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Acute Respiratory Acidosis Decreases Left Ventricular Contractility but Increases Cardiac Output in Dogs

Keith R. Walley, Theodore H. Lewis, and L.D.H. Wood

To understand the cardiovascular response to respiratory acidosis, we measured hemodynamics, left ventricular pressure, and left ventricular volume (three ultrasonic crystal pairs) during eucapnia and respiratory acidosis in 10 fentanyl-anesthetized open-chest dogs. Left ventricular contractility was assessed primarily by measuring the slope (E_{max}) and intercept (V_0) of the left ventricular end-systolic pressure-volume relation determined by combining end-systolic points from a vena caval occlusion and from brief aortic cross-clamping. Respiratory acidosis (pH 7.09, P_{CO_2} 92 mm Hg) reduced contractility by a decrease in E_{max} (11.4 to 9.2 mm Hg/ml, $p < 0.01$) with no change in V_0. Despite this, cardiac output increased (1.7 to 2.1 l/min, $p < 0.01$), and heart rate increased (96 to 121 beats/min, $p < 0.05$), with no change in blood pressure. Systemic vascular resistance fell by 26% ($p < 0.01$). During eucapnia, propranolol reduced E_{max} (11.4 to 4.6 mm Hg/ml, $p < 0.01$) with no change in V_0. After propranolol treatment, respiratory acidosis further reduced E_{max} (4.6 to 3.6 mm Hg/ml, $p < 0.05$) and increased end-systolic volume more than before propranolol ($p < 0.001$). Now cardiac output did not increase even though heart rate increased (81 to 106 beats/min, $p < 0.001$) and systemic vascular resistance fell by 20% ($p < 0.01$). We conclude that the effect of respiratory acidosis on the circulation is to increase venous return (equals cardiac output) in the face of decreased left ventricular contractility. The β-adrenergic response to respiratory acidosis substantially ameliorated the increase in end-systolic volume and supported the increase in venous return but did not alter the associated tachycardia or vasodilation. Respiratory acidosis, like propranolol treatment, decreases contractility by decreasing E_{max}. (*Circulation Research* 1990;67:628–635)

R ecent studies have suggested that respiratory acidosis contributes to cardiovascular dysfunction and mortality in patients who have acute ventilatory failure and patients who receive sodium bicarbonate during resuscitation from cardiac arrest.[1,2] This conclusion is based on isolated myocardial muscle[3–5] and excised heart[6,7] studies, which show that respiratory acidosis directly depresses contractility. Yet, whole-animal studies[8–10] suggest that respiratory acidosis is not depressant to the heart except at very high levels of P_{CO_2} (above 350 mm Hg[10]). These apparently discrepant results

highlight that the cardiovascular effects of respiratory acidosis are important but poorly understood.

A better understanding of the cardiovascular effects of respiratory acidosis may explain the apparent discrepancy. For example, in whole animals it is possible that pump function is maintained by adrenergic cardiovascular reflexes supporting contractility, or alternatively, by enhanced venous return and altered loading conditions in the face of decreased left ventricular contractility. To distinguish between these two possibilities, we measured the left ventricular end-systolic pressure-volume relation (ESPVR) and hemodynamics during respiratory acidosis induced in dogs. The ESPVR was chosen because it is a relatively preload- and afterload-insensitive index of contractility over a wide physiological range.[11,12] To help determine the contribution of β-receptor–mediated reflexes, we repeated measurements before and after β-blockade.

A rightward shift of the ESPVR, interpreted here as decreased contractility, may result from a decrease in slope, E_{max}, as occurs during β-blockade[12] or from an increase in the volume intercept, V_0, as occurs

during hypoxia.[13] Whether the contractile effect of respiratory acidosis is similar to β-blockade or hypoxia is not known. Thus, a second reason for performing this study was to determine the effect of respiratory acidosis on E_{max} and V_0 and to compare this with the effect of β-blockade and hypoxia to gain insight into the mechanism of action of respiratory acidosis on the myocardium.

