Mechanism of decreased left ventricular stroke volume during inspiration in man

MAROUN KARAM, M.D., ROBERT A. WISE, M.D., T. K. NATARAJAN, M.S.,
SOLBERT PERMUTT, M.D., AND HENRY N. WAGNER, M.D.

ABSTRACT Radionuclide ventriculography was performed in 15 healthy subjects during quiet breathing and during inspiration against a 24 cm H2O threshold load with a respiratory gating technique. Inspiratory threshold loading caused an inspiratory decrease in ejection fraction from 64% to 59% (p < .001). Stroke counts proportional to stroke volume decreased by 9.6% (p < .02) due to an increase in end-systolic counts of 15.9% (p < .05). End-diastolic counts decreased in four subjects and increased in three subjects, but the mean counts did not change significantly. These findings suggest that negative pleural pressure causes an impediment to left ventricular ejection comparable to an increase in arterial pressure. Respiratory gating of radionuclide ventriculography during loaded breathing is suggested as a controlled stress on the ventricle for diagnostic purposes.


ANIMAL AND HUMAN STUDIES have shown that left ventricular stroke volume is reduced during inspiration. When pleural pressure changes are increased during inspiration, such as they are in patients with asthma or during breathing against a resistive load, inspiratory stroke volume decreases further,

but the mechanism of this reduction is not clear. Two general categories of explanations for the decrease in stroke volume have been proposed. The first postulates a decrease in end-diastolic volume due to decreased pulmonary venous return and the second explanation postulates an increase in end-systolic volume due to an impediment to left ventricular ejection caused by the negative pleural pressure.

To determine the mechanism of the decrease in stroke volume during loaded breathing, we noninvasively measured the effects of inspiratory threshold loading on relative left ventricular end-diastolic volume, end-systolic volume, and stroke volume in a group of 15 normal subjects using radionuclide ventriculography gated for both the cardiac and the respiratory cycles.

Methods

Population. Fifteen male volunteers who were from 18 to 33 years old were recruited, interviewed, examined, and found to be free of pulmonary, cardiovascular, or other disease. The study protocol was approved by the Johns Hopkins Committee on Human Investigations and informed consent was obtained from each subject before the study.

Inspiratory threshold loading. Figure 1 is a schematic diagram of the inspiratory threshold loading system used in this study. The inspiratory threshold valve consisted of a closed chamber with a weighted plunger. Each subject had to develop a critical negative mouth pressure in order to open the valve and inspire. A threshold pressure of −24 cm H2O was used that was achieved by adding lead weights to the valve plunger. The pressure flow characteristics of the threshold valve and connecting tubing are shown in figure 2. An inspiratory threshold load was used to cause pleural pressure to be reduced by approximately the same degree as mouth pressure, irrespective of changes in tidal volume, respiratory frequency, or inspiratory flow. Studies in two subjects who used an esophageal balloon indicated that the change in mouth pressure was reflected by the change in esophageal pressure within 4 cm H2O over minute ventilation up to 30 l/min.

Radionuclide ventriculography. The technique of gated radionuclide ventriculography used in this laboratory is described in detail elsewhere. Labeling of red blood cells in vivo was performed with 20 mCi of 99mTc pertechnetate injected after prior injection of nonradioactive stannous pyrophosphate. With the subject in the supine position, the gamma camera (Ohio Nuclear, Solon, Ohio) was positioned over the precordium and angled approximately 40 degrees in a left anterior oblique projection to allow the best visual separation of the right and left ventricles. The data acquisition from the region of interest was synchronized with each subject’s electrocardiogram with a physiologic synchronizer (Brattle Instrument Co., Cambridge, MA) interfaced to a dedicated minicomputer (Informatek Simus 4, Norcross, GA). The cardiac cycle was divided into 60 to 85 msec time segments, and counts imaged during each of these.

From the Division of Radiation Health Sciences and Department of Medicine, Johns Hopkins Medical Institutions, Baltimore. Supported in part by NIH grants Nos. HL10342, HL00914, and CA52845.

