et al., 1976). In recent experiments on ventricles, afterload pressure (Weber et al., 1974) and even ventricular wall force (Burns et al., 1973) were kept constant at various levels, and either the constant pressure or force afterload was a major determinant of stroke volume (Weber et al., 1974; Burns et al., 1973). More recently, instantaneous time-varying arterial pressure and ventricular wall force throughout systole (both of which are determined as a result of the complex interaction of the ventricle with the arterial impedance) have been considered to affect stroke volume more directly (Milnor, 1975; Brutsaert and Paulus, 1977). This concept appears reasonable in light of the effect of instantaneous afterload force on instantaneous shortening of cardiac muscle (Braunwald et al., 1976; Brutsaert and Paulus, 1977; Paulus et al., 1976; Abbott and Gordon, 1975). Although experimental study of the effect of time-varying afterload force on the amount of shortening was attempted recently in excised cardiac muscle (Paulus et al., 1976), much remains to be known about the effect of the time-varying afterload pressure on stroke volume of the ventricle.

Our recent studies of left ventricular pressure-volume relationships have shown that the end-systolic pressure-volume relationship under a fixed contractile state is largely independent of preload, afterload, and mode of contraction (Suga et al., 1973; Suga and Sagawa, 1974). Similar evidence has been reported by other investigators (Weber et al., 1974; Burns et al., 1973; Weber et al., 1976). These findings suggest that the end-systolic pressure determines end-systolic volume, and the pressure-volume history before the end of the same systole probably will not directly affect the end-systolic volume. Therefore, stroke volume seems to be determined primarily by the end-systolic pressure when the contraction starts from a fixed end-diastolic volume under a fixed contractile state.

In the present study, we asked whether the entire course of instantaneously changing afterload pressure is important, or whether a particular component, especially the end-systolic pressure, is more
Methods

Surgical Preparation

Twenty-five experiments were performed on the left ventricles of isolated canine hearts. In each experiment, a pair of mongrel dogs of either sex (9-19 kg in body weight) was anesthetized with sodium pentobarbital (30 mg/kg, iv). In the smaller dog (mean body weight = 12 kg) of the pair, an excised cross-circulated heart preparation was instituted, and a thin latex balloon (Qualatex no. 9 helium balloon, prestretched to increase unstressed volume above 60 ml), was fitted in the left ventricle by standard methods (Suga and Sagawa, 1977). The heart preparation was perfused by arterial blood from the larger dog (mean body weight = 15 kg) of the pair at a constant perfusion pressure (75-125 mm Hg, mean = 88 mm Hg) at 35-37°C. Left ventricular thebesian flow was drained by suction via a multi-side hole cannula placed between the balloon and the endocardium. The hearts beat in regular sinus rhythm (74-130 beats/min, mean = 102 beats/min) for 4-6 hours during cross-circulation. The weight of the left ventricle (with the atria and the right ventricular free wall removed) was measured at the end of each experiment. Left ventricular weight ranged from 47 g in a 10-kg dog to 120 g in an 18-kg dog, with a mean of 84 g.

Servo Pump

Figure 1 is a schematic diagram of the volume servo pump system. Details of its design and performance were described previously (Suga and Sagawa, 1977). Briefly, it consists of a rolling-diaphragm cylinder (Bellofram SS-4-F-SM, effective area = 25 cm²) actuated by a permanent magnet shaker (Ling Electronics, model 411). The shaker has a force rating vector of 25 kg, input power of 350 W, and a maximum displacement of ±8.8 mm. It was driven by a power amplifier (Crown DC-300, output power = 310 W). The position of the Bellofram cylinder piston was sensed by a linear displacement transducer (Trans-Tek, model 244-000, frequency response = 3 dB down at 100 Hz) firmly connected between the chassis and the piston rod. A homemade circuit served to compare the volume signal output of the displacement transducer with the piston rod. A negative feedback system was constructed. The system served to displace the diaphragm of the Bellofram cylinder precisely as commanded by the reference signal. The compliance of the diaphragm was as small as 0.6 ml/200 mm Hg, being reduced to this value by application of a negative pressure of 75-100 mm Hg behind the diaphragm.