Materials and Methods

Instrumentation

Ten mongrel dogs (mean weight, 22±3 kg) were anesthetized with thiopental (20–25 mg/kg i.v.) and fentanyl (100 μg/kg). Anesthesia was maintained with an infusion of fentanyl (1 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}).[13,14] After instrumentation, muscle paralysis was induced with vecuronium (0.1 mg/kg initially and 0.05 mg/kg after each experiment set) to avoid reflex respiratory muscle movement during respiratory acidosis. The dogs were intubated and mechanically ventilated with an inspired oxygen concentration of 35% to ensure adequate oxygenation. During instrumentation and during eucapnic measurements, tidal volume was set at 15 ml/kg at a rate adjusted to maintain P_{CO_2} between 35 and 40 mm Hg. Four centimeters of positive end-expiratory pressure was applied to maintain end-expired lung volume. A femoral artery catheter was placed to sample arterial blood and monitor pressure. Right atrial and pulmonary artery catheters were inserted via the right external jugular vein for mixed venous blood sampling, pressure measurement, and cardiac output determination by the thermodilution technique. Thermodilution cardiac output was calibrated against cardiac output measured using the Fick method as described previously.[13]

A midline thoracotomy was performed, and the pericardium was opened wide and sutured in place to form a support for the heart. Left ventricular pressure was measured with an intraventricular catheter (Millar Instruments, Houston) inserted through the apex of the left ventricle. Inflatable cuffs were placed around the superior and inferior venae cavae to allow for transient vena caval occlusion. Aortic occlusions were performed with a vascular clamp. As previously described,[13] ultrasonic crystals were sewn to the anterior, posterior, apical, and free wall epicardium, and ultrasonic crystals were implanted in the myocardium at the base of the left ventricle and in the septum. This allowed simultaneous measurement of an anterior-posterior diameter (D_{ap}), long axis diameter (D_{long}), and a septal–free wall diameter (D_{sf}).

Pressure-Volume Relations

We estimated left ventricular volume (V) as[13,15]

$$V = G \times D_{ap} \times D_{long} \times D_{sf} - V_{myocardium} \quad (1)$$

where G is a geometric factor (if the ventricle were a perfect ellipse $G = \pi/6$) and $V_{myocardium}$ is the volume of myocardium included by the epicardial placement of ultrasonic crystals. We determined G and $V_{myocardium}$

in every dog as the slope and intercept, respectively, of a postmortem volume calibration as follows. At the end of every experiment the heart was excised and a thin-walled latex balloon was sewn into the mitral anulus. Fluid and air between the balloon and endocardium were evacuated so that the known balloon volume equaled left ventricular volume. G and $V_{myocardium}$ were determined as the slope and intercept of the best-fit line relating known balloon volume and $D_{ap} \times D_{long} \times D_{sf}$. The assumption made in this postmortem calibration that the principle axes of deformation of the left ventricle are identical during contraction of the heart in life compared with passive distention after death is supported by previous direct measurements of these axes.[16] The correlation between measured volume and volume calculated from the diameter measurements was excellent (mean $r=0.99$), as it was in previous work using this method.[13] On the average, measured G was 0.46, indicating that the ventricles had geometric properties similar to an ellipse (where $G = \pi/6 \approx 0.52$). $V_{myocardium}$ determined by this postmortem calibration correlated well with left ventricular myocardial weights ($r=0.81$) and with the volume axis intercept of the ESPVR at baseline measured in the alive animal ($r=0.96$). Therefore, in Equation 1, instead of subtracting $V_{myocardium}$ determined postmortem, we subtracted the volume axis intercept of the ESPVR at baseline measured in the alive animal and used this as the zero volume reference for all subsequent measurements of volumes in the alive animal.

As an additional in vivo calibration, we compared stroke volume determined from ultrasonic crystal dimension measurements to stroke volume determined from thermodilution cardiac output measurements. The regression line passes through the origin and shows reasonable correlation ($r=0.76, p<0.001$), but stroke volume determined by thermodilution overestimated stroke volume determined from crystal measurements by 24%. Our data do not indicate why this overestimate occurred, but possibly, the volume of the aortic outflow tract and other regions, which do not fit the ellipsoidal shape assumption, contribute to this.