Address for correspondence: Robert A. Wise, M.D., Division of Pulmonary Medicine, Baltimore City Hospitals, 4940 Eastern Ave., Baltimore, MD 21224.

Received Sept. 1, 1983; revision accepted Jan. 19, 1984.
segments were stored as a separate frame in the computer memory for each picture element.

Previous studies have shown that gamma ray counts acquired over the left ventricle are proportional to left ventricular volume.\textsuperscript{8,9} The standard error of the regression for repeated studies in the same subject in our laboratory and others is 5\% to 6\%.\textsuperscript{11,12}

To study events occurring only during inspiration, we used an additional gating process during threshold loading (figure 3). Mouth pressure was sensed by a transducer interfaced with a physiologic synchronizer (Brattle Instrument Co., Cambridge, MA) that was gated to record cardiac events during inspiration.

Since it was the purpose of our study to examine the effects of pleural pressure on left ventricular function, we used only those beats in which systole was initiated near peak negative mouth pressure. Since the fall in mouth and pleural pressure took 200 to 300 msec after the respiratory gate was closed, some beats may have occurred during a fall in lung volume, but during the period when pleural pressure was negative.

Protocol. The study was performed according to the following protocol: Stage I: A 6 min baseline study was performed in subjects during quiet breathing and results were used as the control data. Stage II: Each subject was instructed to breathe through the threshold load 1 to 2 min to become accustomed to the system. After a short rest period, a 10 min double-gated radionuclide ventriculogram was acquired while the subject was breathing against the load. Inspiratory time as a fraction of the total respiratory cycle time tended to decrease with the load, leading to a period of data accumulation of at least 2 to 3 min, which is sufficient time for data acquisition.\textsuperscript{12}

Two measurements each of heart rate, blood pressure, and pulsus paradoxus, defined as the respiratory variation of systolic blood pressure, were made during both stages with an arm cuff and a mercury sphygmomanometer.

Data acquisition and processing. Regions of interest over the left ventricle were constructed separately for end-diastole and end-systole for both the stage I and stage II data acquisitions. Regions of interest were automatically drawn for end-diastole (region 1), end-systole (region 2), and background (region 3) by a previously described technique.\textsuperscript{13} End-diastole was defined as the frame occurring immediately following the r wave. End-systole was selected as the frame with the minimum counts following end-diastole. A reference sample consisting of a shielded source of \textsuperscript{99m}Tc-labeled red blood cells positioned distant from the heart was used to normalize counts for acquisition time and isotope decay. Ejection fraction (EF) was calculated from the background-corrected end-systolic and end-diastolic counts as follows:

\[
EF = \frac{EDC - ESC}{EDC}
\]

Vol. 69, No. 5, May 1984
Stroke counts (SC) were calculated as the background-corrected difference between end-diastolic and end-systolic counts as follows:

\[ SC = EDC - ESC \]  

(2)

Counts coming from the left ventricle and corrected for background, acquisition time, and isotope decay were used to measure relative left ventricular volume. Results were expressed as a change from control in the same subject in order to minimize the effect of subject-to-subject variations in attenuation.

Statistical analysis. Normalized end-systolic, end-diastolic, and stroke counts, and ejection fraction, heart rate, systolic blood pressure, and pulsus paradoxus during loaded breathing were compared with those during quiet breathing with Student’s t test for paired variates. Statistical significance was inferred when p was less than .05.

Results

A representative normalized time-activity curve for the control and loaded conditions shows an increase in end-systolic counts without a change in end-diastolic counts (figure 4). End-diastolic, end-systolic, and background counts obtained in the subjects are presented in table 1 and expressed as a percent change from control (figure 5). Considering a 12% change in counts to be significant, end-diastolic counts decreased in four subjects, rose in three subjects, and were not clearly changed in eight subjects. In the subjects as a group there was no statistically significant change in end-diastolic counts. Mean end-systolic counts increased by 17.8% (p < .05). There was a mean decrease in stroke counts of 9.6% (p < .02) and background counts increased by 4.2% (p < .05).

