Contractile strength and mechanical efficiency of left ventricle are enhanced by physiological afterload

DANIEL BURKHOFF, PIETER P. DE TOMBE, WILLIAM C. HUNTER, AND DAVID A. KASS
Cardiology Division, Department of Medicine, and Department of Biomedical Engineering, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205

Recent studies have revealed that ejecting beats can generate end-systolic pressures that exceed those of isovolumic beats contracting at the same end-systolic volumes (5, 6, 9, 32, 36). Although the mechanism underlying this apparent increase in contractile state with ejection is unclear, one would anticipate that such augmented work capacity would be accompanied by proportionate increases in metabolic demand and thus myocardial oxygen consumption (MV0₂). However, this metabolic consequence of ejection has not been evaluated previously.

Suga and colleagues (12, 21, 22, 25, 26) introduced a framework for addressing such questions of ventricular energetics that is based on the pressure-volume area (PVA) as an index of total mechanical energy generation by the ventricle. It was shown that at constant contractile state the relation between PVA and MV0₂ is linear (12, 26). Furthermore, under conditions in which the end-systolic pressure-volume relation (ESPVR) was independent of whether ejecting or isovolumic contractions were imposed on the ventricle, the MV0₂-PVA relation was also independent of contraction pattern (25). However, these studies employed artificial ejection patterns that were nonphysiological, leaving the question open as to how the MV0₂-PVA relation and ESPVR are influenced by more physiological afterloads.

The purpose of the present study was twofold. The first goal was to quantify differences in contractile state, as indexed by the slope and volume-axis intercept of the ESPVR, between isovolumic and ejecting contractions under steady-state conditions in isolated canine hearts. The present study differed from previous studies that compared the ESPVRs of isovolumic and ejecting beats (27) in that flow patterns during ejection were determined by the interaction of the isolated ventricle with a more physiological windkessel afterload impedance. The second goal was to determine the metabolic cost of differences detected in contractile performance between isovolumic and ejecting modes of contraction. This was accomplished by comparing MV0₂-PVA relations determined from the isovolumic and ejecting contractions. It was found that the slope of the steady-state ESPVR was generally greater during the ejecting than isovolumic contractions (by as much as 30%), indicating a significant enhancement of contractile state during ejection. However, the slope of the MV0₂-PVA relation was less during ejecting conditions (by as much as 20%), indicating that less oxygen was consumed for any given PVA during ejection. These data suggest that when afterload is provided by a windkessel impedance, the metabolic efficiency of total mechanical energy generation by the ventricle is greater during ejecting than isovolumic conditions.

METHODS

Surgical preparation. A total of eight isolated canine hearts were studied. The procedures used to isolate and support a canine heart were similar to those described by Suga and Sagawa (27). Two mongrel dogs were anesthetized with pentobarbital sodium (30 mg/kg iv). The femoral arteries and veins of one dog (support dog) were cannulated and connected to a perfusion system that was used to supply oxygenated blood to the isolated heart. This dog was medicated with hydrocortisone (500 mg im), diphenhydramine (50 mg iv), and indomethacin (25 mg iv) as required to maintain anesthesia. The support heart was then removed and used for measurement of ventricular energetics. The remaining seven hearts were isolated and connected to a perfusion system that was used to supply oxygenated blood to the isolated heart. This dog was medicated with hydrocortisone (500 mg im), diphenhydramine (50 mg iv), and indomethacin (25 mg iv) as required to maintain anesthesia. The remaining seven hearts were isolated and connected to a perfusion system that was used to supply oxygenated blood to the isolated heart. This dog was medicated with hydrocortisone (500 mg im), diphenhydramine (50 mg iv), and indomethacin (25 mg iv) as required to maintain anesthesia.
A-VOX analyzer was calibrated on two separate occasions against direct measurements provided by a LEX-O2-CON machine.

The temperature of the perfusate was maintained at \( \sim 37^\circ\text{C} \) by a heat exchanger. Pacing electrodes were sutured to atrial tissue to control heart rate at a constant rate throughout each experiment, set at 10–15 beats/min higher than the spontaneous heart rate.

**Impedance loading system.** A servo-system was used to control left ventricular volume. Details of its design and performance have been reported by Suga and Sagawa (28). Physiological afterloading of the isolated ventricles was accomplished by a computer-based system similar to that described in detail previously (33). Briefly, a digital computer was programmed with the differential equations of the three-element windkessel model of aortic input impedance. This model has been shown to provide a reasonable representation of input impedance spectra of real arterial systems for the purpose of simulating many aspects of aortoventricular coupling (4). There are three parameters in the model that determine the impedance spectrum: the characteristic impedance \((R_0)\), the peripheral arterial resistance \((R_a)\), and the arterial compliance \((C_a)\). The computer digitizes the instantaneous LVP and calculates the appropriate instantaneous flow out of the ventricle for the specified aortic impedance. The flow signal is integrated digitally and converted to an analog signal, thus providing the volume command signal for the ventricular volume servo-system. The values of the three windkessel parameters can be changed from the computer keyboard, providing a means of altering afterload impedance. The ventricle fills during diastole in response to a simple computer-simulated preloading circuit consisting of a pressure source and filling resistance (33). When desired, the ventricle can be constrained to contract isovolumetrically by fixing the volume command signal at a constant level.