The volume command signal was generated by a previously described circuit (Suga and Sagawa, 1977). Clamping of end-diastolic and end-systolic volume at desired values was achieved by clamping corresponding voltages of the volume command signal with diodes (Suga and Sagawa, 1977). The left atrial ECG signal was used to trigger the command signal generator.
The balloon placed in the left ventricle was connected via the mitral annulus to the volume servo pump. The balloon and the water housing of the pump were primed with tap water so that no air bubbles remained. The water reciprocated between the ventricle and the pump in synchrony with ventricular contraction in a programmed manner. This pump enabled us to vary the onset and velocity of ventricular ejection while clamping the end-diastolic and end-systolic volumes at chosen values and producing a flow pattern resembling the flow pattern observed normally in vivo. Intraventricular volume was calibrated in each experiment by collapsing the balloon to zero volume and adding a known volume of water to the pump for gain calibration. The resolution of volume measurement was less than 1 ml. Intraventricular pressure was measured with a Konigsberg P21 miniature gauge placed inside the apical end of the balloon, with the diaphragm facing toward the cardiac base. Zero pressure reference was chosen to be the midlevel of the left ventricle placed horizontally in the rig.

End of Systole

The end of mechanical systole must be defined clearly for the present study, since systole has been defined in several different ways by different investigators. Generally, one can define the end of systole as the moment at which some measure of ventricular contraction becomes maximal. The measure of contraction varies with the mode of contraction as follows. In an entirely isovolumic contraction, the end of systole is simply the time at which the ventricular pressure reaches its peak (Fig. 2A). In an entirely isobaric contraction, it is the time at which the ventricular ejection reaches the maximum and therefore the ventricular volume becomes the minimum (Fig. 2B). In an auxobaric contraction, the end of systole is the time at which the ventricular pressure is maximal and the volume is minimal (Fig. 2C). In a natural type of contraction in vivo (Fig. 2D), ejection ends about the time at which the ventricle starts to relax (Suga et al., 1973). Thus, the end of ejection almost coincides with the end of systole. Therefore, the end of systole could not be identified as the end of systole. Neither could the peak pressure be identified as the end of systole, because the peak pressure occurred relatively early in systole. The pressure-volume loop trajectory had a more rounded shoulder at the left upper corner than the natural loop. However, it still was possible to identify the end of systole as the time at which the pressure-volume datum point on the loop touched or came closest to the isovolumic end-systolic pressure-volume relationship curve (Suga and Sagawa, 1974).

In the present study, we attempted to simulate the natural type of ejection as much as possible, so that the end of ejection would coincide with the end of the ventricle's naturally occurring systole (Fig. 3, loops 1 and 2). Figure 3 shows three pressure-volume loops for ejecting contractions with different velocities of ejection from a given end-diastolic volume to a given end-systolic volume. Loops 1 and 2 were obtained when the end of ejection coincided with the end of systole (point A). Loop 3 was observed when we prolonged ejection beyond the end of systole (point B). The end of ejection occurred at point C. This last type of ejection was avoided in the present study. The difference between loops 1 and 2 is that the velocity of ejection for loop 1 was greater during the earlier phase of the ejection period but decreased more rapidly toward the end of ejection. The pressure spike at the upper left corner of loop 1 does not imply that the ventricle developed pressure after ejection was com-

![Figure 2](https://example.com/figure2.png)
End-systolic pressure determines stroke volume/Suga et al.

100
0
0 10 20 30 ml

Figure 3 A picture and a schematic drawing of three pressure-volume loops 1, 2, and 3 with different velocities of ejection. In loops 1 and 2, the end of ejection was made to coincide with the end of natural systole. These two loops have the same end-systolic pressure at the end of ejection (point A) in spite of the difference in the pressure-volume trajectory before the end of systole. In loop 3, ejection was not completed by the end of systole (point B). The end of ejection (point C) was later than the end of systole.

Figure 4 Superimposed pressure and volume tracings of isovolumic (broken) and ejecting (solid) contractions having the same end-systolic volume as the isovolumic volume. The end of systole of the ejecting contraction did not coincide with that of the isovolumic contraction. The former was 19 msec behind the latter in this example.

The end of systole of an ejecting contraction was 10-25 msec (or 5-10% of systolic duration) later than the peak isovolumic pressure at the same end-systolic volume. This observation concerning ventricular contraction was described previously (Suga and Sagawa, 1974) and is consistent with findings for papillary muscle (Braunwald et al., 1976). Because of this difference, we considered it inappropriate to impose on ejecting contractions the same duration that occurs in the entirely isovolumic systole.

