Dissociation of End Ejection from End Systole of Ventricle

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SUMMARY

Previous experiments showed the cases in which end ejection of the ventricle did not always coincide with end systole as identified by the time for Emax corresponding to the maximally contracted pressure-volume relationship line of the ventricle. The purpose of the present study is to obtain a better insight into the ventricular afterloading conditions that enable end ejection to coincide with end systole of the ventricle by a simulation method. The left ventricle was simulated by a time-varying elastance, E(t), and the afterload by a constant pressure connected to the ventricle via a valve with resistance R and inertance L in series. A sinusoidal wave starting from 0 at onset of systole, reaching Emax at end systole, and returning to 0 at end diastole in each cycle was assigned for E(t). Parameters of the system elements were changed individually. Ventricular pressure, volume and flow were computed by solving the system of ordinary differential equations with a time-varying parameter, E(t). Results indicate that end ejection coincides with end systole only when R and L values fall on a specific curve in an R-L domain for a given set of the other system parameters, and otherwise the 2 ends variably dissociate from each other. Consequently, end ejection should not blindly be used as a substitute for end systole when Emax and end-systolic pressure-volume relations are to be assessed.

Additional Indexing Words:
Heart Cardiodynamics Aortic pressure Incisura Aortic flow Dicrotic notch Diastole

As a consequence of our proposal of Emax, i.e., slope of the end-systolic pressure-volume relationship line, as an index of ventricular contractility,1,2 the concept has been applied to assessment of ventricular contractility in various experimental and clinical settings.3,4 A major problem unsolved in this application is how to determine end systole.5,6

End systole has long been practically identified by end ejection according to Wiggers' proposal,7 although some investigators noticed later that end ejection was often no guide to the end of ventricular active contraction.8 Fortunately, there has been no serious problem with the conventional method of

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identifying end systole until Emax is attempted to be assessed. A considerable error in Emax will be produced if ventricular pressure and volume at an erroneously determined end systole are used as end-systolic pressure and volume.

Animal experimental data in literature evidently indicate the examples in which end ejection markedly lagged behind the time at which Emax was observed. Therefore, we consider that end ejection should not tacitly be recognized as end systole of the ventricle in assessing Emax and end-systolic pressure-volume relation.

In the present theoretical study, we attempted to obtain a better insight into whether and how end ejection can coincide with and dissociate from end systole under various ventricular loading conditions. To this end, we used a simulation technique on a digital computer. Results indicate that end ejection can coincide with end systole when the system parameters take special relationships and otherwise dissociate from end systole to various extents.

**Methods**

In the first place, let us explain what we consider end of mechanical systole of the ventricle, since end systole has been identified by different events in cardiac cycle by different investigators. We have defined, based on the ventricular pressure-volume relationships, the end of mechanical systole of the ventricle as a whole as the moment at which some measure of ventricular contraction becomes maximal and relaxation is initiated. Our previous studies of canine left ventricular mechanics indicated that the pressure-volume loop trajectories of both isovolumic and ejecting contractions under a given inotropic background could be approximately enveloped by a linear line in the pressure-volume diagram as shown in Fig. 1. An instantaneous pressure-volume point starting from an end-diastolic point in a given contraction ascends to the enveloping line during contraction, reaches it when contraction is maximal and relaxation is initiated, and descends to the end-diastolic point during relaxation. Our end systole is the moment at which the pressure-volume loop of a contraction reaches or comes nearest to the enveloping line, which can be therefore called the end-systolic pressure-volume relationship line.

By this definition, end systole of an isovolumic contraction corresponds to the time for peak isovolumic pressure (Fig. 2A); end systole of an isobaric contraction to the time for minimal volume (Fig. 2B); end systole of an auxobaric beat to the time for maximal pressure and minimal volume (Fig. 2C); end systole of a normal ejecting contraction to the left upper corner of the pressure-volume loop (Fig. 2D). Even in this type of normal ejecting beat, end systole does not precisely coincide with end ejection, the latter lagging behind end systole by 0–24 msec according to our previous observation. Furthermore, in a markedly round pressure-volume loop trajectory, which was actually observed when the left ventricle was loaded with an artificial loading system, end ejection markedly lagged behind end systole and fell in the middle of relaxation as shown in Fig. 2E. All these end systoles correspond to
Fig. 1. Pressure-volume loop trajectories of several isovolumic and ejecting contractions under a given inotropic background in a canine left ventricle supported by cross circulation. The slant solid line envelops the isovolumic pressure-volume trajectories and the ejecting pressure-volume loop trajectories as well.

