Pressure-Flow Studies in Man: Effect of Respiration on Left Ventricular Stroke Volume

By Jerome Ruskin, M.D., Robert J. Bache, M.D., Judith C. Rembert, Ph.D., and Joseph C. Greenfield, Jr., M.D.

SUMMARY
The pressure gradient technique was used to evaluate effects of respiration on left ventricular stroke volume in 22 patients: 11 normal patients; eight patients with airway obstruction; and three patients with pericardial tamponade. In normals, stroke volume, systolic pressure, and pulse pressure fell an average of 7, 3 and 11% (P < 0.01), respectively, during inspiration. In patients with airway obstruction, these parameters decreased by 25, 12 and 23% (P < 0.001), respectively. After breath-holding, stroke volume also fell immediately with the onset of inspiration in both groups. These results are consistent with a reduction in left ventricular filling during inspiration as the factor primarily responsible for the fall in stroke volume. In patients with pericardial tamponade, variations in left ventricular stroke volume, systolic pressure and pulse pressure were related to: (1) an immediate fall in stroke volume with the onset of inspiration; and (2) a subsequent increase in stroke volume presumably due to an inspiratory increase in right ventricular stroke volume.

Additional Indexing Words:
Ventricular function Pericardial tamponade Pulsus paradoxus Obstructive lung disease

The influence of respiration on left ventricular function has been studied since the technique of cardiac catheterization in man was perfected. Lauson, Bloomfield and Courand found that the systemic arterial systolic, diastolic and pulse pressures were lowest during inspiration, when intrapleural pressure is least, and highest at the peak of expiration when intrapleural pressure is greatest.1 These workers postulated that this finding resulted in part from transmission of the respiratory variations in intrathoracic pressure to the aorta and the arterial tree, and in part from respiratory-related changes in left ventricular stroke volume. The inspiratory drop in systemic arterial pressure has also been ascribed to a delay in transmission through the pulmonary vascular bed for the fall in right ventricular stroke volume which accompanies expiration.2, 3 Pulsus paradoxus, an exaggeration of the inspiratory fall in systemic arterial blood pressure, has been observed in many conditions in man including airway obstruction, pericardial tamponade, marked obesity, tense ascites, hypovolemic shock, and during tilting and Z axis spin in a centrifuge.4-6 A more pronounced expression of one or more of the mechanisms described above has been postulated to be responsible for pulsus paradoxus.2-12

A major difficulty in evaluating these respiratory-related hemodynamic events in man has been the inability to measure both phasic aortic blood pressure and flow; thus, changes in stroke volume have previously been inferred from pressure data. The present study was undertaken to assess directly the effects of respiration on left ventricular stroke volume and to further evaluate the genesis of pulsus paradoxus. The pressure gradient technique13 was used to measure phasic aortic blood flow and pressure during both continuous and interrupted respiration in normal patients and in patients with
pulsus paradoxus due to either airway obstruction or pericardial tamponade.

Methods

Continuous recordings of phasic aortic blood pressure and flow were made during the course of diagnostic cardiac catheterization in 22 adult male patients admitted to the Veterans Administration Hospital, Durham, North Carolina. The nature of the experimental portion of the procedure was discussed with each patient and his informed consent was obtained prior to study. No complications occurred and the only inconvenience to the patient was the prolongation of the catheterization procedure by approximately 30 min.

Patients were grouped according to: (1) the degree of paradoxical pulse which was present with the patient supine during quiet respiration and (2) the clinical diagnosis. Group I consisted of 11 patients with less than 8 mm Hg inspiratory fall in systolic blood pressure who served as normals for this study. Nine of these patients had either coronary artery disease or a myocardial infarction and two patients had pericardial disease. None of these patients had clinical evidence of obstructive lung disease or congestive heart failure at the time of study. Group II consisted of eight patients with airway obstruction secondary to either emphysema, chronic bronchitis, or asthma and a paradoxical pulse greater than 10 mm Hg. None of these patients had evidence of congestive heart failure at the time of study. Group III contained three patients with clinically obvious pericardial effusion secondary to either tuberculous or uremic pericarditis, in whom hemodynamically significant pericardial tamponade was demonstrated by a paradoxical pulse greater than 20 mm Hg.

