Timing and Velocity of Ejection as Major Determinants of End-Systolic Pressure in Isolated Rabbit Hearts

Abdellatif Ezzaher, PhD; Taib El Ouazzani, PhD; Bertrand Crozatier, MD, PhD

**Background** Systolic shortening is known to produce muscle deactivation. The present study was designed to analyze whether the velocity and the timing of ejection play a role on end-systolic pressure-volume relations (ESPVR).

**Methods and Results** In isolated rabbit hearts, left ventricular pressure and volume were recorded and digitized, and left ventricular volume was controlled by a servosystem (4-millisecond cycles) to alter the timing of ejection. A significant deficit in end-systolic pressure was observed when ejection was late in systole with respect to earlier ejection. This was associated with a significantly reduced end-systolic elastance. End-systolic pressure of beats with slow ejection was intermediate between that of the beats with early ejection and that of beats with late ejection with a significantly increased end-systolic volume compared with beats with early rapid ejection. The same results were obtained with hypertrophied hearts (abdominal aortic stenosis). Pressure-volume loop areas were significantly increased in beats with slow ejections and with rapid delayed ejections versus early rapid ejections. No change in the positive peak of dp/dt was observed when the timing and the velocity of ejection were modified.

**Conclusions** ESPVR is modified by the ejection profile, with a decreased end-systolic pressure and an increased pressure-volume loop area related to the velocity and the amount of shortening during the end-systolic phase. These indices of ventricular function thus must be used with caution when the timing of ejection is altered, and the end-diastolic volume-peak dp/dt relation may be a better index of ventricular function. (*Circulation. 1994;90:3055-3062.)*

**Key Words** • systole • pressure-volume relation • pressure • hypertrophy

A number of indices have been proposed for quantifying left ventricular function. The isovolumic and ejection indices of ventricular function were shown to be affected by changes in preload, afterload, and inotropic state. In the early 1970s, Suga et al. and Suga and Sagawa4 defined in isolated canine heart the instantaneous relation between systolic pressure and systolic volume. They showed that the end-systolic pressure-volume relation (ESPVR) was linear and provided a measure of chamber contractile state that was largely insensitive to steady-state loading conditions. ESPVR linearity enabled a simple description in terms of slope (Eₛ) and volume-axis intercept (Vₒ) and allowed the characterization of ventricular contraction by a time-varying elastance model.

The ESPVR was used extensively to quantify ventricular performance of the in situ heart both in experimental studies5-9 as well as in humans. As techniques of ESPVR determination and conditions of experimental preparations have improved, the load-independent feature of ESPVR has been questioned. In a reexamination of ESPVR, Burkhoff et al. showed a contractility-dependent curvilinearity of the relation in isovolumically contracting isolated canine ventricles. An effect of stroke volume and velocity of ejection on end-systolic pressure (ESP) has been demonstrated in isolated canine left ventricles.17 Later, an effect of preload changes18,19 and arterial impedance changes on ESPVR has been also shown in isolated20 and in situ hearts.15

ESP was shown to depend on the velocity of ejection, and studies showed that abrupt changes in left ventricular volume produced a deficit in pressure generation suggesting that the timing of ejection may modify ESP. The purpose of our study was thus to analyze in detail ESPVR and pressure-volume loop areas during altered timing and velocity of ejection.

**Methods**

Twenty-four adult New Zealand White rabbits weighing 2.0 to 4.4 kg (mean, 3.2 kg) were used for the study. Hearts were studied under Langendorff apparatus with a servocontrol of left ventricular volume.

**Servocontrol System of Left Ventricular Volume**

This system was divided into an electromechanical part and a computer system (Fig 1).

