Effect of heart rate on the canine end-systolic pressure-volume relationship

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ABSTRACT Although the rate dependence of isolated muscle contractility is well known, the ventricular end-systolic pressure-volume relationship (ESPVR) has been reported to be insensitive to heart rate. To resolve this contradiction, we used an isolated, ejecting canine heart preparation perfused at a constant coronary arterial pressure. Heart rate was changed from 60 to 200 beats/min in steps of 20 beats/min. At least 10 pressure-volume loops under different filling pressures were obtained at each heart rate in each of six hearts. Over a heart rate range from 60 to 120 beats/min, the slope of the ESPVR (ESPVR) increased significantly from 3.5 ± 0.4 (SE) to 5.3 ± 0.6 mm Hg/ml. In the range between 120 and 180 beats/min there was little change in ESPVR (5.3 ± 0.6 to 5.4 ± 0.6 mm Hg/ml), but at 200 beats/min ESPVR increased slightly to 5.7 ± 0.5 mm Hg/ml. The volume axis intercept (V₀) of the ESPVR changed little over the range of heart rate from 60 to 160 beats/min (10.2 ± 2 ml to 9.4 ± 1.3 ml) but increased to 15.2 ± 1.2 ml at a rate of 200 beats/min. The change in ESPVR with increase in heart rate from 60 to 120 beats/min (i.e., increase in ESPVR without change in V₀) is the same as those seen with a positive inotropic intervention with calcium or catecholamines, whereas the V₀ changes over the range from 160 to 200 beats/min is similar to those seen with regional ischemia. The insensitivity of ESPVR in the midrange may be the result of a balance of positive and negative influences on ventricular contraction or a restricted range for the increase in inotropic state with higher rate.


Physiologists have long been aware that frequency of contraction influences the contractile state of myocardium. The earliest description of this phenomenon has been credited to Bowditch; many investigators have since shown that in isolated muscle preparations and in isovolumically contracting hearts, peak systolic tension or pressure is increased as the frequency of contraction increases.

However, several investigators have questioned the importance of the frequency effect on contractility in vivo. For example, Kavalier et al. showed that the effect was far less marked or absent in unexercised canine papillary muscles beating in situ. Suga et al. showed that changing heart rate over the midrange caused very little change in the end-systolic pressure-volume relationship (ESPVR).

The purpose of this investigation was to reinvesti-
Coronary perfusion is maintained constant with blood from an oxygenator or second support animal. The left ventricle contains a balloon. Ejection and filling of the left ventricle is controlled by a servomotor with a computer-generated volume-command signal.

left ventricles. The left atrium was opened and the chordae tendineae were severed. A metal ring was sutured to the mitral anulus. A water-filled latex balloon connected to a servocontrolled piston pump was placed within the left ventricle through the metal ring. When the surgical preparation was complete, suction was applied through the left ventricular vent so that the balloon and the left ventricle had very nearly the same volume.

The intrinsic heart rate of the isolated heart tended to be between 100 and 120 beats/min. To obtain lower heart rates it was usually necessary to block the atrioventricular (AV) conduction by damaging the AV node with a suture and to pace the heart from the ventricle at the desired low rates.

**Servopump hardware.** The right side of figure 1 shows a schematic representation of the ventricular volume control pump system. Details of its design and performance have been previously reported. Briefly, a linear motor (Ling Electronics, Model 411) controlled the piston position of a rolling-diaphragm cylinder (Bellofram SS-4-F-SM). The latex balloon was secured to a tube connected to the outflow tract of the Bellofram cylinder. The cylinder, connecting tube, and the balloon were all filled with water. A linear displacement transducer (Trans-Tek model 244-000) sensed the position of the piston, producing a signal proportional to the balloon volume. The signal was used in a negative feedback loop for comparison with a volume-command signal from a computer (see below), which represented the desired instantaneous left ventricular volume. The error signal resulting from this comparison was supplied to a power amplifier (Crown DC-300), which in turn drove the linear motor to minimize the difference between the desired and actual left ventricular volume.

