Progressive Hypoxemia Limits Left Ventricular Oxygen Consumption and Contractility


To study the cardiac effects of progressive hypoxemia, we measured the left ventricular end-systolic pressure-volume relation (ESPVR), myocardial oxygen consumption (MVO₂), and myocardial oxygen delivery (MQO₂) in eight thoracotomized dogs anesthetized with fentanyl and droperidol. We specifically looked for evidence of oxygen supply limitation of MVO₂ and depressed contractility (altered ESPVR) during stepwise decreases in inspired oxygen fraction. We hypothesized that the reported relation between MVO₂ and left ventricular pressure-volume area (PVA) may hold when inadequate MQO₂ determines MVO₂, which then may limit PVA, manifested partly as a change in the ESPVR. Initially, as arterial oxygen saturation was decreased from 95 ±3% to 64 ±14%, coronary blood flow increased so that MQO₂ was maintained with no change in myocardial extraction ratio (ER₉ = MVo₂/MQO₂). During this first phase, lactate utilization, PVA, and ESPVR did not change. When oxygen saturation was further reduced, coronary blood flow rose no higher and ER₉ increased, but not enough to maintain MVo₂. Lactate consumption decreased and ST segments rose, signaling a change from aerobic metabolism. MVo₂ decrease was associated with a fall in PVA, which was due to a fall in blood pressure and a significant depression of the ESPVR. Specifically, the volume intercept of the ESPVR increased in all dogs (6.5–20.1 ml, p<0.0001), accounting for two thirds of the increase in end-systolic volume. The slope of the ESPVR decreased during hypoxia (13.3–6.1 mm Hg/ml, p<0.02), accounting for only one third of the observed increase in end-systolic volume. We believe that the evidence of anaerobic metabolism, the decrease in PVA, and the depression of the ESPVR demonstrates onset of oxygen supply limitation of MVo₂. Our data are consistent with the hypothesis that limited MVo₂ may limit PVA. The hypoxic volume intercept alteration of the ESPVR is different from changes in the slope of ESPVR seen with other interventions. This may be analogous to recent observations in isolated muscle that show hypoxic depression in contractility to be different from other interventions. (Circulation Research 1988;63: 849–859)

Evidence of depressed cardiac function is frequently found in patients with acute hypoxemic respiratory failure. In this study, we attempted to demonstrate potential adverse effects of arterial hypoxemia on left ventricular mechanics and to quantitatively show the limit of aerobic myocardial metabolism during acute hypoxemia. Gremels and Starling demonstrated that hypoxia results in a dilated, poorly contracting heart. More recent studies have demonstrated hypoxic depression of indexes of contractility in myocardial tissue and isolated hearts, but similar findings in intact animals are obscured by reflex adjustments of preload, afterload, and sympathetic tone associated with hypoxia. Indeed, intact animals have been shown to maintain or increase cardiac output, heart rate, blood pressure, and the change in left ventricular pressure over time (dP/dt) in the face of progressive hypoxia. To accomplish our goal yet avoid these pitfalls, we used indexes of contractility that are relatively invariant to changes of preload and afterload within wide physiological limits, namely, the left ventricular end-systolic pressure-volume relation (ESPVR).

Whole-body oxygen consumption is maintained constant when oxygen delivery is progressively reduced by increased oxygen extraction. Further reductions in oxygen delivery eventually exceed the
ability of the body or tissue to maintain a constant oxygen consumption, which then falls, and blood lactic acid levels increase.\(^{11,12}\) The heart is very different from the whole body in that the myocardial extraction ratio \((ER_m)\) is high even at normal myocardial oxygen delivery \((MQo_2)\), and myocardial oxygen consumption \((MVo_2)\) is maintained or increased largely by changes in coronary blood flow\(^{13-15}\) and, to a lesser extent, by changes in \(ER_m\) (note that \(ER_m = MVo_2/ MQo_2)\).\(^{16-19}\) Conceivably, at high work loads or at some low myocardial oxygen delivery, the limit of myocardial aerobic metabolism is reached as it is in other organs, so that \(MVo_2\) is determined by inadequate \(MQo_2\). Of course, this does occur in ischemic heart disease, but it has not been demonstrated in the well-perfused left ventricle exposed to global hypoxemia. Accordingly, we examined our data for evidence of onset of oxygen supply limitation of \(MVo_2\).

