Effects of Coronary Arterial Pressure on Left Ventricular End-Systolic Pressure-Volume Relation of Isolated Canine Heart

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SUMMARY. In the excised canine left ventricle, the end-systolic pressure-volume relationship (ESPVR) has been shown to be approximately linear over the working range of loading conditions when coronary arterial pressure (CAP) is maintained constant, independent of loading conditions. To investigate the ESPVR under the more intact physiological condition in which the CAP varies with loading on the left ventricle, we studied the effect of changes in CAP on the ESPVR in 10 excised cross-circulated canine ventricles which were contracting isovolumically. The ESPVR, determined from isovolumic contractions at four different volumes, was reasonably independent of CAP as long as CAP remained above a critical pressure (67.0 ± 22.1 mm Hg). Below this pressure, the slope of ESPVR decreased although the volume axis intercept (V0) remained unaltered. These findings indicate that under physiological conditions, where there is a close coupling of CAP to systolic left ventricular pressure, the ESPVR should become nonlinear in the low preload or afterload regions. When CAP was varied with the left ventricular pressure in five ventricles, the ESPVR indeed became nonlinear in the low-load region. We conclude that the ESPVR in intact conditions is reasonably linear in the physiological load range, but it can be nonlinear in the low-load range.

PREVIOUS studies on excised canine hearts from this laboratory (Suga et al., 1973; Suga and Sagawa, 1974) showed that the left ventricular end-systolic pressure-volume relationship is approximately linear over the working range of the heart, and the slope of the relation line (Emax) is a sensitive index of inotropic state. In those studies, the excised ventricle was perfused by a support dog, and coronary arterial pressure (CAP) was controlled independent of the function and loading conditions of the isolated left ventricle. In the intact animal, however, the ventricle generates CAP, which is, in turn, likely to influence ventricular function under certain circumstances. Therefore, there can be interdependence, i.e., feedback, between CAP and ventricular function.

There have been a large number of experimental studies performed regarding the effect of low CAP on ventricular function. However, the nature of the deterioration of ventricular function at low CAP has not yet been shown in terms of ESPVR. Therefore, we do not know whether CAP affects the ESPVR over an extensive range (including subphysiological and supraphysiological CAP) or only in a low range, whether the effect is independent of loading conditions (i.e., preload and afterload), and what parameters of the ESPVR would be affected predominantly (Emax, V0, or both of them). In order to evaluate the ESPVR of the intact heart preparation, in which the coronary feedback loop is naturally closed, we must know the effect of CAP on the ESPVR. Such information would provide a firm basis to interpret the ESPVR obtained from cardiac patients under normal or abnormal conditions of coronary perfusion.

Because ventricular function is known to deteriorate precipitously at low CAP, we hypothesized that under open-loop conditions, CAP affects the ESPVR significantly only when it is markedly low, and that when the coronary perfusion feedback loop is closed, the ESPVR would become nonlinear in the region of low ventricular pressure and volume. These hypotheses were tested first by determining the effect of altering CAP on the ESPVR under open-loop conditions, and then by obtaining the ESPVR with CAP coupled to systolic ventricular pressure to variable degree (i.e., under closed CAP feedback loop conditions). For technical reasons, the study was limited to the ESPVR determined from isovolumic contractions in isolated canine ventricles.