Experimental Protocol

The inotropic state of the preparation without any intentional inotropic intervention was considered the control contractile state in this study. In some experiments, control inotropy was enhanced, either steadily or transiently, by infusing inotropic agents as described below. End-diastolic volume of the ventricle was set at a value within the range of 10-45 ml, which was accompanied by peak isovolumic pressure of 50-250 mm Hg. End-diastolic pressure was never raised above 25 mm Hg. End-systolic volume was set at another value, which was chosen to allow stroke volumes within the range of 0-25 ml. Under a given set of end-diastolic and end-systolic volumes, the onset and velocity of ejection were varied widely, whereas the flow pattern was adjusted to resemble the normal in situ flow pattern. In choosing these parameters of ejection, we took care to finish ejection at the end of systole, so that the pressure-volume loop trajectory had a clear corner or a small pressure spike at the upper left corner, as explained above (see loops 1 and 2 in Figure 3).

The experimental protocol consisted of four runs as explained below. In 15 ventricles of the total 25 preparations, each run was carried out only once in the middle range of ventricular volume. In the other 10 ventricles, each run was repeated in two or three different ranges of ventricular volume.

Run I (Constant End-Diastolic and End-Systolic Volumes)

Both end-diastolic and end-systolic volumes were set at appropriate values and fixed throughout each run. The onset and velocity of ejection were varied, widely as seen in panels A and B of Figures 5 and 6. This run was undertaken to study the effect of change in the systolic courses of pressure and volume on the end-systolic pressure for a given pair of end-diastolic and end-systolic volumes.

Run II (Constant End-Systolic Volume and Varied End-Diastolic Volume)

End-systolic volume and the onset of ejection were set at appropriate values. End-diastolic volume was varied to cover wide ranges of stroke volume and ejection fraction, as seen in panels C of Figures 5 and 6. This run was undertaken to study...
the effect of stroke volume and ejection fraction on the end-systolic pressure at a given end-systolic volume.

**Run III (Constant End-Diastolic Volume and Varied End-Systolic Volume)**

End-diastolic volume and the onset of ejection were set at appropriate values and fixed throughout the run (panels D of Figures 5 and 6). End-systolic volume was varied widely to study the effect of change in end-systolic volume on end-systolic pressure, namely, the end-systolic pressure-volume relationship.

**Run IV (Transient Enhancement of Contractile State)**

End-diastolic and end-systolic volumes were clamped, and the onset and velocity of ejection were fixed at appropriate values. The flow pattern also was fixed. Contractile state was enhanced transiently by either: (1) postextrasystolic potentiation following a premature beat produced by a mechanical stimulation of the ventricle, (2) intracoronary bolus injection of Ca2+ (0.05–0.2 mm), or (3) intracoronary bolus injection of catecholamines such as isoproterenol, epinephrine, or norepinephrine (0.1–1 μg). This run was undertaken to study effects of acute changes in contractile state on the end-systolic pressure at the same end-systolic volume.

**Data Collection**

Ventricular pressure, volume, and velocity of ejection (i.e., $-dV/dt$) were traced on a strip chart as a function of time, as shown in Figures 5 and 8. These signals were calibrated as described in our previous paper (Suga and Sagawa, 1977). The same pressure and volume signals were recorded on a storage oscilloscope in terms of the pressure-volume loop trajectory, and the loop was photographed on Polaroid film (Figs. 6 and 9). All data in runs I through III were obtained from steady state contractions under different loading conditions. The steady state was reached 2–3 minutes after changes in loading conditions. In runs I through III, only data from stable preparations were analyzed. The criterion of the stability of the preparation was that the peak pressures in the two steady state series of isovolumic contractions at the same volume before and after each run should not be different by more than 5 mm Hg. By this criterion, the number of stable preparations was 10 in run I, 13 in run II, and 10 in run III. The ratio of the number of the successful runs to that of the total performed runs was about 50%.

**Data Analysis**

End-systolic pressure, which was the ventricular pressure at the end of systole as defined above, was read in mm Hg (1 mm Hg = 133.3 Pa in SI units) from the strip chart tracings. In run I, the time from the onset of the rise in ventricular pressure to the onset of ejection was read in msec. It was normalized with respect to the duration of systole of the individual beat, because the duration of systole ranged almost 2-fold, from 144 to 280 msec, in different ventricles. The normalized onset of ejection is dimensionless and less than unity. Peak velocity of ejection was read in ml/sec. It was normalized with respect to the end-diastolic volume in the same beat. This normalization followed the normalization of shortening velocity of muscle with respect to its initial length. The normalized velocity has a dimension of sec$^{-1}$. In run II, the percent ejection fraction was obtained by normalizing stroke volume with respect to the end-diastolic volume. In run III, end-systolic volume was normalized with respect to left ventricular wall volume, with the assumption that the ventricular wall has a specific density of 1. This normalization was done such that the variation among the end-systolic pressure-volume relationship lines due to the wide differences in left ventricular weight could be taken into consideration. The normalized end-systolic volume is dimensionless. These normalized variables were used to pool corresponding data from different hearts for calculation of the average responses.