The pressure gradient technique, used to measure phasic blood flow and pressure in the ascending aorta, is based on an approximate solution of the Navier-Stokes equations of fluid motion which relate the axial pressure gradient to blood flow.13 Details of the instrumental techniques, manometric accuracy requirements and calibration procedures have been described in detail elsewhere.14 The validity of this technique has been demonstrated in a flow generator, in the open-chest dog, and in man, both in this laboratory and in others.15-17

At the conclusion of the diagnostic cardiac catheterization, a specially designed 6.5 French Fox-Fry double lumen catheter18 with lateral pressure taps 4 cm apart was introduced percutaneously into the femoral artery and advanced to the ascending aorta. The lateral pressures were measured with Statham P23Db transducers and Hewlett-Packard 350-100 amplifier systems and the pressure difference obtained with a model 3400 Donner-Systron analog computer. This pressure difference was used to continuously solve the proper equation for phasic blood flow. Aortic blood pressure was recorded directly from the proximal pressure tap of the catheter. The patient's nose was occluded and the phases of respiration were recorded from an air pressure transducer attached to a standard respiratory valve. One lead of the electrocardiogram, usually lead II, was monitored. All data were recorded on a model 4565B Hewlett-Packard optical paper recorder at a paper speed of 100 mm/sec and on a model 3955A Hewlett-Packard FM electromagnetic tape recorder.

To assure that the patients would be able to cooperate during the procedure, they were brought to the laboratory to practice the breathing sequences the day prior to study. Continuous recordings of pressure and flow were obtained in all patients during normal quiet respiration for at least a three-minute period. Similar measurements were then made following a period of voluntary breath-holding lasting 6-10 seconds. Patients were instructed to stop breathing during mid-expiration and to avoid straining. In addition, the duration of the expiratory phase was voluntarily prolonged during several respiratory cycles. In three patients in the normal group an artificial obstruction to breathing was created by partially occluding the lumen of the mouthpiece and the pressure-flow-recordings were repeated during several respiratory cycles. To avoid any possible effects of variations in heart rate, in six patients the heart rate was controlled by right atrial pacing using a bipolar transvenous pacing catheter and a model 5800 Medtronic external pulse generator; in four of these, recordings were made during pacing at two different heart rates.

To facilitate data analysis, each respiratory cycle was divided into three parts and pressure-flow data from a single heart beat were measured during the following: (1) end expiration, (2) early to peak inspiration, and (3) early to mid expiration. The data obtained at end expiration were used as the control for all comparisons. Data obtained during early to peak inspiration were utilized to document the direct effects of the inspiratory fall in intrathoracic pressure on left ventricular output. When possible, respiratory cycles were chosen in which cardiac systole occurred shortly after the onset of inspiration. To determine whether the inspiratory increase of right ventricular filling resulted in subsequent augmentation of left ventricular output, data were analyzed during early to mid expiration, thus allowing a 3 to 6 beat interval for transit through the pulmonary vascular bed. Respiratory cycles were not used if the heart rates varied by more than 2%. Five to ten respiratory cycles were evaluated from each patient and data from approximately 600 heart beats were measured. Stroke volume was obtained by planimetric integration of the area under each flow curve. Zero flow was assumed to be present at the end of diastole. Systolic and diastolic arterial blood pressures were measured directly from the recordings and the pulse pressure was calculated. Standard statistical techniques for paired data analysis were used to evaluate the results. All computations were carried out on a model 1130 IBM digital computer.

Results

Data obtained during continuous respiration from 11 normal subjects are summarized in the top row of table 1. With the onset of inspiration, the

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*U. S. Catheter and Instrument Corp.