If, at some level of hypoxemia, \(MVo_2\) is determined by \(MQo_2\), rather than by its usual determinants—loading conditions and contractility—it is conceivable that loading conditions and contractility may themselves be affected (as they are with regional ischemia). Pressure-volume area \((PVA)\) has been shown to closely correlate with \(MVo_2\) in an isolated heart model and provides a useful energetics framework to examine the effects of hypoxia (Figure 1).\(^{20-21}\) All experimental studies confirming and extending this relation vary \(PVA\) to determine the \(MVo_2\) response. In contrast, we are concerned with the \(PVA\) response when \(MVo_2\) becomes limited by inadequate oxygen supply. Conceivably, the \(MVo_2-PVA\) relation may hold in this circumstance with consequences on pumping function. We discuss our results in this innovative context to show that our data are consistent with (though not proof of) the notion that part of the hypoxic depression of left ventricular contractility is due to energy supply limitation. That is, if supply-limited \(MVo_2\) limits \(PVA\), then one or more of the boundaries of \(PVA\) must change. An increase in diastolic stiffness, a decrease in end-diastolic volume, a decrease in systolic pressure, and a shift to the right of the ESPVR would decrease \(PVA\) (Figure 1). A shift to the right of the ESPVR is interpreted as depressed contractility, which may be accomplished by a decrease in the slope of the ESPVR \((E_{max})\) or by an increase in the volume intercept of the ESPVR \((V_0)\). Previous work has shown that \(E_{max}\) is increased by positive inotropic agents but there is no significant change in \(V_0)\).\(^{22}\) Since hypoxia may not have acted like previously studied myocardial depressants, we tested for changes both in \(E_{max}\) and \(V_0\).

Materials and Methods

Instrumentation

Ten mongrel dogs weighing 22.8 ± 2.0 kg were anesthetized with fentanyl (200 \(\mu g/kg\)) and droperidol (2.5 mg/kg). Anesthesia was maintained with an infusion of fentanyl (1 \(\mu g/kg/min)\)\(^{23}\) as well as with supplemental doses of droperidol as needed. This anesthetic combination was chosen to avoid the cardiac depression and tachycardia associated with pentobarbital and chloralose.\(^{24,25}\) The dogs were intubated and mechanically ventilated with a tidal volume of 15–20 ml/kg at a rate adjusted to maintain arterial PCO\(_2\) at 32 to 40 mm Hg. Sodium bicarbonate was infused as necessary to maintain pH at 7.35 to 7.45. A femoral arterial line was established to draw arterial blood samples and to monitor arterial pressure. A left-ventricular catheter (Millar, Houston, Texas) was placed through a left carotid arterial cut-down. A Swan-Ganz catheter was inserted via the left external jugular vein to draw mixed venous blood samples and to monitor cardiac output through use of the thermodilution technique.

A midline thoracotomy and pericardiectomy were performed and 3 cm of positive end-expiratory pressure were applied to maintain end-expired lung volume. A pair of ultrasonic crystals were sewn to the anterior and posterior epicardium. An epicardial crystal sutured to the apex was paired with a crystal implanted through a small stab wound at the base of the left ventricle, about 3 mm below the atrioventricular sulcus.\(^{26}\) A cuffed, wide-bore \((3.5 \text{ mm i.d.})\) balloon catheter was placed in the coronary sinus by direct palpation to collect all coronary sinus flow. The coronary sinus venous effluent was continuously pumped back into a right femoral venous catheter with a roller pump.
Immediately after the animals died, we confirmed the placement of the coronary sinus catheter and determined the vascular bed drained by a retrograde injection of dye. Dye stained 86% of left ventricles (91 ± 17 g were stained of 104 ± 18 g total left ventricular weight, which included the septum) and 19% of right ventricles (7 ± 3 g of 38 ± 7 g), suggesting that the coronary sinus flow reflected most of the left ventricular blood flow and probably was not contaminated significantly with right ventricular blood flow. Almost all of the unstained left ventricle was accounted for by a region of the septum that was always unstained.