The ESPVR, with slope E_{max} and volume intercept V_0, was determined as the best-fit line through points of maximum elastance from two steady-state beats, two aortic cross-clamp beats, and four beats during the vena caval occlusion (Figure 1). To do this, simultaneous left ventricular pressure and volume measurements were digitally sampled at 250 Hz during steady state and during brief aortic cross-clamping and at 100 Hz during an 8-second vena caval occlusion. The short duration of the vena caval occlusion was chosen to sample data before reflex changes in contractility occurred. Likewise, the aorta was cross-clamped for only one beat to avoid the Anrep effect[17] and reflex changes in contractility. End-diastolic and end-systolic volumes were determined from steady-state pressure-volume loops.
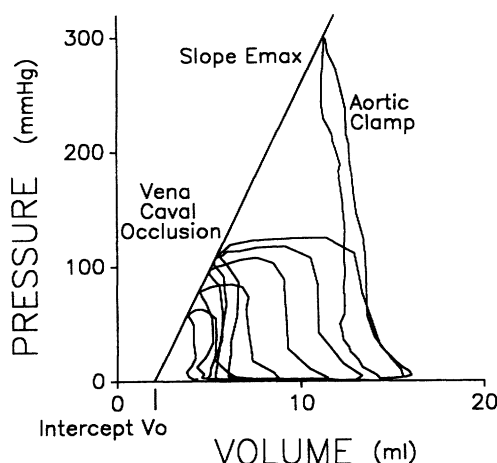
FIGURE 1.   *Left ventricular pressure (ordinate) and left ventricular volume (abscissa) draw pressure-volume loops for six heart beats in one set of one experiment. The end-systolic pressure-volume relation, having slope E_{max} and volume intercept V_0, was determined as the best-fit line through points of maximum elastance from beats during steady state, vena caval occlusion, and aortic cross-clamping.*
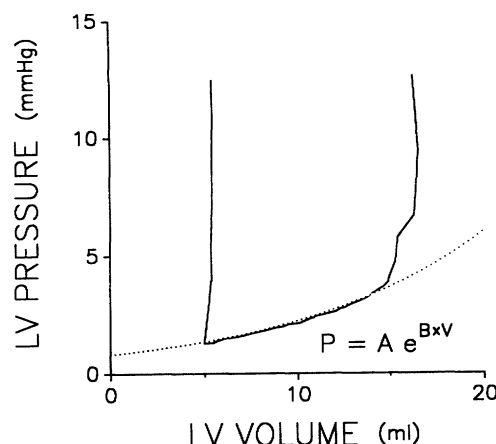

FIGURE 2.   *To test for changes in left ventricular compliance, diastolic pressure-volume points were fit with Equation 2. A typical fit of this equation to the data is illustrated. Neither respiratory acidosis nor β-blockade acutely altered diastolic compliance. Note that the pericardium has been opened in this preparation.*

The ESPVR has been shown to be superior to other indexes of contractility because it is less sensitive to changes in preload and afterload,[11,12] which change during respiratory acidosis. Nevertheless, to facilitate comparison to previous studies, we measured additional ejection phase and isovolumic indexes of contractility. First, the ejection fraction was calculated as end-diastolic volume minus end-systolic volume, all divided by end-diastolic volume. Second, the time derivative of left ventricular pressure (dP/dt) was calculated using the Lagrange five-point formula,[18] and maximum dP/dt was determined. Third, the end-systolic volume at an end-systolic pressure of 100 mm Hg was determined by interpolation of the ESPVR. This combines the information contained in E_{max} and V_0, avoids extrapolation of the data (as is done in determining V_0), and may be a more consistent indicator of variations in the contractile state.[19] To exclude the possibility that ventricular systolic resistance[20] modifies our observations, we measured maximum left ventricular elastance (E_{max-s}) and the volume intercept (V_{0-s}) using the flow-clamp technique reported by Shroff et al[20] to determine the ESPVR. Specifically, we determined the flow-clamp ESPVR as the line through the aortic clamp end-systolic pressure-volume point and an end-systolic point late (8 seconds) after onset of vena caval occlusion. The aortic clamp point was at zero flow, and the measured flow at the late vena caval occlusion point was always less than 35 ml/sec (mean flow, 19 ml/sec).

Diastolic left ventricular pressure (P) and volume (V) curves were fit using the exponential equation

$$P = Ae^{BV} \qquad (2)$$

exactly as described by Alderman and Glantz[21] (Figure 2). The fitted parameters, A and B, provided objective measurements of diastolic stiffness to determine whether there was a change during any intervention.

Experimental Protocol

After instrumentation, the animals were allowed to stabilize for 1 hour. Every subsequent experimental set of measurements was preceded by a 20-minute stabilization period so that measurements were made during steady state. First, measurements were made during eucapnic breathing; second, after induction of respiratory acidosis to approximately pH 7.1; third, after return to stable eucapnic breathing. Then, propranolol (2 mg/kg) was administered to produce β-blockade for the remaining 90 minutes of the experiment. This dose of propranolol has been shown to abolish response to infused β-agonists for 4 hours.[14,22] To confirm β-blockade, we infused 6 μg of isoproterenol at the end of the experiment in two of the dogs and observed no change in heart rate, blood pressure, or the end-systolic pressure-volume point. After the propranolol was administered, measurements were repeated before, during, and after respiratory acidosis, as described for the first three sets of measurements.

