Mechanisms of Pulsus Paradoxus During Resistive Respiratory Loading and Asthma

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To determine the mechanisms of pulsus paradoxus during asthma, six subjects known to have cold air bronchial hyperreactivity were studied while in a quiescent phase of their disease. All were free of significant airway obstruction at the time of study. After placement of an esophageal balloon to estimate intrathoracic pressure, the subjects were assessed during quiet breathing, resistive airway loading and then during a stable period of airway obstruction induced by cold air. Steady state left ventricular volume and performance were measured using radionuclide ventriculography; right ventricular volume was calculated from the stroke volume ratio and right ventricular ejection fraction. Cardiac cycles were segregated according to their occurrence in inspiration or expiration using a flow signal from a pneumotachograph.

Combined inspiratory and expiratory resistance produced pulsus paradoxus and changes in esophageal pressure that were similar to those during asthma and significantly greater than those during quiet breathing. These changes were accompanied by decreases in left ventricular diastolic volume and stroke volume during inspiration, and increases in these variables during expiration; right ventricular volume and stroke volume demonstrated changes reciprocal to those seen in the left ventricle. These data indicate that during periods of increase in airway resistance, abnormal pulsus paradoxus results from an exaggeration in the normal inspiratory-expiratory difference in stroke volume mediated primarily by the effects of intrathoracic pressure on ventricular preload.

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During quiet spontaneous breathing there is a phasic variation in stroke volume, with the smallest left ventricular stroke volume occurring during inspiration (1). This decrease in inspiratory stroke volume has been related to a decrease in left ventricular size during both diastole and systole and accounts for the usual variation in systolic blood pressure with respiration (2–4). Maneuvers that influence intrathoracic pressure have marked effects on left ventricular size and performance (5–11), in part because of the direct effects of intrathoracic pressure on ventricular preload and afterload. Presumably, abnormal pulsus paradoxus (widening of the respiratory variation in blood pressure) during airway obstruction also reflects this influence of intrathoracic pressure on cardiac function.

Published data relating to the manner in which intrathoracic pressure affects left ventricular function are complicated by a number of factors. Studies assessing left ventricular function have employed a variety of methods that differ in their sensitivity to geometry and in their capacity to detect rapid alterations in ventricular function (5–11). There have also been differences with respect to the integrity of the pericardium and thoracic structures that affect the degree of interaction among the cardiac chambers (12,13). Finally, maneuvers under investigation such as the Valsalva or Mueller maneuver or continuous positive pressure breathing may involve mechanisms other than those operational during tidal breathing.

We utilized radionuclide ventriculography gated to respiratory flow to study steady state respiratory maneuvers in human subjects that closely approximate the pleural pressure changes seen in clinical asthma; we then induced asthma in these same subjects using cold air inhalation. We hypothesized that during asthma, increases in airway resistance

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promote pulsus paradoxus by exaggerating respiratory swings in intrathoracic pressure. This, in turn, induces sequential inspiratory-expiratory differences in right and left ventricular preload which result in a pronounced increase in the usual variation in stroke volume seen throughout respiration. To test this hypothesis, we studied six volunteers who had inducible airway obstruction, with the specific intent of comparing the cardiovascular effects of resistive airway loading with asthma.

Methods

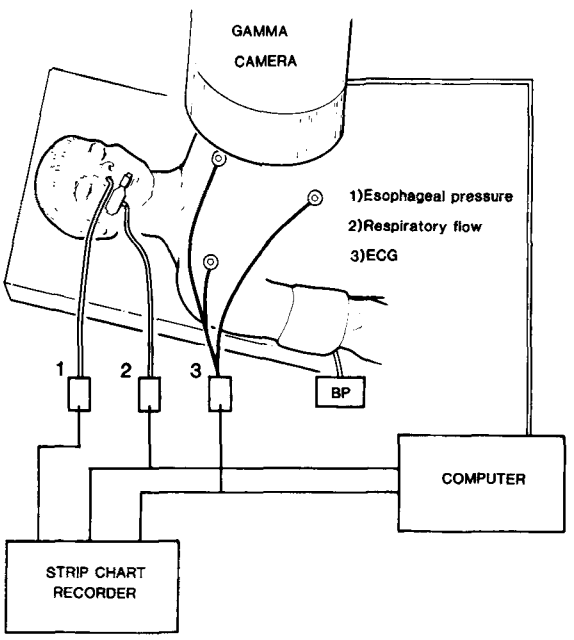
Study patients. Six asymptomatic individuals (aged 19 to 35 years; three male, three female) with asthma served as subjects for this investigation. All subjects were experienced in the measurement of pulmonary function, having participated in other studies. Each was in a stable phase of his or her disease, and none took daily medication at the time of this study. All medications, including methylxanthines and sympathomimetic agents, were withheld for at least 24 hours before each bronchial challenge. All subjects were free of known cardiovascular disease and all had a normal cardiac examination and electrocardiogram at rest. Each subject gave informed consent before participation in these investigations in accordance with the guidelines of the Committee on Human Studies of Brigham and Women's Hospital, where all studies were performed.