**Electromechanical Part**

The electromechanical part was similar to that described by Sagawa et al.23 It was represented by a linear motor (GW 20, Gearing and Watson; maximal acceleration, 60 g; maximal velocity, 1.52 m/s; force, 100 N; maximal displacement, 10 mm) and a Foucault current displacement transducer (FGP Instrumentation; course, 7.5 mm; precision, 1 μm; maximal displacement, 7.62 mm; frequency response, DC-10 kHz). This part was connected to a Plexiglas cylinder positioned vertically in front of the axis of the linear motor and connected to an intraventricular balloon. The pump and the balloon were both filled with Vaseline oil. This liquid was selected because its viscous properties allow an adequate displacement of the
pump that was demonstrated by preliminary tests. Because of the liquid continuity, the displacements generated by the linear motor were transmitted to the cylinder and then to the balloon inserted into the left ventricle. In turn, these movements were controlled by the displacement transducer, which indicated the position of the axis of the cylinder and thus reflected the corresponding volumic variations. A microprocessor instantly controlled ventricular volume values by sending signals to a power amplifier (SS 100, Gearing and Watson; maximal power, 100 W RMS [watt root mean square]; frequency range, DC-10 KHz; maximal output voltage, 10 V; maximal current, 11 A; input voltage, 0 to 1 V; maximal distortion, 0.75%; maximal, noise-signal ratio, 70 dB). Signals were amplified and transmitted to the linear motor.

**Computer System**

The computer system allowed the execution of volumic cardiac cycles of isolated rabbit hearts. It received pressure and volume information from the heart to analyze the response of the heart during different cardiac cycles. The computer program was divided into three parts running on an IBM-PC 386 with arithmetic microprocessor (33 MHz, 32 bits) and a DT 2801 Data Translation card.

The first part (in Turbo C language) consisted of acquisition of data to generate waves and to control parametric values (heart rate, volume, pressure). The second part of the program (in assembly language INTEL) triggered the servo-control volumes and digitized ventricular pressure obtained by the pressure transducer and the volume signals obtained by the displacement transducer. Data were stored on hard disk in the third part of the procedure for subsequent digital and graphic analysis.

**Volume Waveform Generation**

Chosen end-diastolic and end-ejection volumes were given in the first part of the procedure along with the values of the stimulation rate and time parameters.

Volume control during a cardiac cycle was similar to that described by Sunagawa et al. The cardiac cycle was defined by five different phases: isovolumic contraction (from T0, electrical stimulus to T1, onset of ejection), ventricular shortening (from T1 to T2 by pulling the cylinder from the balloon according to a previously given parabolic formula with steps of 4-millisecond intervals until the end-ejection point was obtained), isovolumic relaxation (T2-T3), ventricular filling (T3-T4, according to a parabolic formula filling the ventricular balloon to end-diastolic value by pushing the cylinder), and diastolic phase (T4-T0), during which ventricular volume did not vary. Servocontrol of volume was obtained by a numerical approach, taking into account the calculated command value and the difference between previous theoretical and measured values.

Digital data of the calculated command were converted into analog data to be detected by the motor-cylinder system. Its displacements allowed the heart to execute the cardiac cycle as defined in the first part of the program.

Because each experiment was performed with a new balloon that caused new experimental conditions, the first phase of the study consisted of the determination of the resolution of volume measurement. For this purpose, the computer simulated a volumic cardiac cycle. The volumic error was obtained from the difference between theoretical and experimental curves obtained with the balloon alone. Stability parameters were modified to obtain the best adjustment that allowed a maximal error between 10 and 15 μL, which was fixed during all the experiments.

**Experimental Protocol**

Hearts were rapidly removed from the thoraces after the rabbits were killed. Each heart was immediately suspended by a cannula inserted into the aorta and was perfused with a modified Krebs-Henseleit solution of (in mmol/L) 118 NaCl, 4.7 KCl, 25 NaHCO3, 2.5 CaCl2, 1.2 KH2PO4, and 11 glucose and bubble-oxygenated with 95% O2-5% CO2 (pH 7.4; Po2, 600 mm Hg). Perfusion pressure was maintained at 70 mm Hg throughout the experiment. It was shown in preliminary experiments that the preparation was stable for at least 1 hour.