Methods

Surgical Preparation

Ten pairs of mongrel dogs weighing 18.1–26.3 kg (21.9 ± 1.9 kg) were used under anesthesia with sodium pentobarbital (30 mg/kg, iv). The chest of one dog was opened under artificial ventilation. The subclavian artery and right atrium were cannulated and connected to the femoral arteries and veins, respectively, of a support dog. The azygos vein, superior and inferior vena cavae, brachiocephalic artery, and descending aorta were ligated. Cross-circulation was completed by ligation of the pulmonary hilus.
was removed from the chest, the pericardium removed, the left and right ventricles vented, the chordae tendineae cut, and the apex of a thin balloon was pulled out through a small opening in the left ventricular apex. A plastic adaptor to which the balloon was mounted was sewn to the mitral valve annulus. A diagram of the perfused isolated ventricle appears in Figure 1. The space between the balloon and the ventricular wall was minimized by applying continuous suction through the vent in the apex. The balloon adaptor then was connected to a servo-pump system, which was previously described elsewhere (Suga and Sagawa, 1977). It consisted of a high performance linear motor (Ling Electronics, model 411) and a bellow piston pump (Bellofram, SS-4-F-SM-UM). A constant volume of tap water filled the pump and balloon. Movement of the linear motor, which changed the balloon volume, was measured by a linear variable differential transformer (Transtek, 244-000) attached to the piston shaft. This servo-pump system allowed us to control the ventricular volume precisely throughout the cardiac cycle. A disc oxygenator (Pemco model 7109) was placed in parallel with the support dog, so that oxygenated blood could be received from either the support dog or the oxygenator, as desired. CAP was measured via a catheter placed just distal to a coronary perfusion cannula in the aortic root. A servo-controlled perfusion pump (Harvard model 1215) maintained mean CAP at any selected value. Coronary arterial blood temperature was maintained approximately at 37°C with a water bath and heat exchanger.

CAP, left ventricular pressure and volume, and the support dog's arterial pressure were recorded on a pen recorder (Gould 2800), digitized on line by a computer (Data General, Nova 1220) and also stored on an FM magnetic tape recorder. Only selected portions of the digitized data were permanently recorded on magnetic tape for future data analysis. The ESPVRs were also monitored on line on an X-Y storage oscilloscope (Tektronix model #5103).

Experimental Conditions and Protocol

In the early phase of this series of experiments, we studied both isovolumic and ejecting contractions. However, we found that when the contractile state became poor with a very low CAP, the adjustment of the command signal for the ventricular volume servo-pump to obtain a physiologically shaped ejecting pressure-volume (P-V) loop became difficult. This was primarily because of the hardware limitations of the volume servo-pump. Furthermore, susceptibility of the ventricle to arrhythmia increased with a low CAP, which made the adjustment even more difficult. Therefore the present analysis is limited to the data from isovolumic contractions.

At the beginning of each experiment, a ventricular volume was selected which gave a peak isovolumic pressure between 80 and 120 mm Hg with a mean CAP of 80 mm Hg. The ventricular volume was fixed at this value while CAP was varied over the range from 30 to 120 mm Hg to determine at what CAP the peak isovolumic pressure began to fall. Once this critical coronary pressure was known, CAP was set at one of several levels above and below this critical value, and the ESPVR was determined from peak isovolumic pressures at four volumes repeatedly under different CAP's. A typical set of experimental data are shown in Figure 2. Pressure and volume were recorded over a number of cardiac cycles at each of the four volumes (27.5, 22.5, 17.5, and 12.5 ml in Figure 2) under the highest CAP, and then the volume was returned to the same initial volume of the run. This procedure took about 5 minutes. If the pressure at the beginning and end of the run did not differ by more than 5%, we accepted the data; otherwise the data were discarded. The CAP then was lowered, and several minutes later when the preparation stabilized, the pressure measurements were repeated at the same four volumes. The procedure was repeated until a sufficiently low range of CAP was covered (90, 75, 40, and 30 mm Hg in Figure 2).

In five hearts, we validated the prediction from the open-loop analysis of CAP effect on the ESPVR through a direct observation of the closed-loop effect of CAP on ESPVR by setting CAP equal to the peak systolic pressure or a constant fraction of it during the determination of the ESPVR over a variety of ventricular volumes.

Data Analysis

Mean CAP was obtained directly from the strip chart recording. The ESPVR was determined by computer in the following manner. A stable portion of data containing at least three beats was selected at each of the four volumes studied by an interactive editing procedure. The "end-systolic" point was determined at each volume by finding the maximum P-V ratio. A least square linear regression analy-
FIGURE 2. Example of end-systolic pressure-volume relationship (ESPVR) lines under various coronary arterial pressures (CAP). ESPVR was determined using left ventricular peak systolic pressure (LVP) of isovolumic contractions obtained at four different ventricular volumes with a constant CAP. When CAP was lowered from 90 to 40 mm Hg, the slope of ESPVR decreased slightly from 5.1 to 4.9 mm Hg/ml. When CAP was further lowered to 30 mm Hg, the slope decreased markedly to 3.0 mm Hg/ml, though the volume intercept of the relationship line remained approximately constant.

sis was made of these four pressure points over the volumes.

