Editorial:
The End-systolic Pressure-Volume Relation of the Ventricle: Definition, Modifications and Clinical Use

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BASIC RESEARCH on the ventricular pressure-volume loop diagram has been revived. Several investigators proposed that the relationship of end-systolic pressure (or wall stress) to end-systolic volume (or some dimension) may be useful in evaluating the contractile state of the heart. Grossman et al. published an important clinical study in 1977; many others followed. At the 1980 annual meetings of the American Heart Association and American College of Cardiology, at least 11 papers were presented concerning the end-systolic relationship between pressure and volume, pressure and thickness, and wall stress and normalized volume. Several significant studies have also appeared in the past 5 years; a dozen clinical studies have been published. With this popularity, the original meanings of end-systolic pressure-volume relation and its parameters (e.g., $E_{\text{max}}$, $m$, $V_0$ and $V_d$) have become ambiguous. Sometimes they were purposely modified to attempt to improve their value and other times just to make the measurement easy. Whatever the reason, it seems appropriate to review these modifications with reference to the proponents' original ideas about fundamental aspects.

Isovolumic Pressure-Volume Relation

Frank determined the relation curve of isovolumic peak pressure to volume in the frog ventricle and showed that it was highly nonlinear, indicating a descending portion in the large volume region. Recent investigators of isolated canine hearts, however, demonstrated a rectilinear relation between the pressure and volume (fig. 1), with only one exception. In the human heart, isovolumic contraction is difficult to obtain. A few investigators have made special efforts to examine the linearity of end-systolic pressure-volume relation by subjecting patient's heart to three loading conditions. In the physiologic range studied, the pressure-volume relation was found to be linear. (See figure 1 of Mehmel et al. in this issue.)

Those studies on isolated canine hearts indicated that the left upper corner of the pressure-volume loops of ejecting contractions come so close to the isovolumic pressure-volume relation line that, as an approximation, the rectilinear isovolumic pressure-volume relation line can be considered uniquely representing an end-systolic state of the ventricle under the given constant contractile state irrespective of the mode of contraction and the loading conditions during ejection. However, this is an approximation reduced from data on isolated canine ventricle, and its validity for the human heart and the intact canine ventricle must be verified. In fact, dependence of the end-systolic pressure-volume relation upon preload or ejection fraction was shown in the isolated canine ventricle (as suggested by the greater distance between the solid line and broken line for the large ejection beat in figure 1). Put in a more general way, the load dependence or independence of the end-systolic pressure-volume relation of ejecting ventricles must be validated in closed-chest animal preparations. The present view of the importance of the short-term history dependent difference in end-systolic pressure-volume relation line varies from entirely negligible to small but statistically significant when stroke volume is large.

Suga and Sagawa designated the slope of the relation line end-systolic elastance $E_{\text{es}}$, or the maximum elastance, $E_{\text{max}}$. The latter appeared an appropriate term because the slope $E(t)$ of the regression line of instantaneous ventricular pressures on volumes specified at a time in systole increased with time, reaching a maximum $E_{\text{max}}$ and decreasing thereafter. Earlier, they had called $E_{\text{max}}$ the end-systolic pressure-volume ratio, but no longer use this term because it could be confused with the ratio of pressure to absolute volume ($P/V$). Although this latter ratio has been called $E_{\text{max}}$, or analyzed under different names, it is not $E_{\text{max}}$ because the end-systolic pressure-volume relation line does not extrapolate to the origin, but intersects with the volume axis at a finite positive value ($V_o$ in figure 1). Thus,

$$E(t) = \frac{P(t)}{[V(t) - V_d(t)]} \quad (1)$$

or, according to the end-systolic formula used by Grossman et al.,

$$E_{\text{es}} = \frac{P_{\text{es}}}{m} (V_{\text{es}} - V_o) \quad (2)$$

Although $V_o$ varies with time from its end-diastolic value (often referred to as " unstressed volume") to its end-systolic value, it varies little near end-systole and can be treated as a constant if the interest is confined to $E_{\text{max}}$. Suga and associates originally called this end-systolic $V_o$ because it appeared to represent a functionally dead volume at
which the ventricle cannot generate any supra-atmospheric pressure. Sunagawa et al. measured how the end-systolic and end-diastolic pressure-volume relation curves course in the negative pressure region, and found that the two curves converge at a point with a negative pressure coordinate of $-15$ to $-20$ mm Hg and a volume coordinate only mildly less than $V_e$ (fig. 1). They call this volume by $V_e$ because at this volume the ventricle cannot develop any systolic pressure.