**Impedance loading system.** The ventricular volume-command signal for the volume control servosystem is generated by the interaction between left ventricular pressure signal and a specially designed hybrid computer. The left ventricular pressure, measured by a Konigsburg pressure transducer (P-21) placed inside the balloon, served as the input to an analog computer programmed to solve differential equations that describe both the ventricular preloading and afterloading circuit. The characteristics of this system have been previously described. It allows the ventricle to fill from a fixed pressure source through a preloading system and eject into an afterloading system with precisely controlled afterload resistance, compliance, and characteristic impedance.

Coronary perfusion pressure and left ventricular volume and pressure were recorded simultaneously on a strip chart. Pressure-volume loops were recorded on a storage oscilloscope (Techtronix, Model 5111) and photographed.

**Protocol.** Left ventricular diastolic pressure was set to produce a peak systolic pressure between 100 and 120 mm Hg at a control coronary perfusion pressure of 80 mm Hg against a control set of arterial impedance parameters (resistance = 3.0 mm Hg-sec/ml, compliance = 0.4 ml/mm Hg, characteristic impedance = 0.2 mm Hg-sec/ml) and at a heart rate of 120 beats/min. The filling pressure, controlled by the computer, was then lowered over 10 sec until the peak systolic pressure became less than 20 mm Hg. The filling pressure was then returned to its initial value.

This was repeated for heart rates of 60, 80, 100, 120, 140, 160, 180, and 200 beats/min. At each heart rate we waited until steady state was reached before recording data. The sequence of the heart rates was varied from heart to heart, and the initial condition was recreated at the end of the sequence to determine whether the contractile state of the preparation changed during the experiment. When a clear change was recognized, the data from the heart was discarded.

**Data analysis.** The Polaroid pictures of the oscilloscope tracing of pressure-volume loops were used to measure the slope and volume axis parameters of the ESPVR. The ESPVR was traced, the tracing calibrated, and the slope and intercept determined from the tracing. The (dP/dt) max was determined by numerical differentiation of the digitized pressure recording (LSI 11/34 16 bit minicomputer). The (dP/dt) max for corresponding volumes at each heart rate was determined by interpolation with a linear least-squares regression of (dP/dt) max on end-diastolic volume.

**Statistical analysis.** For each heart, linear regression was applied to the slope vs heart rate relationship and the intercept vs heart rate relationship of the ESPVR over the heart rate ranges from 60 to 120, 120 to 160, 160 to 200 beats/min. An analysis of variance was applied to compare the slopes of the linear regression over these three ranges. Significance was defined at the p < .01 level.

An analysis of variance and covariance with repeated measures (BMDP statistical package) was used for comparison of (dP/dt) max.

**Results**

Figure 2 shows an example of the data from a single heart. The eight panels in the top and middle rows present pressure-volume tracings recorded on the oscilloscope for heart rates from 60 to 200 beats/min. The bottom three panels show the superimposed ESPVR lines for the three heart rate ranges of 60 to 120, 120 to 160, and 160 to 200 beats/min. Notice that in the range from 60 to 120 beats/min there is a progressive increase in the slope of the ESPVR (E') with increase in heart rate but little change in the volume.
axis intercept ($V_0$). In the heart rate range from 120 to 180 beats/min there is little change in either the slope or the intercept of the ESPVR line. Over the heart rate range above 180 beats/min there is a progressive, almost parallel rightward shift of the ESPVR.