Protocol. Each subject was studied on 2 days. On the first day, bronchial challenge testing was performed using the technique of isocapnic hyperpnea with cold air (14). Pulmonary function was measured before and after isocapnic hyperpnea at increasing levels of ventilation so that a dose-effect relation could be defined for cold air. The challenge was stopped when the postchallenge forced expiratory volume in 1 second fell more than 25% from the prechallenge baseline.

On the second study day, baseline pulmonary function was again measured. Subjects then underwent radionuclide ventriculography under four conditions: during unimpeded tidal respiration, during inspiratory resistive loading, during inspiratory and expiratory resistive loading and after bronchial challenge with cold air (asthma). The resistive loads were applied by tightening screw clamps on rubber tubing attached to the inspiratory and expiratory parts of a Rudolph valve through which the subjects breathed. The magnitude of the inspiratory resistance varied from subject to subject but in all cases sufficient to produce visible recruitment of accessory respiratory muscles (sternocleidomastoid) and a minimum of 10 mm Hg pulsus paradoxus. Because the loads were alinear and varied with airflow, subjects were coached to maintain a stable respiratory pattern during each of the first three respiratory maneuvers. After the loaded breathing, the subjects underwent bronchial challenge with cold air performing isocapnic hyperpnea for 4 minutes at a level of ventilation previously determined to produce a 25% fall in 1 second forced expiratory volume. Three minutes after completing the challenge, pulmonary function was again measured and ventriculography was performed. At the completion of imaging, a final measurement of pulmonary function was made. All data collection was completed within 120 minutes of the radionuclide injection.

Measurements (Fig. 1). At baseline and during all cardiac gating, heart rate, blood pressure and esophageal pressure were monitored. An electrocardiographic signal provided a continuous recording of heart rate. This electrocardiographic signal was also used for cardiac gating (see later). Systemic arterial pressure was obtained with a sphygmomanometer. Esophageal pressure was monitored continuously using a Hyatt type balloon (Young Rubber Co.) attached to PE200 tubing. The balloon was placed in the middle third of the esophagus at the beginning of the study. Esophageal pressure was recorded continuously on chart paper using a Validyne MP45 transducer and a Hewlett-Packard 8805B amplifier. Each maneuver required 15 to 20 minutes to complete. After a stable breathing pattern was established, a minimum of two measurement of blood pressure, pulsus paradoxus and heart rate and five measurements of peak positive and negative esophageal pressures were recorded over each of three 5 minute intervals. For the purpose of this study, pulsus paradoxus was measured by first recording the highest systolic pressure heard

Figure 1. Experimental set-up during radionuclide imaging. The heart was imaged in the modified left anterior oblique projection with a gamma camera/computer system. Electrocardiographic data and the respiratory flow rate were also sampled by the computer. The electrocardiogram (ECG), respiratory flow and esophageal pressure were recorded on a strip chart. Blood pressure (BP) was measured with a sphygmomanometer.



during three expiratory cycles only, and subsequently by the systolic pressure at which Korotkoff sounds were audible throughout the respiratory cycle. These were averaged to provide the values for that maneuver.

During all cardiac imaging, subjects breathed through a mouthpiece attached to a pneumotachograph and a Rudolph valve. The pneumotachograph in combination with the transducer and amplifier provided a mouth flow signal that was recorded on chart paper and was simultaneously transmitted to a computer.

Pulmonary function measurements in all cases included measurements of forced expiratory volume and flow made on a waterless spirometer. The 1 second forced expiratory volume was calculated with standard techniques and the average of two trials was used in data analysis.