Respiratory acidosis was induced by increasing the inspired CO_2 fraction without altering ventilator settings. In five dogs, an additional set was added after the non–β-blocked respiratory acidosis set. In this additional set, P_{CO_2} was increased further to observe the effect of severe respiratory acidosis (pH 6.9).

At each set, measurements were made of arterial blood gases, hematocrit, and temperature. Right atrial pressure, pulmonary artery pressure, aortic pressure, left ventricular pressure, ultrasonic crystal diameters, and thermodilution cardiac output (repeated three times) were measured during steady state at end expiration. Then, left ventricular pres-

TABLE 1. Variables Related to Arterial Blood Gas Measurements in 10 Dogs

	Before β-blockade		After β-blockade	
	Eucapnia	Respiratory acidosis	Eucapnia	Respiratory acidosis
pH	7.42±0.02	7.09±0.04*	7.42±0.01	7.09±0.02*
P_{CO_2} (mm Hg)	38±2	92±9*	39±2	94±9*
P_{O_2} (mm Hg)	158±36	155±32	157±18	161±24
Temperature (°C)	37.5±0.4	37.7±0.4*	37.9±0.4	38.2±0.4*
Hematocrit (%)	41±3	44±3†	42±6	43±6

Values are mean±SD.
*$p<0.01$ vs. eucapnia (*t* test).
†$p<0.05$ vs. eucapnia (*t* test).

sure and diameters were sampled during a one-beat aortic cross-clamp repeated twice. Finally, left ventricular pressure and diameters were sampled during an 8-second vena caval occlusion.

Data Analysis

We used a repeated-measures analysis of variance with two trial factors[23] to test the null hypotheses that E_{max} and V_0 did not change. When a significant difference was found at the $p<0.05$ level, specific differences between sets were identified by a *t* test corrected for multiple comparisons with the procedure of Holland and DiPonzio Copenhaver.[24] The same analysis was performed on variables listed in Tables 1–3 to highlight changes in measured variables. No difference was found in any measured variable from the eucapnic set before initiation of respiratory acidosis to the eucapnic set after recovery from respiratory acidosis. Therefore, to simplify presentation in tables and figures, we averaged data from the eucapnic sets. Data are summarized as mean±SD throughout the text and tables.

Results

Elevation of the inspired CO_2 fraction produced a constant respiratory acidosis (Table 1) within 10 minutes, and reduction of the inspired CO_2 fraction reversed the respiratory acidosis as quickly. All changes in hemodynamics and left ventricular mechanics appeared to follow P_{CO_2} levels closely, with no observed time lag. No important changes in arterial oxygenation or hematocrit occurred (Table 1). We noticed that in all dogs temperature rose slightly during respiratory acidosis and then decreased on return to eucapnic breathing (Table 1). We adjusted our heating circuit to minimize these temperature changes.

Before β-blockade, respiratory acidosis (pH 7.09, P_{CO_2} 92 mm Hg) reduced left ventricular contractility by a 19% decrease in E_{max} ($p<0.01$) (Figure 3, Table 2), resulting in a 2.3-ml increase in end-systolic volume ($p<0.05$, Table 3). V_0 did not change. End-diastolic volume increased approximately the same amount (2.8 ml) as end-systolic volume so that stroke volume was unchanged. The increase in diastolic volume was accompanied by a small but not significant rise in end-diastolic pressure along an un-

changed diastolic pressure-volume relation, as measured by the unchanged exponential fitting parameters A and B (Table 3). Severe respiratory acidosis (pH 6.89±0.03, P_{CO_2} 162±22 mm Hg) reduced left ventricular contractility by decreasing E_{max} a further 21% ($p<0.01$) with no change in V_0.

