

Mitral and Aortic Blood Flows during Spontaneous Respiration in Dogs

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Left sided hemodynamic events during respiration remain a controversial subject. Left ventricular (LV) hemodynamic events were evaluated during obstructed and partially obstructed inspiration in anesthetized dogs acutely instrumented with mitral (\dot{Q}_m) and ascending aortic (\dot{Q}_a) flow probes. This allows classification of the inspiratory decrease in LV stroke volume as either a diastolic event (e.g., ventricular interdependence) in which case the LV inflow volume ($\int \dot{Q}_m$) should decrease before the LV outflow volume ($\int \dot{Q}_a$), or a systolic event (e.g., afterload or contractility) in which case outflow ($\int \dot{Q}_a$) should decrease before inflow ($\int \dot{Q}_m$). During either unobstructed ($n = 8$) or partially obstructed ($n = 5$) spontaneous ventilation, $\int \dot{Q}_m$ reached both its inspiratory minimum and expiratory maximum prior to the associated minimum and maximum values for $\int \dot{Q}_a$ in 80% or more of the respiratory cycles. Thus, a diastolic event dominates both in reducing the subsequent LV outflow during the inspiratory fall in intrathoracic pressure and in increasing LV outflow during the expiratory increase in intrathoracic pressure. However, because a diastolic event did not occur first at all times, a systolic event must also be present. If a rapid change in intrathoracic pressure occurred during diastole, $\int \dot{Q}_m$ invariably immediately increased. If a rapid change in intrathoracic pressure occurred during systole, $\int \dot{Q}_a$ could change independently of the preceding $\int \dot{Q}_m$. Both systolic and diastolic mechanisms contribute to the inspiratory fall in LV output. These mechanisms will not be clearly delineated without evaluating the effects of intrathoracic pressure within a single cardiac cycle. (Key words: Animal: dog, Heart, left ventricle; Ventricular interdependence; Pulsus paradoxus; Cardio-respiratory interactions.)

LEFT SIDED hemodynamic events during spontaneous ventilation, e.g., pulsus paradoxus, particularly with airway obstruction, have been a focus of controversy among physiologists for over a century.¹ The anesthesiologist is routinely required to care for patients with variable degrees of airway obstruction. Many of these patients have primary left ventricular (LV) dysfunction. The clinical implications of airway obstruction on left sided hemo-

dynamic events depend on the basic pathophysiology. We have studied the hemodynamic events during respiration by determining the instantaneous changes in LV inflow and outflow throughout each respiratory cycle. Although there is no argument that an inspiratory decrease in pleural pressure will increase systemic venous return and right ventricular (RV) output, there is considerable discussion regarding the physiologic mechanism(s) responsible for the simultaneous decrease in LV output.¹⁻⁴ The measurement of mitral valve blood flow allows the major hypotheses for the decrease in LV output to be grouped as diastolic or systolic events. Thus, during inspiration any primary pooling of blood in the pulmonary vascular bed or left atrium, leftward ventricular septal shift (ventricular interdependence), or pulmonary compression of the heart (heart-lung interdependence) will first reduce the integrated mitral inflow volume ($\int \dot{Q}_m$) and hence LV end-diastolic volume and then the subsequent LV stroke volume measured as the integrated ascending aortic flow ($\int \dot{Q}_a$). Conversely, an inspiratory increase in LV afterload or decrease in inotropic state will primarily reduce LV stroke volume causing an increase in the LV end-systolic volume. The increased LV volume as the next diastolic period begins will result in an initially higher LV diastolic pressure and hence reduce mitral flow. With this information the decrease in LV output can be ascribed to either a diastolic (preload) event or a systolic (afterload/contractility) event. Because both increases and decreases in LV volumes have been associated with the decrease in LV output and arterial pressure during a decrease in intrathoracic pressure,¹⁻⁴ the simultaneous measurements of both $\int \dot{Q}_m$ and $\int \dot{Q}_a$ should allow determination of whether diastolic or systolic mechanisms dominate in determining the change in LV output. A consistent pattern in which changes in $\int \dot{Q}_m$ always preceded changes in $\int \dot{Q}_a$ would mean that diastolic events dominate in determining LV output. A consistent pattern of changes in $\int \dot{Q}_a$ always preceded changes in $\int \dot{Q}_m$ would mean that systolic events dominate. If both diastolic and systolic events significantly contribute to the decrease in LV output, then a consistent temporal relationship between changes in $\int \dot{Q}_m$ and $\int \dot{Q}_a$ would not be expected during every respiratory cycle.

Methods

Eight mongrel dogs weighing 25-35 kg were anesthetized with sodium pentobarbital (30 mg/kg iv). Following

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intubation of the trachea with a 10-mm endotracheal tube, the lungs were ventilated with a positive pressure volume ventilator (Harvard Apparatus Co., So. Natick, Massachusetts). Pentobarbital (65–130 mg iv every 60–90 min) was used to maintain anesthesia but permit spontaneous ventilatory efforts. Arterial and venous catheters and an arterial cannula for cardiopulmonary bypass were inserted. An electrocardiogram was obtained from limb leads and a left thoracotomy was performed. Following anticoagulation (heparin 300 U/kg), the vena cava was cannulated, and complete cardiopulmonary bypass instituted utilizing a bubble oxygenator (Bard Co., Santa Ana, California). The circuit was primed with approximately 500 ml of blood and 6% Dextran added as needed. The coronary circulation was perfused from an aortic cannula with an ice-cold cardioplegic solution until the heart was palpably cold and the coronaries visually cleared of blood. Through a left atrial incision the circular (50 or 55 mm circumference) electromagnetic flow probe (Carolina Medical Electronic Instruments, Inc., King, North Carolina) was sewn directly over the mitral valve annulus such that on visual and manual inspection the probe was firmly seated. The electrical cable from the mitral valve flow probe and a left atrial high fidelity catheter (Millar Inc., Houston, Texas) were brought out through the appendage. A high fidelity manometer (Königsberg Instrument Co., Pasadena, California) and calibrating saline-filled catheter were placed in the LV through the apical dimple. The high-fidelity catheters were initially stabilized and calibrated *in vitro* in a water bath at 35° C and adjusted *in vivo* to match the saline-filled catheter pressures measured with Statham P23b transducers (Gould, Inc., Cleveland, Ohio). An electromagnetic flow probe (In Vivo Metric Inc., Healdsburg, California) was securely placed around the ascending aorta. Cardiopulmonary bypass was discontinued, and anticoagulation antagonized with protamine sulfate (1 mg/100 U of heparin). Intermittent arterial blood gases were obtained and appropriate adjustments were made in the ventilator settings, or sodium bicarbonate was given to correct abnormalities. The minimal left atrial pressure compatible with hemodynamic stability during spontaneous ventilation was studied in each dog. In three dogs a degree of postbypass myocardial depression was evident throughout the period of data collection, requiring an epinephrine infusion to stabilize the circulatory status sufficiently to allow spontaneous respiration. In four dogs following acquisition of data at low LV filling pressures associated with stable hemodynamic conditions, a combination of gradual temporal deterioration and plasma volume loading elevated LV end-diastolic pressure allowing comparison of the hemodynamic events during both conditions. In three dogs a bilateral cervical vagotomy was performed to slow the respiratory rate.