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### Table 1

**Hemodynamic Data***

<table>
<thead>
<tr>
<th>Groups</th>
<th>N (11 patients)</th>
<th>SV (cm³)</th>
<th>S/D BP (mm Hg)</th>
<th>PP (mm Hg)</th>
<th>DE (sec)</th>
<th>SV (cm³)</th>
<th>S/D BP (mm Hg)</th>
<th>PP (mm Hg)</th>
<th>DE (sec)</th>
<th>SV (cm³)</th>
<th>S/D BP (mm Hg)</th>
<th>PP (mm Hg)</th>
<th>DE (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>55 ± 5</td>
<td>117 ± 8/80 ± 6</td>
<td>37 ± 3</td>
<td>0.24 ± 0.01</td>
<td>51 ± 5</td>
<td>113 ± 7/78 ± 6</td>
<td>33 ± 3</td>
<td>0.23 ± 0.01</td>
<td>57 ± 4</td>
<td>118 ± 8/80 ± 6</td>
<td>38 ± 3</td>
<td>0.24 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Airway obstruction</td>
<td>57 ± 6</td>
<td>129 ± 3/87 ± 3</td>
<td>43 ± 2</td>
<td>0.25 ± 0.01</td>
<td>43 ± 6</td>
<td>113 ± 2/79 ± 3</td>
<td>33 ± 2</td>
<td>0.23 ± 0.01</td>
<td>56 ± 6</td>
<td>130 ± 3/85 ± 3</td>
<td>45 ± 2</td>
<td>0.26 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>33</td>
<td>90/70</td>
<td>20</td>
<td>0.21</td>
<td>22</td>
<td>75/62</td>
<td>13</td>
<td>0.19</td>
<td>30</td>
<td>102/73</td>
<td>29</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>F.W.</td>
<td>35</td>
<td>142/90</td>
<td>52</td>
<td>0.20</td>
<td>21</td>
<td>120/83</td>
<td>37</td>
<td>0.17</td>
<td>45</td>
<td>150/88</td>
<td>62</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>O.M.</td>
<td>28</td>
<td>140/120</td>
<td>20</td>
<td>0.19</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>37</td>
<td>150/116</td>
<td>34</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Mean values and the standard error of the mean are listed for stroke volume (SV), systolic/diastolic blood pressure (S/D BP), pulse pressure (PP), and duration of ejection (DE). P values listed for the normal and airway obstruction groups reflect comparison using paired data analysis of results obtained at peak inspiration (panel B) and early/mid expiration (panel C) to those obtained at end expiration (panel A). NS denotes P > 0.05. In the pericardial tamponade group, individual data are listed from each of the three patients.

### EFFECT OF RESPIRATION ON STROKE VOLUME

<table>
<thead>
<tr>
<th>Mean stroke volume</th>
<th>Decrease in stroke volume</th>
<th>Systolic blood pressure</th>
<th>Pulse pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>11g</td>
<td>3% (P &lt; 0.01)</td>
<td>8% (P &lt; 0.01)</td>
<td>10% (P &lt; 0.01)</td>
</tr>
</tbody>
</table>

A typical recording from patient H.M., with bronchial asthma, is illustrated in Figure 1. Data from the eight patients having respiratory obstruction are summarized in Table 1. The changes in respiratory rate and blood pressure were not statistically significant for one to two breaths/min. These findings persisted for one to two breaths/min. During continuous inspiration, the respiratory rate varied from 70 to 18 per minute. The mean heart rate in the normal group was 78 ± 3 beats/min and in the five patients who was 96 ± 4 beats/min. The mean heart rate in the normal group was 78 ± 3 beats/min and in the five patients who was 96 ± 4 beats/min. The mean heart rate in the normal group was 78 ± 3 beats/min and in the five patients who was 96 ± 4 beats/min.
cycle as were noted during the control heart rate. In the three normal patients in whom airway obstruction was artifically produced, hemodynamic changes occurred which were similar to those in patients with naturally occurring airway obstruction.

In the bottom section of table 1, individual data from three patients having pericardial tamponade are listed. Respiratory rates ranged from 12 to 20 per minute in these patients. In each patient the onset of inspiration was accompanied by a marked drop in stroke volume, systolic blood pressure and pulse pressure; in fact, in one patient, ejection was absent during early inspiration. Recordings from this patient, O.M., are illustrated in figure 2. A marked increase above the control values of stroke volume, systolic blood pressure and pulse pressure occurred during early and mid expiration in these three patients. In the bottom panel of figure 2, recordings were obtained following a period of breath-holding. These demonstrate that a relatively constant stroke volume of 25 cm³ occurred during the latter part of inspiration; following the onset of expiration the stroke volume increased to 41 cm³. Similar hemodynamic changes were noted in the other two patients.