After a 10-minute recovery period under Langendorff apparatus, a compliant fluid-filled latex balloon connected to a catheter was inserted through the left atrial appendage into the left ventricular cavity along with a 6F Millar catheter for high-fidelity pressure measurement. The pressure in the balloon alone represented the reference pressure (0 mm Hg). The apex of the left ventricle was perforated, allowing the adjustment of the balloon into the left ventricular cavity and a venting of venous return from the Thebesian veins.

The basal frequency of isolated hearts was too high to allow sufficiently long periods of servocontrol. We thus removed the right atrium and crushed the atrioventricular node to perform ventricular pacing at a rate of 100 beats per minute (600-millisecond cycles). Experiments were performed after stabilization of the preparation for about 15 minutes. Total duration of each run was 10 seconds.

In a first protocol, we used 5 isolated hearts in which end-diastolic and end-ejection volumes were fixed at 1.4 mL and 1.2 mL, respectively, with a fixed velocity of ejection (Fig 2). The onsets of ejection were varied from 60 to 160 milliseconds by steps of 20 milliseconds, and the corresponding end ejections were varied from 150 to 230 milliseconds. This allowed us to obtain five different contractions (Fig 2). This
run was undertaken to study the effect of changes in the
timings of ejection on the end-systolic pressure-volume points.

A second protocol in 13 isolated hearts consisted of the
comparison between three contractions: (1) an early ejection,
(2) a late ejection with the same velocity of shortening as in the
first protocol, and (3) a contraction with a slow ejection.

The beat with a small velocity of ejection had the same onset
of ejection as the beat with early ejection and the same end
ejection as the beat with delayed ejection. This run was
undertaken to study the effect of changes in the velocity of
ejection on the end-systolic pressure-volume points. End-dia-
stolic volume and end-ejection volume were fixed at 1.4 mL
and 1.2 mL, respectively. In 5 of these 13 hearts, end-diastolic
volume was progressively increased to 2 mL by 0.05-mL incremen-
ts, with corresponding increases in end-ejection vol-
ume to maintain stroke volume constant. This was performed
to obtain the whole ESPVR to measure end-systolic elastance
and volume-axis intercept.

A third protocol was designed to analyze whether the results
obtained in normal hearts were reproduced in hypertrophied
hearts. For this purpose, an abdominal aortic stenosis was
performed in 6 rabbits. Rabbits were first anesthetized with
etomidate (2 mg/kg, Janssen). The abdominal aorta was
surgically ligated just below the diaphragm. A ligature
was tightened around both the aorta and an adjacent piece of
polyethylene catheter (Biotrol, outer diameter, 2.42 mm),
which was immediately withdrawn. The obtained aortic steno-
sis was ~50%. Animals were killed 2 weeks after this inter-
dention. Ventricular performance was studied under Langen-
dorff apparatus by the comparison of three different
contractions as in the second protocol (early, late, and slow
systolic shortenings).

Data Analysis

To obtain a high stability of the run during each step of the
experiments, only the 15th beat that preceded the last beat of
the run was analyzed. Digital and analog analytic of this beat
was performed by four parameters: volume, pressure, pressure-vol-
ume ratio as a function of time, and positive peak dp/dt. The
peak pressure-volume ratio indicated end systole. The
values of these parameters were digitized every 4 milliseconds.
The time duration of ejection was measured by subtracting the time
of the onset of contraction (time at which ventricular volume
began to decrease) from the time of end ejection (time at
which ventricular volume reached its minimum).

ESPVR was analyzed by linear regression of ESP versus
end-systolic volume (ESV), which was pressure and volume at
end systole.25 E was the slope and V, the axis intercept of this
relation. The same pressure and volume signals were visual-
ized on an oscilloscope in terms of pressure-volume loop
trajectory. The area pressure-volume loops were analyzed by
planimetry.

The mean±SEM was calculated for each parameter in each
group (first, second, and third protocols). Comparisons with
parameters of the beats with early ejection and that of beats
with different timings or velocities of ejections were made by a
one-way ANOVA. In the first protocol consisting of 5 hearts
with five different ejection timings, data were analyzed using a
randomized complete block analysis. When an overall statisti-
cal significance was found by the F test, paired t tests were
used to compare two different contractions using the Bonfer-
roni correction for multiple means. Differences were consid-
ered statistically significant at P<.05.