Bronchial challenge. Two studies, 1 to 8 weeks apart, were performed on each subject. Subjects inhaled dry compressed air that was cooled to subfreezing temperatures by passage through a heat exchanger. End-tidal carbon dioxide was monitored continously with a Gould capnograph and carbon dioxide was added to the inspiratory circuit in quantities sufficient to maintain end-tidal carbon dioxide concentrations at rest eucapnic levels. Expired gas was directed into a target balloon that was evacuated by a vacuum pump through a calibrated rotameter at a constant rate. By instructing subjects to breathe so as to keep the target balloon filled, their minute ventilation could be exactly determined. On the first study day the challenge ventilation was set at a level determined from the subject's predicted maximal voluntary ventilation, calculated as 35 times the baseline 1 second forced expiratory volume. After control measurements of forced expiratory volumes and flows, the subjects inhaled subfreezing air at 20% of the maximal voluntary ventilation for 4 minutes. Three minutes after completion of the isocapnic hyperpnea, pulmonary function measurements were repeated. If the 1 second forced expiratory volume was 75% or more of the baseline volume, the challenge was repeated in the same manner but the target ventilation was increased progressively to 40, 60 and 80% of maximal voluntary ventilation. The challenge was stopped when the postchallenge 1 second forced expiratory volume fell more than 25% from the prechallenge baseline. From these data, a dose-effect relation was plotted for cold air, and interpolated ventilation expected to produce a 25% fall in 1 second forced expiratory volume was used on the second study day. The challenge on the second study day was conducted in an identical manner but only a single level of ventilation was used.

Radionuclide ventriculography. Data collection and analysis were performed on a Digital Equipment Corporation GAMMA-11 nuclear medicine computer system with an 800/1,600 bits/inch tape drive. A multi-channel analog to digital converter (AR11) was used to sample the electrocardiographic and respiratory signals.

The patient was positioned in the modified left anterior oblique projection (30° cephalic position of the detector). The cardiac image was marked on the gamma camera display to facilitate precise positioning of the patient during each intervention. The electrocardiogram and the respiratory flow signal were sampled every 10 ms. From a display of the respiratory signal, the user selected inspiratory and expiratory thresholds. Values above the inspiratory thresholds were considered to be inspiration; values below the expiratory threshold were considered to be expiration; those values that fell in between were considered neither inspiration nor expiration. Electrocardiographic cycles were segregated and the entire cycle was assigned to either inspiration or expiration based on the respiratory signals at the time of the occurrence of the R wave.

Data analysis. After the inspiratory and expiratory thresholds had been set, the data collection was begun. The data were collected in list mode directly on a 2,400 foot (720 m) magnetic tape. Approximately 17 million counts were collected per intervention in each subject. During the data collection, an RR interval histogram was produced for both inspiration and expiration.

The data were reformatted by selecting a range of RR intervals for inspiration and expiration. Any RR interval falling outside of the selected range was discarded. The left ventricular ejection fraction was measured with a user-drawn, fixed region of interest (15). The right ventricular ejection fraction was calculated from the apical two-thirds of the ventricule, again with a user-drawn, fixed region of interest (16). The right ventricular outflow tract was not included because of overlap with other cardiac chambers. The background for both ventricles was calculated automatically. The end-diastolic area of the left ventricle was obtained from the size of the left ventricular region of interest. This area was taken as an index of volume.

Multiple measurements of heart rate, blood pressure, pulsus paradoxus and esophageal pressure were made during each respiratory maneuver. The average of these measurements was taken as the value for that intervention in each patient. These data were then combined to provide an average value for the group. To calculate left ventricular area, the end-diastolic area was determined by planimetry using the computer. The inspiratory diastolic area in the baseline state was assigned a value of 100 in each subject and all other areas were expressed as a percent of that value. Ejection fraction was calculated utilizing the count-based method (end-diastolic counts − end-systolic counts)/(end-diastolic counts − background). Right ventricular diastolic volume was calculated from the formula

$$\frac{\text{Normalized left ventricular diastolic volume}}{\text{Stroke volume ratio}} \times \frac{\text{Left ventricular ejection fraction}}{\text{Right ventricular ejection fraction}}.$$