Measurements

Left ventricular pressure, \( p_L \), was measured with the intraventricular Millar catheter. Left ventricular chamber volume (\( V_{wh} \)) was estimated as

\[
V_{wh} = \frac{\pi}{6} \times D_{long} \times D_{ap} \times D_d - V_{myocardium} \tag{1}
\]

where \( D_{long} \) is the apex-base diameter, \( D_{ap} \) is the anterior–posterior diameter, \( D_d \) is the unmeasured septal–fremwall diameter estimated as \( D_{ap} \), and \( V_{myocardium} \) is the myocardial muscle volume. To improve this volume estimate, we used the following additional information. At the end of every experiment, the heart was excised and a thin-walled latex balloon was sewn in the mitral anulus. Fluid and air between the balloon and endocardium was evacuated so that the known balloon volume equaled left ventricular volume. The heart was floated in saline to avoid nonhomogeneous distortion of ventricular shape. Ultrasonic crystal dimensions were measured at many known balloon volumes to calibrate the ventricular volume estimate (Figure 2). Furthermore, we used the information that the left ventricular volume does not change during the isovolumic phases of the cardiac cycle. The "improved" estimate of ventricular volume is

\[
V_{wh} = G \times D_{long} \times D_{ap} \times D_d - V_{myocardium} \tag{2}
\]

where \( G \) is not assumed to be \( \pi/6 \) but is determined in each heart as the slope of the volume calibration curve. \( D_{long} \) and \( D_{ap} \) are measured in Equation 1. \( D_d \) is a dimensionally correct combination of \( D_{long} \) and \( D_{ap} \) that takes into account the impossibility of exact crystal placement and best fits the condition of constant isovolumic volumes (see "Appendix"). \( V_{myocardium} \) is determined from the intercept of the volume calibration curve in each heart. The entire analysis was done using both volume estimates with no difference in the conclusions. Because the second volume estimate contained more information and correlated best with independent stroke volume measurements, we report volumes estimated using the second method.

Figure 2 shows a typical calibration plot of postmortem left ventricular volume versus the volume estimated as the product of ultrasonic crystal dimensions. The slope of this regression line is \( G \) from Equation 2. The standard deviation in estimating \( G \)

is small, suggesting that changes in estimated volume very accurately reflect changes in actual volume. Since the \( Y \) intercept (\( V_{myocardium} \) from Equation 2) is an extrapolation, the standard deviation in estimation of this value is relatively larger even though this value correlated \( r=0.49 \) with myocardial mass (Table 1). For all sets of data from all dogs, the ultrasonic crystal volume correlated with stroke volume calculated from cardiac output and heart rate (ultrasonic crystal stroke volume = \( 0.63 \times \) Fick stroke volume + 4.8 cm\(^3\), \( r=0.63, p<0.05 \) (Table 1). 

\( E_{max} \) and \( V_0 \) were determined at each stage during a vena caval occlusion (Figure 3). A steady-state pressure-volume loop was also recorded at each stage. PVA was determined exactly as previously described. 20, 21 That is, PVA is the area on the left ventricular pressure-volume diagram bounded below by diastole, on the right by isovolumic systole, above by the ejection phase of systole, and on the left by a line connecting the end-systolic point to \( V_0 \) determined during the baseline set (Figure 1). Note that the left-hand boundary of PVA is the same as the ESPVR only when \( V_0 \) is equal to the normoxic baseline \( V_0 \).

\( MVO_2 \) and \( MQO_2 \) were determined from coronary sinus flow and arterial and coronary venous oxygen content. Coronary sinus flow was determined directly by a timed collection. Coronary sinus pressure may influence the pressure-flow characteristics of the coronary circulation unless coronary sinus pressure is maintained below the coronary venous vascular waterfall pressure. 28, 29, 30 Accordingly, we kept the outflow level of the coronary sinus catheter below the right atrium. To demonstrate that coronary sinus pressure was below the waterfall pressure, we repeated the timed collection in all exper-

![Figure 2. Volume calculated from ultrasonic crystal dimensions is compared with volume inside an intraventricular balloon during a postmortem calibration for a typical dog. Half of the volume calibration plots were better (higher correlation coefficient, R) than the one shown and half were worse. The y axis intercept is the myocardial muscle volume and the slope of the line is G (Equation 2).](http://circres.ahajournals.org/lookup/fig/2017/45311/Walley-767-399222.jpg)
Protocol

In eight dogs, sets of measurements were collected first on room air and subsequently at progressively lower inspired oxygen fraction (FIO2). The dog was allowed to stabilize at the new FIO2 for 20 minutes prior to each set of measurements. At each set coronary sinus flow, arterial oxygen content, mixed venous oxygen content, coronary sinus oxygen content, FIO2, mixed expired oxygen fraction, and minute ventilation were measured. Then PaO2 and the ultrasonic crystal diameters were sampled at 500 Hz and stored in digital format during a 5-second apnea at end expiration. Finally, both the superior and inferior venae cavae were occluded and PaO2 and diameters were sampled at 100 Hz during a 10-second apnea at end expiration. Typically, seven to 10 sets were collected in each dog before death, which occurred at an FIO2 of 10.6% (range, 6.8%-12.4%).