A change in end-systolic pressure at a given end-systolic volume in runs I and II was expressed in terms of end-systolic pressure deficit $\Delta P$ (mm Hg), which was defined to be equal to end-systolic pressure in control contraction minus end-systolic pressure in the contraction of interest at the same end-systolic volume. In run I, the control contraction was the contraction with a minimal time to the onset of ejection or a minimal peak velocity of ejection, whereas in run II the control contraction was the isovolumic contraction (with zero ejection fraction). The mean ± SEM of the end-systolic pressure deficit $\Delta P$ (mm Hg) was calculated from the data in runs I and II, pooled as follows. For run I, the normalized onset of ejection was classified into four intervals: 0–0.2, 0.2–0.4, 0.4–0.6, and 0.6–0.8; the normalized peak velocity was classified into five intervals: 0–5, 5–7.5, 7.5–10, 10–12.5, and more than 12.5 sec$^{-1}$. For run II, ejection fraction was classified into 0 (isovolumic), 10–20, 20–30, 30–40, 40–50, 50–60, 60–70, and 70–80%. In each run, data on the end-systolic pressure deficit were pooled for each of the classified intervals from all runs in different hearts.

For run III, end-systolic pressures were plotted against the normalized end-systolic volumes in individual hearts, to study the end-systolic pressure-volume relationship normalized for the size of the ventricle. Since the relationship appeared quasilinear over the tested pressure range except below 50 mm Hg, a linear regression analysis was used for the data above 50 mm Hg to calculate the slope $E_{max}$ of individual relationship lines (Suga et al., 1973).

**Results**

Figure 5 (panels A through D) shows typical examples of simultaneous recordings of ventricular
pressure, volume, and flow in runs I through III under a stable contractile state. From these tracings, onset and peak velocity of ejection and end-diastolic and end-systolic volumes were measured. Listed at the bottom of each panel are the varied parameter values. The flow pattern resembles that measured in intact normal dogs. Panels A and B indicate that both end-diastolic and end-systolic volumes were clamped precisely at the specified volumes in spite of the marked changes in the pressure and volume courses during systole in run I. Panels C and D indicate that end-systolic volume in run II and end-diastolic volume in run III were clamped precisely at the specified volumes in spite of the marked changes in stroke volume. The arrows in Figure 5 indicate the end of systole with which the end of ejection was made to coincide. The end-systolic pressures at the arrows were almost the same in spite of the changes in the onset and velocity of ejection in run I. However, they tended to decrease with the increases in end-diastolic volume and, hence, stroke volume and ejection fraction in run II. In run III, the end-systolic pressures markedly decreased with the decreases in the end-systolic volume.

Figure 6 (panels A through D) shows the ventricular pressure-volume loop trajectories in runs I, II, and III. Lettering and numbering are the same as for Figure 5. The arrows mark the end of systole. The negative pressures in early diastole in some beats were not due to the excessive suction of the ventricular volume by the pump, but to the nature of the diastolic pressure-volume relationship of the ventricle.
through III. Data in the corresponding columns and panels of Figures 5 and 6 are from the same experiments. In panel A, the onset of ejection was varied over a wide range with a relatively constant peak velocity of ejection. With the advance of the onset of ejection from loop 1 to loop 4, the ventricular pressure at the onset of ejection decreased, and the pressure-volume trajectory during ejection phase shifted downward. However, all the pressure-volume trajectories during the ejection phase converged closely into a single pressure-volume datum point (arrow) at the end of systole. In panel B, the peak velocity of ejection was varied widely. The onset of ejection was almost unchanged. The pressure-volume trajectory during the ejection phase was convex upward for a relatively low peak velocity of ejection. It became convex downward in loop 2, and the downward convexity increased with the increase in the peak velocity of ejection from loop 3 to loop 5. However, the pressure-volume trajectories converged closely into a single pressure-volume datum point (arrow) at the end of systole. These results show that the end-systolic pressure at a constant end-diastolic volume in differently loaded contractions was little changed by the wide variation of the systolic course of contraction in the pressure-volume plane when the contractions started from the same end-diastolic volume. Run I was repeated under a steadily enhanced contractile state by infusing Ca\(^{2+}\) into the coronary perfusion tube at a rate of about 0.35 mM/min, which increased the end-systolic pressure at a given volume by about 50%. Under the enhanced contractile state, we observed the independence of the end-systolic pressure from the systolic course of contraction, just as in the control state.