Fig. 2. Pressure (P) and volume (V) curves of ventricle as a function of time in cardiac cycle, and their pressure-volume loop trajectories in an entirely isovolumic (A), purely isobaric (B), auxobaric (C), normally ejecting (D), and unnaturally ejecting (E) contraction. The slant dashed lines in the pressure-volume diagrams are the end-systolic pressure-volume relationship lines. The solid circles correspond to end systole. The open circles to peak pressure. Symbol X indicates end ejection in (E). Note the dissociation of end ejection from end systole in (E).

the moment at which left ventricular pressure-volume ratio E(t) takes maximal value E_{max}.^{1,2)}

In the present simulation, the left ventricle was modeled as a time-varying elastance E(t) according to our previous studies.^{1,2)} For the sake of simplicity but
without losing the essence, the time-varying elastance \( E(t) \) was formulated as a sinusoidal wave: \( E(t) = 0.5 \times E_{\text{max}} \times [\sin(2\pi f t - 0.5\pi) + 1] \). This \( E(t) \) function starts from 0 at time \( t=0 \) (sec) = end diastole or onset of systole, reaches \( E_{\text{max}} \) (mmHg/ml) at time \( t=0.5/f \) (sec) = end systole, and returns to 0 at \( t=1/f \) (sec) = end diastole, repeating this cycle at a frequency of \( f \) (Hz). At onset of systole, the ventricle was assumed to be filled up to end-diastolic volume of \( V_{\text{ed}} \) (ml). Ventricular pressure \( P(t) \) can then be formulated as \( P(t) = E(t) \times V(t) \) by the definition of \( E(t) \),\(^{1}\) where \( V(t) = V_{\text{ed}} - \int_{0}^{t} I(t) \, dt \), and \( I(t) = -dV(t)/dt = \) ventricular output flow. A small ventricular systolic unstressed volume \( V_{d} \)\(^{1}\) was neglected without affecting results of simulation in terms of timing of end ejection.

The ventricle model was connected to an afterload via a valve having a forward resistance \( R \) (mmHg sec/ml) and an inertance \( L \) (mmHg sec\(^2\)/ml) in series, as shown in Fig. 3. The aortic valve was assumed to stop a reverse flow and remain closed in each cardiac cycle once it was closed at the onset of reversed flow. The afterload was assumed to be a constant pressure drain \( P_{a} \) (mmHg). This afterloading condition is equivalent to the situation in which the ventricle is connected to an infinitely-large-compliance chamber via a tubing with \( R \) and \( L \). Fig. 3 illustrates the simulation system by electrical symbols. Although this simulation is a very much simplified representation of the actual system, we consider that the fundamental hemodynamic characteristics of the ventricle-afterload interaction system are preserved for the present purpose.

The differential equations describing the system are: \( dI(t)/dt = L^{-1} \times [E(t) \times V(t) - P_{a} - R \times I(t)] \) and \( dV(t)/dt = -I(t) \) during ejection, and \( dV(t)/dt = 0 \) before ejection starts and after ejection ends. This set of ordinary differential equations was solved simultaneously using the Runge-Kutta method on a digital computer (Digital, Minc-11). The integration step was 5 msec. Computed \( P(t) \), \( V(t) \), and \( I(t) \) were printed on a printer and also displayed on an oscilloscope, from which hard copies were made. From \( I(t) \), end ejection was determined as the time when \( I(t) \) became zero or negative for the first time in cardiac cycle.

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**Fig. 3.** Electrical representation of the simulated system. \( E(t) = \) time-varying elastance of the left ventricle; \( P(t) = \) ventricular pressure; \( V(t) = \) ventricular volume; \( I(t) = \) ventricular output flow; \( P_{a} = \) constant afterload pressure; \( R = \) viscous resistance around the aortic valve; \( L = \) inertance of the blood column between the ventricle and the afterload.
Each parameter of the system elements was varied while the other parameters were kept unchanged, and the relationship between end ejection and end systole was analyzed.