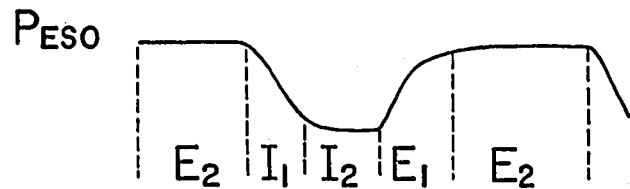


FIG. 1. Schematic representation of the categorization of the respiratory cycle based on the esophageal pressure. E₂ = end expiration those beats occurring when esophageal pressure has plateaued during expiration; I₁ = early inspiration, those beats occurring as esophageal pressure falls toward its minimum values; I₂ = peak inspiration, those beats occurring as esophageal pressure approaches and reaches its minimum values; E₁ = early expiration, beats occurring as esophageal pressure increases toward the baseline values at end expiration.

A saline-filled pulmonary artery catheter was inserted in the pulmonary artery directly or a right atrial catheter positioned from the right external jugular vein. The bypass cannulae were removed and the pericardium loosely reapproximated with interrupted sutures allowing any accumulated blood to drain. Bilateral pleural tubes were inserted, the cables and catheters brought out through the chest wall, the chest closed airtight, and the pleural space evacuated by hyperinflation and pleural suction. Spontaneous ventilation was resumed with the dogs breathing an oxygen-enriched gas mixture. A thin latex esophageal balloon, 7 cm long, with 0.5 ml of air over PE190 tubing with multiple side holes and an unstressed volume over 3 ml, was positioned in the distal one-third of the esophagus.

All pressure measurements were referenced to the midchest level with the dog lying in the right lateral decubitus position. Flow probe signals were filtered with a 10 or 30 Hz cutoff with synchronized gating to improve signal acquisition.

DATA ACQUISITION AND REDUCTION

Recordings were made at 100 mm/s paper speed in eight dogs during unobstructed spontaneous respiration and during partial inspiratory obstruction obtained by partially occluding the inspiratory port of a one-way valve attached to the endotracheal tube. In three dogs frequent arrhythmias during partial inspiratory obstruction precluded evaluation. At least four beats following an arrhythmia were rejected. As in our prior studies the respiratory cycle was divided into four parts^{5,6} (fig. 1).

Net LV inflow ($\int \dot{Q}_m$) was determined by integrating the total positive area above zero mitral flow obtained during systole and subtracting the negative deflection in early systole as the mitral valve closed. This seemed a reasonable approach based on prior studies relating the flow probe signal to mitral valve motion.^{7–11} LV output ($\int \dot{Q}_a$) was determined by planimetry of the area under the aortic flow trace. LV inflow and output volumes were

averaged for each phase of the respiratory cycle and the end-expiratory values assigned a relative value of 100% for comparison with the other phases of respiration. The zero flow was checked for each flow probe at the conclusion of the study following cessation of cardiac activity produced with an overdose of pentobarbital and potassium chloride.

The critical element of this study was comparison of the timing of the changes in LV inflow and outflow during respiration. To improve the signal for data reduction, the gain of the aortic and mitral flows were adjusted frequently to give the largest signal that remained within the pen range over the entire respiratory cycle.

RATIONALE FOR ANALYSIS

The relatively slow fall in pleural pressure during inspiration frequently made a consistent sharp change in either $\int \dot{Q}_m$ or $\int \dot{Q}_a$ difficult to define. Although small decreases in both $\int \dot{Q}_m$ and $\int \dot{Q}_a$ were immediately apparent when pleural pressure decreased, discerning whether $\int \dot{Q}_m$ or $\int \dot{Q}_a$ decreased first proved to be exceedingly difficult. This was in part because it was not unusual that a small degree of respiratory variation in both $\int \dot{Q}_m$ and $\int \dot{Q}_a$ was still present in late expiration, *i.e.*, a slow decline in both $\int \dot{Q}_m$ and $\int \dot{Q}_a$ was often present just prior to the inspiratory decrease in pleural pressure. This complex set of cyclically interacting factors can be evaluated by determining which integrated flow (*i.e.*, $\int \dot{Q}_m$ or $\int \dot{Q}_a$) reached its minimum and maximum first. That is, if preload conditions exclusively determined the respiratory variation in LV output, then $\int \dot{Q}_m$ should always reach its maximum and minimum values before $\int \dot{Q}_a$ and *vice-versa* if a change in afterload or contractility solely determined the change in LV output. We choose to analyze our results in this fashion because it allows a clear yes or no answer as to whether diastolic or systolic events dominate in determining the respiratory-induced changes in LV output. If there exists only a diastolic event altering LV output, then changes in $\int \dot{Q}_m$ should precede changes in $\int \dot{Q}_a$ at all times. If a systolic event determines the changes in LV output, then changes in $\int \dot{Q}_a$ always should precede changes in $\int \dot{Q}_m$.

We determined the temporal sequence of the maximum and minimum $\int \dot{Q}_m$ and $\int \dot{Q}_a$ during each respiratory cycle. Every respiratory cycle was given equal weight in this analysis because a single respiratory cycle differing from the others precludes changes in either $\int \dot{Q}_m$ or $\int \dot{Q}_a$ from preceding the other 100% of the time.

STATISTICAL ANALYSIS

The parameters, esophageal pressure, transmural vascular pressures (relative to esophageal pressure), heart rate, and integrated mitral and ascending aortic blood

flows were measured for each cardiac cycle and grouped into the appropriate phase of the respiratory cycle. These data were then statistically analyzed by an analysis of variance (ANOVA) for repeated measures with Duncan's multiple range tests applied to define differences within the phases of the respiratory cycle.

The number of respiratory cycles in which $\int \dot{Q}_m$ or $\int \dot{Q}_a$ reached its respective minimum or maximum first were compared by paired *t* tests for both unobstructed and partial inspiratory obstruction conditions. The average integrated mitral and aortic flows as a percent of their end-expiratory values (E_2) were meaned for each dog and an ANOVA with repeated measures carried out. When a *P* value less than 0.05 was found, a Duncan's multiple range test was performed between the flows for each part of the respiratory cycle.

Results

The characteristic pattern of mitral blood flow during apnea was consistent with reports of other groups.⁷⁻¹¹ Both early passive filling and late active filling were observed with slow heart rates. At fast heart rates separation of the two components was not evident.