Results

Open-Loop ESPVR

The relationship between CAP and left ventricular peak isovolumic pressure at a given volume is shown in panel A of Figure 3. In general, left ventricular peak systolic pressure is remarkably insensitive to changes in CAP as long as the latter pressure remains within a relatively high range. In a lower CAP range, however, the left ventricular peak pressure is dependent on CAP. By inspection, we estimated the critical CAP at which the transition of ventricular pressure from CAP independence to dependence occurred (open circles in panel A). The average critical CAP was found to be 67.0 ± 22.1 (SD) mm Hg at which the left ventricle generated an average peak pressure of 94.5 ± 12.3 (SD) mm Hg at an average volume of 28.5 ± 10.8 (SD) ml. When the CAP-left ventricular peak pressure relationship was expressed with the CAP normalized to the critical pressure and left ventricular peak pressure normalized to its value at the critical CAP, the independence and dependence of the peak systolic pressure on CAP became clearer as shown in panel B of Figure 3.

The effect of CAP on E\textsubscript{max} obtained from isovolumic contractions is summarized in Figure 4. When CAP was above the critical CAP (open circles in panel A of Figure 4), E\textsubscript{max} was relatively insensitive to CAP. However, when the CAP was lowered below the critical CAP, E\textsubscript{max} depended on CAP. Again this feature became clearer when E\textsubscript{max} and CAP were nor-

malized to their values at the critical CAP (panel B in Figure 4). The average E\textsubscript{max} at the critical CAP was 4.4 ± 1.4 (SD) mm Hg/ml.

Panel A of Figure 5 explains our new terminology. We used to designate the volume axis intercept \(V_d\), but now we designate this \(V_o\) and \(V_d\) for the point at which no pressure is generated above the diastolic pressure. The relationship between the volume axis intercept \(V_o\) of the ESPVR line obtained from isovolumic contractions and CAP is shown in panel B of

FIGURE 3. Panel A: The effect of coronary arterial pressure (CAP) on peak left ventricular pressure (LVP) of isovolumic contractions are shown. LVP is relatively insensitive to CAP when CAP is high. In the low CAP range, LVP becomes more sensitive to CAP. Note the inflexion points, i.e., critical CAP’s (open circles), below which the LVP becomes CAP dependent. Panel B: CAP-LVP relationship after normalizing CAP values with respect to the critical CAP of each ventricle (open circle) and LVP values to the LVP at the critical CAP of each ventricle. Dependence of LVP on CAP below the critical CAP is more clearly demonstrated here than in Panel A.
CAP is approximately the same as aortic pressure, factors which influence aortic pressure (such as contractility, preload, or afterload impedance), also influence CAP and, as shown in the open-loop analysis of ESPVR, CAP becomes one of the major determinants of cardiac contractility when it is low. Therefore, in intact situations, the coupling between the left ventricular pressure and CAP forms a feedback loop.

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Closed-Loop ESPVR

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which can affect ventricular contractility. We can predict the ESPVR with feedback from the result of our open-loop analysis.

Panel A in Figure 6 shows a schematic open-loop ESPVR and panel B illustrates how we can predict the closed-loop behavior from the open-loop ESPVR data. In this example, the critical CAP is assumed to be 60 mm Hg. Each of the lines in the figure represents the ESPVR under a constant CAP. If the left ventricular peak pressure and the mean CAP are equal, all of the ESPVR lines will superimpose on the solid line until the left ventricular pressure and the mean CAP become lower than the critical CAP. When the CAP is lowered to 50 mm Hg, the ESPVR will have to shift to the relation line labeled "50" in Figure 6B. When the CAP is further lowered to 40 mm Hg, the ESPVR will further shift to the relation line labeled "40."