**Experimental protocol and measurements.** The sequence of afterload and preload setting that comprised one complete experimental run was as follows. The left ventricle was initially constrained to contract isovolumically, and data were acquired at four or five different preload volumes. The ventricle was then allowed to eject against a specified afterload impedance, and data were acquired at four or five different afterload volumes. Finally, we returned to isovolumic conditions and obtained recontrol data at the different preload volumes. Stability of the preparation for each run was judged during the experiments by comparing peak systolic pressures of beats at identical volumes from the initial and recontrol isovolumic periods. If these pressures varied by \(>10\%\), the data were excluded, and the entire run was repeated. This was the only criterion for excluding data. This entire sequence was repeated for as many different \(R_a\) values as possible in each experiment. For data included for analysis, it was assumed that the preparation was stable during the time period of one full experimental run. However, baseline conditions may have fluctuated from one experimental run to the next in which the afterload resistance being tested was varied.

Values of \(C_a\) and \(R_a\) of the windkessel model were fixed at 0.4 mmHg/ml and 0.2 mmHg·s·ml\(^{-1}\), respectively. \(R_a\) was varied in a random order from one run to the next.
so as to provide ejection fractions of ~10, 20, 30, 40, or 50%. As detailed below, it was not possible to collect data for each ejection fraction (EF) in every heart. After each change in preload or afterload, between 2- and 3-min equilibration time was required to assure that data were obtained at steady state. Recorded signals included LVP, left ventricular volume (LVV), CAP, CBF, AVO2, and a surface electrocardiogram (ECG). Signals were digitized at a sampling rate of 200 Hz, stored on diskettes, and analyzed off-line. Several beats of data were recorded at each preload setting tested.

At the end of each experiment, the weights of the right ventricular free wall and the left ventricle (left ventricular free wall plus septum) were measured.

Data analysis. Each group of data consisted of pressure-volume (P-V) loops recorded at the four or five different preloads but at the same afterload, along with their corresponding CBFs and AVO2s. These raw data were ultimately reduced to parameter values that describe two linear relationships, as follows.

The first relationship is the ESPVR

\[ P_{es} = E_{es} \left( V_{es} - V_0 \right) \]  

where \( P_{es} \) and \( V_{es} \) are the measured end-systolic pressures and volumes, respectively, and \( V_0 \) is the initial volume. Initial estimates of \( P_{es} \) and \( V_{es} \) were defined as the point on the P-V loop at which the LVP-to-LVV ratio was maximum for a given beat. Linear regression analysis was applied to these data, which yielded an initial guess of the volume axis intercept of the ESPVR (\( V_{o} \)). A second iteration was then performed to determine \( P_{es} \) and \( V_{es} \), which were defined as the point on the P-V loop at which the LVP/[LVV-\( V_0 \)] was maximum. \( E_{es} \) (the slope) and \( V_0 \) (the volume axis intercept) of the ESPVR were determined by applying linear regression analysis to these end-systolic P-V points obtained at a given afterload.

The second relationship to be evaluated was the M\( \text{Vo}_2\)-PVA relationship

\[ \text{M\( \text{Vo}_2\) = A PVA + B} \]  

where M\( \text{Vo}_2\) and PVA were determined from each loop, and \( A \) was the slope, and \( B \) was the intercept. PVA was determined by numerical (computer) integration of the area bounded by the ESPVR, the systolic portion of the P-V loop, and the end-diastolic P-V relation (EDPVR; 21). For this purpose, the EDPVR was fit by

\[ P_{ed} = a + bV_{ed} \]  

The parameters of this equation did not vary significantly with afterload conditions. The offset parameter, \( a \), usually took on a negative value, indicating that at small preload volumes, \( P_{ed} \) values were <0 mmHg.

The M\( \text{Vo}_2 \) of the entire heart, [i.e., of the LV plus right ventricle (RV), expressed in ml O2/beat] was calculated as CBF–AVO2/heart rate (HR). The slope, \( a \), and intercept, \( B \), of Eq. 2 were determined by linear regression analysis applied to the data. However, M\( \text{Vo}_2 \) determined in this manner represents the sum of the oxygen consumed by the work-performing LV plus the unloaded, but still oxygen consuming, RV. In Eq. 2, we were only interested in that portion of the oxygen consumed by the LV. To correct for this we assumed that the RV was mechanically unloaded (i.e., not performing any external work) and consumed an amount of the total O2, measured when the LV is also mechanically unloaded, that was proportional to its weight. Accordingly, \( B \) was multiplied by the scaling factor \( W_{LV}/(W_{LV} + W_{RV}) \), where \( W_{LV} \) is the weight of the LV, and \( W_{RV} \) is the weight of the RV free wall. Finally, for comparison of M\( \text{Vo}_2 \) between hearts, \( B \) was also normalized to 100 g of LV weight. In contrast, \( A \) is independent of both the LV-to-RV mass ratio and absolute LV mass.