Table 1. Baseline Hemodynamic Variables

Case	Heart Rate (min $^{-1}$)	Blood Pressure (mm Hg)	Pulsus Paradoxus (mm Hg)	Esophageal Pressure (mm Hg)		LVEF(%)		RVEF(%)	
				I	E	I	E	I	E
Vol	153 ± 17.5	143 ± 12.7	169 ± 13.2†	129 ± 10.8*†	164 ± 9.6†	129 ± 12.1*†	163 ± 9.9†	136 ± 4.9*	
EF (%)	40.3 ± 3.4	38.2 ± 2.8	37.8 ± 2.1	42.5 ± 1.7*†	39.2 ± 2.1	43.2 ± 2.2†	40.2 ± 2.7	43.8 ± 2.5†	
SV	59.3 ± 2.9	55 ± 2.3	67 ± 5.0†	54.7 ± 5.1*	68.1 ± 5.0†	55.2 ± 4.3*	68.3 ± 5.5†	58.2 ± 2.3*	
SVR	1.25 ± 0.05	1.31 ± 0.09	1.20 ± 0.06	1.45 ± 0.09*†	1.15 ± 0.10	1.36 ± 0.11	1.15 ± 0.07	1.42 ± 0.09*	

*$p < 0.05$ versus inspiration; †$p < 0.05$ versus corresponding baseline values. E = expiration; EF = radionuclide ejection fraction; I = inspiration; SV = normalized right ventricular stroke volume; SVR = ratio of left ventricular to right ventricular stroke volume; Vol = normalized right ventricular diastolic volume.

Statistics. Statistical analysis to compare changes among interventions utilized a blocked one-way analysis of variance and a Neuman-Keuls to compare each maneuver with baseline. A paired *t* test was used to compare airway function before and after cold challenge and to compare inspiratory with expiratory values within maneuvers for radionuclide-based measurements. All results are expressed as mean ± 1 SEM.

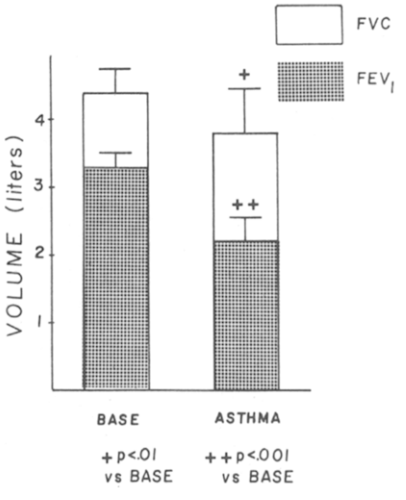
Results

Baseline values. Baseline hemodynamic values for each subject are shown in Table 1. Two patients (Patients 5 and 6) had a diastolic pressure that was slightly elevated. All had normal values for pulsus paradoxus (mean 4.5 ± 1.0 mm Hg) and left ventricular ejection fraction (inspiration 76 + 3.2% expiration 76 ± 4.9%; p = NS). Right ventricular ejection fraction was somewhat lower than that reported by others but there were no differences between inspiratory (40.3 ± 3.4%) and expiratory (38.2 ± 2.8%) values. During inspiration, esophageal pressure fell below atmospheric pressure (mean −5.5 ± 1.5 mm Hg) and during expiration it rose toward atmospheric pressure (mean −0.7 ± 0.9 mm Hg) in all subjects.

Airway function. The use of isocapnic hyperpnea with cold air successfully induced airway obstruction in all patients. The response of the group is illustrated in Figure 2. Initial values for forced vital capacity (mean 4.4 ± 0.41 liters), timed vital capacity after 1 second (mean 3.3 ± 0.27 liters) and ratio of the timed to total vital capacity (0.76 ± 0.007) were greater than 80% of predicted values in all subjects. After cold challenge, both forced vital capacity and 1 second forced expiratory volume fell in all patients (mean 4.0 ± 0.63 liters for forced vital capacity; mean 2.7 ± 0.54 liters for 1 second forced expiratory volume). The 1 second timed/forced vital capacity ratio also declined to 0.65 ± 0.09. All changes were significant ($p < 0.01$ after versus before challenge). No significant changes in heart rate of blood pressure measured during expiration were observed with either respiratory loading or asthma in any subject.