Thus the closed-loop ESPVR becomes curvilinear in the region where the peak left ventricular pressure is below the critical CAP. This relationship is altered by changing the degree of coupling. In the closed-loop experiment to be described next, we varied the coupling between CAP and left ventricular pressure by changing the ratio of mean CAP to the peak left ventricular pressure. Although it is not illustrated in Figure 6, if the mean CAP is adjusted to 80% of the peak left ventricular pressure, the nonlinearity of ESPVR will start when the left ventricular pressure drops below 75 mm Hg (critical left ventricular pressure) instead of 60 mm Hg. If the coupling is 60%, the critical left ventricular pressure will be 100 mm Hg. A low coupling ratio makes the critical left ventricular pressure higher and the slope of ESPVR steep or even negative in the low ventricular pressure region.

To validate the above prediction based on the result of this open-loop analysis, closed-loop experiments were performed in five ventricles. The coupling ratio was fixed at unity in two ventricles but widely varied in three ventricles from 40% to 100% by steps of 20%. Figure 7 shows the representative closed-loop ESPVR obtained from isovolumic contractions under a wide variety of coupling ratios in the three ventricles. The ESPVR of a ventricle which showed the highest critical CAP (80 mm Hg) among the three ventricles preceding open-loop analysis is shown in panel A. The closed-loop ESPVR of this ventricle showed an obvious curvilinearity when the CAP was lowered below 80 mm Hg even though the CAP was equal to the peak isovolumic left ventricular pressure (i.e., the coupling ratio was 100%). With very low CAPs, the slope of the relationship curve became even negative; i.e., the curve extended from the upper left to the lower right. This negative slope occurred at a higher P-V region when mean CAP was made equal to a smaller fraction (80, 60, to 40%) of left ventricular pressure. Panel C in Figure 7 shows the ESPVR of a ventricle with the lowest critical CAP (40 mm Hg) among these three. The closed-loop ESPVR of the ventricle was reasonably linear even in the low perfusion pressure range. However, the slope of ESPVR eventually became negative when the coupling ratio was decreased to as little as 40%. Panel B presents the ESPVR of a ventricle which showed an intermediate critical CAP (60 mm Hg) in the preceding open-loop analysis. The closed-loop ESPVRs are in general more vertical than the open-loop ESPVRs, indicating that the ESPVR is sensitive to CAP; yet they are not as curvilinear as these ESPVRs in panel A. Therefore closed-loop ESPVRs shown in panel B show characteristics between those of the ventricles shown in panels A and C. It is impressive that, despite the likely time-dependent variation in contractile state of those ventricles over the more than 1-hour period encompassing the open-loop analysis and the closed-loop runs, we still can see the qualitative difference in the closed-loop ESPVR between the ventricles corre-
FIGURE 7. Three examples of closed-loop end-systolic pressure-volume relationship (ESPVR) experiments. A dark thick line represents open-loop ESPVR at the CAP of 100 mm Hg. Each number at the bottom of the ESPVR curve indicates the coupling ratio. The closed-loop ESPVR are obtained by coupling CAP to 100% (1.0), 80% (0.8), 60% (0.6), and 40% (0.4) of left ventricular pressure. Panel A: The closed-loop ESPVR curves of a ventricle which had the critical CAP of 80 mm Hg in the open-loop analysis. In the 100% coupling condition, the ESPVR was relatively linear when CAP was above 80 mm Hg. When CAP was lowered below 80 mm Hg, the nonlinearity became obvious. The nonlinearity was clearer when the coupling ratio was smaller. Panel B: The closed-loop ESPVR curves of a ventricle which showed the critical CAP of 60 mm Hg in its open-loop analysis. The ESPVR curves are sensitive to the CAP as well as the coupling ratio, which made the closed-loop ESPVR curves nearly vertical. However, the sensitivity is less than the ventricle shown in Panel A. Panel C: The closed-loop ESPVR of a ventricle which showed the critical CAP of 40 mm Hg in the open-loop analysis. Compared with the ventricles shown in A and B, the ESPVRs are relatively insensitive to CAP and the coupling ratio until the coupling ratio becomes as small as 0.4. With the very low coupling ratio, the slope of ESPVR became slightly negative.