Results of recent studies have suggested that the EF correlates with the difference in contractile performance between isovolumic and ejecting beats (9, 32). Therefore, data from different hearts were grouped according to EFs for the purpose of statistical analyses. However, when defined in the standard way as the ratio between stroke volume (SV) and end-diastolic volume (EDV), EF can vary with preload volume when afterload resistance is fixed. The selection of a particular EDV at which to define EF for purposes of pooling data between hearts would therefore be arbitrary. In contrast, the ratio between SV and (EDV-Vs), defined as the “effective ejection fraction” (EF\( \text{eff} \)), is independent of EDV in theoretical models (34). Linear regression analysis applied to the data of the present study obtained under ejecting conditions at various preload and afterloading conditions confirmed that this was the case; although there was a statistically significant relation between EF and EDV (\( P < 0.001 \)), EDV did not influence EF\( \text{eff} \) (\( P > 0.05 \)). Therefore, data from all hearts were pooled and grouped according to deciles of EF\( \text{eff} \) as specified in Table 1.

Mean (±SD) values of slopes and intercepts of the ESPVRs and M\( \text{Vo}_2\)-PVA relations of data acquired under ejecting conditions and during initial and final isovolumic runs are presented for each EF\( \text{eff} \) group. Statistical differences between relations measured under isovolumic and ejecting conditions were determined within each group using the pooled data and a two-way analysis of variance (ANOVA).
of covariance with experiment number and loading conditions coded as categorical parameters. Within each EF_eff group, the three statistical comparisons of the measured relations were the following: initial isovolumic vs. ejecting run; ejecting vs. final isovolumic run; and initial vs. final isovolumic run. The P values of the statistical tests were adjusted by the Bonferoni correction to account for the multiple comparisons. All statistical calculations were performed using commercially available computer software (SYSTAT, Evanston, IL).

After the data were pooled, only three experiments contained runs with EF_eff ranging between 40 and 50% (group 4, Table 1), and therefore these data were not subjected to the comparison analysis outlined above.

In addition to the analysis outlined above, the net effects of afterload on ventricular pressure-generating capability and M\(\text{\textit{V}}_{02}\) were also quantified by comparing \(P_{\text{es},0}\) and M\(\text{\textit{V}}_{02}\) at specified volumes and Pvas, respectively, for ejecting and isovolumic beats. \(P_{\text{es},0}\) was estimated from the ESPVRs measured under isovolumic and ejecting conditions at a test volume (V\text{\textit{test}}) that was 15 ml greater than the V\text{\textit{s}} of the initial isovolumic run. Thus end-systolic pressures for the initial isovolumic run (\(P_{\text{es,ISO,0}}\)), the ejecting run (\(P_{\text{es,EJ,0}}\)) and the final isovolumic run (\(P_{\text{es,ISO,5}}\)) were determined and compared as follows:

\[
\begin{align*}
P_{\text{es,ISO,0}} &= E_{\text{es,ISO,0}} (V_{\text{test}} - V_{\text{es,ISO,0}}) \\
P_{\text{es,EJ,0}} &= E_{\text{es,EJ,0}} (V_{\text{test}} - V_{\text{es,EJ,0}}) \\
P_{\text{es,ISO,5}} &= E_{\text{es,ISO,5}} (V_{\text{test}} - V_{\text{es,ISO,5}})
\end{align*}
\]

where \(V_{\text{test}} - V_{\text{es,ISO,0}} + 15\), and the subscripts ISO,0, EJ, and ISO indicate parameter values obtained from the initial isovolumic run, the ejecting run, and the recontrol isovolumic run, respectively. The final end-systolic pressure for isovolumic conditions (\(P_{\text{es,ISO}}\)) was defined as the average of the ISO, and ISO values. Finally, the difference in end-systolic pressure between isovolumic and ejecting conditions expressed as a percent (\(\Delta P_{V_{s},+15}\)) was defined as

\[
\Delta P_{V_{s},+15} = 100 \left( \frac{P_{\text{es,EJ}} - P_{\text{es,ISO}}}{P_{\text{es,ISO}}} \right) \quad (5)
\]

\(\Delta P_{V_{s},+15}\) was plotted as a function of EF_eff for every ejecting condition tested.

In a similar fashion, the effect of afterload on M\(\text{\textit{V}}_{02}\) was determined for a Pva value of 2,500 mmHg

\[
\begin{align*}
\text{Load Dependence of ESPVR and M\(\text{\textit{V}}_{02}\) - PVA Relation}
\end{align*}
\]

- **RESULTS**
  - A total of 32 ESPVRs and M\(\text{\textit{V}}_{02}\)-PVA relations were obtained under ejecting conditions from the eight hearts studied. The values of EF_eff explored in each experiment are shown in Table 1. Table 1 also summarizes how data from different hearts were grouped according to EF_eff values and provides the mean (±SD) EF_eff and afterload resistance values (\(R_a\)) used within each group. Heart rate averaged 152 ± 12 beats/min, right ventricular free wall mass averaged 52 ± 8 g, and left ventricular mass averaged 133 ± 17 g.
  