Figure 6 illustrates left ventricular ejection fraction during control and loaded breathing. In each of the 15 subjects ejection fraction decreased; the mean decrease was from 64% to 59% (p < .001).

Results for heart rate, blood pressure, and pulsus paradoxus are illustrated in figure 7. There was no statistically significant change in heart rate or end-expiratory systolic or diastolic blood pressure. Pulsus paradoxus was not measurable with the cuff technique during quiet breathing but averaged 20 mm Hg during loaded breathing (p < .001).

Discussion

The results of this study indicate that inspiration against a threshold load decreases relative left ventricular stroke volume and ejection fraction primarily as the result of an increase in end-systolic volume without any concomitant change in end-diastolic volume.

In general, there are two potential mechanisms for a decreased stroke volume — a decrease in end-diastolic volume or an increase in end-systolic volume. A decrease in end-diastolic volume may be attributable to a phase lag in respiratory variation of systemic venous return, primary pooling of blood in the lung during inspiration, or the mechanism of ventricular interdependence whereby the filling of the left ventricle is impeded by the distension of the right ventricle. An increase in end-systolic volume could be attributed either to an increase in afterload or a decrease in contractility.

End-diastolic volumes did not change in a consistent manner and therefore could not account for the fall in stroke volume in all of our subjects. This variability may reflect the biphasic nature of end-diastolic volume.
They showed that in early inspiration end-diastolic volume fell, presumably due to impingement by the distended right ventricle. In late inspiration, end-diastolic volume rose, presumably as a consequence of the increased systemic venous return delayed through the pulmonary circuit or the effect of the impaired left ventricular ejection. The variability among our subjects may reflect the random variation in allocation of systoles between early and late inspiration, or may reflect a variable degree of ventricular interdependence or respiratory variation in venous return. It is

![Graph](http://circ.ahajournals.org/)

**FIGURE 4.** Representative normalized time-activity curve during control quiet breath (left) and inspiration against the 24 cm H₂O load (NPP, right). In this example, there was little change in end-diastolic counts (EDC) and increase in end-systolic counts (ESC) leading to a fall in stroke counts (SC) and ejection fraction (EF).