Discussion

Effect of Coronary Arterial Pressure on ESPVR

It has been well known that left ventricular function is influenced in a complex way by changes in coronary circulation. Deterioration of ventricular function can result from a decline in the slope of ESPVR (E\text{max}) rightward shift in \(V_0\) or a combination of both mechanisms. This study showed that in the isolated ventricle, neither the slope of the ESPVR nor the volume axis intercept obtained from isovolumic contractions changed as long as CAP was higher than a critical pressure. Below the critical pressure, ventricular function deteriorated. We showed that the mechanism responsible for this deterioration caused by acute hypoperfusion imposed on fresh, isolated ventricles was a decline in the slope of ESPVR, not a rightward shift of the ESPVR (increase in \(V_0\)).

There have been many publications that investigated the effect of coronary perfusion on ventricular function. However, to our knowledge, none of those authors have dealt with the relationship between CAP and the ESPVR with the exception of Abel and Reiss (1970). These investigators showed the effects of CAP on the ESPVR using isolated, isovolumically contracting canine ventricles. Over a wide range of CAP from 45 to 175 mm Hg, the left ventricular peak pressure progressively increased with the CAP exhibiting no plateau except at an extremely high CAP. Therefore, there was no clear critical CAP below which ventricular function became CAP dependent. The ESPVRs obtained by these authors were reasonably linear, but both the slope and the volume axis intercept of the relationship were dependent on the CAP. We did not see such an extensive sensitivity of ESPVR on CAP in our ventricles. However, we did observe that the isovolumic ESPVR became highly sensitive to CAP after prolonged perfusion (2-4 hours). The mechanism of this time-dependent change in the CAP sensitivity is not clear. Daniel (1973) and Downey (1976) showed that when coronary arterial flow or CAP was varied, left ventricular function changed little if coronary flow remained above a critical level, but declined if coronary flow decreased below the critical level. Since the average critical CAP in our data was 67.0 ± 22.1 mm Hg, which is about the same coronary pressure below which coronary autoregulatory reserve is exhausted (Shaw et al., 1962; Lekven et al., 1973; Downey, 1976), it is tempting to conjecture that the deterioration of left ventricular function below the critical pressure is related to loss of autoregulatory reserve of the coronary vessels. In the isolated ventricle or a similar preparation which requires extensive surgical manipulation, it is widely known that coronary autoregulation is likely to be lost sooner or later. Therefore, the loss of clear critical pressure after prolonged perfusion could be explained by the loss of coronary autoregulation.

Closed-Loop ESPVR

Beneken et al. (1969) has, while keeping mean left atrium pressure constant, compared the effect of mean aortic pressure changes on cardiac output under a constant CAP and under a CAP which equaled to and therefore changed with mean aortic pressure. They found that cardiac output was inversely related to mean arterial pressure when CAP was maintained at
a constant value. However, when CAP was equal to mean arterial pressure, cardiac output first increased with increases in mean aortic pressure until the latter reached about 100 mm Hg, and thereafter cardiac output decreased with further increases in aortic pressure. Since the heart rate in their data appears to be reasonably constant despite changes in mean arterial pressure, the cardiac output changes can be attributed to alterations of stroke volume. The present data allow us to interpret the findings by Beneken et al. as follows. With a constant CAP, stroke volume will decrease with an increase in the afterload pressure (mean aortic pressure in their study) because of the constant ESPVR. However, when the coronary feedback loop is closed, the increase in mean aortic pressure also increases the contractility if the control aortic and coronary pressure are in very low range. Depending upon the magnitude of the increase in contractility via the increase in CAP relative to the magnitude of the afterload effect of the increased aortic pressure, it is conceivable that an increase in mean aortic pressure leads to an increase in stroke volume. On the other hand, in the relatively high aortic pressure range (i.e., when CAP is higher than the critical CAP), the contractility will no longer be a function of CAP and stroke volume will decrease with a further increase in the mean aortic pressure. Thus the bidirectional change in cardiac output observed by changing mean arterial pressure with the closed coronary feedback loop can be interpreted as a manifestation of the nonlinear ESPVR observed in the present analysis.