  Examples of P-V loops, ESPVRs, and M\(\text{\textit{V}}_{02}\)-PVA relations obtained from the initial isovolumic period and subsequent ejecting conditions from a representative experiment are shown in Fig. 1 (these data are from Expt 6 in Table 1). The data from the recontrol isovolumic period were nearly identical to the initial isovolumic data. The ejecting data in Fig. 1, left, were obtained with an afterload resistance of 8.0 mmHg·s·ml⁻¹, which resulted in an average EF_eff of 13.9%. The total ejection fraction (i.e., SV/EDV) was 11% at the highest preload and 7% at the lowest preload. There was essentially no difference in the steady-state ejecting and isovolumic ESPVRs; the slopes of both ESPVRs were 4.7 mmHg·100 g·ml⁻¹ in this example. The M\(\text{\textit{V}}_{02}\)-PVA relation measured under ejecting conditions fell slightly below that measured under isovolumic conditions (Fig. 1, bottom left), but these differences were neither physiologically nor statistically significant.

In contrast, when ejecting data were obtained at lower afterload resistances, and thus at higher ejection fractions, significant differences were observed between the two ESPVRs and M\(\text{\textit{V}}_{02}\)-PVA relations. As shown in Fig. 1, top right, an afterload resistance of 0.8 mmHg·s·ml⁻¹ and an EF_eff of 57.9% (total EF of 48% at the highest preload and 40% at the lowest preload) resulted in an ESPVR that fell above the isovolumic relation. \(E_{es}\) was 4.6 mmHg·100 g·ml⁻¹ under isovolumic conditions and

**FIG. 1.** Representative P-V data showing influence of afterload on ESPVRs and M\(\text{\textit{V}}_{02}\)-PVA relations. Neither ESPVR nor M\(\text{\textit{V}}_{02}\)-PVA relation differed significantly between isovolumic and ejecting conditions with small effective ejection fraction (EF_eff) left, whereas ESPVR was steeper and M\(\text{\textit{V}}_{02}\) was shallower with large EF_eff than during isovolumic conditions right. See text for further explanations and definitions.
5.7 mmHg·100 g·ml⁻¹ under ejecting conditions; $V_o$ changed little between the two conditions (7.0 vs. 6.5 ml). The MVO₂-PVA relation (Fig. 1, bottom right) determined under ejecting conditions fell below that determined under isovolumic conditions. The slope of the relation decreased by 24% from $2.75 \times 10^{-3}$ to $2.10 \times 10^{-3}$ ml O₂·mmHg⁻¹·ml⁻¹, with little change in the intercept value (0.049 vs. 0.053 ml O₂/beat).

**Influence of afterload on steady-state ESPVR.** The influence of afterload on the steady-state ESPVR is summarized by $E_{F_{eff}}$ group in Fig. 2. The mean (±SD) $E_{es}$ (Fig. 2, top) and $V_o$ (bottom) of the initial isovolumic run (ISO₁), the ejecting run (EJ), and the recontrol isovolumic run (ISO₂) are shown for each group. The relations measured under isovolumic and ejecting conditions were compared statistically using analysis of covariance. Statistically significant differences in slopes or elevations (i.e., the vertical displacement of the curves from the horizontal axis) of the relations are denoted by symbols in respective panels. Recall that with analysis of covariance, a statistically significant difference in either the slopes or elevations of the two relations being compared signifies that the relations are different.

With only one exception, there were no differences between the ESPVRs of the initial and final isovolumic relations. This would be expected in view of the data exclusion criterion used during the experiment (see METHODS). However, within group 3 ($E_{F_{eff}}$ from 30.0 to 39.9%), there was a small but statistically significant difference in the elevations of these two ESPVRs.

The ESPVRs measured during ejecting conditions fell above those measured during both the initial and final isovolumic runs in groups 2, 3, 5, and 6. These were manifested as either statistically significant differences in slopes or elevations, as detailed in Fig. 2. Even when present, differences in average $V_o$ values between isovolumic and ejecting beats were small (<2 ml). However, the increases in average $E_{es}$ values were large and on the order of 30% in several of the groups. Within group 1, there was a small but statistically significant difference between the ejecting and second isovolumic ESPVRs, with the former falling slightly above the latter. A numerical summary of the data corresponding to Fig. 1 is presented in Table 2. Statistical analysis was not applied (na) to group 4, as detailed in METHODS, due to the fact that $n = 3$ in this group.