Can one disregard $V_e$ because it appears to be small (5–10 ml in the left ventricle of a 20-kg dog)? Definitely not. In abnormal ventricles, it may become very large temporarily during acute regional ischemia or chronically in infarcted hearts. The $V_e$ results from a linear extrapolation of the end-systolic pressure-volume data obtained over a limited volume interval in human subjects, so it may vary widely from patient to patient (see table 1 of Mehl et al.) despite their effort to collect three pressure-volume data points in each patient. If $V_e$ were disregarded and a single pressure-volume data point were connected with the origin, the resultant slope value ($\text{pseudo } E_{\text{max}}$) could be vastly different from those slope values $K_{\text{ee}}$ listed in the table. The significance of shift of $V_e$ in diseased hearts is unclear, so it is even more important to attempt to acquire at least two pressure-volume data points from each patient under a constant inotropic background and determine the $V_e$ value specific to the patient's condition.

Ovviating Load Alteration

Because it is not easy to change afterload and obtain multiple pressure-volume data points in a given subject while maintaining a constant contractility by pharmacologic denervation, attempts have been made to obviate alteration of load. Spann et al. applied a regression analysis to end-systolic pressure-volume data points collected from a group of patients, but only one pressure-volume point from each patient, and termed the slope of such regression lines estimates of $E_{\text{max}}$. This is a misnomer, even though they normalized the volume variable with respect to body surface. The meaning of the slope of such regression lines is different from the $E_{\text{max}}$ or $m$ parameter in equation 1 or 2, respectively. There is a well-established high correlation between body size, cardiac output and ventricular volumes in a wide range of animal species; the similar correlation among adults in a given animal species is rather poor. For this reason, the normalization of volume with respect to body surface area is of doubtful significance.

Rousseau et al. proposed that late systolic stress values within a single beat correlate linearly with corresponding volumes and that the regression coefficient might be a good approximation of the real end-systolic stress-volume relation. However, the time course of systolic pressure-volume and stress-volume trajectory is strongly dependent on afterload impedance and the contractile property of myocardium. From this principle it is difficult to accept the proposal.

Two animal experiments have been reported that attempt to estimate peak isovolumic pressure from an ejection beat, obviating the need to alter the loading condition. One estimation is based on the assumption that an isovolumic pressure curve can be reasonably approximated by an elevated sine wave and makes use of the isovolumic systolic and diastolic portions of a pressure curve from ejecting ventricle. Connecting this estimated peak pressure-volume point with the measured end-systolic pressure-volume data point will yield an end-systolic pressure-volume relation line, which is similar to the broken line in figure 1.

Another attempt assumes a viscoelastic model for the ventricle and estimates the model parameter values from instantaneous pressure and volume data of a given beat. The model comprises a time-varying elastance $E(t)$ and a pressure-dependent viscous resistance. Again, once the elastance parameter is identified, multiple peak isovolumic pressure points can be easily calculated and the end-systolic pressure-volume points connected to yield the slope parameter, $E_{\text{max}}$. Both methods are said to predict the peak isovolumic pressure within $\pm 5\%$ of the actual pressure, so their potential for clinical estimation of $E_{\text{max}}$ should be pursued.

End-systole vs End-ejection

Iizuka warned of the probable confusion and consequent misuse of the end-systolic pressure-volume relationship because of the hazy distinction between end-ejection and end-systole among cardiologists. When ejection of blood begins and ends depends not only on the time course of the myocardial contractile process, but also on external loading conditions. For example, if an extremely efficient counterpulsation was performed, the ventricle would be assisted to continue ejecting blood even after the active process passed its peak. In contrast, if the coun-
terpulsation were out of phase, it would easily bring ejection to an end even before the peak of active contraction is reached. Therefore, a term must be established that indicates the end of active contractile process independent of loading condition. Izukatsu proposed contraction and end-contraction for systole and end-systole. Suga and I feel that it is premature to abandon the term systole entirely.