Results

When left ventricular pressure was expressed as a
function of left ventricular volume (Fig 3), differences in
the shape of the pressure-volume loops were observed.
Pressure progressively increased during systole in the
beat with early rapid ejection. In contrast, pressure
decreased during systole in the beat with late rapid
ejection. This decrease was larger when ejection was
more delayed. The pressure-volume trajectory did not
converge toward a single pressure-volume end-systolic
point.

ANOVA showed a significant difference between
beats for each measured parameter but not between
hearts. These results were reproduced in 5 hearts
(Table 1). There was a substantial deficit in ESP when
ejection was late in systole (101.8±12.1 mm Hg) with
respect to earlier ejection (125.7±13.1 mm Hg, P<.02).
In contrast, ESV was not affected by changes in the
timing of ejection. During changes in the timing of
ejection, the positive peak dp/dt remained unchanged.
Measurements of pressure-volume loop areas showed a
nonsignificant trend toward an increase when ejection
was delayed (Table 1). The timing of ejection also
affected the time at which ESP was reached (t,). When
ejections occurred later during systole, t rose. The
The maximal value was observed in the beat with the most delayed ejection (212.8±7.1 versus 157.6±6.3 milliseconds in the beat with the earliest ejection, *P<.005). End ejection occurred long before end systole (124.8±2.0 and 157.6±6.3 milliseconds, respectively, *P<.002) when ejections were early in systole. In contrast, end systole and end ejection were not different when ejections were late in systole (Table 1).

To determine whether the velocity of shortening during the end-systolic phase was responsible for the depression of ESP, we compared beats with early rapid ejection, slow ejection, and delayed rapid ejection. Table 2 shows hemodynamic parameters obtained in these three different conditions. Since the duration of ejection was similar in early and delayed rapid ejections for the same stroke volume (0.2 mL), mean velocity of ejection was similar in these two types of beats (3 μL/ms) and significantly larger than in the slow ejecting beat (1.9 μL/ms), which had the same stroke volume but a larger ejection duration (Table 2). Fig 4 illustrates left ventriculat pressure and volume data of these three ejecting beats obtained in an isolated rabbit heart preparation. Three steady-state ejecting beats are superimposed. The shape of left ventricular pressure changed with the altered timing and velocity of ejection. Late in systole, the decline of pressure of the beat with slow ejection was intermediate between that of the beat with early rapid and delayed rapid ejection. When left ventricular pressure was expressed as a function of left ventricular volume (Fig 5), the altered timing of ejection (shown in this protocol by early rapid and delayed rapid ejection) always produced the same influence in the shape of pressure during systole as in the first series of experiments. Pressure during this phase was increased in the beat with slow ejection as compared with the beat with late rapid ejection, but it was smaller than pressure in the beat with rapid early ejection. The pressure-volume trajectory during systole also did not converge toward a single end-systolic pressure-volume point.

The means of 13 experiments are shown in Fig 6. There was a significantly decreased ESP in the beat with a delayed ejection (87.0±4.6 mm Hg) as compared with the beat with earlier ejection (96.0±4.2 mm Hg). In contrast, the beat with slow ejection showed an ESP of 89.5±4.9 mm Hg, which was intermediate between that of the beat with early ejection and the beat with late ejection, but the differences were not statistically significant. However, ESP was significantly increased in beats with slow ejections as compared with beats with early rapid ejection. In contrast, ESP was not different between beats with slow and rapid delayed ejections. This shows that although the velocity of ejection was slower in the intermediate beat than in the beat with early ejection, an ESP deficit with an increased ESP was observed in the beat with a slower ejection, indicating that ESP deficit is due to ventricular ejection during the end-systolic phase. Furthermore, this pressure deficit was larger in the beat with delayed rapid ejection in end systole, showing that velocity of shortening in this phase is the factor that produces the ESP decrease.