Figure 3 shows the pooled data from six hearts. The top panel shows the slope of the ESPVR ($E_{es}$) and the bottom panel shows its volume axis intercept ($V_0$) over the entire heart rate range. The small bars are standard error of the mean. Over the range from 60 to 120 beats/min $E_{es}$ increased significantly with heart rate ($3.5 \pm 0.4$ to $5.3 \pm 0.6$ mm Hg/ml; $p < .0001$, $n = 6$); from 120 to 160 beats/min there was no further increase in $E_{es}$ ($5.2 \pm 0.6$ mm Hg/ml; $p = \text{NS}$, $n = 6$); and at 200 beats/min there was a slight further increase in $E_{es}$ ($5.7 \pm 0.5$ mm Hg/ml; $p < .01$, $n = 6$). $V_0$ was decreased slightly over the heart rate range of 60 to 120 beats/min ($10.1 \pm 2.0$ to $9.2 \pm 1.5$ ml; $p < .01$, $n = 6$), changed very little over the range 120 to 160 beats/min ($9.4 \pm 1.3$ ml; $p = \text{NS}$, $n = 6$), and increased to $15.2 \pm 1.2$ ml at a heart rate of 200 beats/min.

The influence of heart rate on the time to end-systole ($T_{es}$) is shown in figure 4. There was a significant shortening of $T_{es}$ from $237 \pm 26.4$ (SD) msec at the heart rate of 60 beats/min to $140 \pm 20.5$ msec at 200 beats/min.
beats/min. \( T_{es} \) is defined as the time from end-diastole (detected by a threshold rise in dP/dt) to the time at which the pressure-volume loops reached the point that was used for drawing the ESPVR line of an individual beat.

Figure 5 shows the \((dP/dt)_{\text{max}}/\text{heart rate} \) relationship. There was a statistically significant increase in \((dP/dt)_{\text{max}} \) over the heart rate range of 60 to 120 beats/min (1192 ± 309 to 1850 ± 368 mm Hg/sec; \( p < .001, n = 6 \)). Over the heart rate range 120 to 160 beats/min there was a variable upward trend that was not significant, and from 160 to 200 beats/min there was a downward trend that was not statistically significant (2163 ± 432 to 2011 ± 380 mm Hg/sec; \( p = \text{NS}, n = 6 \)).

Discussion

We have shown that in the isolated canine left ventricle, the influence of heart rate on the ESPVR depends on the range over which heart rate varied. Within the range between 60 to 120 beats/min there was a steady increase in \( E_{es} \) with insignificant variations in \( V_0 \). In the middle range (120 to 180 beats/min) there was very little change in either \( E_{es} \) or \( V_0 \) of the ESPVR, and over the range above 180 beats/min there was a rightward shift of the relationship with increase in heart rate.

The influence of heart rate on cardiac contractility has been extensively studied and reviewed. A significant influence has been shown in isolated muscle strips, isolated hearts, intact anesthetized animals, and conscious animals. Species differences have been shown, as well as differences with the presence or absence of anesthesia. In this study we confined our interest to the influence of heart rate on the pumping function of the left ventricle.

Mitchell et al. studied the effect of heart rate on areflexic canine hearts under right heart bypass with controlled aortic pressure and cardiac output. They demonstrated that over the range from 60 to 180 beats/min, the mean rate of pressure rise increased, stroke power increased, and dP/dt increased. However, stroke work remained nearly constant over the entire range.

Lendrum et al. studied the effect of heart rate in isovolumically contracting dog hearts. In their preparation the heart remained in situ, and heart rate was not controlled but changed spontaneously. Monroe and French used an isolated heart compressing air. They reported one heart in which heart rate was changed from 30 to 254 beats/min in four steps. An increase in the slope of the ESPVR was seen with each step of increase in heart rate. In contrast, Suga et al. using an isolated ejecting canine heart, found that the slope of the ESPVR increased only slightly and inconsistently among different hearts. They reported an increase of 0.54 ± 0.84 mm Hg/ml per 100 beats/min increase in paced heart rate. These studies all suggest that there is a shift to the left of the ESPVR with increasing heart rate but have not convincingly demonstrated the quantitative difference in these shifts over different heart rate ranges.

Our study has the advantage of using an isolated heart, free of the influence of reflex and external factors, ejecting at physiologic preload, and under precisely controlled afterload impedance. These factors, along with precise volume measurements, allowed us to measure ventricular chamber function accurately. In addition, we controlled coronary perfusion pressure precisely, removing another confounding variable.