**Influence of afterload on $MVO_2$-PVA.** The results of a similar analysis carried out on the $MVO_2$-PVA relations are summarized in Fig. 3 and Table 2. In no case did the relations measured during the initial and final isovolumic conditions differ. In groups 3, 5, and 6, the slopes of the $MVO_2$-PVA relations, $A$, measured under ejecting conditions were significantly less than those measured from both the initial and final isovolumic periods. $A$ increased by almost 25% in groups 5 and 6 on moving from ejecting to isovolumic conditions and to a lesser degree in the other groups. There was no physiologically significant influence of afterload on the intercept of the $MVO_2$-PVA relation, $B$.

**Net impact of load on contractile state and $MVO_2$.** The net impact of afterload on $P_{es}$ generation and $MVO_2$ as a function of $E_{F_{eff}}$ is summarized in Fig. 4. In Fig. 4, top, the percent difference in $P_{es}$ between isovolumic and ejecting conditions at a volume 15 ml greater than $V_o$ ($\Delta P_{V,+15}$, Eq. 5) is plotted as a function of $E_{F_{eff}}$ for all ejecting conditions tested. Each symbol denotes data from a different experiment. For most hearts, $\Delta P_{V,+15}$ increased to a maximum of ~35% as $E_{F_{eff}}$ increased to ~60% and tended to plateau or decrease with higher $E_{F_{eff}}$ values. Data from one heart (Fig. 4, open inverted triangles) were anomalous in that $\Delta P_{V,+15}$ increased steadily as $E_{F_{eff}}$ increased.

As noted above, the points on Fig. 4 were determined for a left ventricular volume 15 ml greater than the $V_o$ within each heart. Neither the general shape nor magnitude of this relation was influenced significantly by the choice of the volume at which this comparison was made. This was because there was relatively little impact of afterload conditions on $V_o$ values.

The percent difference in $MVO_2$ between ejecting and isovolumic conditions at a PVA of 2,500 mmHg·ml·100 g⁻¹ ($\Delta MVO_2$, Eq. 3) is plotted as a function of $E_{F_{eff}}$ in Fig. 4, middle. As indicated by these data, $MVO_2$ was less during ejecting conditions than during isovolumic conditions, and the difference became greater as $E_{F_{eff}}$ increased. At the highest $E_{F_{eff}}$ values, where $A$ decreased by an average of ~21% (Fig. 3, Table 2), $MVO_2$ at a PVA of 2,500 mmHg·ml·100 g⁻¹ decreased by an average of ~13%. Data from one heart were anomalous (filled
LOAD DEPENDENCE OF ESPVR AND MV\textsubscript{O}\textsubscript{2}-PVA RELATION

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>EF\textsubscript{eff}</th>
<th>(E_m) mmHg\textsubscript{mL}^{-1}\textsubscript{100 g}</th>
<th>(V_m) mL</th>
<th>(A) \textsubscript{10^{-5}}</th>
<th>(B) \textsubscript{10^{-5}}</th>
<th>MV\textsubscript{O}\textsubscript{2} ml O\textsubscript{2}\textsubscript{mL}^{-1}\textsubscript{100 g}^{-1}</th>
<th>MV\textsubscript{O}\textsubscript{2} ml O\textsubscript{2}\textsubscript{beat}^{-1}\textsubscript{100 g}^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>17.0 ± 1.7</td>
<td>4.6 ± 0.8</td>
<td>4.4 ± 0.7</td>
<td>13.0 ± 3.5*</td>
<td>13.3*</td>
<td>2.6 ± 0.3</td>
<td>2.5*</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>27.2 ± 2.0</td>
<td>5.0 ± 0.9</td>
<td>4.3 ± 0.7</td>
<td>13.2 ± 2.5</td>
<td>13.3</td>
<td>2.6 ± 0.4</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>35.1 ± 2.6</td>
<td>4.7 ± 0.6</td>
<td>4.8 ± 0.7</td>
<td>12.9 ± 11.0*</td>
<td>9.8 ± 2.4‡</td>
<td>0.009 ± 0.008</td>
<td>0.009 ± 0.009</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>40.9 ± 3.3</td>
<td>5.6 ± 0.9</td>
<td>4.4 ± 0.7</td>
<td>10.0 ± 14.1</td>
<td>3.0 ± 2.6</td>
<td>0.045</td>
<td>0.045 ± 0.048</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>56.0 ± 2.2</td>
<td>4.6 ± 1.2</td>
<td>4.5 ± 0.6</td>
<td>13.0 ± 13.1</td>
<td>11.8</td>
<td>2.7 ± 2.1‡</td>
<td>0.007 ± 0.008</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>65.5 ± 2.7</td>
<td>4.1 ± 0.7</td>
<td>4.6 ± 0.7</td>
<td>13.1 ± 12.3‡</td>
<td>12.8</td>
<td>2.7 ± 2.1‡</td>
<td>0.048 ± 0.050</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of studies contributing to pooled data set; ISO\textsubscript{1} and ISO\textsubscript{2}, initial and final isovolumic runs, respectively; \(E_m\), slope of end-systolic pressure-volume relation; \(V_m\), volume axis intercept; \(A\), slopes, and \(B\), intercepts of MV\textsubscript{O}\textsubscript{2}-PVA relations; EF\textsubscript{eff}, ejecting run. *EJ different than ISO\textsubscript{1}; †EJ different than ISO\textsubscript{1} and ISO\textsubscript{2}; ‡EJ different than ISO\textsubscript{1}; §ISO\textsubscript{2} different from ISO\textsubscript{1}. For all statistically significant differences, \(P < 0.05\).