Despite decreased contractility, cardiac output increased by 23% ($p<0.01$), with a similar increase in heart rate (26%, $p<0.05$, Table 3). Mean aortic pressure did not change, so systemic vascular resistance (difference between mean aortic pressure and right atrial pressure divided by cardiac output) decreased by 26% ($p<0.01$), suggesting arterial vasodilation. A further effect of respiratory acidosis on the peripheral vascular bed resulted in an increase in
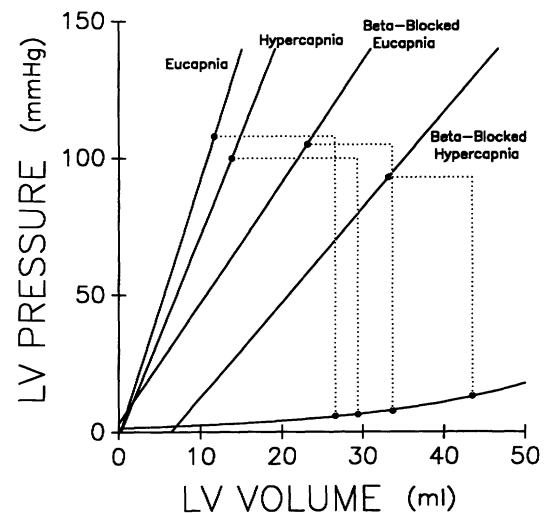

FIGURE 3. *Average end-systolic pressure-volume relations for all experimental conditions are illustrated as continuous lines, as is the invariant diastolic pressure-volume relation. The interrupted lines connect closed circles, indicating the end-diastolic volume and end-systolic pressure for each condition. Before β-blockade, respiratory acidosis decreases contractility (decrease E_{max} with no change in V_0), and end-systolic volume increases. Stroke volume is maintained by an equal rise in end-diastolic volume along essentially the same diastolic pressure-volume relation. After β-blockade, respiratory acidosis decreases stroke volume slightly, but both end-systolic and end-diastolic volumes are markedly increased. LV, left ventricular.*

TABLE 2.   Measures of Left Ventricular Contractility in 10 Dogs

	Before β-blockade		After β-blockade	
	Eucapnia	Respiratory acidosis	Eucapnia	Respiratory acidosis
E_{max} (mm Hg/ml)	11.4±5.5	9.2±4.6*	4.6±0.8	3.6±0.8*
V_0 (ml)	0.2±1.3	0.3±2.6	−0.7±4.8	6.4±5.5*
End-systolic volume at 100 mm Hg (ml)	11.0±4.2	13.8±5.2*	22.4±6.8	35.3±9.6*
Maximum dP/dt (mm Hg/sec)	2,990±780	2,790±850*	1,550±250	1,410±290*
Ejection fraction (%)	47±11	42±12†	22±9	15±7*
E_{max-s} (mm Hg/ml)	10.8±5.4	8.7±4.0*	4.7±1.3	3.8±0.9*
V_{0-s} (ml)	1.5±3.4	1.0±3.9	2.0±6.0	8.1±5.4*

Values are mean±SD.
*$p<0.01$ vs. eucapnia (*t* test).
†$p<0.05$ vs. eucapnia (*t* test).

venous return (equals cardiac output) at an unchanged right atrial pressure despite decreased left ventricular contractility.

During eucapnic breathing, β-blockade reduced contractility by a 50% decrease in E_{max} ($p<0.01$) with no change in V_0 (Figure 3, Table 2). The decrease in E_{max} resulted in a 9.4-ml increase ($p<0.01$) in end-systolic volume (Figure 4, Table 3). End-diastolic volume increased less (4.3 ml) along an unchanged diastolic pressure-volume relation, so stroke volume decreased significantly. Cardiac output and heart rate fell at the same blood pressure (Table 3).

During β-blockade, respiratory acidosis further reduced E_{max} by 22% ($p<0.01$) (Figure 3, Table 2). V_0, which previously had not changed, now increased to 6.4±5.5 ml above baseline V_0 ($p<0.01$). The combination of decreased E_{max} and increased V_0 resulted in a large increase (10.3 ml, $p<0.01$) in end-systolic volume despite a 13% fall in mean aortic pressure ($p<0.01$). Stroke volume fell significantly,

but the decrease was attenuated by the fall in aortic pressure and by an increase in end-diastolic volume along an unchanged diastolic pressure-volume relation. The decrease in aortic pressure was partly accounted for by a 20% decrease in systemic vascular resistance ($p<0.01$). Under these β-blocked conditions, cardiac output did not increase even though heart rate increased and mean aortic pressure fell.