Esophageal pressure. The effect of each intervention on esophageal pressure and pulsus paradoxus is demonstrated in Figure 3. During inspiration, all maneuvers resulted in a significant reduction in esophageal pressures (inspiratory resistive loading = −10.5 ± 3.4; inspiratory and expiratory resistive loading = −14.8 ± 5.5; asthma = −16.3 ± 9.7 mm Hg) (all $p < 0.05$ versus baseline). Expiration was associated with changes in esophageal pressures that were relatively small and achieved statistical significance only during asthma. Pulsus paradoxus was increased above baseline values for all three interventions (12.8 ± 1.8, 17.5 ± 2.5 and 15.2 ± 2.9 mm Hg, respectively) (all $p < 0.05$ versus baseline). These changes were qualitatively similar in all subjects. Fluctuations in esophageal pressure (expiratory-inspiratory) for each inter-

Figure 2. Airway function before (BASE) and after (ASTHMA) cold air challenge in the six subjects. The 1 second forced expiratory volume (FEV_1) falls more than forced vital capacity (FVC), resulting in a decline in the FEV_1/FVC ratio from 0.76 ± 0.007 to 0.65 ± 0.09 ($p < 0.01$). The reduction in FEV_1 for the group was 19%.



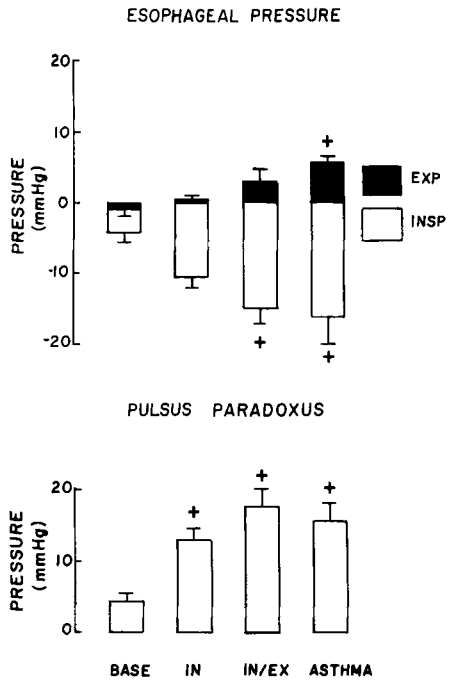


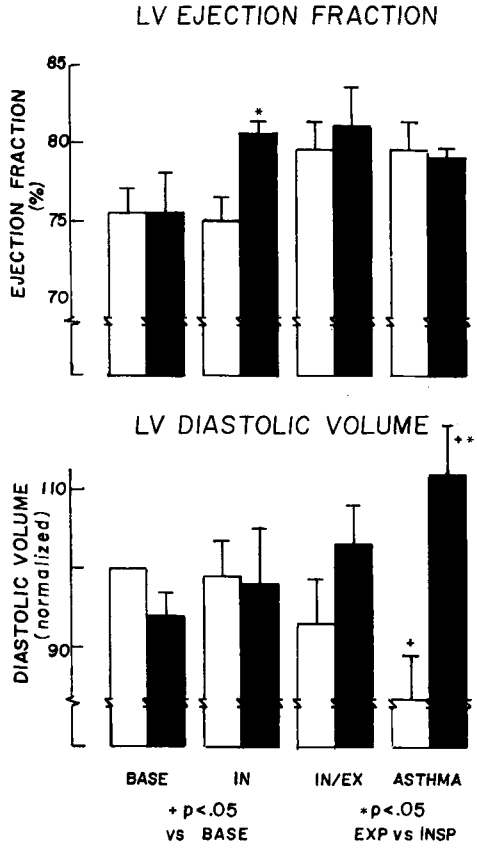
Figure 3. Alterations in esophageal pressure and pulsus paradoxus for the group. **Top,** There is a decline in inspiratory (INSP) pressure (**open bars**) and a smaller increase in expiratory (EXP) pressure (**solid bars**) resulting in a progressively wider swing in esophageal pressure between inspiration and expiration. The magnitude and configuration of pressure changes in inspiratory and expiratory resistive loading (IN/EX) are similar to those during cold air-induced asthma. **Bottom,** The development of exaggerated pulsus paradoxus (>10 mm Hg) is seen with all interventions. Thus, combined inspiratory (IN) and expiratory airway resistive loading closely duplicates changes in esophageal pressure and pulsus paradoxus seen with asthma. $^{+}p < 0.05$ versus baseline.

vention bore a direct, nearly linear correlation to the amount of pulsus paradoxus (amount of pulsus = 0.6 × [change in esophageal pressure] + 4.4; r = 0.83).