### TABLE 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>EDC</th>
<th>ESC</th>
<th>SC</th>
<th>BKG</th>
<th>EF</th>
<th>PP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>I</td>
<td>II</td>
<td>I</td>
<td>II</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>1</td>
<td>27051</td>
<td>20169 (75)</td>
<td>5412</td>
<td>5949 (110)</td>
<td>21639</td>
<td>14220 (66)</td>
</tr>
<tr>
<td>2</td>
<td>19221</td>
<td>16332 (85)</td>
<td>4988</td>
<td>4993 (100)</td>
<td>14233</td>
<td>11339 (80)</td>
</tr>
<tr>
<td>3</td>
<td>36794</td>
<td>35592 (97)</td>
<td>15340</td>
<td>16475 (107)</td>
<td>21454</td>
<td>19117 (89)</td>
</tr>
<tr>
<td>4</td>
<td>26476</td>
<td>22083 (83)</td>
<td>8405</td>
<td>10239 (122)</td>
<td>18071</td>
<td>11844 (66)</td>
</tr>
<tr>
<td>5</td>
<td>26104</td>
<td>20766 (80)</td>
<td>13100</td>
<td>11038 (84)</td>
<td>13004</td>
<td>9728 (75)</td>
</tr>
<tr>
<td>6</td>
<td>32782</td>
<td>34619 (106)</td>
<td>9744</td>
<td>13363 (137)</td>
<td>23038</td>
<td>21256 (92)</td>
</tr>
<tr>
<td>7</td>
<td>33610</td>
<td>31990 (95)</td>
<td>12742</td>
<td>12619 (99)</td>
<td>20868</td>
<td>19371 (93)</td>
</tr>
<tr>
<td>8</td>
<td>28288</td>
<td>30868 (109)</td>
<td>8375</td>
<td>10954 (131)</td>
<td>19913</td>
<td>19914 (100)</td>
</tr>
<tr>
<td>9</td>
<td>22896</td>
<td>28694 (125)</td>
<td>6443</td>
<td>10774 (167)</td>
<td>16453</td>
<td>17919 (109)</td>
</tr>
<tr>
<td>10</td>
<td>26940</td>
<td>27170 (101)</td>
<td>6836</td>
<td>8373 (121)</td>
<td>20104</td>
<td>18797 (93)</td>
</tr>
<tr>
<td>11</td>
<td>42622</td>
<td>43351 (102)</td>
<td>19216</td>
<td>19790 (103)</td>
<td>23406</td>
<td>23561 (101)</td>
</tr>
<tr>
<td>12</td>
<td>34198</td>
<td>38440 (112)</td>
<td>17900</td>
<td>20296 (114)</td>
<td>16298</td>
<td>18144 (111)</td>
</tr>
<tr>
<td>13</td>
<td>19327</td>
<td>24917 (129)</td>
<td>5790</td>
<td>8504 (147)</td>
<td>13537</td>
<td>16413 (102)</td>
</tr>
<tr>
<td>14</td>
<td>29130</td>
<td>28694 (98)</td>
<td>13989</td>
<td>15724 (112)</td>
<td>15141</td>
<td>12970 (86)</td>
</tr>
<tr>
<td>15</td>
<td>24227</td>
<td>25585 (106)</td>
<td>10817</td>
<td>12063 (112)</td>
<td>13410</td>
<td>13522 (101)</td>
</tr>
<tr>
<td>Mean</td>
<td>28644</td>
<td>28618</td>
<td>10606</td>
<td>12077</td>
<td>18038</td>
<td>16541</td>
</tr>
<tr>
<td>± SEM</td>
<td>±6434</td>
<td>±7398</td>
<td>±4597</td>
<td>±4498</td>
<td>±3680</td>
<td>±4062</td>
</tr>
</tbody>
</table>

All counts are corrected for background activity and acquisition time. Values in parentheses are percentages of control.

1 = control; II = loaded breathing; EDC = end-diastolic counts; ESC = end-systolic counts; SC = stroke counts; BKG = background counts/pixel; PP = pulse paradoxus with loaded breathing.
possible that subjects who make greater use of their diaphragms during loaded breathing would have a greater increase in abdominal pressure than subjects who use their intercostal muscles. The increased abdominal pressure could lead to a greater increase in venous return and right ventricular distension. Since our subjects were healthy, we cannot say what effect loaded inspiration would have on end-diastolic volume in subjects with pericardial disease in whom ventricular interdependence would tend to be exaggerated.

The most frequently noted cause for a decrease in stroke volume is an increase in end-systolic volume. Although the possibility of a decrease in contractility cannot be excluded, there is no evidence for a change in the activity of the autonomic nervous system, as evidenced by the absence of any changes in heart rate or blood pressure during loaded breathing. Furthermore, studies in animals have shown that vagotomy does not appear to alter respiratory variation in stroke volume.4

We favor the explanation offered by several other authors1,6 that the afterload is increased due to the negative pleural pressure. Although the term “afterload” has been defined in several ways,17 we use it in this context to mean systolic wall stress. According to the modification of Laplace’s law for thick-walled prolate ellipsoid18

\[ S = \frac{P_{TM}}{r} \left(1 - \frac{r^3}{1^2 \left(2r + t\right)}\right) \]  