Discussion

The effects of respiration on left ventricular stroke volume have been studied in chronically instrumented dogs. Guntheroth et al. found an 11% respiratory variation in left ventricular stroke volume in lightly anesthetized intact dogs. Hoffman et al., however, noted that left ventricular stroke volume varied little in the awake dog during quiet respiration but did fall with deep inspiration. Prior to the data presented in this report, no systematic study of the effects of respiration on left ventricular stroke volume in man was available. Goldblatt et al. found the end-diastolic distance between clips

Figure 1

Pressure and flow recordings from a patient having obstructive lung disease. ECG, pressure difference (Δp/Δz), timing of respiration, aortic blood flow, and aortic blood pressure are displayed from top down in each panel. The stroke volume, cm³, is listed under each flow curve. In panel (A), obtained during normal rhythmic respiration, both stroke volume and blood pressure fell during inspiration. Data in panel (B) were recorded during the latter part of a six-second period in which respiration had been suspended in mid-expiration. Both stroke volume and blood pressure fall in the first heart beat after the onset of inspiration.
sutured to the left ventricular surface to undergo little change during quiet respiration. Gabe et al., using a catheter tip velocity probe, found mean aortic blood flow velocity to change ±20% during three respiratory cycles in one patient during exaggerated respiration. Although it is probable that the variation in stroke volume in normal patients is related to the depth of inspiration and, hence, the degree of negative intrathoracic pressure, we did not attempt to quantify changes in intrathoracic pressure in the present study. Therefore, a detailed study of the relationship between left ventricular stroke volume and the depth of respiration, i.e., changes in intrathoracic pressure, could not be undertaken. The average change in stroke volume of 10% found in our normal patients was accompanied by a 5 mm Hg change in systolic pressure during the respiratory cycle. This variation in systolic blood pressure is consistent with that usually found clinically in normal patients during quiet respiration.

Obviously, one of the major factors which might influence left ventricular stroke volume in normal subjects during the respiratory cycle is the variation in filling time of the ventricle due to sinus arrhythmia. In our patients, this factor was eliminated either by choosing respiratory cycles in which the R-R interval varied only minimally, or by controlling the heart rate by right atrial pacing.

Several mechanisms have been postulated for the variations seen in blood pressure and stroke volume during the respiratory cycle. Based on their findings of a decreased aortic blood flow during inspiration in an experimental animal model, Shabetai et al.,

 concluded that the inspiratory decrease in aortic pressure was due in part to direct transmission of negative intrathoracic pressure to the aorta, and in part to a reduced left ventricular stroke volume. This reduction in left ventricular stroke volume may occur because the inspiratory decrease of intrathoracic pressure results in redistribution of blood into the more compliant left atrium and pulmonary veins at the expense of reduced filling of the less compliant left ventricle. Another mechanism which has been postulated is that the inspiratory increase in right ventricular output affects left ventricular stroke volume during the succeeding expiration. According to this mechanism, the inspiratory decrease of left ventricular stroke volume results from delayed transmission through
the pulmonary vasculature of the expiratory decrease in right ventricular output and should be followed by an increase in left ventricular stroke volume as the inspiratory augmentation of right ventricular output reaches the left ventricle. This would appear on the left side as a subsequent transient increase in left ventricular stroke volume which might best be seen during early expiration. Although such an "overshoot" of left ventricular stroke volume was seen in four of the normal patients during quiet continuous respiration, it was of minimal degree and no such "overshoot" could be demonstrated in the other four patients of this group. Consequently, when the group was considered as a whole, no statistically significant "overshoot" of left ventricular stroke volume resulting from transmission of the inspiratory augmentation of right ventricular output to the left ventricle could be demonstrated.