Two additional dogs were not made hypoxic and identical measurement sets were collected on room air over a time course identical to the hypoxic experiments to rule out major time-related changes in this surgical preparation. These two animals were stable with no change in blood pressure or cardiac output over 4 hours. Vo deviated from the baseline measurement by 0.3 ±0.9 ml on all sets while E^, slope of the line; Vo, volume intercept.

Statistical Analysis

To summarize our data, we present it in seven stages, for which steady-state measurements were obtained in all eight studies. Compared with the first set of values obtained on room air, most of the observed changes occurred in the final three sets, with few statistically significant changes prior to this. For experiments that lasted for more than seven sets, data from stage 2 up to the final three sets were averaged pairwise. For example, set 2 and 3, set 4 and 5, and set 6 and 7 were averaged in a
TABLE 2. Variables Affecting Arterial Oxygenation in Eight Dogs

<table>
<thead>
<tr>
<th>Stage</th>
<th>FIO2 (%)</th>
<th>PACO2 (mm Hg)</th>
<th>Arterial oxygen content (mLO2/dl)</th>
<th>PACO2 (mm Hg)</th>
<th>pH</th>
<th>Hct (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21.0±0.5</td>
<td>81±3</td>
<td>13.7±3.7</td>
<td>38±2</td>
<td>7.40±0.05</td>
<td>32±8</td>
</tr>
<tr>
<td>2</td>
<td>16.6±1.7*</td>
<td>61±13*</td>
<td>12.1±2.8</td>
<td>37±2</td>
<td>7.42±0.02</td>
<td>31±5</td>
</tr>
<tr>
<td>3</td>
<td>14.0±0.5*</td>
<td>50±6*</td>
<td>11.2±2.6</td>
<td>35±1</td>
<td>7.42±0.04</td>
<td>32±7</td>
</tr>
<tr>
<td>4</td>
<td>12.7±1.0*</td>
<td>43±6*</td>
<td>10.6±1.6*</td>
<td>36±3</td>
<td>7.42±0.03</td>
<td>34±6</td>
</tr>
<tr>
<td>5</td>
<td>12.0±1.2*</td>
<td>41±8*</td>
<td>9.9±1.3*</td>
<td>36±2</td>
<td>7.41±0.03</td>
<td>34±6</td>
</tr>
<tr>
<td>6</td>
<td>11.3±1.4*</td>
<td>36±8*</td>
<td>8.8±1.6*</td>
<td>36±3</td>
<td>7.38±0.03</td>
<td>34±6</td>
</tr>
<tr>
<td>7</td>
<td>10.6±1.6*</td>
<td>36±9*</td>
<td>9.0±2.2*</td>
<td>34±6</td>
<td>7.41±0.08</td>
<td>36±5</td>
</tr>
</tbody>
</table>

Mean±SD.

*Different from baseline stage 1 p<0.01.

We tested the null hypothesis that hypoxia does not change Emax and V0 with a nonparametric repeated-measures analysis of variance (Friedman test). When a significant difference was found (p<0.05), a Mann-Whitney test with a Bonferroni correction identified specific differences. The same analysis with parametric statistics was performed for the data shown in Table 2, Table 3, and Figure 4 to highlight changes in measured parameters. Data are summarized as mean±SD throughout.

Results

The reductions in FIO2 were chosen to produce approximately equal reductions in arterial oxygen content at each stage (Table 2). PACO2, pH, and hematocrit were maintained constant. As FIO2 was decreased from 21% to 12%, heart rate and cardiac output were relatively constant and arterial pressure fell slightly (Table 3). During this initial phase of hypoxia, MVO2 was maintained by an increase in coronary blood flow so that ERm did not change from the initial value of 65% (Figure 4). On the average, MVO2 and PVA were constant at 53±2 ml O2/kg/min and 197,000±16,000 mm Hg/ml/min. There were no significant changes in lactate consumption, ST segments, or contractility as measured by V0 and Emax during this initial phase.