We observed no change in positive peak dP/dt in the three types of beats (Table 2). Measurements of the pressure-volume loop areas (Fig 6) showed a significant increase in beats with slow ejections and with rapid delayed ejections compared with early rapid ejections. The timing of ejection always affected the time at which ESP was reached. End ejection was reached before end systole with early rapid ejection. End systole was delayed in late rapid ejection, and the difference between end systole and end ejection was only 14 milliseconds in delayed rapid ejections (Table 2).

The whole ESPVR for different timings and velocities of ejection was analyzed in 5 hearts. The x-axis intercept (Vt) tended to be decreased when ejection was delayed.

### Table 1. Hemodynamic Parameters in Response to Altered Timing of Rapid Ejections (n=5)

<table>
<thead>
<tr>
<th>Ejection</th>
<th>ESV, mL</th>
<th>ESP, mm Hg</th>
<th>PP, mm Hg</th>
<th>dP/dt, mm Hg/s</th>
<th>Area, mm Hg×mL</th>
<th>tE, ms</th>
<th>tS, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>1.175±3.3</td>
<td>125.7±13.1</td>
<td>127.6±13.3</td>
<td>1700±139.3</td>
<td>12.8±0.9</td>
<td>124.8±2.0</td>
<td>157.6±6.3</td>
</tr>
<tr>
<td>Intermediate 1</td>
<td>1.178±3.3</td>
<td>119.8±11.9</td>
<td>125.6±13.3</td>
<td>1698±119.5</td>
<td>15.7±1.2</td>
<td>142.4±1.6†</td>
<td>168±1.3</td>
</tr>
<tr>
<td>Intermediate 2</td>
<td>1.186±4.3</td>
<td>115.4±12.7</td>
<td>130.8±13.8</td>
<td>1751±127.6</td>
<td>16.5±1.0</td>
<td>167.2±2.3†</td>
<td>180±4.2</td>
</tr>
<tr>
<td>Intermediate 3</td>
<td>1.190±6.3</td>
<td>109.5±10.5</td>
<td>136.4±13.5</td>
<td>1774±126.2</td>
<td>16.2±1.0</td>
<td>193.6±3.7†</td>
<td>203±7.4*</td>
</tr>
<tr>
<td>Delayed</td>
<td>1.203±1.0</td>
<td>101.8±12.1*</td>
<td>136.3±13.9</td>
<td>1751±112.5</td>
<td>15.9±1.3</td>
<td>212.6±2.3†</td>
<td>212.8±7.11</td>
</tr>
</tbody>
</table>

ESV indicates end-systolic volume; ESP, end-systolic pressure; PP, peak pressure; dP/dt, peak of the time derivative of left ventricular pressure; Area, pressure-volume area; tE, time of end ejection; and tS, time at which ESP is reached.

Values are mean±SEM. Comparisons with early ejection: *P<.02, †P<.005.

### Table 2. Hemodynamic Parameters in Response to Altered Timing and Velocity of Ejection (n=13)

<table>
<thead>
<tr>
<th>Ejection</th>
<th>EDP, mm Hg</th>
<th>EDV, mL</th>
<th>PP, mm Hg</th>
<th>dP/dt, mm Hg/s</th>
<th>tE, ms</th>
<th>ed, ms</th>
<th>tS, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early rapid</td>
<td>14.1±3.1</td>
<td>1.429±0.008</td>
<td>99.8±4.2</td>
<td>1196.95</td>
<td>117±8.5</td>
<td>64.8±2.4</td>
<td>185±8.3</td>
</tr>
<tr>
<td>Slow</td>
<td>15.7±3.5</td>
<td>1.432±0.008</td>
<td>103.5±4.3</td>
<td>1289.79</td>
<td>172.9±8.8*</td>
<td>108.4±4.0*</td>
<td>199±3.7</td>
</tr>
<tr>
<td>Delayed rapid</td>
<td>15.1±4.0</td>
<td>1.429±0.008</td>
<td>115.4±4.8*</td>
<td>1258±82</td>
<td>210.5±6.4*</td>
<td>67.2±2.0</td>
<td>224±8.2*</td>
</tr>
</tbody>
</table>

EDP indicates end-diastolic pressure; EDV, end-diastolic volume; PP, peak pressure; dP/dt, peak of the time derivative of left ventricular pressure; tE, time of end ejection; ed, ejection duration; and tS, time at which end-systolic pressure is reached after end diastole.