where \( S \) = midwall stress; \( P_{TM} \) = transmural ventricular pressure; \( r \) = midwall radius; \( t \) = wall thickness; \( l \) = longitudinal axis. Thus, wall stress must increase with an increase in transmural pressure at a constant size and shape. Several studies1,4,6,22 have shown that inspiration is accompanied by an increase in transmural aortic systolic and presumably left ventricular systolic transmural pressure. This decrease in pleural pressure is not identical to change in arterial resistance since the relationship between arterial pressure gradient and flow would not be altered. The effect of a fall in pleural pressure would, however, be identical to an increase in the critical back pressure to arterial flow. During systole aortic blood flow (\( \dot{Q} \)) is a function of aortic pressure (\( P_A \)), the critical arterial back pressure (\( P_B \)), and the arterial resistance (\( R_A \)), so that

\[ \dot{Q} = \frac{P_A - P_B}{R_A} \]  

The critical back pressure can be defined as the pressure in the aorta at which flow would stop. Several studies have shown this pressure to be higher than venous pressure and it is thought to be due to smooth muscle tone in the small arterioles acting like a Starling resistor.19-21 The left ventricular transmural pressure

\[ \Delta \text{EDC} \text{ NS} \quad \Delta \text{ESC} \quad \Delta \text{SC} \quad \Delta \text{BKG} \quad p < .05 \quad p < .05 \quad p < .02 \]
(PLVTM) is the pressure gradient across the wall and depends on aortic and pleural pressure so that
\[ P_{\text{LVTM}} = P_A - P_{PL} \]  
(Solving equations 4 and 5 for aortic pressure and setting them equal yields)
\[ P_{\text{LVTM}} = QR_A + P_B - P_{PL} \]

Thus, the transmural pressure of the left ventricle can be increased by increasing arterial resistance, blood flow, or the critical back pressure or decreasing pleural pressure. It should be noted, however, that the effect of increasing back pressure or decreasing pleural pressure are quantitatively identical, but of opposite sign.

Although we found that systolic blood pressure fell by approximately the same amount as pleural pressure, we consider it likely that aortic transmural pressure may still have increased. Blood pressure measurement with the cuff technique may not have been sufficiently precise to detect a change. Also, we do not know the exact timing of hemodynamic and pleural pressures for accurate calculation of transmural pressure. Numerous invasive studies have demonstrated that aortic pressure during inspiration falls less than pleural pressure, causing a net increase in aortic transmural pressure.1, 4, 22, 32

We also noted in our study that there was a significant, albeit small, increase in background counts with loaded inspiration. Background counts reflect the amount of blood per unit of lung volume measured adjacent to the left ventricle.23, 24 We did not measure end-expiratory lung volumes during this study; however, it seems likely that our inspiratory loading study was performed at lung volumes the same or higher than those at control. If this were the case and there were no changes in pulmonary blood volume, then we would have expected background counts to fall during inspiration. In fact, the opposite occurred, indicating an increase in pulmonary blood volume. There are three possible mechanisms for the increase in pulmonary blood volume with inspiration: an increased inflow to the lung from the right ventricle, decreased outflow from the lung to the left ventricle, or both. A number of studies have demonstrated that inspiration is associated with an increase in right ventricular stroke volume.4, 25-27 The effects of inspiration on pulmonary venous return have been much less well researched. It has been reported that during spontaneous inspiration, pulmonary venous return usually increases,28, 29 whereas under conditions of cardiac tamponade it decreases.30 Thus, the mechanism of elevated pulmonary blood volume can be accounted for at least partly by an increased inspiratory inflow from the right ventricle.

An additional factor may have been an increase in transmural left ventricular filling pressure.1, 22 There is also a question of whether the increased pulmonary blood volume is due to primary pooling of blood in the lung, which further exaggerates the inspiratory fall in stroke volume. This appears not to be the case since the greatest increases in pulmonary blood volume are not associated with the greatest falls in end-diastolic volume.