Left ventricular function. Changes in inspiratory and expiratory left ventricular diastolic volumes and ejection fraction for each maneuver are shown in Figure 4. Changes in ejection fraction due to all interventions were small (<5% versus baseline) and did not achieve statistical significance. No significant changes in ejection fraction between inspiration and expiration occurred during any maneuver except inspiratory resistive loading. Values for *inspiratory diastolic volumes* decreased (93 ± 5.8 for inspiratory and expiratory resistive loading and 87 ± 5.3 for asthma) and *expiratory diastolic volumes* increased (103 ± 5.1 and 112 ± 5.4, respectively) with successive interventions; statistical significance for these values was present during asthma ($p < 0.05$ versus respective baseline). These changes resulted in expiratory volumes exceeding inspiratory volumes during both inspiratory and expiratory resistive loading ($p < 0.01$ expiration versus inspiration). In summary, inspiratory and expiratory resistive loading and asthma resulted in left ventricular diastolic volumes that, relative to quiet breathing, were larger during expiration (when esophageal pressures were above baseline) and smaller during inspiration (when esophageal pressures were below baseline).

Left ventricular stroke volume (diastolic volume × ejection fraction) and end-systolic volume (diastolic volume − stroke volume) were derived from the measured values and are shown in Figure 5. Although changes in systolic volume were small, there was a tendency for left ventricular systolic volume during all interventions to be smaller than that during quiet breathing. Changes in stroke volume relative to baseline were largest during inspiratory and expiratory resistive loading and asthma, and expiratory values exceeded inspiratory values for both interventions ($p < 0.01$ expiratory versus inspiratory). Therefore, during interventions in which the largest swings in esophageal pressure were evident, dif-

Figure 4. Changes in inspiratory (**open bars**) and expiratory (**solid bars**) left ventricular (LV) ejection fraction and left ventricular diastolic volumes. Although there is a tendency for ejection fraction in both phases of respiration to increase somewhat with airway obstruction, these changes are not statistically significant. In contrast, inspiratory diastolic volume decreases while expiratory volume increases especially during inspiratory and expiratory resistive loading (IN/EX) and asthma, demonstrating that there are substantial differences in preload during these two phases of respiration with airway obstruction. Abbreviations and open and solid bars as in Figure 3.



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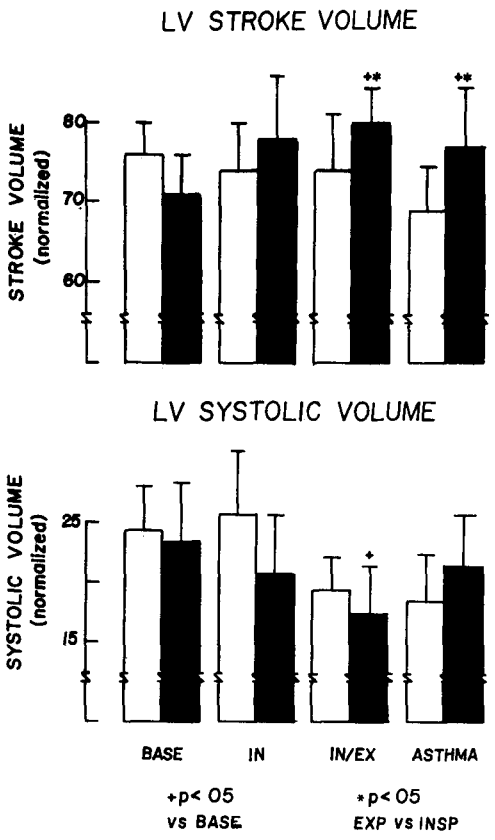

Figure 5. The variables from Figure 4 were used to calculate left ventricular (LV) stroke volume and systolic volume during inspiration (**open bars**) and expiration (**solid bars**). With resistive loading and asthma, stroke volume falls during inspiration and increases during expiration leading to a large inspiratory-expiratory difference seen during inspiratory and expiratory resistive loading (IN/EX) and asthma. As a result, systolic volumes remain the same or fall during both inspiration and expiration. See text for explanation. Abbreviations as in Figure 3.

ferences in stroke volume between expiration and inspiration were also the largest.