The transient response observed in LVP to changes in preload and to switches from ejecting to isovolumic conditions were very similar in direction and magnitude to those reported previously (32, 35). Examples of these transients are shown in Fig. 5. Contractile strength rose for several minutes after an increase in preload, whereas it fell for several minutes after a preload decrease (Fig. 5A). In this example, the magnitude of the LVP transient after the volume increase (from 14 to 37.5 ml) was ~25 mmHg (33% increase over the peak pressure measured immediately after the volume change). With a preload decrease (from 37.5 to 22 ml) the LVP transient was ~10 mmHg (20% below peak pressure after volume reduction). Such pressure transients after preload changes were observed independent of whether the hearts were contracting isovolumically as in the example shown, or ejecting.

The transient in contractile strength observed on switching from ejecting to isovolumic contractions at nearly the same end-systolic volume (Fig. 5B) mimicked in many ways the transients observed with a decrease in upright triangle in Fig. 4) in that there was relatively little impact on MV\textsubscript{O}\textsubscript{2} despite an EF\textsubscript{eff} of ~70%.

Unlike the \(\Delta P\textsubscript{Ej,15}\) values, the percent difference in MV\textsubscript{O}\textsubscript{2} values between isovolumic and ejecting conditions did depend on the choice of the PVA; the larger the PVA, the greater the percent differences. This dependency derives from the relatively large offset value of the MV\textsubscript{O}\textsubscript{2}-PVA relation (i.e., \(B\)) that did not vary with afterload. A PVA value of 2,500 mmHg\textsubscript{mL}^{-1}\textsubscript{100 g}^{-1} falls within the typical range for an ejecting isolated canine heart but probably underestimates the value for a more intact model in which the contractility is higher. Only at very small and nonphysiological PVA reference values would the change in MV\textsubscript{O}\textsubscript{2} become insignificant.

The correlation between \(\Delta P\textsubscript{Ej,15}\) and \(\Delta MV\textsubscript{O}\textsubscript{2,2500}\) is shown in Fig. 4, bottom. The more that ejecting contractile performance exceeded isovolumic performance the more that ejecting MV\textsubscript{O}\textsubscript{2} decreased below isovolumic MV\textsubscript{O}\textsubscript{2}.

 transient response to changes in loading conditions.

The present study focused on an analysis of steady-state left ventricular properties. It is important to note that after a change in preload, left ventricular contractile strength did not stabilize for periods as long as 3–4 min. Similar transients have been observed after changes in length of isolated cardiac muscle and have been shown to be associated with increased calcium release to the myofilaments under the steady-state conditions (1, 16). Because calcium cycling accounts for a significant amount of total energy demands, these transients may impact significantly on contractile performance and MV\textsubscript{O}\textsubscript{2}.

The transient responses observed in LVP to changes in preload and to switches from ejecting to isovolumic conditions were very similar in direction and magnitude to those reported previously (32, 35). Examples of these transients are shown in Fig. 5. Contractile strength rose for several minutes after an increase in preload, whereas it fell for several minutes after a preload decrease (Fig. 5A). In this example, the magnitude of the LVP transient after the volume increase (from 14 to 37.5 ml) was ~25 mmHg (33% increase over the peak pressure measured immediately after the volume change). With a preload decrease (from 37.5 to 22 ml) the LVP transient was ~10 mmHg (20% below peak pressure after volume reduction). Such pressure transients after preload changes were observed independent of whether the hearts were contracting isovolumically as in the example shown, or ejecting.

The transient in contractile strength observed on switching from ejecting to isovolumic contractions at nearly the same end-systolic volume (Fig. 5B) mimicked in many ways the transients observed with a decrease in
LOAD DEPENDENCE OF ESPVR AND M\textsubscript{VO\textsubscript{2}}-PVA RELATION

**FIG. 4.** Top: percent difference in steady-state $P_e$, measured under isovolumic and ejecting conditions at a volume 15 ml greater than $V_0$ (\(\Delta P_{e,\text{+15}}\)) as a function of $E_F$ for all hearts at all afterloads studied (see Eq. 5). Middle: percent difference in steady-state $M\text{VO}_{2}$ under isovolumic and ejecting conditions at a PVA of 2,500 mmHg·ml·100 g\(^{-1}\) shown as a function of $E_F$ (\(\Delta M\text{VO}_{2,2500}\); see Eq. 6). Bottom: degree to which $P_e$ increased on ejecting beats correlated with the degree to which $M\text{VO}_{2}$ decreased on ejecting beats compared with isovolumic beats. See text for further explanation and definitions.

preload (32). $P_e$ was generally less on the initial isovolumic beat than on the preceding steady-state ejecting beats; $P_e$ then increased for a several beats, exhibited a broad plateau, and then declined significantly, usually falling well below the value for the initial isovolumic contraction. In this typical example, $P_e$ on the steady-state isovolumic contractions was \(-14\) mmHg less than on the first isovolumic beat and \(-30\) mmHg less compared with the maximum peak pressure attained during the transient. Thus such transients can be large in magnitude and long in duration.