Recently, Isoyama and his associates (1981) compared the cardiac output under open and closed coronary loop conditions using isolated canine ventricles. The afterload on these ventricles was a hydraulic impedance loading system. When the coronary circulation was maintained by a constant flow pump, cardiac output monotonically increased with decreases in peripheral resistance of the loading system. When CAP was made equal to the "aortic" pressure, cardiac output increased with decreases in the peripheral resistance as long as CAP was above 65 mm Hg. Below this peripheral resistance level, cardiac output decreased with decrease in peripheral resistance. Therefore there was an optimum peripheral resistance at which cardiac output becomes maximal. The monotonous increase in cardiac output with decreases in the peripheral resistance under the open coronary loop condition can be explained by the constant ESPVR. When the coronary loop is closed by equalizing the CAP to arterial pressure, the ESPVR becomes nonlinear below the critical CAP. This characteristic effect of CAP on ESPVR determines an optimal afterload resistance at which the cardiac output becomes maximal.

Physiological Implication of Curvilinear ESPVR

What does the negative slope of the lower part of the curvilinear ESPVR mean for the circulatory system performance? Suppose that the CAP happened to fall into the negative slope region of the ESPVR curve because of an excessive reduction in the pre- and/or afterload for the left ventricle. Once the ventricle moves into this region, the low CAP reduces the contractility which tends to further lower CAP in the face of increasing end-systolic volume and decreasing ventricular pressure. This cyclic event is likely to lead to a catastrophic deterioration of ventricular function. Therefore, the negative slope of ESPVR suggests the potential risk of a vicious cycle. As shown in Figure 7, the left ventricular systolic pressure below which the ESPVR bends downward and then towards the lower right is rather low if the coupling ratio is near unity (i.e., when mean CAP is close to left ventricular systolic pressure) and the critical CAP is low. Under physiological conditions, the high coupling ratio and low critical CAP, which is likely to be much lower than that measured in isolated ventricles, make the left ventricular function quite stable despite variable loading conditions. When the coupling ratio is low, i.e., CAP is only a small fraction of left ventricular systolic pressure, the left ventricular systolic pressure that can trigger the vicious cycle becomes higher, rendering left ventricular performance unstable even with small changes in loading conditions. Several pathological conditions, such as narrowing of the major coronary arteries, aortic stenosis, aortic regurgitation, and IHSS, can decrease the coupling ratio of CAP to the left ventricular systolic pressure. Under these conditions, CAP can reach the critical level which triggers the vicious cycle even when left ventricular systolic pressure is relatively high, and these patients would be much more prone to a catastrophic deterioration of ventricular function than people with the normal coupling ratio.

Once this vicious cycle is triggered, the ventricle would not likely recover from it by its own ability. However, some devices can assist the ventricle to escape from the catastrophe. For example, intra-aortic balloon pumping augments the left ventricular pressure and CAP coupling ratio by increasing CAP during diastole and decreasing afterload during systole (Weber and Janicki, 1974). If this assist device works optimally, CAP can be maintained virtually independent of ventricular function, and, as a result, ventricular function will become stable.

The ESPVR (or concept of ESPVR) has been used clinically to evaluate left ventricular function (Grossman et al., 1977; Marsh et al., 1979; Merillon et al., 1981; Mehmel et al., 1981). In order to determine the ESPVR, at least two P-V loops under different loading conditions are required at a constant contractility. The investigators avoided changes in contractility associated with changes in loading conditions through the reflex system by using pharmacological blockades of autonomic efferent signals to the heart (Marsh et al., 1979; Mehmel et al., 1981). However, the results of the present study indicates that, even if all reflex controls of cardiac contractility are blocked, the assumption of constant contractility under different left ventricular loading conditions may not necessarily be true if the ventricle is operating in a range sensitive to coronary perfusion pressure. The nonlinearity of ESPVR can
be more prominent in diseased hearts, in which the assessment of ventricular function is more crucially needed than in healthy hearts. If one determines ESPVR from only two P-V loops, the potential non-linearity cannot be disclosed. As shown in Figures 6 and 7, if one picks up two P-V loops in the nonlinear ESPVR range, the value of $E_{\text{max}}$ thus estimated could be an overestimation for the normal P-V range. Therefore, unless the linear ESPVR is otherwise confirmed, determination of the ESPVR from multiple P-V loops (Mehmel et al., 1981) is highly desirable.

The present results were obtained under highly controlled conditions with the heart isolated, denervated, contracting isovolumically, and under steady state conditions. The effect of closing the coronary feedback loop on the ESPVR in the more physiological ejecting heart, including the transient response, remains to be determined.

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