To further evaluate the contribution of respiratory-related alterations of right ventricular output to the observed variations of left ventricular stroke volume in normal subjects, inspiratory changes of left ventricular stroke volume were observed following a period of breath-holding. This period of apnea allowed phasic respiratory alterations of right ventricular output to subside so that left ventricular stroke volume equilibrated at a steady value. Following a period of apnea, left ventricular stroke volume decreased with the first heart beat after the onset of inspiration. Since the period of breath-holding had eliminated any preceding respiratory-related alterations of right ventricular output, this immediate inspiratory decrease of left ventricular stroke volume must have occurred as a primary left-sided phenomenon. The fact that the inspiratory decrease of left ventricular stroke volume following a period of apnea was identical in magnitude with that observed during continuous respiration indicated that any contribution to respiratory-related alterations of left ventricular stroke volume by preceding alterations of right ventricular output during continuous respiration must have been minimal. Thus, it seems most likely that the inspiratory fall in left ventricular stroke volume in normal subjects results from transient inspiratory pooling of blood in the pulmonary veins with a resultant decrease in left ventricular filling.

It is of interest that the inspiratory fall in stroke volume was proportionately the same in the three normal patients and one patient with obstructive lung disease in whom the heart rate was increased to 150 beats/min by atrial pacing. Thus, the abbreviated diastolic filling time associated with tachycardia did not alter the respiratory-related changes in left ventricular stroke volume.

The pulsus paradoxus which is present in patients with airway obstruction has been ascribed by Dornhorst et al.9 to direct transmission to the thoracic aorta of the increase in the magnitude and rate of change of the negative intrathoracic pressure which is present in these patients. This hypothesis was supported by Shabetay et al.12 who found that in anesthetized dogs the paradoxical pulse associated with airway obstruction created by partially occluding an endotracheal tube was not accompanied by abnormal variations of left ventricular stroke volume. Shabetay et al.12 also found that brachial artery blood velocity in a patient with chronic airway obstruction did not undergo respiratory variations commensurate with the observed variations in arterial pressure. Lange and Tsagaris, on the other hand, using pulse pressure as an index of stroke volume in a patient with pulsus paradoxus due to airway obstruction, concluded that there was a brief decrease in left ventricular filling caused by increased pulmonary vascular storage of blood during inspiration.2 The 25% average inspiratory fall in left ventricular stroke volume and the concomitant 23% decrease in pulse pressure in our patients with obstructive lung disease is in keeping with the conclusions of these investigators. Although the exaggerated fall in systolic blood pressure in these patients may be explained in part by direct transmission to the thoracic aorta of the abnormally great increase in negative intrathoracic pressure associated with inspiration, there was always a concomitant marked fall in left ventricular stroke volume. In patients with airway obstruction, as in the normal patients, no definite overshoot in stroke volume following the inspiratory fall could be demonstrated. Thus, a definite role of changes in right ventricular stroke volume in the genesis of pulsus paradoxus could not be demonstrated.

Many theories have been advanced to explain the paradoxical pulse observed in patients with pericardial tamponade.3, 8, 3, 9, 7, 21 The one factor common to all theories is that a decrease in left ventricular filling and subsequent stroke volume occurs during inspiration. The responsible mechanism has not been further elucidated by the data from our patients. The marked respiratory variation in left ventricular stroke volume in our patients with pericardial tamponade resulted from: (1) an immediate fall in stroke volume with the onset of inspiration, and (2) a marked increase in stroke volume...
EFFECT OF RESPIRATION ON STROKE VOLUME

volume several heart beats later. Following breath-holding the onset of inspiration resulted in an immediate decrease in left ventricular stroke volume, systolic blood pressure, and pulse pressure. This was followed in two to three heart beats by a marked increase in these parameters (fig. 2), presumably subsequent to the enhancement of right ventricular stroke volume during the preceding inspiration. As noted above, this finding was not demonstrated in normal patients or patients with airway obstruction but was quite marked in patients with pericardial tamponade. These results support the concept that during pericardial tamponade augmentation in right ventricular filling during inspiration interferes with left ventricular filling. It is possible that pooling of blood in the pulmonary veins during inspiration may additionally decrease left ventricular filling and contribute to the paradoxical pulse seen in patients with pericardial tamponade. Gabe et al. studied the aortic blood velocity in one patient with pericardial tamponade and found an average change of 80% in "relative left ventricular stroke volume" during the respiratory cycle. These data and the conclusions recorded by these investigators are similar to those outlined above.

Acknowledgments

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