**DISCUSSION**

The influence of afterload on the steady-state ESPVR and the $M\text{VO}_{2}$-PVA relation were investigated in isolated canine hearts with afterload provided by a three-element windkessel model. At “effective” ejection fraction [\(E_F\)] greater than \(-30\)%, the ESPVRs measured during ejecting conditions indicated a significant enhancement of contractile state over those measured during isovolumic conditions. The magnitude of this effect could become relatively large: at an $E_F$ of 60%, contractile strength averaged \(-35\)% greater during ejecting than isovolumic conditions. When $E_F$ was \(>20\)% the slopes of the corresponding $M\text{VO}_{2}$-PVA relations decreased on switching from isovolumic to ejecting conditions with no significant influence on the intercept.

FIG. 5. Original tracing showing relatively large and long transient in LVP after clusages in ventricular volume during isovolumic contractions (A) and after a switch from ejecting to isovolumic contractions near end-ejection volume. Top: 1 cm equivalent to 0.4 s during fast recordings and to 40 s during slow recordings. Bottom: 1 cm equivalent to 0.4 s during fastest recordings and, in order, 5, 10 (starting at 1st arrow), 20 (2nd arrow), and 40 s (3rd arrow) during slower paper speeds. See text for further explanation and definitions.

This result indicates that at a given value of PVA, $M\text{VO}_{2}$ was less when the heart was ejecting than when it was contracting isovolumically. Moreover, these differences in both contractile strength and $M\text{VO}_{2}$ at fixed PVA grew progressively as $E_F$ increased up to \(-60\)% (Fig. 3). Only when $E_F$ increased \(>60\)% did the differences in steady-state contractile strength tend to plateau or decline. Finally, there was a close correlation between the increase in contractile strength and the decrease in $M\text{VO}_{2}$ between isovolumic and ejecting conditions.

**Afterload and $M\text{VO}_{2}$-PVA relation.** Results of previous studies have supported the notion that the relationship between PVA and $M\text{VO}_{2}$ is independent of afterload conditions (22-26, 31). These previous studies were performed under experimental conditions in which afterload did not alter the ESPVR. However, several recent investigations, as well as the data from the present study, indicate that there are conditions under which the ESPVR can be influenced by afterload to a much greater
energy expended by the ventricle during a beat (i.e., energy counted for in previous interpretations of the $\text{MVO}_2$-PVA relation may reflect alterations in performance at and it is possible that the phenomenon observed in the present study suggest that ventricular contraction is more efficient under ejecting than isovolumic conditions despite the fact that enhanced contractile strength, as observed during ejection, would normally be expected to increase $\text{MVO}_2$.

Enhancement of ventricular performance during ejection has previously been related to a length dependence of activation, which involves at least two factors. First is the length dependence of calcium release (1, 2). For an ejection beat to have the same $V_{es}$ or PVA as an isovolumic beat, it must have a higher preload volume. If calcium release increases with preload (under steady-state conditions), then more calcium would be released on the ejecting beat, possibly contributing to greater strength during the entire contraction. A second factor contributing to length dependence of activation is increased affinity of myofilaments for calcium (8). By this mechanism, a greater proportion of released calcium would be bound to myofilaments on the ejecting than isovolumic contractions resulting in a stronger contraction. However, both of these mechanisms would be anticipated to increase energy demand, since either increased calcium availability or myofilament calcium uptake would be accompanied by increased energy utilization by greater numbers of cross-bridge interactions.

An alternative hypothesis may involve a favorable effect of muscle shortening on cross-bridge interactions. The existence of such a mechanism is suggested by results from isotonically contracting muscles showing that, at the same starting length, force generated on shortening contractions can exceed force generated on isometric beats late in systole despite the decrease in muscle length (20). The energetic consequences of this enhancement of strength have not been evaluated but need not be associated with increased energy demands if, as a consequence of shortening, more force can be generated for a given amount of calcium release and number of cross-bridge interactions.

However, any conclusions about microscopic phenomena derived from the present data remain speculative, and it is possible that the phenomenon observed in the present study may reflect alterations in performance at a more global level. For instance, one factor not accounted for in previous interpretations of the $\text{MVO}_2$-PVA relation is the amount of internal mechanical energy expended by the ventricle during a beat (i.e., energy for torsion, muscle shortening under unloaded conditions, etc.). It is conceivable that afterload could influence the contributions of such factors to overall energy demands and effect a change in the $\text{MVO}_2$-PVA relation. The degree to which they may account for the changes observed in the present study is not known.