Right ventricular function. Table 2 summarizes alterations in relative right ventricular diastolic volumes, ejection fraction and stroke volume. During the baseline state, inspiratory diastolic volume and stroke volume tended to be larger than expiratory values. With loaded breathing and asthma, inspiratory diastolic volumes increase significantly over both baseline and expiratory volumes, achieving statistical significance in all interventions. These changes, most marked during inspiration, are in contrast to those occurring in the left ventricle, which were more prominent during expiration. The measured stroke volume ratios reflect the increase in left ventricular stroke volume during expiration, when right ventricular stroke volume remained unchanged from baseline.

Discussion

The purpose of this study was to examine the mechanisms by which airway obstruction produces pulsus paradoxus. Resistive loading was used to simulate airway obstruction, a method successfully employed by other investigators (17); however, the induction of asthma in humans is unique in the cardiovascular literature. The combination of inspiratory and expiratory resistive loading most closely reproduced changes seen during our asthma intervention and will be emphasized for comparisons. This similarity is evident in the amount of pulsus paradoxus and the magnitude and direction of changes in esophageal pressure. It seems likely that the changes in esophageal pressure reflect those in intrathoracic pressure and represent a characteristic response to an increased resistance to air flow.

Role of intrathoracic pressure in pulsus paradoxus. The linear correlation between the inspiratory-expiratory change in esophageal pressure and the magnitude of pulsus paradoxus suggest that these two variables are coupled. The data from this study indicate that the sequential effects of intrathoracic pressure on ventricular preload are responsible for pulsus paradoxus during resistive airway loading and asthma. Specifically, loaded inspiration and the resulting fall in intrathoracic pressure result in an increase in right ventricular diastolic volume and stroke volume. During expiration, several cardiac cycles later, left ventricular diastolic volume and stroke volume increase while right ventricular volumes return to baseline values. Furthermore, it is conceivable that the inspiratory increase in right ventric-

Table 2. Right Ventricular Function Data

	Baseline		Inspiratory Resistance		Inspiratory and Expiratory Resistance		Asthma	
	I	E	I	E	I	E	I	E
Vol	153 ± 17.5	143 ± 12.7	169 ± 13.2†	129 ± 10.8*†	164 ± 9.6†	129 ± 12.1*†	163 ± 9.9†	136 ± 4.9*
EF (%)	40.3 ± 3.4	38.2 ± 2.8	37.8 ± 2.1	42.5 ± 1.7*†	39.2 ± 2.1	43.2 ± 2.2†	40.2 ± 2.7	43.8 ± 2.5†
SV	59.3 ± 2.9	55 ± 2.3	67 ± 5.0†	54.7 ± 5.1*	68.1 ± 5.0†	55.2 ± 4.3*	68.3 ± 5.5†	58.2 ± 2.3*
SVR	1.25 ± 0.05	1.31 ± 0.09	1.20 ± 0.06	1.45 ± 0.09*†	1.15 ± 0.10	1.36 ± 0.11	1.15 ± 0.07	1.42 ± 0.09*

*$p < 0.05$ versus inspiration; †$p < 0.05$ versus corresponding baseline values. E = expiration; EF = radionuclide ejection fraction; I = inspiration; SV = normalized right ventricular stroke volume; SVR = ratio of left ventricular to right ventricular stroke volume; Vol = normalized right ventricular diastolic volume.

ular diastolic volume is part of a generalized increase in the volume of right-sided intrapericardial structures (that is, right atrium and pulmonary arteries) that enhances ventricular interaction and contributes to the accompanying decrease in left ventricular preload and stroke volume. Both an increase in left ventricular preload observed with the expiratory phase and a decrease observed with the inspiratory phase make important contributions to phasic differences in stroke volume during loaded breathing and asthma.

Comparison with previous studies. The correlation of left ventricular diastolic volume with changes in intrathoracic pressure has been documented in other studies although the precise mechanisms may be complex. In comparing other studies with ours, we have emphasized those in which the pericardium is intact and subjects were breathing spontaneously. Such conditions permit increases in lung volume to accompany subatmospheric changes in intrathoracic pressure and maximize the opportunity for pulmonary-cardiac-pericardial interactions.