Additional isovolumic and ejection phase indexes of contractility (Table 2) support the observation that respiratory acidosis depressed contractility. The increase in end-systolic volume during respiratory acidosis was greater after β-blockade (10.3±3.8 ml) than before (2.3±2.9 ml) ($p<0.001$) even though end-systolic pressure decreased more after β-blockade than before (Table 3). After β-blockade, respiratory acidosis also resulted in a greater decrease in ejection fraction ($p<0.05$), and a greater increase in end-systolic volume interpolated at an end-systolic pressure of 100 mm Hg ($p<0.001$). There were no signif-

TABLE 3.   Hemodynamics and Left Ventricular Mechanics in 10 Dogs

	Before β-blockade		After β-blockade	
	Eucapnia	Respiratory acidosis	Eucapnia	Respiratory acidosis
Heart rate (beats/min)	96±27	121±34*	81±20	106±6†
Mean aortic pressure (mm Hg)	108±10	100±8	107±11	93±11†
Cardiac output (l/min)	1.68±0.6	2.06±0.8†	1.11±0.4	1.20±0.4
Systemic vascular resistance (mm Hg/l/min)	70±24	51±16†	106±40	84±36†
Right atrial pressure (cm H_2O)	4.4±1.2	4.5±1.3	5.4±1.6	6.6±1.6*
Left ventricular end-diastolic pressure (mm Hg)	5.8±1.5	6.3±2.0	7.5±1.6	13.0±2.8†
Left ventricular end-diastolic volume (ml)	26.6±6.6	29.4±8.2	33.7±7.0	43.5±7.9†
Left ventricular end-systolic volume (ml)	14.6±4.6	16.9±5.4*	26.3±5.5	36.6±6.2†
Diastolic parameter A (mm Hg)	1.4±1.2	1.2±1.1	1.1±0.8	1.0±0.7
Diastolic parameter B (ml⁻¹)	0.10±0.04	0.08±0.03	0.08±0.02	0.07±0.02

Values are mean±SD.
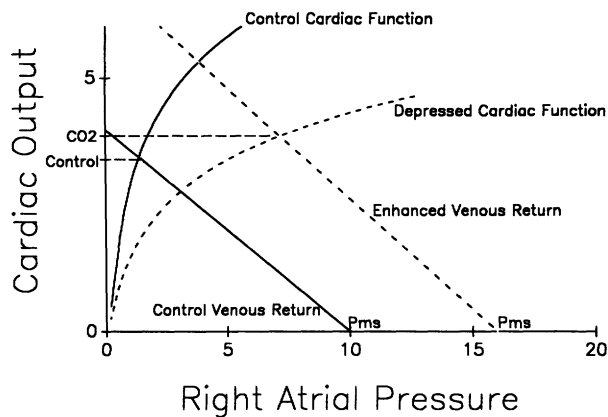*$p<0.05$ vs. eucapnia (*t* test).
†$p<0.01$ vs. eucapnia (*t* test).

FIGURE 4. *Schematic cardiac function and venous return curves are before β-blockade illustrated for control (continuous lines) and respiratory acidosis (interrupted lines). Respiratory acidosis increases mean systemic pressure (P_{ms}) from 10 to 16 mm Hg, as occurs during epinephrine infusion, but decreases contractility so that hypercapnic venous return curves intersect the decreased cardiac function curve at a higher cardiac output and right atrial pressure than in control conditions. Respiratory acidosis also increases heart rate, which moves the decreased cardiac function curve toward the control position without increasing contractility much, so the increased right atrial pressure during respiratory acidosis is ameliorated.*

icant differences in percent change in E_{max}, E_{max-s}, and maximum dP/dt nor in absolute change in E_{max}, E_{max-s}, and maximum dP/dt. Changes of E_{max-s} and V_{0-s} are similar to changes of E_{max} and V_0, thereby excluding the possibility that systolic ventricular resistance contributes significantly.

Discussion

Our results demonstrate that acute respiratory acidosis (pH 7.09, P_{CO_2} 92 mm Hg) decreased left ventricular contractility and increased end-systolic volume by 2.3 ml, but stroke volume was maintained because end-diastolic volume increased as much. Despite decreased contractility, respiratory acidosis increased cardiac output by 23% associated with a similar increase in heart rate. After β-blockade, similar respiratory acidosis further decreased left ventricular contractility and increased the end-systolic volume by 10.3 ml. Now respiratory acidosis did not increase cardiac output even though heart rate increased and systemic vascular resistance decreased as much as before β-blockade. Taken together, these findings are consistent with the hypothesis that respiratory acidosis stimulates β-adrenergic reflexes[25,26] to increase venous return[27,28] and to ameliorate the reduction of cardiac pumping function induced by myocardial intracellular acidosis.[29,30]