SPONTANEOUS UNOBSTRUCTED VENTILATION

A total of 85 inspirations were analyzed in eight dogs. $\int \dot{Q}_m$ reached its minimum value before $\int \dot{Q}_a$ in 68 inspirations (80%), and $\int \dot{Q}_a$ reached its minimum first in 17 inspirations (20%). Data without arrhythmias were available during expiration in 78 of the 85 respiratory cycles to evaluate which integrated flow reached its respective maximum first (table 1). In 66 respiratory cycles (85%) $\int \dot{Q}_m$ reached its maximum before $\int \dot{Q}_a$, whereas $\int \dot{Q}_a$ reached its maximum prior to $\int \dot{Q}_m$ in 12 respiratory cycles (15%). Thus, $\int \dot{Q}_m$ led $\int \dot{Q}_a$ both in reaching its minimum ($P < 0.02$) and maximum ($P = 0.01$) values during a complete respiratory cycle. However, in only one of eight dogs was a completely consistent pattern with $\int \dot{Q}_m$ leading $\int \dot{Q}_a$ observed for every respiratory cycle. Because one integrated flow did not lead the other 100% of the time, both diastolic and systolic events must determine the respiratory variation in LV output.

Within the respiratory cycle $\int \dot{Q}_m$ significantly decreased during both early ($P < 0.01$) and peak inspiration ($P < 0.01$) compared to end expiration (fig. 2). Compared to its minimum in early inspiration, $\int \dot{Q}_m$ significantly increased at peak inspiration ($P < 0.05$). $\int \dot{Q}_m$ was maximum in early expiration. In contrast, $\int \dot{Q}_a$ although significantly decreasing during inspiration ($P < 0.01$), did not significantly increase back toward baseline values until early expiration ($P < 0.01$). Thus, changes in LV inflow on the average preceded the changes in LV output.

With rapid respiratory rates the quasi-square wave

TABLE 1. Number Of Respiratory Cycles in which $\int \dot{Q}_m$ or $\int \dot{Q}_a$ Reach Their Respective Minimum and Maximum Values First

Dog	Minimum		Maximum		LVFP _{tm} (mmHg)
	$\int \dot{Q}_m$	$\int \dot{Q}_a$	$\int \dot{Q}_m$	$\int \dot{Q}_a$	
Spontaneous unobstructed respiration					
1*	2	3	5	0	7.5
2	2	3	4	1	3.1
3	10	0	5	4	14.1
4	13	0	8	1	21.9
5*	2	0	1	0	19.1
6*	7	2	8	1	10.0
7	17	6	18	4	17.5
8	15	3	17	1	13.9
Total	68	17	66	12	
Grand total	85 ($P < 0.02$)		78 ($P = 0.01$)		
Per cent	80	20	85	15	
Partial inspiratory obstruction					
1*	2	3	3	2	7.9
3	20	5	17	6	19.5
4	26	0	21	5	23.8
5*	12	0	10	0	14.2
7	6	0	6	0	15.8
Total	66	8	57	13	
Grand total	74 ($P = 0.06$)		70 ($P < 0.05$)		
Per cent	89	11	81	19	

* Postvagotomy; LVFP_{tm} = transmural LV filling pressure at E₂.

changes in pleural pressure occasionally allowed evaluation of acute decreases and increases in esophageal pressure beginning in either diastole or systole. Figure 3 demonstrates the effects of such rapid changes in pleural pressure on $\int \dot{Q}_m$ and $\int \dot{Q}_a$. From an inspiratory minimum $\int \dot{Q}_m$ increases prior to an increase in $\int \dot{Q}_a$ at the end of the first respiratory cycle. During the second inspiration $\int \dot{Q}_a$ clearly decreases independently of any prior decrease in $\int \dot{Q}_m$, whereas in early expiration $\int \dot{Q}_a$ begins to increase prior to the expiratory increase in $\int \dot{Q}_m$. During the third and fourth respiratory cycles with the rapid expiratory increase in esophageal pressure, $\int \dot{Q}_m$ increases independently of any prior increase in $\int \dot{Q}_a$. Except for the second inspiration, when $\int \dot{Q}_a$ reaches its minimum value first, $\int \dot{Q}_m$ leads in reaching its respective inspiratory minimum and expiratory maximum for the four respiratory cycles.

A slower respiratory rate is illustrated in figure 4 in which two consecutive inspirations demonstrate typical patterns of respiratory variation in the two flow traces. In both $\int \dot{Q}_m$ reaches its inspiratory minimum and expiratory maximum prior to $\int \dot{Q}_a$. The rapidity with which $\int \dot{Q}_m$ changes with an increase in esophageal pressure is evident in the second respiratory cycle (S₂) in which a substantial portion of an 12% increase in $\int \dot{Q}_m$ from the previous beat is accounted for by the late diastolic

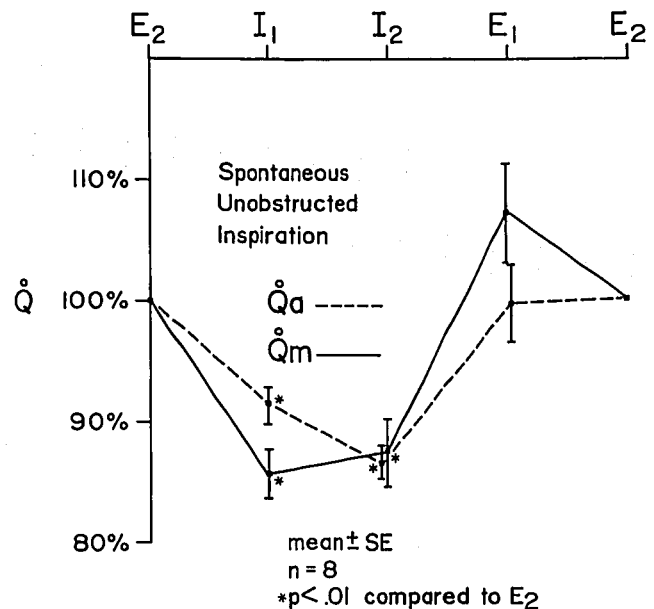


FIG. 2. Summary of results of the changes in LV output measured as the integrated ascending aortic flow (\dot{Q}_a) and LV inflow measured as the integrated mitral flow (\dot{Q}_m) during a complete spontaneous unobstructed inspiration. End expiration (E₂) is arbitrarily assigned a value of 100%, for comparison to early inspiration (I₁), peak inspiration (I₂), and early expiration (E₁). Both flows significantly decrease during the fall in pleural pressure with a change in lung volume.