Values are mean±SEM. Comparisons between slow ejections and delayed rapid ejections with early rapid ejections: *P<.001.
or slower, but the changes were not statistically significant. In contrast, $E_{es}$ was significantly decreased when ejection was late during systole as compared with early ejection ($37 \pm 7.1$ mm Hg/mL versus $87.9 \pm 8.8$ mm Hg/mL, $P < .03$, Fig 7).

Results obtained with hypertrophied hearts were similar to those found with normal hearts (Table 3). Aortic stenosis induced a significant left ventricular hypertrophy as judged by the left ventricular to body weight ratio (1.66±0.01 g/kg in control hearts and 2.25±0.14 g/kg in hypertrophied hearts, $P < .001$). Late ejection induced a significant decrease in ESP (18 mm Hg) as compared with early ejection and, compared with slow ejection, ESP was not significantly different from that measured during early ejection, although ESV was significantly increased. Similarly, with normal hearts, pressure-volume area was significantly increased in slow ejections as compared with early ejections and more in late ejections.

**Discussion**

Taken together, our results show that both the velocity and the timing of ejection play a role in ESPVR since beats with slow ejections and late rapid ejections have a lower ESP than beats with early rapid ejections in both normal and hypertrophied hearts. Factors that produce...
a decrease in ESP appear to be the velocity and/or the amount of shortening during the end-systolic phase. In contrast with ESP behavior, the pressure-volume area is larger when ejection takes place in the late systolic phase.

**Effects of Ejection Timing on the Dissociation Between End Ejection and End Systole**

The analysis of ESPVR requires a clear definition of the end of systole. In this study, end systole was the time corresponding to the peak of the pressure-volume ratio. 25 End systole may be different from end ejection. In vivo, ejection ends at a time close to that when the ventricle starts to relax. 3 Thus, end ejection almost coincides with end systole. Therefore, end systole can be identified as the left upper corner of the pressure-volume loop trajectory. However, in certain conditions, end ejection does not necessarily coincide with end systole, 4 and ejection continues well beyond the expected end-systolic point. In our study, we found that the time points of end systole and end ejection depended on the timing of ejection. Both the end-systolic time and the end ejection time increased when ejections occurred late in systole. We noted that end ejection occurred long before end systole when ejections were early in systole, and this difference disappeared when ejection was late in systole (Table 1). The absence of time difference between end systole and end ejection was always accompanied with a depression of ESP.

Many studies found that the time at which end systole was reached increased from isovolumic to ejecting beat. 3,25,26 This parameter was considered by Hunter 25 as a measure indicating the positive influence that ejection exerted on pressure development. Our study showed an increase of t 0 in ejecting beats with delayed ejection as compared with the beats with early ejection, which were associated with a depression of ESP. This opposite result can be due to the utilization of different reference beats because Hunter 25 compared ejecting beats with isovolumic beats only.

**Effects of Altered End Ejection Timing on ESPVR**

We attribute the decreased ESP in rapidly ejecting beats during the late systolic phase to an inactivation caused by systolic shortening because E m was significantly decreased in these beats (Fig 7). The effect of the velocity of ejection on ESPVR was shown in the early studies by Suga and Yamakoshi. 17 Among possible mechanisms, Suga and Yamakoshi 17 quoted an uncoupling effect of shortening, viscoelastic properties, some viscous resistance against deformation among myocardial fibers, or inadequate oxygen supply during larger contractions. None of these hypotheses can be excluded. In contrast with the effect of velocity of ejection on ESPVR, the effect of the timing of ejection was not recognized in early experiments. Suga et al 17,27 showed that the shift of the onset of ejection had little effect on ESP. In their first article, Suga and Yamakoshi, 17 by examining ejecting beats with different timings of ejection, showed that the shift of the onset of ejection had little effect on ESP only when the onset was very early or very late during systole. However, if instead of the isovolumic beat early ejecting beats were taken as the reference, no difference between ESPs was observed between ejecting beats. This was confirmed in another study. 27 The difference with our results, which show a progressive fall in ESP when the onset of ejection is delayed, cannot be attributed to a difference in models because methods used in these studies and in ours are similar. However, in the studies by Suga et al, 17,27 the onset but not the end of ejection was modified.