Effect of Respiratory Acidosis on Left Ventricular Contractility

We found that respiratory acidosis directly decreases left ventricular contractility in this whole-animal preparation in accord with isolated muscle studies[3–5] and excised heart studies.[6,7] Because preload and afterload are known to change during respiratory acidosis,[8–10] we chose to measure the ESPVR as a relatively preload- and afterload-insensitive indicator of contractility.[11,12] Had we chosen, as others previously have, cardiac output,[8,9] left ventricular minute work,[8] or even left ventricular function curves[10] (we found that cardiac output was increased at the same right and left atrial pressures) as an index of contractility, we would have concluded that contractility was not depressed during respiratory acidosis from the present data, identical to previous whole-animal studies of respiratory acidosis when P_{CO_2} was less than 350 mm Hg.[8–10] Our measurements of pressure-volume trajectories demonstrate decreased contractility and show that the increase in cardiac output, left ventricular minute work, and left ventricular function curve are accounted for by increased preload, decreased afterload, and increased heart rate associated with the effect of respiratory acidosis on the peripheral circulation and cardiovascular reflexes. Thus, the difference between in vitro and whole-animal studies may be partly accounted for by the previous use of indexes of contractility in whole-animal studies that were confounded by changes in preload, afterload, and heart rate.

When the β-receptor response is blocked, the rightward shift of the ESPVR during respiratory acidosis is even more pronounced (Figure 3), as indicated by a greater increase in end-systolic volume after β-blockade (10.3 ml) than before (2.3 ml) ($p < 0.001$). This suggests that the known adrenergic response to respiratory acidosis[25,26] negates some of the direct reduction of contractility but does not completely prevent it. The hypothesis that contractility decreased more during respiratory acidosis after β-blockade than before β-blockade is supported by the greater increase in the end-systolic volume interpolated from the ESPVR to a pressure of 100 mm Hg (an index that incorporates both E_{max} and V_0) and the greater fall in ejection fraction. Little support for or against this hypothesis is given by the nonsignificant differences in percent change in E_{max}, E_{max-s}, and maximum dP/dt and absolute change in E_{max}, E_{max-s}, and dP/dt during respiratory acidosis before and after β-blockade. These tests in this setting were less sensitive indicators of changes in contractility. Furthermore, maximum dP/dt is a preload-dependent index of contractility, and preload increased during respiratory acidosis. We favor the interpretation of these data to indicate that myocardial contractility is better preserved when the β-adrenergic system is intact, because the end-systolic ventricle dilated less before β-blockade than after. Yet these data do not equivocally exclude the possibility that the contractility response of the left ventricle to respiratory acidosis was the same before and after β-blockade, and we note that the heart rate response to respiratory acidosis was unaltered by β-blockade.

A second reason for conducting this study was to determine the effect of respiratory acidosis on E_{max} and V_0 and to compare this to the effect of propranolol and to the previously reported effect of hypoxia.[13] Inotropic agents affecting intracellular calcium concentration have been shown to change E_{max} with no significant change in V_0.[12] Respiratory acidosis and hypoxia contrast these agents at the cellular level as they both can decrease contractility without altering intracellular calcium transients.[31] In a whole-animal preparation, we previously found that hypoxic reduction of left ventricular contractility is quite different from other inotropic agents in that progressive hypoxia resulted in a large increase in V_0.[13] Because part of the depressant effect of hypoxia is thought to be due to the concomitant intracellular acidosis,[29,30] we wondered if the intracellular acidosis induced by respiratory acidosis would also increase V_0. We found that respiratory acidosis did not result in an increased V_0 at a pH of 7.1 nor at a pH of 6.9. Respiratory acidosis, like propranolol treatment, resulted in a decrease in E_{max}. Accordingly, we conclude that hypoxia and respiratory acidosis do not mediate all of their myocardial depressant effects in the same way.

Effect of Respiratory Acidosis on Venous and Arterial Circulation

Despite an increased end-systolic volume caused by reduced myocardial contractility, stroke volume does not decrease, and cardiac output actually increases during respiratory acidosis before β-blockade. Because the passive diastolic pressure-volume filling curve did not change, the increase in diastolic filling and cardiac output must be attributable to factors outside the heart, namely, an increase in factors promoting venous return. Either mean systemic pressure increases or resistance to venous return decreases during respiratory acidosis[32] (Figure 4). A rise in mean systemic pressure may be caused by increased circulating catecholamines[27,28] associated with respiratory acidosis.[25,26] A fall in resistance to venous return conceivably could be caused by redistribution of blood flow to fast time constant vascular beds.[33] Our observation that propranolol administration attenuates the ability of the peripheral circulation to increase venous return suggests that at least part of the effect of respiratory acidosis on venous return is mediated by β-receptors.