Individual and statistical data from 14 runs on 10 hearts are shown in panels A and B of Figure 7. The 10 hearts in panel A were not necessarily the same as the 10 hearts in panel B. Panel A indicates that the end-systolic pressure at a given end-systolic volume was only mildly suppressed by extensively delaying the onset of injection. The normalized onset of ejection corresponded to different times in systole which ranged from 144 to 280 msec (mean = 203 msec) on 10 ventricles. As compared to the end-systolic pressure with the normalized onset of ejection between 0 and 0.2, the end-systolic pressure deficit \(\Delta P\) was 1 ± 1 (SEM) mm Hg for 0.2-0.4, 6 ± 3 mm Hg for 0.4-0.6, and 12 ± 3 mm Hg for 0.6-0.8. However, Wilcoxon’s signed rank test (Hollander and Wolfe, 1973) showed none of these to be statistically significant at the 5% level. The insignificant pressure deficit for the range of 0.6-0.8 could be due to the small number of the samples. Panel B of Figure 7 indicates the average deficit of the end-systolic pressure plotted as a function of the normalized peak velocity. The unit-normalized velocity ranged from 14 to 45 mls/sec (mean = 29 mls/sec) in different runs and ventricles. The deficits were as small as 2 ± 1, 6 ± 5, 7 ± 5, and 10 ± 4 mm Hg for normalized peak velocities of 5-7.5, 7.5-10, 10-12.5, and above 12.5 sec\(^{-1}\), respectively, as compared to the end-systolic pressure for the normalized peak velocity of ejection of 0-5 sec\(^{-1}\). None of these pressure deficits was statistically significant at the 5% level by Wilcoxon’s signed rank test. The insignificant deficit for the range of above 12.5 sec\(^{-1}\) could be due to the small sample number.

Panel C of Figure 6 was obtained in one ventricle with a constant end-systolic volume in run II under a control contractile state. End-diastolic volume was increased from the isovolumic condition. Therefore, stroke volume and ejection fraction were increased from zero. These changes were accompanied by a slight suppression of the end-systolic pressure at a given end-systolic volume as indicated by the two arrows: the top arrow for the isovolumic, and the lower one for loop 4 with the largest stroke volume. Similar responses were observed under the Ca\(^{2+}\)-enhanced (0.35 mM/min) contractile state. The pressure deficit for a given ejection fraction was not affected appreciably with changes in the onset and velocity of ejection, as was determined in run I. Individual and statistical data from 16 runs in 13 hearts in run II are shown in panel C of Figure 7. They indicate that an increase in ejection fraction beyond 40-50% consistently caused a suppression of the end-systolic pressure. The end-systolic pressure deficit was 2 ± 2 mm Hg for an ejection fraction of 20-30%, 3 ± 2 mm Hg for 20-40%, 6 ± 3 mm Hg for 40-50%, 14 ± 3 mm Hg for 50-60%, 13 ± 4 mm Hg for 60-70%, and 17 ± 4 mm Hg for more than 70%, as compared to the isovolumic end-systolic pressure (25-155 mm Hg, mean = 110 mm Hg). Wilcoxon’s signed rank test showed that the pressure deficit for ejection fractions above 40% is statistically significant at the 5% level. Since it seemed that the pressure deficit for a given ejection fraction was greater when the peak isovolumic pressure was higher, we studied the correlation between the pressure deficit for the ejection fraction of 40-50% (\(\Delta P_{45}\), mm Hg) and the isovolumic pressure at the same end-systolic pressures in 14 runs in run II. The correlation coefficient between them was 0.801, and was statistically significant at the 1% level. The linear regression equation was \(\Delta P_{45} (\text{mm Hg}) = 0.0977 \times (\text{isovolumic pressure}) - 0.527\). There was no significant correlation between the pressure deficit and the end-systolic volume. We then normalized the pressure deficits with respect to the isovolumic pressure in individual runs and obtained the percent pressure deficits. The percent deficit was 1% for an ejection fraction of 20-30%, 2% for 30-40%, 5% for 40-50%, 7% for 50-60%, 14% for 60-70%, and 20% for 70%.