An effect of the timing of ejection on ESPVR is in agreement with other studies and can be explained by systolic properties of the left ventricle such as elasticity, resistance, and deactivation. Hunter et al, 21 using flow-pulse techniques, showed that deactivation was larger in end systole with a larger resistive component when flow was applied late during systole. Similar results have been shown by Shroff et al. 22 They reported the effects of different timings of flow (early and late in systole) on pressure generation. They showed that ventricular pressure decreased with flow and that this decrease was larger in late systole. Studies by Hunter et al 21 and Shroff et al 22 did not analyze the ESPVR, but their results are in agreement with ours since both studies showed an increased resistive component associated with a deactivation induced by late pulses or flow that could produce the decreased ESP observed in our study.

The effects of an altered timing of ejection on ESP also could be mediated through changes in the systolic left ventricular pressure waveform, since pressure was increasing during a large part of systole and reached its peak close to the middle of systole when ejection occurred late during systole (Fig 4). This mid systolic zone may represent the transition zone proposed by Brutsaert et al, 28 in which contraction load is converted into relaxation load. This zone may have a major

**Table 3. Hemodynamic Parameters in Response to Altered Timing and Velocity of Ejection in Hypertrophied Hearts (n=6)**

<table>
<thead>
<tr>
<th>Ejection</th>
<th>EDP, mm Hg</th>
<th>EDV, mL</th>
<th>ESV, mL</th>
<th>ESP, mm Hg</th>
<th>PP, mm Hg</th>
<th>dP/dt, mm Hg/s</th>
<th>Area, mm Hg×mL</th>
<th>t 0, ms</th>
<th>ed, ms</th>
<th>t 0, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early rapid</td>
<td>16.8±2.3</td>
<td>1.422±0.02</td>
<td>1.156±0.002</td>
<td>114.2±10</td>
<td>116.8±10.5</td>
<td>1187±174</td>
<td>12.5±2.6</td>
<td>90±10.7</td>
<td>68±0.0</td>
<td>184.7±12</td>
</tr>
<tr>
<td>Slow</td>
<td>17.5±3.8</td>
<td>1.439±0.002</td>
<td>1.163±0.003*</td>
<td>108.5±10.8</td>
<td>113.8±10.8</td>
<td>1364±183</td>
<td>21.0±3.1†</td>
<td>142.7±8.7†</td>
<td>108±2.3†</td>
<td>215.3±8.2†</td>
</tr>
<tr>
<td>Delayed rapid</td>
<td>16.5±2.7</td>
<td>1.435±0.0008</td>
<td>1.176±0.005*</td>
<td>95.8±21.2†</td>
<td>126.7±11.9</td>
<td>1351±160</td>
<td>27.1±2.2†</td>
<td>202±8.4‡</td>
<td>68±1.8</td>
<td>226±7.1*</td>
</tr>
</tbody>
</table>

EDP indicates end-diastolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume; ESP, end-systolic pressure; PP, peak pressure; dP/dt, peak of the time derivative of left ventricular pressure; Area, pressure-volume area; t 0, time of end ejection; ed, ejection duration; and t 0, time at which ESP is reached.