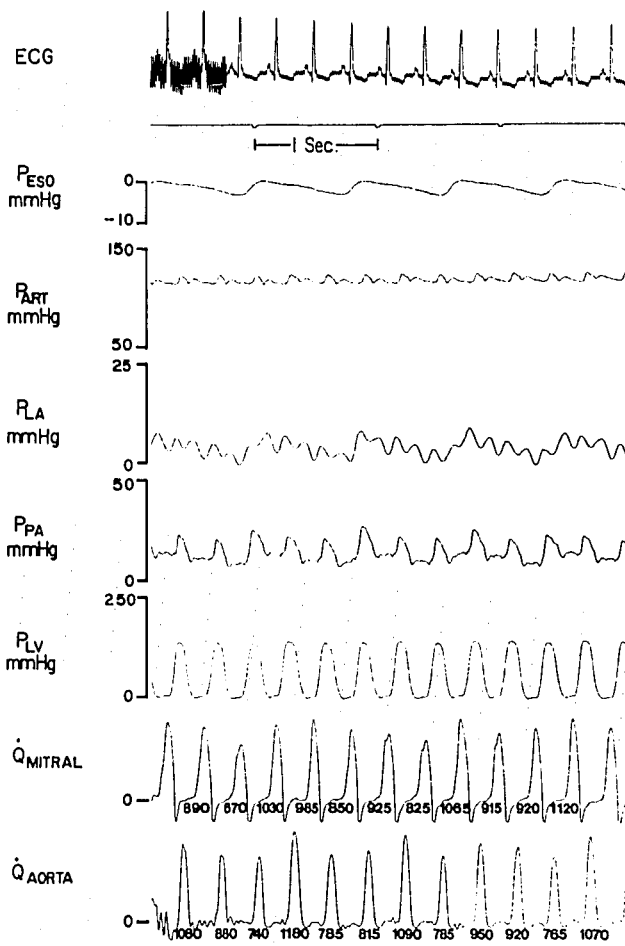


FIG. 3. Four spontaneous breaths at a rapid respiratory rate. During each respiratory cycle as indicated by the changes in the esophageal pressure (P_{ESO}), large changes in both mitral (Q_{MITRAL}) and ascending aortic (Q_{AORTA}) flows are evident. The integrated area under each flow trace is given in arbitrary units to facilitate comparison of the sequential changes. Data at this respiratory rate were not used for statistical analysis. Most importantly, during the second inspiration a large decrease in aortic flow (1,180 to 785) is preceded by only a minimal change in mitral flow (1,030 to 985) consistent with a systolic event affecting LV output independently of changes in preload. ECG = electrocardiogram; P_{ART} = arterial pressure; P_{LA} = left atrial pressure; P_{PA} = pulmonary arterial pressure; P_{LV} = left ventricular pressure; dog 1, prevagotomy.

increase in $\int \dot{Q}_m$ to the right of the vertical line. This can be compared to the first respiratory cycle (S_1) in which the 18% increase in $\int \dot{Q}_m$ as expiration occurs earlier in diastole increases both the early peak and late mitral flow.

During the inspiratory decrease in esophageal pressure (mean, 3.7 mmHg), there were significant increases at peak inspiration in the transmural LV end-diastolic ($P < 0.05$) and transmural right atrial ($P < 0.05$) pressures. The average end-expiratory transmural LV end-diastolic pressure was 14.0 mmHg (range, 3.1–21.9 mmHg). The

transmural aortic diastolic pressure increased during either early or peak inspiration in seven of eight dogs, with the early expiratory value being less than either early ($P < 0.01$) or peak ($P < 0.05$) inspiratory values (table 2).

PARTIAL INSPIRATORY OBSTRUCTION DURING SPONTANEOUS VENTILATION

A total of 74 inspirations were analyzed in five dogs. $\int \dot{Q}_m$ reached its minimum value before $\int \dot{Q}_a$ in 66 inspirations (89%) and $\int \dot{Q}_a$ reached its minimum first in eight inspirations (11%) (table 1). Expiratory data without arrhythmias were available in 70 of the 74 respiratory cycles. In 57 respiratory cycles (81%) $\int \dot{Q}_m$ reached its expiratory maximum value prior to $\int \dot{Q}_a$, whereas $\int \dot{Q}_a$ reached its expiratory maximum prior to $\int \dot{Q}_m$ in 13 respiratory cycles (19%). Although $\int \dot{Q}_m$ significantly led $\int \dot{Q}_a$ in reaching a maximum value ($P = 0.026$), on the average $\int \dot{Q}_m$ led $\int \dot{Q}_a$ in reaching a minimum value in only four of the five dogs ($P = 0.06$), dog 1 with the lowest LV end-diastolic pressure being the exception. As with spontaneous unobstructed inspiration, because changes in $\int \dot{Q}_m$ did not precede changes in $\int \dot{Q}_a$ 100% of the time, both diastolic and systolic events must determine the respiratory variation in LV output.

Within the respiratory cycle $\int \dot{Q}_m$ was significantly less during both early and peak inspiration compared to either early or end expiration ($P < 0.01$ for all comparisons). In contrast, $\int \dot{Q}_a$ was only significantly less at peak inspiration compared to end expiration ($P < 0.01$) (fig. 5).

The first $\int \dot{Q}_m$ after the expiratory increase in esophageal pressure always acutely increased, followed by an increase in the ensuing $\int \dot{Q}_a$ (fig. 6). During a prolonged inspiration after a vagotomy (fig. 7), $\int \dot{Q}_m$ gradually increased to baseline values over eight beats, and then markedly increased by 31% during the first diastolic period during expiration. This rules out a phase lag in ventricular outputs due to pulmonary transit time as the cause of the acute expiratory increase in $\int \dot{Q}_m$. When a rapid expiratory increase in esophageal pressure occurred during systole, $\int \dot{Q}_a$ did not always immediately increase (fig. 6). At other times as in figure 7, the 17% increase in $\int \dot{Q}_a$ immediately after the expiratory increase in esophageal pressure is not completely attributable to the 8% increase in $\int \dot{Q}_m$ in the prior diastolic period.

During the inspiratory decrease in esophageal pressure (mean, 6.0 mmHg) there was a significant increase in the transmural LV end-diastolic pressure with peak inspiratory values being significantly greater than both end-expiratory and early inspiratory values ($P < 0.05$). The average end-expiratory transmural LV end-diastolic pressure was 16.2 mmHg. The transmural aortic diastolic pressure increased during inspiration in four of the five