The mechanism of the frequency range–dependent difference in the effect of heart rate is not revealed from our data. It has been previously suggested that activation has both a positive and a negative inotropic effect. Both effects are most probably mediated through alteration in calcium release and sequestration.

There is evidence that the positive inotropic effect results from increased calcium availability related to

![FIGURE 4](image4.png)

**FIGURE 4.** The influence of heart rate on the time to end-systole (\( T_{es} \)).

![FIGURE 5](image5.png)

**FIGURE 5.** The influence of heart rate on \((dP/dt)_{\text{max}}\).
accumulation of the calcium entering the cell with each beat. The negative inotropic effect may relate to the finite time required for "mechanical restitution." For a given time constant of mechanical restitution, a shorter duration of electrical diastole allows only a smaller fraction of the "potential" contractile strength to become available on excitation of the ventricle. These factors, together with other factors such as limited coronary reserve, and metabolic limitations probably contribute to the different heart rate responses over different frequency ranges.

Increased heart rate shortened the duration of the Tₑ, over the entire range of heart rates studied (figure 4). The disparity between the influence of heart rate on the time course of contraction and the maximum chamber stiffness is particularly apparent in the midrange (120 to 160 beats/min), where no change in the ESPVR and yet significant decrease in Tₑ occurred. This is consistent with the findings of Suga et al.,14 who reported a significantly shortened Tₑ but no substantial effect of Eₑmax. It is also consistent with the findings of Mitchell et al.,12 who showed that increased dP/dt with increased heart rate was not associated with increased stroke work.

Our data for dP/dt showed a trend similar to that shown in the ESPVR data. That is, over the lower heart rate range there was a significant increase in dP/dt with heart rate, in the middle range there was no significant influence of heart rate on dP/dt, and in the high range there was a trend toward decreasing dP/dt (although not statistically significant). It should be noted that (dP/dt)ₑₑ has a strong dependence on preload. Preload is altered by heart rate changes, so a valid comparison of dP/dt and heart rate cannot be made without correcting for this load dependence as was done in our analysis.

The shift of the ESPVR in a nearly parallel manner with heart rate increase above 180 beats/min is very similar to the change previously shown in regional ischemia.22 We have no evidence, however, that regional ischemia was present, nor is there an a priori reason to believe so. An alternative explanation would be that the shape of the heart has changed at the higher heart rate, leading to the ESPVR shift. Further studies are needed to elucidate the mechanism of these changes.

The ESPVR is being used as an index of left ventricular pump function in patients. Several pressure-volume loops under different loading conditions are presently required for measurement of the ESPVR. Because heart rate may change unintentionally during the load manipulation, the present information on the significant influence of change in heart rate itself in the physiologic (low) range on the ESPVR becomes of importance. Unless it is clear that a patient is undergoing evaluation in a range where the ESPVR is insensitive to changes in heart rate, it will be best to ensure, by pacing if necessary, that the heart rate does not vary during the measurement of ESPVR. If extrapolation of the present results to humans is allowed, any significant change in heart rate should be strictly avoided in the low range.

The sensitivity of the ESPVR to heart rate may be useful as an index of the metabolic state of cardiac muscle, since changes in the balance between oxygen demand and calcium delivery will probably lead to changes in the response of the ESPVR to heart rate. Differences between responses of patients with and without regional ischemia have already been demonstrated.23 Thus the difference in the response of ESPVR to changes in heart rate have the potential to add diagnostic information in patients.

The tightly controlled conditions in this study are the major limitation for extrapolating the results of this study to intact animals or patients. Many of the controlled factors (reflex activity, changing hormonal background, changing coronary perfusion pressure) could significantly modify the response of cardiac performance to changes in heart rate.

Further studies are needed to quantify these changes in patients and to determine the influence of disease states on the sensitivity of ESPVR to heart rate.

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