Panel D of Figure 6 was obtained from a ventricle with a constant end-diastolic volume in run III. The onset of ejection was made to occur at a constant interval after the onset of contraction. Since we already knew that a change in the onset of ejection did not significantly affect the end-systolic pressure.
at a given volume, we did not study the effect of the change in the onset of ejection on the end-systolic pressure in run III. The decreases in end-systolic volume were always accompanied by proportional decreases in end-systolic pressure, as indicated by arrows. These changes yielded an end-systolic pressure-volume relationship curve which was slightly concave to the volume axis in this and some other ventricles, but largely linear in the rest. After the end-systolic volumes were normalized relative to the left ventricular wall volume of individual ventricles, the end-systolic pressure was plotted against the normalized end-systolic volume in panel D of Figure 7. This figure shows that the end-systolic pressure-volume relationship is largely linear over a wide range from 50 to 150 or 200 mm Hg of end-systolic pressure in 10 ventricles, each contracting from a given end-diastolic volume (14–45 ml, mean = 30 ml). The mean slope (E_max) of the linear regression lines, fitted to the end-systolic pressure-volume points above 50 mm Hg in the control contractile state, was 432 ± 43 (SEM) in terms of mm Hg/unit-normalized end-systolic volume, corresponding to 7.7 ± 0.8 mm Hg/ml end-systolic volume. When the contractile state was enhanced in two ventricles by a continuous infusion of Ca^{2+} at a rate of about 0.35 mM/min, E_max increased to 1100–1300 mm Hg/unit-normalized end-systolic volume, or 13–17 mm Hg/ml. These values for E_max in both control and Ca^{2+}-enhanced contractile states were comparable to those previously reported (Suga et al., 1973; Suga and Sagawa, 1974; Suga et al., 1976). The data in run III confirmed the validity of our contention (Suga et al., 1973; Suga and Sagawa, 1974) that the end-systolic pressure is uniquely determined by the end-systolic volume in such a special case, in that contractions started from a given end-diastolic volume.

The high sensitivity of the end-systolic pressure at a given end-systolic volume to the enhancement of the contractile state was demonstrated by the following observations. Figure 8 (panels A through C) shows representative tracings from run IV. Figure 9 (panels A through D) shows representative
Figure 8. Effects of enhancement of contractile state on the end-systolic pressure at the same end-systolic volume in a 50-g left ventricle. Panel A: postextrasystolic potentiation following an extrasystole produced by a mechanical stimulation of left ventricular surface. The reason that the systolic pressure of the extrasystolic beat was higher than the control and the postextrasystolic potentiated beats is that the ventricle was filled by the pump during its early systole in a manner which does not occur naturally. Panel B: a bolus of Ca\(^{2+}\) (0.1 mM) was injected into the coronary perfusion tube. Panel C: a bolus of isoproterenol (0.1 \(\mu\)g) was injected into the coronary flow.

Figure 9. Effect of enhanced contractile state on end-systolic pressure as observed on the pressure-volume trajectory. Panels A, B, and C correspond to the panels with the same letters in Figure 8, although they are not from identical runs. In panel D, in a control contractile state after a run with a transiently enhanced contractile state similar to that in panel B, end-systolic volume was increased so that end-systolic pressure increased to the same level as in the enhanced contractile state. The arrows mark the end-systolic pressure-volume data points under the control contractile state. The circles mark those under the enhanced contractile state. The triangle in panel D marks the end-systolic pressure-volume datum point at the increased end-systolic volume under the control contractile state.
pressure at a given end-systolic volume in contractions from a fixed end-diastolic volume. Note that these changes in the end-systolic pressure at a given end-systolic volume far exceeded the variations in the end-systolic pressure due to the changes in the systolic pressure and volume courses in runs I and II.

Panel D of Figure 9 shows that the end-systolic volume of the ventricle in an enhanced contractile state (marked by the circle) was significantly smaller than that in the control contractile state (marked by the triangle) when the end-systolic pressures in the two states were matched. Therefore, stroke volume under the enhanced contractile state was greater even when the end-diastolic volume and the end-systolic pressure were unchanged. This clearly indicates that, when we analyze the effect of afterload on stroke volume, the variation of the contractile state of the ventricle has to be minimized.

Discussion

The present results indicate that, for contractions from a fixed end-diastolic volume under a stable contractile state, the ventricular end-systolic volume, not the entire systolic course of ventricular contraction, is the predominant determinant of the end-systolic pressure of the ventricle. In other words, given a preload and a contractile state, the end-systolic pressure-volume relationship of the ventricle is almost independent of the systolic pressure-volume course. This is expected from our previous results (Suga et al., 1973; Suga and Sagawa, 1974). However, the present study further indicates that we must limit our earlier notion (Suga et al., 1973; Suga and Sagawa, 1974), that end-systolic pressure at a given end-systolic volume is independent of end-diastolic volume, to those beats with relatively small ejection fractions, and state that when ejection fraction is large, the end-systolic pressure will be somewhat smaller than that of isovolumic beats.