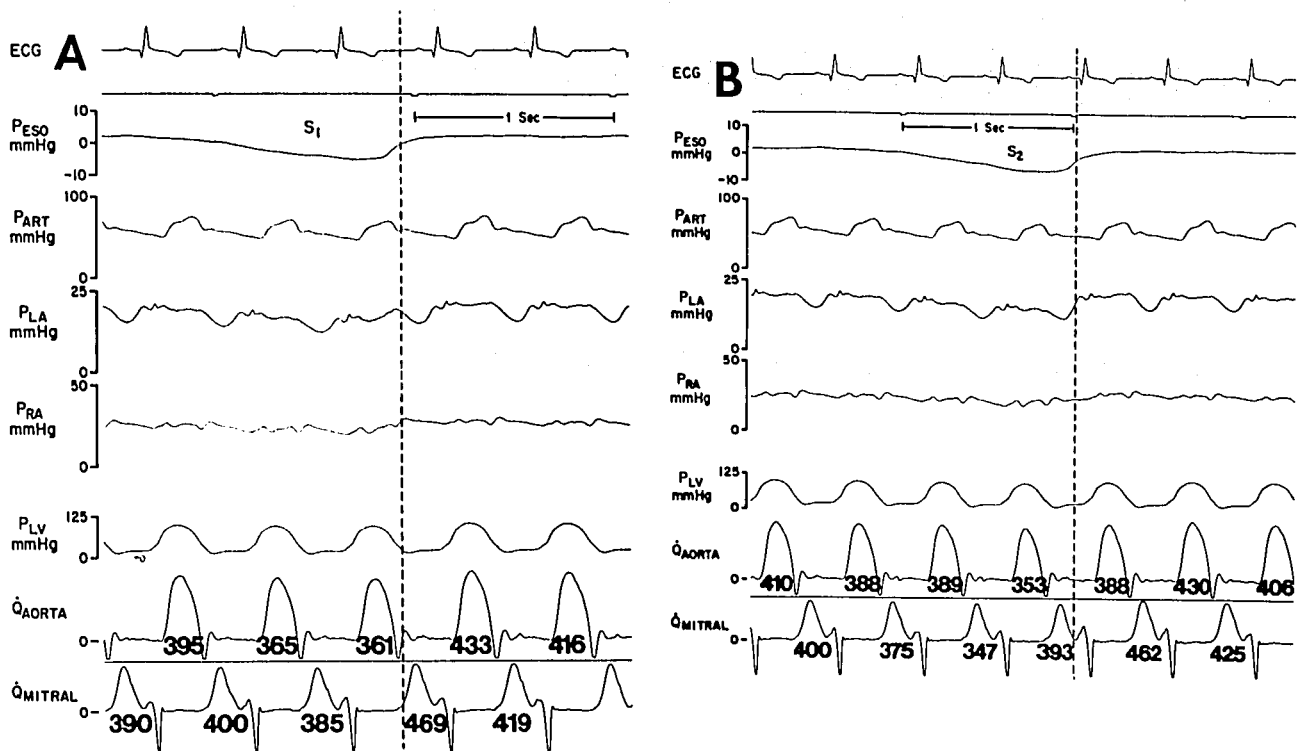


FIG. 4. Two consecutive spontaneous unobstructed inspirations with the increase in esophageal pressure (P_{ESO}) demarcated by the vertical dashed line in both breaths in dog 6 postvagotomy. *A.* During the fall in esophageal pressure (S_1) both ascending aortic (Q_{AORTA}) and mitral flow (Q_{MITRAL}) decrease. The increase in esophageal pressure occurs during diastole with an obvious increase in mitral flow immediately apparent, the increase in aortic flow following. *B.* During the following inspiration (S_2) there is again a decrease in both ascending aortic and mitral flows, but the expiratory increase in esophageal pressure now occurs in late diastole. The increase in area under the mitral flow trace is evident to the right of the vertical line. Ascending aortic flow then exhibits a similar increase. The minimal and maximal mitral flows precede the respective minimal and maximal aortic flows during both respiratory cycles. Diastolic events clearly dominate in determining LV output changes. The elevated left sided diastolic pressures and low arterial pressure reflect a presumptive degree of LV dysfunction. The ECG demonstrates normal sinus rhythm, arterial pressure (P_{ART}), left atrial pressure (P_{LA}), right atrial pressure (P_{RA}), and left ventricular pressure (P_{LV}) are all measured relative to atmosphere.

dogs. The transmural pulmonary artery systolic pressure significantly increased at peak inspiration, whereas in both dogs with right atrial lines the transmural right atrial pressure increased during inspiration (table 3).

CRITIQUE OF THE PREPARATION

Insertion of the electromagnetic flow probes requires extensive surgery. Despite this, the study conditions pro-

TABLE 2. Spontaneous Unobstructed Respiration

	E ₂	I ₁	I ₂	E ₁
P _{ARTim} systolic (mmHg) (n = 8)	111.2 ± 13.0	110.4 ± 12.7	107.4 ± 11.9	110.2 ± 13.0
P _{ARTim} diastolic (mmHg) (n = 8)	68.5 ± 10.0	70.4 ± 10.4	69.7 ± 9.5	66.9 ± 9.9
P _{LAim} (mmHg) (n = 8)	12.3 ± 2.2	12.5 ± 2.0	14.1 ± 1.7	12.9 ± 2.2
P _{LVim} diastolic (mmHg) (n = 8)	14.0 ± 2.6	14.3 ± 2.5	15.8 ± 2.3*	14.7 ± 2.6
P _{RAim} (mmHg) (n = 5)	12.9 ± 1.7	13.1 ± 1.5	15.4 ± 1.4*	14.4 ± 2.2
Heart rate (beats/min) (n = 7)	137.8 ± 9.0	138.3 ± 9.1	138.6 ± 9.5	138.7 ± 9.4

Values are given as mean ± SE.

* $P < 0.05$ compared to E₂.

P_{ARTim} systole = arterial systolic transmural pressure; P_{ARTim} diastole = arterial diastolic transmural pressure; P_{LAim} = left atrial a-wave

transmural pressure; P_{LVim} = left ventricular end-diastolic transmural pressure; P_{RAim} = right atrial a-wave transmural pressure; E₂ = end expiration; I₁ = early inspiration; I₂ = peak inspiration; E₁ = early expiration.

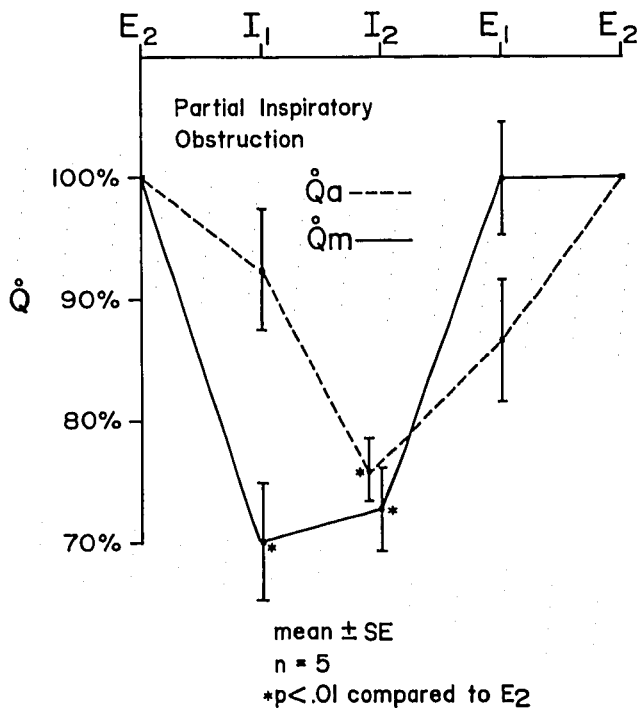


FIG. 5. Summary of results of changes in LV output measured as the integrated ascending aortic and LV inflow measured as the integrated mitral flows obtained during partial inspiratory obstruction. Abbreviations as in figure 2.