Further reduction of FIO2 below 12% during the final two stages resulted in significant changes in many variables signaling a change in both metabolism and function. During this extremely hypoxic phase, coronary blood flow did not increase further to maintain MVO2 (Figure 4). Indeed, coronary blood flow decreased in part because of the fall in blood pressure. MVO2 and PVA decreased (by 17% and 23%, respectively, at stage 7), associated with reduced cardiac output and blood pressure (Table 3). Extraction ratio finally rose when the coronary flow fell in stage 6, associated with a fall in lactate consumption (Figure 4). In four of eight dogs the myocardium became a lactate producer, signaling anaerobic metabolism. ST segments rose in seven of eight dogs and fell in the other dog so that the average deviation from baseline in the second phase was significant and probably reflected myocardial ischemia. The ESPVR became acutely depressed. Thus, when coronary blood flow could no longer increase to maintain ERm, there was an approximately simultaneous change in oxygen metabolism.
lactate metabolism, electrophysiological function, and contractility of the left ventricle.

These metabolic and functional changes define two parts to the MVO2–MQO2 relation similar to the aerobic and anaerobic phases of the whole body (Figure 5). Whole body oxygen consumption became supply limited at a critical oxygen delivery of 9.3 ml O2/kg/min consistent with published values.11,12 The heart differs from the whole body during the initial phase in that oxygen consumption is not a constant (the plateau of Figure 5) but variable (top panel of Figure 6). Analogous to the whole body, the anaerobic second phase of the MVO2–MQO2 relation is distinguished from the first by an increased ERm, altered lactate metabolism, and a decrease in MVO2 associated with a decrease in MQO2 (Figure 4 and the bottom panel of Figure 6).

In each experiment the reduction in PVA at stages 6 and 7 was associated with the reduction in MVO2. The units of PVA and MVO2 can be converted to joules (1 mm Hg · ml = 1.33 × 10⁻⁴ J and 1 ml O₂ = 20.2 J approximately). Therefore, the fraction of MVO2 that is converted to PVA can be calculated. The efficiency ratio, PVA/MVO2, decreases slightly as MVO2 decreases (first stage, 27%, to last stage, 17%), consistent with published results in isolated hearts.20,21 To account for the decrease in PVA, we examined its four boundaries (as illustrated in Figure 1). There was no measurable change of the diastolic pressure-volume relation (the bottom boundary) in this open-chest, open-pericardium preparation. Specifically, there was no change in diastolic pressure when measured at a volume of 20 ml greater than baselineVo (pressure at volume = Vo + 20 ml in Table 3). The right-hand boundary, marked by end-diastolic volume, increased in the late stages (Table 3) and therefore influenced the calculated value of PVA but did not account for the observed decrease in PVA. Indeed, an isolated increase of the right-hand boundary would increase PVA. Therefore, the observed decrease in PVA was due to concurrent changes of the other boundaries. The top boundary, related to end-systolic pressure, decreased slightly with progressive hypoxia because of a decrease in systemic vascular resistance and, preterminally, because of a decrease in cardiac output. This accounts for part of the decrease in PVA. The rest of the reduction in PVA...
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Hypoxemia Depresses Contractility

Figure 5. Whole body oxygen consumption oxygen delivery data from all dogs are pooled and best fit lines are drawn. A plateau aerobic phase and an oxygen supply dependent phase are evident. The critical oxygen delivery is 9.3 ml O2/kg/min.

is caused by a rightward shift of the left-hand boundary, which is related to a fall in contractility. 

V₀ did not remain equal to baseline V₀ (p<0.0001) when the dogs became severely hypoxic (Table 3 and Figure 7). Thus, the left-hand boundary of PVA (a line joining baseline V₀ to the hypoxic end-systolic pressure-volume point) did not coincide with the measured ESPVR in this circumstance. Table 3 demonstrates that when compared at the same end-systolic pressure, end-systolic volume increased compared with baseline. (For comparison, at the same end-systolic pressure, a baseline end-systolic volume was determined from the baseline ESPVR read at the hypoxic end-systolic pressure.) The increase in V₀ was equal to two thirds of the increase in end-systolic volume. Only the remaining third of the increase in end-systolic volume was caused by a decrease in Eₘₐₓ (p<0.05). In fact, at hypoxic stage 6, Eₘₐₓ increased in four dogs even when an increase in V₀ had resulted in a dilated, depressed left ventricle.

Discussion

These observations suggest that progressive hypoxemia reaches the limits of myocardial aerobic metabolism when coronary blood flow is maximized. Further reduction in arterial oxygen saturation reduces MQO₂, and MVO₂ decreases associated with anaerobic metabolism despite increased oxygen extraction. In turn, this oxygen supply limitation and anaerobic metabolism is associated with reduced PVA output of the ventricle in accord with the conservation of energy. The associated depression of the ESPVR is largely due to an increase in V₀ with some decrease in Eₘₐₓ.