**Results**

Fig. 4 indicates $E(t)$, $P(t)$, $V(t)$, and $I(t)$ curves in one cardiac cycle for $E_{\text{max}}=4 \text{ mmHg/ml}$, $f=2 \text{ Hz}$, $R=0.06 \text{ mmHg sec/ml}$, $L=0.001 \text{ mmHg sec}^2/\text{ml}$, $P_a=100 \text{ mmHg}$, and $V_{\text{ed}}=50 \text{ ml}$ ($1 \text{ mmHg}=1.33 \times 10^4 \text{ dyne/cm}^2$). End systole was $250 \text{ msec}$ from onset of systole. The resulting end ejection was $250 \text{ msec}$, being coincidental with end systole.

Fig. 5 indicates similar data for a decreased $R$ of $0.005 \text{ mmHg sec/ml}$ with all the other parameters unchanged from the previous case. End ejection preceded end systole by $40 \text{ msec}$.

Fig. 6 depicts a third set of similar data for an increased $R$ of $0.01 \text{ mmHg sec/ml}$ and increased $L$ of $0.01 \text{ mmHg sec}^2/\text{ml}$ with all the other parameters unchanged. End ejection lagged behind end systole by $75 \text{ msec}$.

Fig. 7 shows on an $R$-$L$ plain a curve that relates specific $R$ and $L$ values that enabled end ejection to coincide with end systole. This curve was ob-
tained by repeating many simulation runs similar to Figs. 4 through 6 with R and L varied and all the other parameters unchanged as specified in the legend of the figure. In the R-L region on the left side of the curve, end ejection
Fig. 7. R-L relation curve that makes end ejection coincide with end systole. This particular curve was obtained for $P_a=100$ mmHg, $V_{ed}=50$ ml, $E_{max}=4$ mmHg/ml, and $f=2$ Hz.

Fig. 8. Dependence of end ejection on afterload pressure $P_a$. $V_{ed}=50$ ml, $E_{max}=4$ mmHg/ml, $R=0.06$ mmHg sec/ml, $L=0.001$ mmHg sec$^2$/ml, End systole = 250 msec.

precedes end systole to various degrees. In contrast, end ejection lags behind end systole to a certain extent in the R-L region on the right side of the curve. The end systole-end ejection discrepancies ranged up to 100-150 msec for combinations of extremely large and/or small R and L.

The simulation also indicated that the particular R and L values that made end ejection coincide with end systole for a given set of the other system parameters did no longer make them coincide with each other for different sets of the system parameters. An example is shown in Fig. 8. A change in $P_a$ was accompanied by a marked shift of end ejection while all the other parameters were kept unchanged.

Thus, all the present results evidently indicated that end ejection coin-
cided with end systole of the ventricle only under limited circumstances and otherwise end ejection variably dissociated from ventricular end systole.

**DISCUSSION**

The results of the present simulation help us to generalize previous experimental observations that end ejection of the real ventricle did not always coincide with end systole. Although the degree of the dissociation of end ejection from end systole in the simulation may not quantitatively predict that of the actual ventricle in vivo because of the simplifying assumptions used, the present results probably suggest the existence of corresponding phenomena in vivo at least qualitatively.

From both previous experimental and present theoretical pieces of evidence supportive of dissociable ends of ejection and systole, we consider that end systole of the ventricle should not always be identified by end ejection. This contention is consistent with Remington's contention that the end of ejection is clearly no guide to the end of active muscle contraction. This Remington's statement was based on his own earlier experimental observation that, when an aortic occlusion was released during a beat, ejection could begin late and continue through almost the whole of the period of decreasing tension. He also mentioned, "while this terminology (i.e., systole) might be questioned, we are without the tools to describe ventricular performance in a way which would allow use of a more precise substitute." Since our previous experimental results indicated existence of end systole characteristic of both a given ventricle and its inotropic background but relatively independent of its pre- and afterloading conditions, we consider that end systole can now be defined more specifically than before, independent of end ejection which can shift as a result of the ventricle-afterload interaction. Although the end systole of the ventricle can now be defined explicitly as the time for $E_{\text{max}}$, its determination is not as easy as the determination of end ejection by the dicrotic notch of aortic pressure curve or by the onset of the second heart sound. Nevertheless, it is now clear that, at least for the assessment of $E_{\text{max}}$ and the end-systolic pressure-volume relationship, end ejection should not blindly be used as the substitute for end systole of the ventricle.

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