vided adequate and clinically relevant information in dogs in the immediate postcardiopulmonary bypass period. Initially, each study was performed with the lowest LV filling pressure compatible with hemodynamic stability during spontaneous ventilation. In three dogs an epinephrine infusion was required to obtain hemodynamic stability sufficient to allow spontaneous ventilation. In four dogs data obtained early in the study period (and then at the conclusion of the study with gradual deterioration of ventricular performance and/or plasma volume loading) permitted comparison of the patterns of changes in $\int \dot{Q}_m$ and $\int \dot{Q}_a$ during a respiratory cycle at different LV transmural filling pressure (table 4). We choose to separate low and high filling pressure at 12 mmHg because multiple studies of ventricular interdependence have found that at this pressure with pericardial constraint present, ventricular interaction is always significant.^{1,12} Because we made no measurements of the end-systolic pressure-volume relationships during the experimental protocols, no definitive statement can be made regarding ventricular function.¹³ Our clinical evaluation suggested that LV dysfunction was usually present when LV filling pressures greater than 15 mmHg prior to any inotropic support were required in the immediate postbypass period. Thus, 12 mmHg represents a reasonable separation point reflecting lesser and greater degrees of ventricular inter-

dependence, and probably lesser and greater degrees of ventricular dysfunction. Despite the differing physiologic status of each dog, and even within the same dog over time, the fact that we observed similar patterns of change in $\int \dot{Q}_m$ and $\int \dot{Q}_a$ suggests that the separate diastolic and systolic mechanisms altering LV output are present over a wide range of clinically relevant conditions.

Intravenous barbiturate anesthesia was used rather than inhalational agents because we have used it in all our prior studies of cardiopulmonary interactions in dogs. Intravenous opiates were not used because spontaneous ventilation was required. Neural and humoral mechanisms clearly influence the steady state influence of respiration on the cardiovascular system.^{14,15} Although these rela-

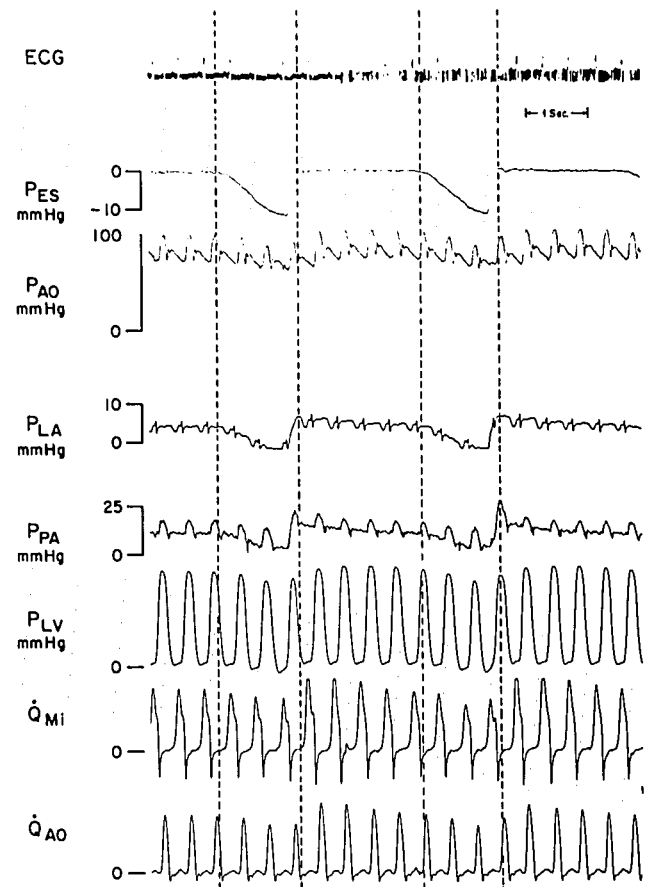


FIG. 6. Two consecutive respiratory cycles during partial inspiratory airway obstruction (dog 1 postvagotomy). Vertical dashed lines demarcate the two periods during which esophageal pressure is reduced during inspiration. Both integrated mitral (\dot{Q}_{MI}) and ascending aortic (\dot{Q}_{AO}) flows diminish during the inspiration and increase with expiration. There is a large expiratory increase in mitral flow preceding the large increase in aortic flow in both respiratory cycles. Although the rapid increase in esophageal pressure occurs during systole in the second breath, there is little effect on aortic flow. These two respiratory cycles demonstrate the dominance of mitral flow leading aortic flow during partial inspiratory obstruction. Abbreviations as in previous figures.

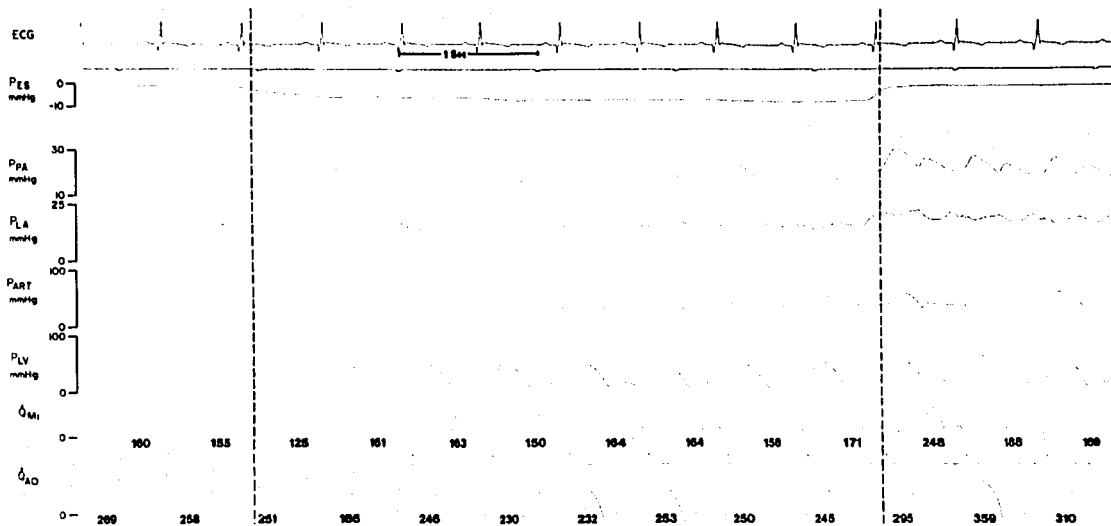


FIG. 7. Recording during a single prolonged inspiratory effort during partial inspiratory obstruction in a dog following bilateral vagotomy (dog 5). Abbreviations as in previous figures. The numbers under each flow trace reflect the volume area in arbitrary units. During inspiration there is a decrease in both mitral and aortic flows reaching their respective minimum early during the inspiration and then gradually increasing as a new equilibrium is reached. The total inspiratory period is demarcated between the two vertical dashed lines. Eight beats occur during this inspiration with the rapid expiratory increase in esophageal pressure occurring immediately prior to a systolic LV ejection. The immediate increase in Q_a during the first systole of expiration can only partially be attributed to the increase in the preceding Q_m .