Measurement of Volumes and Coronary Sinus Blood Flow

As Slinker and Glantz point out, measurement of left ventricular volume is difficult since this signal cannot be transduced directly but can only be inferred from dimension measurements. Our volume estimate, calibrated in every dog by postmortem examination and in vivo (Table 1 and Figure 2), compares favorably with other measures of left ventricular volume made in intact dogs. V₀ deviated 0.3±0.9 ml over seven normoxic sets in two time-control dogs. This difference and the standard deviation of the difference are more than an order of magnitude less than the change in V₀ reported here. Thus, we believe that our methods are capable of detecting the difference in V₀ even though the measurement of V₀ is more difficult as it is an extrapolation. We measured coronary sinus blood flow by direct collection because we believe it is the most accurate measure of absolute flow. Measurement of flow at different downstream pressures confirmed that we maintained downstream pressure below the coronary venous waterfall pressure so that the measurement did not alter.
Progressive Hypoxemia Limits Left Ventricular Aerobic Metabolism

Progressive hypoxemia resulted in supply limitation of whole-body oxygen consumption (Figure 5) as in Cain's whole-body studies. The analogous relation of MVO$_2$ to MQ$_2$ has not previously been directly reported but can be determined in part by examining published data. Some investigators find no change in ERm while others find an increase in ERm in moderate hypoxemia or when MVO$_2$ is increased by exercise. However, no previous global left ventricular investigation has examined the full range of the MVO$_2$-MQ$_2$ relation to demonstrate the onset of limitation of MVO$_2$ by inadequate MQ$_2$, the coincident onset of anaerobic metabolism, and the critical limit of myocardial oxygen extraction. Similar to the whole-body oxygen delivery-oxygen consumption relation there appears to be an aerobic and an anaerobic phase. During the initial phase adequate oxygen delivery is maintained in the face of progressive hypoxemia by increased coronary blood flow, keeping ERm constant (first four stages of Figure 4). During these initial stages of hypoxia we found no changes in the ESPVR, cardiac output, ECG, or lactate consumption, suggesting that the left ventricle was functioning aerobically. We think that during this initial phase MVO$_2$ determined MQ$_2$ through autoregulation of coronary blood flow. Like the whole body, the anaerobic second part of the MVO$_2$-MQ$_2$ relation is distinguished from the first by increasing ERm, lactate production, and MVO$_2$ decreasing with MQ$_2$ (Figure 4 and Figure 6 bottom panel). Accordingly, we believe that during this second phase MVO$_2$ demonstrates oxygen supply limitation similar to that seen in the whole body and in other isolated tissues. We also found that with decreasing MVO$_2$ during this oxygen supply limited phase left ventricular contractility decreased, cardiac output fell, and the ECG demonstrated ischemic changes. In no dog did we find significant depression of contractility before onset of supply limitation of MVO$_2$ nor did we find preservation of contractility after onset of supply limitation of MVO$_2$ and anaerobic metabolism. This is consistent with the notion that function is largely dependent on energy from aerobic metabolism and function is limited when MVO$_2$ is limited by inadequate oxygen supply.

Effects of Hypoxia on Contractility Mediated via MVO$_2$-PVA Relations

Hypoxia depresses isolated myocardial tissue contractility and in the limit some level of hypoxia must depress cardiac contractility in situ. Yet our hemodynamic results are similar to previously published results and do not necessarily imply any cardiac depression until the terminal set. The basis of hemodynamic changes is complex and may be due to reflex changes of preload, peripheral vascular properties, and cardiac performance. To distinguish between these possibilities, we measured left ventricular pressure, volume, and the ESPVR—a measure of contractility that is relatively invariant to changes of preload and afterload within wide physiological limits.