Further discussion on the limit of the load independence of the end-systolic pressure-volume relationship is in order. We observed some deficit in end-systolic pressure when the onset of ejection approached the end of systole, or when the peak velocity of ejection was relatively high (Fig. 7), although the deficit was not statistically significant. In natural conditions of the heart in vivo, the normalized onset of ejection ranges from 0.15 to 0.30 (Wiggers, 1921), and the normalized peak velocity is below 7–10 sec⁻¹, according to our estimation from the documented data (Noble et al., 1966). Considering these ranges, we conclude that the end-systolic pressure deficit is little affected by physiological changes in the onset and velocity of ejection under natural conditions. In contrast, ejection fraction can vary by up to 70% under natural conditions (Wildenthal and Mitchell, 1969). With an ejection fraction near the upper limit of the physiological range, a statistically significant magnitude of the end-systolic pressure deficit of 13–17 mm Hg, or 14–20% of the peak isovolumic pressure, was observed in the present study. Therefore, if the end-systolic pressure of a ventricle decreases by 14–20% as it ejects from a greater end-diastolic volume to the same end-systolic volume as before, it will be difficult to judge whether the decrease in end-systolic pressure is caused by a change in end-diastolic volume and, consequently, in ejection fraction, or by a change in the contractile state. However, a similar magnitude of change in the end-systolic pressure can be ascribed to a change in the contractile state if the end-systolic, end-diastolic, and hence stroke volume and ejection fraction are unchanged as in run IV.

Suga and Yamakoshi (1977) performed a similar study concerning the effects of ejection fraction and of the onset and velocity of ejection on end-systolic pressure. There are obvious differences between the two studies in the effects of changes in the onset and velocity of ejection on the end-systolic pressure. These effects, measured in terms of end-systolic pressure deficit, were statistically significant in the previous study, in contrast to the present results. The reason for the different results seems to lie in the different patterns of ejection flow. The flow pattern in the previous study, in which the active pump was air-driven and not servo-controlled, was quite different from the present pattern, gradually increasing to the peak flow and rapidly decreasing to zero. The difference in the timing of the peak flow in systole seems critical in terms of effects on ventricular performance, according to Brady’s (1965) finding that a quick length change given to an isometrically contracting heart muscle in the latter half of the contraction phase of a twitch produced a much greater uncoupling effect on myocardial activation than a similar length change given in the first half. Although the onset and peak flow were comparable between the previous and present studies, the peak velocity of ejection occurred much earlier in the present study (with the more normal flow pattern) than in the previous study (with the less natural flow pattern).

The dependence of the end-systolic pressure on stroke volume was observed alike in the previous study (Suga and Yamakoshi, 1977) and in the present one. As was already discussed in the previous paper, the stroke volume dependence of the end-systolic pressure at a given end-systolic volume is probably in part a manifestation of the uncoupling effect of myocardial shortening on activation which Brady (1965), among others, observed in excised myocardium, and which we recently confirmed in situ canine papillary muscle (Suga et al., 1977). Besides the uncoupling effect, the viscoelastic properties (stress relaxation and creep) and the load-dependent changes in contractile state that were observed in the in situ papillary muscle (Suga et al.,
the stroke volume of the end-systolic pressure at a given end-systolic volume.

Extending the interpretation of the present findings one step further, we would state that, for a given end-diastolic volume and a contractile state, the end-systolic pressure, not the entire systolic pressure and volume courses, primarily determines the end-systolic volume, and hence the stroke volume, of the left ventricle. This interpretation with reversed dependent and independent variables is plausible for the following reason. We changed ventricular volume as if it were the independent variable, and measured changes in ventricular pressure as if it were the dependent variable. However, ventricular pressure and volume are known to depend on each other, as indicated by the unique interdependence among the force, shortening velocity, and length of heart muscle (Braunwald et al., 1976; Brutsaert and Paulus, 1977). In fact, in the present experiments, a chosen volume command signal produced both a unique pressure change and a unique pressure-volume trajectory, and this pressure change did uniquely require the chosen volume change in a given ventricle under a given contractile state. Therefore, although we used volume control, the same results could have been obtained even if pressure control had been used to produce primarily the same pressure change as resulted under volume control and the resultant volume change had been observed. We submit that the same pressure-volume trajectory results whether pressure or volume is varied as the independent variable. With this reversibility in mind, panels A, B, and D of Figure 6 show that an identical end-systolic volume, and hence an identical stroke volume, are obtained when the ventricle contracts from the same end-diastolic volume and the same pressure is loaded at the end of systole at which the ejection is over. They further show that the end-systolic volume decreases and stroke volume increases when the end-systolic pressure is decreased. These situations hold regardless of the systolic pressure-volume course. Therefore, we conclude that the end-systolic pressure, not the entire systolic pressure-volume course, is the predominant determinant of stroke volume for ventricular contractions starting from the same end-diastolic volume under a given contractile state.