tionships may be altered by anesthesia, our focus of concern is within a single respiratory cycle, a time frame minimizing reflex or humoral effects.¹⁶

A degree of pericardial constraint has been found to exist under normal conditions.¹⁷ Multiple studies clearly document the influence of pericardial constraint.^{17,18} For this reason studies were performed with the pericardium reapproximated following instrumentation accepting that this is not precisely the same constraint had the pericardium not been surgically violated. Based on our prior studies, we would expect that both the influence of ven-

tricular interdependence and the influence of any change in afterload on the subsequent LV inflow would have been diminished if we had removed the pericardium.¹⁸

Although the coronary ostia are proximal to the ascending aortic flow probe, it seems unlikely coronary flows would change within a single systole to completely account for the observed variation in $\int Q_a$.¹⁹ Although diastolic filling time and contractility vary with heart rate, statistical analysis shows that the heart rate did not change.

There is little question that human and canine thoracic anatomy have substantial differences that could limit ex-

TABLE 3. Partial Inspiratory Obstruction

	E ₁	I ₁	I ₂	E ₂
P _{ART_{tm}} systolic (mmHg) (n = 5)	112.9 ± 12.7	114.0 ± 11.6	111.7 ± 11.1	110.8 ± 11.4
P _{ART_{tm}} diastolic (mmHg) (n = 5)	75.4 ± 11.7	76.8 ± 11.6	79.7 ± 10.8	75.5 ± 9.9
P _{LA_{tm}} (mmHg) (n = 5)	14.1 ± 2.5	13.5 ± 2.5	15.5 ± 2.4	15.0 ± 2.5
P _{LV_{tm}} diastolic (mmHg) (n = 5)	16.2 ± 3.0	16.2 ± 3.3	17.9 ± 3.4*	17.4 ± 2.8
P _{PA_{tm}} systolic (mmHg) (n = 3)	21.9 ± 1.1	22.2 ± 1.0	24.0 ± 0.7†	23.5 ± 0.9
P _{PA_{tm}} diastolic (mmHg) (n = 3)	16.3 ± 1.2	16.0 ± 1.6	17.2 ± 1.2	17.3 ± 0.6
P _{RA_{tm}} (mmHg) (n = 2)	11.6 ± 5.0	9.9 ± 3.6	12.7 ± 4.9	13.6 ± 7.2
Heart rate (beats/min) (n = 4)	134.0 ± 20.7	133.3 ± 20.9	138.8 ± 21.1	134.0 ± 20.4

Values are given as mean ± SE.

P_{ART_{tm}} = arterial transmural pressure; P_{LA_{tm}} = left atrial a-wave transmural pressure; P_{LV_{tm}} = left ventricular end-diastolic transmural pressure; P_{PA_{tm}} = pulmonary arterial transmural pressure; P_{RA_{tm}} = right

atrial a-wave transmural pressure.

* $P < 0.05$ compared to E₂.

† $P < 0.01$ compared to E₂.

TABLE 4. Mitral ($\int \dot{Q}_m$) and Aortic ($\int \dot{Q}_a$) Flows at Low (≤ 12 mmHg) and High (> 12 mmHg) LV End-diastolic Transmural Pressures during Unobstructed Respiration

Dog LVEDP _{mm}	$\int \dot{Q}_m$ (%)			$\int \dot{Q}_a$ (%)				
	E ₁	I ₁	I ₂	E ₁	E ₂	I ₁	I ₂	E ₁
5 Low	100	100.0	109.0	130.0	100	89.5	93.0	105.5
5 High	100	78.0	93.0	131.5	100	92.0	89.3	128.5
6 Low	100	94.7	93.3	104.8	100	92.6	90.4	98.2
6 High	100	87.0	94.5	115.0	100	91.5	88.0	102.0
7 Low	100	89.6	93.1	105.6	100	90.0	90.3	103.6
7 High	100	76.4	71.6	85.3	100	97.5	80.5	85.4
8 Low	100	93.3	96.5	114.9	100	90.8	92.4	99.9
8 High	100	86.8	89.8	108.5	100	94.1	85.7	98.8

trapolation of these results to the human particularly with regard to mechanical heart-lung interdependence during a change in lung volume.²⁰ Many of the mechanical cardiorespiratory events, however, are likely to be applicable to understanding human physiology until measurements in humans can be made to confirm or refute the relevance of our findings.

Discussion

The results of this study demonstrate for the first time in the intact cardiorespiratory system that during spontaneous ventilation separate systolic and diastolic LV events contribute to the inspiratory fall and expiratory rise in LV output. Our results suggest that the confusion in the literature surrounding the mechanism of variation in LV output and arterial pressure (pulsus paradoxus) during spontaneous ventilation should be expected^{1-3,21,22} because at least two different mechanisms operate within different parts of a single cardiac cycle. A diastolic mechanism decreases LV end-diastolic volume during a decrease in intrathoracic pressure (*i.e.*, $\int \dot{Q}_m$ decreases). This factor alone should lead to a decreased LV output ($\int \dot{Q}_a$) during the decrease in pleural pressure and, secondary to a reduced preload, result in a diminished LV end-systolic volume.²³ In contrast, a systolic event reducing LV output during a decrease in intrathoracic pressure initially will increase the end-systolic volume and therefore the ensuing end-diastolic LV volume. Thus, increases, decreases, or balanced changes in LV volumes that have been previously reported would be predicted to occur depending on the relative dominance of the separate diastolic and systolic events.^{1-3,21,22} Under the current experimental conditions a diastolic event was the dominant but not exclusive factor varying LV output.