Respiratory acidosis increased heart rate, and we propose that this promoted venous return. The increase in heart rate results in a decreased stroke volume. Because systolic pressure and volume do not change substantially with heart rate, the smaller stroke volume means end-diastolic pressures and volumes will be reduced. The associated reduction in atrial pressure is an important factor promoting venous return.[32] Thus, we conclude that increased heart rate associated with respiratory acidosis allowed end-diastolic pressures to be maintained

despite depressed systolic contractility, thereby promoting venous return.

Respiratory acidosis has a known vasodilator effect.[8,9,33] Our data reflect this as a decrease in systemic vascular resistance. While propranolol treatment results in an increase in systemic vascular resistance by blocking the vasodilating vascular β-receptors, β-blockade does not substantially alter the percent change in systemic vascular resistance produced by respiratory acidosis. This is consistent with a direct vasodilating effect of carbon dioxide on the resistance arterial vessels.

In summary, the net effect of respiratory acidosis on the circulation is to increase cardiac output in the face of decreased left ventricular contractility by an increase in factors promoting venous return and by a fall in systemic vascular resistance. After β-blockade, contractility falls more markedly and the venous return response is attenuated, suggesting that contractility and venous return are substantially supported by the adrenergic response to respiratory acidosis.

Effect of Anesthesia, Pericardiectomy, and Ventilation

At the relatively low starting heart rates in this study, we observed an increase in heart rate during respiratory acidosis. Heart rate response has been shown to depend on the starting heart rate and anesthetic agent.[34] Specifically, respiratory acidosis decreases initially high heart rates but increases low heart rates.[34] By testing the chronotropic effect of respiratory acidosis with different anesthetic agents before and after vagotomy, atropine injection, decapitation, destruction of the sinus node, and denervation of the carotid sinus, the same authors suggest that the chronotropic effect of respiratory acidosis involves both peripheral and central receptors acting through vagal efferents. To the extent that our β-blockade was complete, our results also suggest that the stimulus to increased heart rate must involve more than just reflex sympathetic response, because we observed increased heart rate during respiratory acidosis even after β-blockade.

Despite differences in heart rate observed in this and other studies, using various anesthetics and starting heart rates, our results are similar in observing hypercapnic increases of cardiac output and cardiac function[8–10,35] despite decreased contractility.[3–7,35] Therefore, the specific choice of anesthetic appears not to alter the main conclusions.

Thoracotomy and pericardiotomy alter the diastolic pressure-volume relation by mechanical interaction of the heart, pericardium, and lungs; yet, systolic function is not markedly affected.[16] Therefore, the finding of decreased systolic contractility during respiratory acidosis is not likely to be an artifact of the surgical preparation. Conversely, venous return is influenced by diastolic pressures and conceivably would be different in a closed-chest model. In particular, intact pericardium may raise atrial pressure and limit venous return more than in our study, especially when reduced contractility

raises end-systolic volume such that end-diastolic volume must increase to maintain stroke volume. Nevertheless, studies done in open-chest[35] versus closed-chest[8] preparations appear to have a similar result, increased venous return during respiratory acidosis. Likewise, mechanical ventilation may influence the interaction of heart and lungs and alter diastolic function. In the present study, we attempted to avoid influence of mechanical interaction of the heart and lungs by keeping ventilator settings constant (only the inspired CO_2 fraction was changed) and by reducing contact between heart and lungs by using a pericardial support for the heart.

Clinical Implications

These data are far removed from clinical studies but highlight some potentially important ideas. Common clinical indexes of cardiac pumping function (cardiac output, arterial pressure, etc.) may mask significant depression of myocardial contractility that occurs during acute respiratory acidosis. The effect of respiratory acidosis on contractility and venous return may be even more important in patients having attenuated ability to mount a reflex sympathetic response, because the compensatory response depends to some extent on β-adrenergic reflexes. Because the depression of contractility is rapidly reversible after normalization of P_{CO_2}, an effective treatment is to reverse the respiratory acidosis by increasing alveolar ventilation.

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