Values are mean±SEM. Comparisons between slow ejections and delayed rapid ejections with early rapid ejections: *P<.05, †P<.01, ‡P<.001.
importance in the control of mechanical performance of the left ventricle during subsequent relaxation. The depressed ESP observed in our study when ejections occurred late during systole could be explained by the predominance of factors related to relaxation load, thus inducing a premature relaxation (Fig 4). The effect of the timing of ejection on relaxation was also demonstrated by Hori et al., who showed in isolated canine heart and in intact canine heart that ejection timing rather than peak left ventricular pressure may primarily regulate ventricular relaxation rate. Similar results were found by Gillebert and Lew.

Another mechanism that could explain the decreased ESP in beats with rapid late ejections is the effect of changes in the ventriculoarterial coupling, since ESP was shown to be directly proportional to arterial elastance. However, this mechanism probably can be excluded because arterial elastance was also shown to be closely approximated to the ratio between total peripheral resistance and cycle length. Both parameters were not modified by changes in the ejection timing because peripheral resistance was fixed by the experimental apparatus and heart rate was maintained constant during the whole experiment.

Effects of Ejection Timing on Pressure-Volume Area

Both the velocity of ejection and the time at which shortening takes place influence ESPVR (Fig 6). The velocity of ejection in the late systolic phase appears to be the major determinant of ESP decrease. However, an opposite phenomenon must be considered: that is, the increased ESP produced by ejection so that ESP is a balance between opposing effects of ejection. When ejection is late during systole, ventricular dimensions remain at end-diastolic values during early systole, inducing an increased peak systolic pressure and longer sarcomere lengths than those obtained with early ejections. The resulting length-dependent activation probably increases ventricular function. Conversely, late systolic shortening induces a loss in ESP through deactivation and an increased resistive element. These balanced effects can induce an increase in the pressure-volume area when the early events predominate, such as what is observed in Fig 6, but may be compensated by the late systolic events, inducing a nonsignificant increase in pressure-volume area as it was in the first series of experiments in which a delay of ejection did not produce a statistically significant increase of the pressure-volume area (Table 1).

An increase in the pressure-volume area also has been obtained without altering the timing of ejection by withdrawal of a ventricular volume performed with a volume servopump connected to an isolated canine heart. The onset of the withdrawal was always set at end systole in isovolumic contraction, that is, at peak isovolumic pressure. Suga showed that an optimal speed of withdrawal during the decrease in left ventricular pressure produced an increase in the pressure-volume area by conversion of potential energy into external mechanical work. Our study is in agreement with these results because our most delayed rapid ejection occurred at the beginning of left ventricular pressure load decrease. However, the increase in pressure-volume area was observed not only in beats with rapid late ejection but also in beats with slow ejection as compared with the beat with early ejection.

Conclusions

ESPVR appears to be markedly modified by ejection. The late systolic shortening produced in our study probably is not observed in physiological conditions, but it may exist in pathological situations such as aortic stenosis or hypertrophic cardiomyopathy. In these cases, the utilization of ESPVR for the evaluation of cardiac function may lead to errors when the ejection pattern is modified by mechanical or pharmacological interventions. The same conclusion applies to the derived analysis proposed by Glower et al., that is, the stroke work–end-diastolic volume (EDV) relation. In contrast, our study shows that peak positive dP/dt was not altered by changes in the timing and velocity of ejection. This could be expected because it is measured in the isovolumic phase, although an effect of the mode of ejection of the previous beats could have been detected. The dP/dt max–EDV relation, which has been proposed by Little as an index of contractile function based on the same principles as those of the elastance model, thus appears as insensitive to the timing and velocity of ejection and is probably a better way for evaluating ventricular function when the ejection pattern is modified.

Acknowledgments

Dr Ezaher is the recipient of a fellowship grant of the Fondation pour la Recherche Médicale. We acknowledge P. Roche and J.L. Lechien (CEA, Orsay, France), who designed and built the servocontrol system.

References


Timing and velocity of ejection as major determinants of end-systolic pressure in isolated rabbit hearts.

A Ezzaher, T el Ouazzani and B Crozatier

_Circulation_. 1994;90:3055-3062
doi: 10.1161/01.CIR.90.6.3055

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/6/3055

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ 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_ is online at:
http://circ.ahajournals.org//subscriptions/