Afterload and steady-state ESPVR. The ESPVR was introduced initially as a load-independent characterization of ventricular performance (30). The first modification of this paradigm was provided by evidence that the ESPVR measured under ejecting conditions with large stroke volume (and therefore large ejection fractions) fell below that measured under isovolumic conditions. Two processes are believed to contribute to this flow-dependent decrease in pressure-generating capability: shortening deactivation and internal ventricular resistance (10, 11, 19, 29, 36). More recent studies, however, revealed that with various afterloads, $P_{es}$ generation of ejecting contractions can exceed those measured under isovolumic conditions (9, 11, 32, 36). This finding has led to the proposed existence of a process opposing these negative effects of ejection.

The findings of the present study pertaining to the influence of afterload on the ESPVR extend these recently appreciated positive effects of ejection on $P_{es}$, Hunter (9) evaluated the difference in $P_{es}$ between ejecting contractions and the first beat after a switch to isovolumic contractions at the same $V_{es}$. The results of that study demonstrated an inverted parabolic relation between $EF$ and the difference between $P_{es}$ on the steady state ejecting beat and the first isovolumic beat. This curve peaked at an $EF$ of $\sim 30\%$, and crossed back through zero difference at an $EF$ of $\sim 50\%$. Sugiyama et al. (32) demonstrated that after a switch from ejecting beats to isovolumic contractions at the same $V_{es}$, peak LVP increased for a few beats but subsequently declined significantly to a new steady value that was well below the peak pressure on the first isovolumic beat (as in Fig. 5B). The present results indicate that the impact of such transients, typified in the tracing of Fig. 5B, on the steady-state ESPVR can be substantial and mainly manifest as changes in $E_{es}$ with little effect on $V_{es}$.

The features of the experimental conditions that dictate whether and how afterload will influence the contractile strength are not known. As noted above, reported results are quite variable, with some studies showing no effect of afterload (30), others showing a decrease in strength with ejection (3, 10, 14, 19, 29), and still others suggesting enhancement of strength with ejection (5, 6, 9, 32, 36).

Maughan et al. (14), using the same experimental preparation as in the present study, demonstrated that the ESPVR shifted rightward as afterload resistance was decreased (i.e., no significant change in slope but an increase in $V_{es}$). The major difference between this earlier study and the present study relates to the sequence of data collection. In the earlier study, ventricular preload pressure was set, and afterload resistance was varied quickly between three values. Preload was then changed, and the procedure was repeated. There was no particular consideration given to the relatively long period of time required to reach steady-state contractile performance...
after switching afterload resistances or preload volume.

Results of several studies of hearts in open or closed chest dogs (3, 7) have suggested that the ESPVR measured from a low afterload is positioned to the right of the ESPVR measured from a high afterload resistance (opposite to the present study). However, many differences exist between the isolated heart preparation and the heart in situ that may influence how ventricular performance is modulated by load. In intact animals, 1) ESPVRs are determined from transient reductions in preload, 2) coronary perfusion pressure varies with pre- and afterloading conditions, 3) the range over which ejection fraction can be varied is limited, and 4) baseline inotropic state is greater than in isolated hearts. This list is by no means complete, and other factors may contribute to differences in results obtained from the isolated and in situ hearts.

On the other hand, results of at least three studies not performed on isolated canine hearts have shown that contractile strength on ejecting beats can exceed strength on isovolumic beats (5, 6, 36). One of these (6) was performed on intact anesthetized, β-blocked dogs with afterload resistance varied by controlling flow through two arteriovenous fistulas. With afterload pressure maintained constant, it was found that $V_{\text{es}}$ decreased markedly with the fistulas open (decreased resistance, increased oxygen consumption and total energy liberated by the ventricle, as quantified by the PVA index, is also affected by afterload. The direction of the changes suggest that the ejecting contractions are stronger and more efficient than isovolumic contractions. Such a conclusion is intriguing and, if also true at the microscopic level, may lead to new ideas about the energetics of muscular contraction. The influence of load on the strength and efficiency of contraction may be influenced by experimental conditions and therefore might differ quantitatively for the isolated heart and for the heart in situ for a multitude of reasons. The interpretation of increased efficiency is dependent on the assumption that the PVA provides an index of total mechanical energy liberation during a beat that is independent of the mode of contraction.

We are grateful to Dr. M. L. Weisfeldi for invaluable comments and suggestions. We thank Kenneth Rent for excellent technical assistance, without which this study would not have been possible. We are also grateful to Dr. D. Jones and D. Flock for assistance in making LEX-O₂-CON measurements.

This work was supported by National Heart, Lung, and Blood Institute Grant HL-18912. D. Burkhoff was supported by a postdoctoral fellowship from the American Heart Association, Maryland Affiliate.

Address for reprint requests: D. Burkhoff, Div. of Cardiology, Carnegie 568, The Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205.

Received 24 August 1988; accepted in final form 9 August 1990.

REFERENCES