We make novel use of the recently described relation between MVO$_2$ and PVA to develop an energetics analysis of our data to help test the possibility that the observed depression of the ESPVR can be accounted for by oxygen (and therefore energy) supply limitation. All studies confirming and extending this relation vary PVA to determine the MVO$_2$ response. Here we explore the PVA response (and the ventricular mechanics comprising the boundaries of PVA) when MVO$_2$ becomes limited by an inadequate oxygen supply. Since MVO$_2$ is related to metabolic energy input (1 ml O$_2$ = 20.2 J), and PVA has been identified as total mechanical energy output, we speculate that at a given contractile state PVA may correspond one-to-one to MVO$_2$ (that is, a change in PVA will force a change in MVO$_2$ and a change in MVO$_2$ will force a change in PVA). Thus, when progressive hypoxia begins to limit MVO$_2$ then PVA must also decrease. Indeed, we found that decreases in MVO$_2$ were associated with decreases in PVA. The observed decrease of PVA was due to depression of contractility, as measured by the left-hand boundary of PVA, and a decrease of systolic ejection pressure, the upper boundary of PVA. The right-hand boundary of PVA, marked by end-diastolic volume, increased and positively influenced the calculated value of PVA but less than the decrease in PVA effected by the left-hand and upper boundaries.
Suga and associates\textsuperscript{20,21} demonstrated the relation between \(\text{MVO}_2\) and PVA as illustrated in Figure 1 by artificially varying PVA over a wide range in isolated hearts. Note that at an extrapolated PVA of zero a basal \(\text{MVO}_2\) remains. We did not independently try to manipulate PVA thus we did not define the \(\text{MVO}_2\)-PVA relation nor the \(\text{MVO}_2\) intercept accurately. Nevertheless, our PVA/\(\text{MVO}_2\) ratios through the range of normoxia to extreme hypoxia are in accord with published data.\textsuperscript{20,21} Because we did not subtract a basal \(\text{MVO}_2\) in calculating PVA/\(\text{MVO}_2\), we observe an expected decrease in this ratio as \(\text{MVO}_2\) and PVA decrease with hypoxia.

The \(\text{MVO}_2\) intercept has been shown to increase with positive inotropic agents.\textsuperscript{21} Thus, the \(\text{MVO}_2\)-PVA relation data collected under a variety of loading and contractility conditions indicate that if contractility is significantly increased, PVA may decrease while \(\text{MVO}_2\) stays approximately the same. Alternatively, if contractility decreases, PVA may increase while \(\text{MVO}_2\) stays the same. Applied to this hypoxia study, when \(\text{MVO}_2\) is limited by inadequate \(\text{MVO}_2\), contractility could increase at the expense of decreased PVA or contractility could decrease associated with an increase in PVA. Our data indicate that the latter strategy is followed in that contractility is observed to decrease, possibly with the benefit of maximizing PVA. However, even with a decrease in the \(\text{MVO}_2\) intercept, the PVA would eventually have to decrease as \(\text{MVO}_2\) became very low. Thus, the speculation that the relation between \(\text{MVO}_2\) and PVA may hold during progressive hypoxemia can account for the observed decrease in contractility based on this energetics analysis. That is, either contractility decreases as a strategy to preserve PVA (from the \(\text{MVO}_2\)-PVA relation) or as PVA is forced to decrease contractility decreases because it is related to the left-hand boundary of PVA. Our data are consistent with, but by no means proof of, this hypothesis.

**Hypoxemia, Increased \(V_o\), and Contractile Mechanics**

Decrease in contractility due to an increase in \(V_o\) to the extent observed here was a new and surprising result. Virtually all studies have shown that changes in contractility have been due to changes in \(E_{\text{max}}\).\textsuperscript{22} However, a recent study of ischemia from decreased perfusion pressure observes an increase in \(V_o\).\textsuperscript{37} Schroff et al\textsuperscript{38} have also recently demonstrated that ventricular systolic resistance may result in decreased ejection when ejection velocity increases. Ventricular systolic resistance is consistent with recent observations in isolated hearts\textsuperscript{39} showing an increase of \(V_o\) (although much less than seen here with hypoxia) with decreased afterload. It follows that one explanation for our results is that ventricular resistance increased with hypoxia. Contracture due to hypoxia may account for or be related to such an effect. However, this sort of contracture observed as an increase in resting tension in isolated muscle preparations\textsuperscript{4} occurs at \(P_O_2\) values (<6 mm Hg) lower than arterial and coronary sinus \(P_O_2\) values measured here. Although major changes of left-ventricular geometry may alter estimates of \(V_o\) and \(E_{\text{max}}\), we do not think that this is the case in this study. Thoracotomy and pericardiectomy do not substantially alter left-ventricular dynamic geometry\textsuperscript{34} and septal shift was unlikely as right ventricular pressures did not rise.