The specific mechanisms associated with each event cannot be definitely determined with this preparation. To the extent that esophageal pressure accurately reflects the correct ventricular surface pressure,¹⁷ an increase in the transmural LV end-diastolic pressure mitigates against

a primary pooling of blood in the pulmonary vascular bed. Although the use of esophageal pressure may overestimate the transmural pressures, a qualitative increase in transmural pressures undoubtedly occurred because the decrease in pressures relative to atmosphere was less than the decrease in esophageal pressure. This is consistent with either the presence of ventricular interdependence or heart-lung interdependence (pulmonary compression of the heart).^{18,20} With ventricular interdependence acute changes in right heart pressures influence LV compliance, a process markedly enhanced by the presence of pericardial constraint.^{18,20} Acute increases in right heart volume will cause a paradoxical transient reduction in $\int \dot{Q}_m$, whereas acute reductions in right heart volume will cause a transient increase in $\int \dot{Q}_m$.²⁴ Increases in the transmural right atrial pressure associated with presumptive increases in systemic venous return are consistent with ventricular interdependence being a significant factor. Heart-lung interdependence would appear to be less important because reducing lung volume change by partial inspiratory occlusion or even complete inspiratory occlusion precluding any change in lung volume yields similar findings.²⁵ Individual traces in which an expiratory quasi-square wave increase in esophageal pressure occurred early in diastole appeared to influence the entire diastolic period, whereas an expiratory increase in late diastole resulted in an increase in late diastolic filling (fig. 4). This suggests that changes in intrathoracic pressure may alter LV filling almost instantaneously. An increase in lung volume cannot be the cause of a decrease in pulmonary venous return. An isolated increase in lung volume in zone III conditions, which predominantly existed in these studies with an LV end-diastolic pressure of 14 mmHg, would lead to an increase, not the observed decrease in $\int \dot{Q}_m$.²⁶ We conclude that diastolic ventricular interdependence is a major factor in reducing LV output during a fall in pleural pressure under our experimental conditions. However, it does not explain all of the variation in $\int \dot{Q}_a$. Some factor other than a change in preload alone is influencing the subsequent LV stroke

volume because changes in $\int \dot{Q}_m$ do not determine $\int \dot{Q}_a$ at all times.

The two systolic factors that independently alter LV output are changes in contractility and afterload. We cannot rule out a change in contractility, but the rapidity of such large immediately reversible changes in LV output mitigates against a reflexly mediated event. The more likely mechanism is an acute change in LV afterload, increasing as pleural pressure falls and decreasing as pleural pressure rises.¹ Recent studies in our laboratory confirm that a transient decrease in pleural pressure confined to systole will reduce LV output and distend the intrathoracic aorta consistent with an effective increase in arterial afterload.²⁷ The decrease in LV output during the fall in pleural pressure with spontaneous unobstructed inspiration was associated with an increase in the transmural aortic diastolic pressure in seven of eight dogs, and in four of five dogs during partial inspiratory obstruction. These results are consistent with an increased impedance for arterial blood leaving the thorax. Because a major component of the peak systolic pressure reflects a resistive component proportional to the stroke volume, a sufficient inspiratory reduction in preload reducing the stroke volume *via* the Starling mechanism could preclude an increase in systolic pressure even with the afterload increased. Similarly, an expiratory increase in preload should tend to increase the next $\int \dot{Q}_a$ regardless of any decrease in afterload. If the rapid expiratory rise in pleural pressure occurs during systole, the increase in $\int \dot{Q}_a$ could reflect the balance between the effect of an acute decrease in afterload and any change in $\int \dot{Q}_m$ during the preceding diastolic period when pleural pressure was low (figs. 6 and 7).

Figures 3 and 7 strongly support the influence of an independent systolic mechanism affecting LV output during changes in pleural pressure. The large decrease in $\int \dot{Q}_a$ during the second inspiration in figure 3 occurs after a minimal decrease in the preceding $\int \dot{Q}_m$. During the prolonged inspiration in figure 7 $\int \dot{Q}_m$ has increased gradually to baseline values, whereas $\int \dot{Q}_a$ is still below baseline. The rapid increase in $\int \dot{Q}_a$ at the beginning of expiration is out of proportion to the small increase in the preceding $\int \dot{Q}_m$. Both observations are consistent with an increased afterload during the fall in pleural pressure contributing to a reduced LV output, with the stored blood volume then being ejected during expiration as the afterload is reduced.

To the extent that the end-systolic pressure-volume relationship is a straight line for a constant inotropic state,¹⁵ equal decreases in afterload during systole should produce the same increase in LV output regardless of the initial LV end-diastolic volume. However, the same change in afterload should have a much greater effect on the output of the failing compared to the normal ventri-

cle.¹⁵ Although this leads to the prediction that changes in afterload should then dominate during changes in pleural pressures with elevated LV end-diastolic pressures, we observed no difference in the dominance of $\int \dot{Q}_m$ leading $\int \dot{Q}_a$ in dogs over a wide range of LV filling pressures. Indeed, the dogs with the lowest transmural filling pressures had the LV outflow reaching its minimum before inflow during inspiration at least as often as those dogs with elevated transmural pressures (table 1). In four dogs in which flows were obtained at differing LV filling pressures, little difference in the pattern of change during a respiratory cycle was found. These results are consistent with our prior studies demonstrating that the influence of both ventricular interdependence and changes in afterload are enhanced at elevated ventricular pressures with pericardial constraint present.²⁰ This suggests that LV dysfunction with elevated ventricular volumes and end-diastolic pressures should lead to a synergistic interaction between ventricular interdependence and afterload during inspiration to produce the reduced LV output.

Our results suggest that the mechanical effects of an inspiratory decrease in pleural pressure could contribute to the production of pulmonary edema associated with airway obstruction.²⁸ According to the Starling equation for fluid flux across a membrane,** an increase in hydrostatic pressure will increase edema formation. The increase in LV diastolic pressure produced by a leftward septal shift and an increased LV afterload at the same time pulmonary arterial pressure is increasing due to hypoxic pulmonary vasoconstriction would produce an increased hydrostatic pressure within the pulmonary vascular bed. Hypoxic pulmonary vasoconstriction would further increase the propensity toward edema formation by afterloading the RV. This would enhance the leftward septal shift, raising the LV end-diastolic pressure. Thus, in the relatively noncompliant pulmonary vascular bed, as pleural pressure decreases, pulmonary edema would occur as pulmonary arterial inflow increases and outflow decreases.^{4,***}

In conclusion, the simultaneous measurements of mitral and ascending aortic flows demonstrated that both diastolic and systolic factors altered LV output during acute changes in pleural pressure. This was most likely due to diastolic changes in ventricular interdependence and systolic changes in LV afterload. These results help to resolve many controversies over the cause of the inspiratory decrease in arterial pressure (pulsus paradoxus) and explain why, depending on the experimental/clinical conditions, multiple investigators have observed apparently contradictory results in terms of changes in LV volumes.^{1-3,21,22}

** Wise RA: Effect of circulatory mechanics on hydrostatic forces producing pulmonary edema. *J Crit Care* 1:247-256, 1986.

Our results explain why these controversies cannot be resolved during studies comparing steady state conditions or individual respiratory cycles because diastolic events would reduce and systolic events increase LV volumes. It is only when a change in pleural pressure is restricted to either diastole or systole that the individual mechanisms can be evaluated.

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