Lacking a unanimous definition of systole, I submit to define the end-systole generally as the instant at which some measure of the active contractile process reaches a maximum. With this definition, either the time for peak isovolumic pressure or end of ejection under a constant pressure is obviously end-systole. Those who wanted to distinguish end-systole from end-ejection had difficulty in defining end-systole when the ventricle ejects against falling pressure as in the normal beat. By using the time-varying volume elastance E(t), as described in equation 1, however, one can define end-systole as the time at which E(t) becomes maximum, including ejecting beats under variable pressure. That left ventricular ejection normally ends very shortly after the end of systole, as defined above, is coincidental; there is no a priori reason to be so. In fact, Maughan et al. presented evidence that because of the very small pulmonary vascular resistance, the right ventricular ejection goes on far beyond the end-systole. Using computer simulation, Suga showed that even the human ventricular ejection proceeds far beyond the time for E max when peripheral resistance is abnormally small (fig. 2).

Therefore, if one blindly uses such end-ejection pressure-volume data points to estimate E max, the error can be quite large.

In all of the clinical studies cited except two, the measured “end-systolic” pressure-volume relation lines are different from that which Suga et al. defined originally. Most investigators use dicrotic notch pressure in the artery for end-systolic pressure. Some use peak systolic pressure in the ventricle or aorta. Nivatpumin et al. compared in 35 patients the maximum P/V value (not E max, as Suga et al. defined) against the ratio of the peak ventricular pressure to the minimum systolic volume, and found that the two slope parameters correlated highly (r = 0.99), though the latter was about 10% greater than the maximum P/V. Marsh et al. also found a close correlation between the slope parameter determined with peak ventricular pressure and the slope with dicrotic notch pressure against end-systolic ventricular dimension in human subjects with no obvious cardiac diseases. All of these efforts to make estimation of E max noninvasive should be encouraged. However, when pressure and volume data are taken at two instants of time, the ratio is no longer an end-systolic volume elastance. Until the value and limitations of each of noninvasive modifications are established, precise report of the actually measured variables and their relations is warranted to avoid unnecessary confusion. The aortic pressure wave form must also be examined; if a large difference is evident between the peak and dicrotic notch pressure (as in aortic regurgitation), it is imperative to use the pressure at the instant of time at which ventricular volume is determined.

Conclusion

Proposals have been made from several laboratories that information implied in the end-systolic pressure-volume relation be explored for evaluating ventricular function. Many attempts have been made toward this goal and diverse modifications have been developed. The importance of the end-systolic pressure-volume relation seems to be strongly indicated. Three laboratories reported a linear relation between end-systolic pressure and volume in the physiologic range of human left ventricle. Its slope has been shown in many studies to separate poorly contracting ventricles from normal ones more sharply than ejection fraction or end-systolic volume. The volume intercept V o also varies with the state of the heart, though the variation is much less consistent among the reports. This inconsistency may be the result of inaccurate volume measurement or may indi-
cate our ignorance of what to measure or calculate. A preliminary observation in the author’s laboratory suggests a unique importance of $V_0$ in canine ventricles rendered regionally ischemic. As Noble$^{66}$ pointed out, simultaneous consideration of $V_0$ with $E_{\text{max}}$ will make the end-systolic pressure-volume relation of more informational value.

Studies must be continued as to why some investigators obtain such highly negative $V_0$ values and others do not, and why the pressure-dimension relation or wall stress-length relation shows parallel shift as opposed to the slope change, which is more frequently seen in the pressure-volume relation with inotropic interventions.$^{9, 86, 89} Because it is not easy to change loading conditions without provoking reflex changes in contractility of the heart in human subjects, the methods to estimate peak isovolumic pressure from ejecting ventricular pressure-volume data of a single beat is of prime importance. A method to allow repeated accurate measurement of ventricular volume in intact animals must be established to close the gap of information between excised heart data and information on diseased hearts in man. Finally, it is also very important to explore an appropriate way to normalize the slope and volume intercept values for a given purpose.$^1$ With all the information, limitations of the end-systolic pressure-volume relation will become more clear and its value should be far greater.

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