Settle et al. (18) studied subjects with chronic obstructive lung disease and pulsus paradoxus using two-dimensional, echocardiography. They noted a reduction in left ventricular diastolic septal to free wall dimension during inspiration, an observation duplicated when two normal subjects developed exaggerated pulsus paradoxus while subjected to resistive respiratory loading. They postulated that a geometric change in the configuration of the left ventricle due to an inspiratory septal shift toward the left ventricle contributed to their observation. Similar results were obtained by Jardin et al. (19) using a more refined analysis of two-dimensional echocardiograms obtained during an asthmatic episode associated with increased pulsus paradoxus. In their study, no measurements were made during an asymptomatic period or with loaded breathing. The inspiratory-expiratory difference in esophageal pressures for their group was somewhat larger than that in ours. Left ventricular diastolic cross-sectional area during inspiration was reduced by 32% (and end-systolic by 24%) compared with expiratory values, supporting an important influence of alterations in preload to the markedly reduced stroke volume in inspiration relative to expiration. Their right ventricular diastolic areas were 42% larger during inspirations than during expiration, demonstrating the importance of ventricular interaction in reducing left ventricular preload. In our study, left ventricular diastolic volumes during inspiration were reduced by an average of 21% whereas right ventricular diastolic volumes were increased by 20%.

Animal studies by several investigators (20,21) have clearly demonstrated that the inspiratory reduction in intrathoracic pressure is exaggerated during loaded breathing and that, during spontaneous ventilation, this exaggeration in inspiratory pressure is associated with a decrease in left ventricular diastolic size, altered geometry (due to right and left ventricular interaction) and a decrease in left ventricular stroke volume. An increment in left ventricular afterload due to the increase in transmural left ventricular pressures during systole is also said to contribute to the reduction in stroke volume during loaded inspiration (22). However, in our study, end-systolic volume tended to decrease despite negative intrathoracic pressures, indicating that increases in afterload were not a significant factor and that changes in preload were largely responsible for the observed cyclic variations in stroke volume.

Critique of methods. We used a respiratory gating technique to segregate cardiac cycles according to their occurrence during inspiration or expiration. Unlike the study of Karam et al. (22) where a peak negative mouth pressure was used as the trigger, we used a flow signal. With our system, gated equilibrium radionuclide angiography requires several minutes of data collection to obtain images of adequate quality. Although cold air challenge provides a fairly stable reduction in ventilation, the time over which data can be collected is limited. During this limited time, cycles during both inspiration and expiration must be collected. Limiting data collection to early inspiration, a time when effects on cardiac function are maximal, might have increased the magnitude of the observed changes but might also have required a period of collection beyond the stable reduction in airway function. Furthermore, rather than using diastolic and systolic counts or a calculated volume based on counting a sample volume during each intervention, we used an area method for estimating volumes. We believed this to be the most effective method to overcome the inter-subject variability in study duration and loss of isotope from the blood pool. Right ventricular volume estimates were back-calculated from stroke volume ratios, left and right ventricular ejection fractions and left ventricular normalized volumes. Changes occurring in total intrapericardial volume during loaded inspiration may make uncertain contributions to right ventricular counts during diastole and systole.

We are aware that a direct measurement of intrathoracic pressure and specifically, pericardial pressure, would have been preferable to esophageal pressure. However, because we were not calculating intracardiac transmural pressure, our results would not have been substantially altered by a more direct measurement. In addition, the investigators were experienced in the use of esophageal balloons and the interpretation of pressure recordings. Given the overall health of the volunteers, a more invasive method could not be justified.

Conclusion. The magnitude of pulsus paradoxus closely parallels inspiratory-expiratory changes in esophageal pressure, probably as a result of the effects of intrathoracic pressure on right and left ventricular preload and subsequently on stroke volume. During asthma, the response of the bellows to combined inspiratory-expiratory airway resistance is associated with a decrease in left ventricular preload and stroke volume during inspiration and an increase

in both during expiration. These changes in left ventricular preload and stroke volume are accompanied by reciprocal changes in corresponding right ventricular measurements. These data indicate that during inspiration, the decrease in intrathoracic pressure and the resulting increase in right ventricular (and perhaps right atrial and venous) diastolic volumes enhance ventricular interaction and reduce left ventricular preload and stroke volume. Increase in total lung volume during asthma may further enhance ventricular interaction. After expiration, the effects of the increase in right ventricular preload on its stroke volume are evident as an increase in left ventricular preload at a time when right ventricular diastolic volume is nearer to baseline levels. The increase in left ventricular preload leads to an increased stroke volume. It is the inspiratory-expiratory difference in left ventricular stroke volume that accounts for the arterial pulsus paradoxus during airway obstruction.

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