We interpret the result in run II (panel C of Figure 6) to indicate that a somewhat lower end-systolic pressure is needed to obtain the same end-systolic volume in contractions from a larger end-diastolic volume. It could be interpreted further that an increase in end-diastolic volume does not produce an increase in stroke volume by the same amount when the ventricle is loaded with the same end-systolic pressure. The data in Figure 9 indicate that the ventricle under an enhanced contractile state can eject the same stroke volume from the same end-diastolic volume against a markedly increased end-systolic pressure load, and that it can eject more stroke volume than under the control contractile state from the same end-diastolic volume against the same end-systolic pressure load. Therefore, we conclude that the end-systolic pressure can determine stroke volume almost uniquely only when the end-diastolic volume and contractile state are specified. When these two factors change, stroke volume will change despite a constant end-systolic pressure.

The conclusion from the present study is expected to be valid for normally loaded ventricles in situ for the following reasons. In the normal left ventricle ejecting blood into the normal arterial system through the normal aortic valve, the end of ejection almost coincides with the end of systole, and the ventricle starts to relax isovolumically at the end of systole (Suga et al., 1973; Wiggers, 1921). This physiological situation was simulated in the present experiment as explained in Methods. Therefore, we can extrapolate from the experimental results to ejecting contractions of in vivo ventricle and consider that end-systolic volume is determined by the end-systolic pressure as in the present preparation. However, when the ventricle is presented with an abnormal afterload without an intact valve intervening, stroke volume is not necessarily determined by the end-systolic pressure, because ventricular ejection can continue for a while after the relaxation starts, due to the inertia of the ejected blood. A typical example of this abnormal situation was observed in our previous preparation (Suga and Sagawa, 1974).

More explanation seems necessary for the applicability of the above interpretation of the present results to the naturally loaded left ventricle in vivo. The isolated ventricle under controlled experimental conditions differs from the in situ ventricle ejecting against the natural arterial system, in that end-systolic pressure in the latter cannot be independent of preceding pressure and volume changes within the same beat, because ventricular pressure and volume changes affect each other via the arterial impedance (Milnor, 1975). Therefore, end-systolic pressure and thereby stroke volume are likely to be correlated more or less with many cardiovascular parameters under natural circumstances. Thus, many previous studies reported that stroke volume changed with the outflow resistance (Imperial et al., 1961; Wilcken et al., 1964), aortic pressure (Levy et al., 1963; Scher et al., 1968), elastic properties of the outflow system (Salisbury et al., 1962), and aortic impedance (Urschel et al., 1968; Elzinga and Westerhof, 1973). Moreover, in dogs with intact reflexes, the contractile state, (another major determinant of stroke volume) changes with the changes in afterload pressure (Suga et al., 1976). These complex situations are bound to modify the relationship between the end-systolic pressure and stroke volume observed in the present study. There is direct evidence supportive of the present
conclusion. Paulus et al. (1976) applied a variety of time-varying afterload forces to excised cardiac muscle preparations. Their data indicate (although it is not mentioned in the paper) that the amounts of shortening from the same initial length were identical when the muscle forces at the end of shortening were identical, no matter how widely instantaneous afterload force and velocity of shortening were varied during the shortening phase. Similar independence of the afterload force at the end of shortening from the velocity of shortening has been reported in twitching skeletal muscle (Edman, 1975). In both cardiac and skeletal muscles, the insensitivity of contractile force to the course of shortening was observed only when the total amount of shortening remained unchanged (Edman, 1975; Meiss and Sonnenblick, 1972). When the total amount of shortening increases, contractile force at the end of shortening at a given length decreases (Edman, 1975; Meiss and Sonnenblick, 1972). Therefore, the pressure-volume characteristics of the left ventricle observed in the present study seem to be the manifestations of those basic contractile properties of striated muscle.

References

Edman KAP: Mechanical deactivation induced by active shortening in isolated muscle fibers of the frog. J Physiol (Lond) 246: 255-275, 1975
Wiggers CJ: Studies on the consecutive phases of the cardiac cycle. II. The laws governing the relative durations of ventricular systole and diastole. Am J Physiol 66: 439-459, 1921
End-systolic pressure determines stroke volume from fixed end-diastolic volume in the isolated canine left ventricle under a constant contractile state.

H Suga, A Kitabatake and K Sagawa

Circ Res. 1979;44:238-249
doi: 10.1161/01.RES.44.2.238

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/44/2/238.citation

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

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

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