As another potential explanation we considered that the global parameters, \(E_{\text{max}}\) and \(V_o\), may reflect underlying myocardial properties, particularly in this global hypoxic intervention, which did not result in confounding segmental differences in contraction. The integration over space and time of individual myocardial tissue force-length properties results in the global pressure-volume relation. Thus, a shift of the force-length properties would shift the global ESPVR, other things being equal. Therefore, consider the muscle fiber force-length relation as follows. It is well known that increased intracellular calcium frees more actin-myosin fibers of tropinin-tropomyosin so that more force can be generated shifting the force-velocity relation upward. Yet the maximum rate of shortening of each actin-myosin fiber, \(V_{\text{max}}\), is not increased\textsuperscript{40,41} (Figure 8, left-hand panel, solid lines). Since \(V_{\text{max}}\) does not change with an increase in intracellular calcium, a hypothetically unloaded contraction from the same diastolic point with a similar time course will have the same end point, \(V_o\). On the other hand, for any nonzero afterload the ventricle will contract further in the same time because an increase in intracellular calcium concentration increases shortening velocity at any given load. The result in a shift to the left of the ESPVR with no change in volume intercept is an increase in \(E_{\text{max}}\) (Figure 8). An increase in \(E_{\text{max}}\) with no change in \(V_o\) is exactly what has been found with interventions that alter myocardial intracellular calcium concentrations.\textsuperscript{22} A second type of change of the ESPVR may occur if \(V_{\text{max}}\) is decreased. Then the hypothetical unloaded contraction starting from the same diastolic point will not contract as far, resulting in an increase in \(V_o\). At the global level, hypoxic increase in \(V_o\) is exactly what we have observed. At the isolated muscle fiber level, it is conceivable that hypoxia could result in a decrease, in a rate-limiting step represented by \(V_{\text{max}}\), either by limitation of energy substrate or by other effect on actin-myosin ATPase.

The identification of these two types of dilated cardiomyopathy—decreased \(E_{\text{max}}\) and increased \(V_o\)—is not without precedent in studies of isolated muscle. Allen and Orchard\textsuperscript{42} describe interventions that change myocardial muscle force in two distinct ways. Changes in intracellular calcium concentration produced by inotropic agents such as digitalis glycosides change force by altering intracellular
calcium concentration and the number of actin-myosin fibers free to react. On the other hand, hypoxia and acidosis produce depression of force without concomitant changes in intracellular calcium concentration. We suspect there may be a fairly direct connection between these two types of myocardial force changes and global E_max and V_o changes. This conjectured relation between E_max and numbers of actin-myosin cross-bridges on the one hand and V_o and isolated muscle V_LV on the other is testable and may stimulate thought and investigation into the relation between actin-myosin properties and global cardiac mechanics.

Appendix

During isovolumic contraction and relaxation, volume does not normally change yet shape changes dramatically. This information may be used to test volume estimating procedures or volume estimating procedures may be improved by incorporating this additional information. We estimate

\[ V_V = G \times D_{ap} \times D_{long} \times D_{af} - V_{myocardium} \]  

(1)

with G and V_{myocardium} measured from a postmortem calibration curve and D_{ap} and D_{long} measured directly. Ultrasonic crystal placement can never be exactly along principle directions of shortening since these directions change during the cardiac cycle. Rather than estimate D_{af} as D_{ap} we assume that D_{af} is better estimated as a combination of D_{ap} and D_{long}. To maintain dimensional correctness we write

\[ D_{af} = D_{ap}^X \times D_{long}^{(1-X)} \]  

(4)

where X is an exponent between 0 and 1. During an isovolumic phase where volume is a constant (V_c), we substitute Equation 4 into Equation 1 and rearrange:

\[ (V_c + V_{myocardium})/G = D_{ap}^{(1-X)} \times D_{long}^{(2-X)} \]

Note that the left-hand side of the equation is a collection of constants. When logarithms of both sides are taken and rearranged:

\[ \log(D_{ap}) = \frac{(2-X)}{(1+X)} \times \log(D_{long}) + \log((V_c + V_{myocardium})/G)/(1+X) \]

This is in the linear form "y = mx + b" where y = \log(D_{ap}) and x = \log(D_{long}). A log-log plot of D_{ap} versus D_{long} thus has a slope depending only on the unknown X.

\[ \text{slope} = \frac{(2-X)}{(1+X)} = \frac{\text{change of log}
(D_{ap})}{\text{change of log}(D_{long})} \]

To find the slope we measured \(\frac{\text{change of log}
(D_{ap})}{\text{change of log}(D_{long})}\) for all isovolumic phases in each dog and took the average value to calculate X for each dog. Now Equation 1 with \(D_{af} = D_{ap}^X \times D_{long}^{(1-X)}\) gave a volume estimate that incorporated the additional averaged information that volume does not change during isovolumic phases.

References


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