Our finding that inspiration against a load decreases left ventricular stroke volume during inspiration has been previously reported in the literature1, 2, 4 and correlated well with our observed inspiratory decrease in pulse pressure during loaded breathing. Although there has been general agreement on the effect of a fall in pleural pressure on left ventricular stroke volume, there is little agreement on whether this is due to a reduction in end-diastolic volume or to an increase in end-systolic volume. Buda et al.,31 using radiopaque markers, and Scharf et al.,32 using geometric radionuclide techniques in normal subjects, found increases in end-systolic and end-diastolic volumes during the late phase of a Mueller maneuver.

In contrast, Brinker et al.,33 Jardin et al.,34 and Brenner and Waugh35 noted a decrease in end-diastolic area during the study, by echocardiographic techniques, of inspiratory efforts in humans.

In dogs Summer et al.,1 using sonomicrometer measurements of the anterior-posterior axis, observed increased left ventricular end-systolic dimension with no change in left ventricular end-diastolic dimension during spontaneous inspiration. Wead and Norton,2 using a mechanical cross-sectional area transducer,
found that normal inspiration caused a fall in end-systolic and end-diastolic areas, but that inspiratory resistance caused increases in these parameters. Scharf et al.,4 using radiopaque beads in dogs, found that end-diastolic volumes fell in early and rose in late inspiration during both normal and resistance loaded inspiration. Olsen et al.36 have measured three sonomicrometer dimensions in dogs instrumented over a long term and have found that inspiration causes an increase in end-systolic volume but no change in end-diastolic volume. Robotham et al.,37 using three axis endocardial sonomicrometers, showed that spontaneous inspiration caused deformation of the ventricle, with a tendency of the septal-to-lateral dimension to narrow and the anteroposterior dimension to widen.

It is possible, then, that the variation in the findings of these studies was due to alterations in the geometry of the ventricles during respiration that were not accounted for by the techniques used. The technique used in our study requires no assumptions about the shape or geometry of the ventricle with respiration. The major assumptions necessary for use of our technique are that the radioactive counts over the left ventricular region of interest are proportional to blood volume and that attenuation of gamma rays does not vary during the study.

The findings of this study have clinical relevance in several different settings. First, they may explain the presence of paradoxical pulse in patients with severe asthma in whom negative swings in pleural pressure are markedly accentuated. A similar degree of negativity of pleural pressure accompanies inspiration during obstructive sleep apnea and may impair left ventricular function in patients with that condition. Moreover, the reduced lung compliance and hyperpnea of acute left ventricular failure could contribute even further to the deterioration of the patient’s cardiac status through negative pleural pressure swings. In contrast, the salutary effect of positive pressure ventilation in cardiogenic pulmonary edema may, in part, be due to elevation in pleural pressure.38, 39

Since loaded inspiration acts on the left ventricle mainly by impeding emptying, it could possibly be used as a controlled stress on the left ventricle. Scharf et al.40 have used the Mueller maneuver as a controlled stress to demonstrate the presence of abnormal wall motion in patients with coronary artery disease. The putative advantage of our technique is that a sudden fall in pleural pressure would be analogous to a sudden increase in aortic pressure. The sudden imposition of this load would allow study of the ventricular response before reflex or mechanical adaptation could occur. Thus, loaded breathing might be used as a simple and safe method of subjecting the heart to controlled stress as a diagnostic tool in the evaluation of left ventricular pressure-volume relationships. We would expect subjects with impaired ventricular function to have greater increases in end-systolic volume during loaded inspiration.

In summary, then, our findings suggest that the fall in stroke volume that occurs during loaded inspiration is due to a transient impediment to left ventricular ejection. The use of respiratory maneuvers may provide a useful controlled stress on the left ventricle for diagnostic purposes.

We appreciate the excellent secretarial assistance of Mrs. Brenda Jordan.

References

CIRCULATION
Mechanism of decreased left ventricular stroke volume during inspiration in man.
M Karam, R A Wise, T K Natarajan, S Permutt and H N Wagner

Circulation. 1984;69:866-873
doi: 10.1161/01.CIR.69.5.866

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/69/5/866

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally
published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the
Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further
information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/