The Effects of Large Negative Intrathoracic Pressure on Left Ventricular Function in Patients with Coronary Artery Disease

Steven M. Scharf, M.D., Ph.D., Jesus A. Bianco, M.D., Donald E. Tow, M.D., and Robert Brown, M.D.

SUMMARY Using first-pass radionuclide ventriculography, we evaluated the effects of decreases in intrathoracic pressure (Mueller maneuver [M] to −20 to −30 cm H₂O) in 14 patients with and five patients without coronary artery disease (CAD) and in 12 normal control subjects. In the patients without CAD, control ejection fraction was 0.53 ± 0.06 (SEM) and control heart rate was 83 ± 6 beats/min. These did not change during M. In the patients with CAD, control ejection fraction was 0.37 ± 0.03 and heart rate was 82 ± 7 beats/min. During M, heart rate did not change, but ejection fraction decreased to 0.33 ± 0.03 (p < 0.01). Examination of regional wall motion abnormalities showed akinesis of at least one myocardial segment in nine of 14 patients with CAD, but in none of the patients without CAD, nor in any of the 12 previously studied normal subjects (retrospectively analyzed). These data are consistent with the hypothesis that the Mueller maneuver acts to increase afterload placed on the left ventricle. Furthermore, in patients with CAD, the Mueller maneuver may have induced localized myocardial ischemia or unmasked areas of preexisting marginal function.

A DECREASE in mean pleural pressure is one of the major consequences of acute airway obstruction.¹⁻³ This effect should act to enhance venous return. However, when pleural pressure decreases relative to aortic pressure, left ventricular (LV) emptying could be impaired.⁴⁻⁶ As intrathoracic pressure decreases, aortic pressure does not decrease as much as intrathoracic pressure. Therefore, aortic transmural pressure (aortic referenced to pleural pressure) and LV transmural pressure increase. The effect is equivalent to increasing aortic pressure (i.e., increasing afterload) at constant intrathoracic pressure. In support of this hypothesis, recent studies have demonstrated an increase in LV end-diastolic and end-systolic size during sustained decreases in pleural pressure both in man and experimental animals.⁷⁻⁹ We reasoned that in patients with cardiac disease, the effect of decreasing pleural pressure would be more severe because an increased afterload depresses LV function in such patients.¹⁰⁻¹⁴ Accordingly, using radionuclide ventriculography before and during a Mueller maneuver, we evaluated the effects of sustained negative intrathoracic pressure on LV performance in patients with and without known coronary artery disease (CAD). These responses were compared with those from a previously studied³ group of 12 young, normal volunteers.

Methods

Patient Selection

Nineteen patients undergoing first-pass radionuclide ventriculography were asked to undergo an additional study during the Mueller maneuver after giving informed consent. Of these, 14 had clinical diagnoses of CAD and five had other diagnoses. These five underwent radionuclide ventriculography to evaluate cardiac status as part of a diagnostic evaluation. Tables 1 and 2 show the clinical profiles of these two groups of patients. Thirteen of the 14 patients with CAD had confirmation by coronary angiography or well-documented (by enzymes and ECG evolution) previous myocardial infarctions (MIs). The other CAD patient had classic exercise-induced angina pectoris, relieved with nitrates. Of the five patients with a diagnosis other than CAD, only one underwent catheterization, which revealed normal coronary arteries. None of the others had clinical evidence of ischemic heart disease by history or ECG.

Mueller Maneuver

In addition to a study performed during quiet breathing, all patients performed a Mueller maneuver as follows: After placement of nose clips, the patients breathed through a mouthpiece attached to an aneroid gauge, which they could read. After two deep inhalations, they exhaled to resting lung volume (functional residual capacity), a valve was turned to close off the airway and a negative pressure of −20 to −30 cm H₂O at the mouth was generated and maintained for at least 15 seconds. The subjects were instructed not to use the buccal muscles to generate this pressure, and had practiced the maneuver several times before the studies. Lung volume remained constant, so pleural pressure decreased as much as mouth pressure. The order of performing the rest (control) and Mueller maneuvers was randomized so that half the patients

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performed the control radionuclide angiogram first and half performed the Mueller maneuver first.

First-pass Radionuclide Ventriculography

The details of performing radionuclide ventriculography along with validation of our techniques have been published. Briefly, radionuclide angiograms were performed in the 30° left anterior oblique position with the detector angulated at a 30° caudal tilt. A bolus of 20 mCi of 99mTc sodium pertechnetate was injected intravenously. Injection was done at 4–6 seconds after the start of the Mueller maneuver. The passage of the radionuclide through the heart and lungs was monitored with a multicrystal gamma scintillation camera (Baird Atomic System 77) interfaced with a computer. Data were acquired at 40 frames/sec for 20 seconds after injection. The LV phase of the study was readily identified by anatomic configuration and temporal appearance of the radioactivity. The transit of the bolus was replayed and examined as a series of 1-second analog images, each representing 40 summed 25-msec frames. The LV region of interest was flagged with a magnetic pen by a trained observer, who was unaware of which study, rest or Mueller maneuver, was being examined. Time-activity curves for the left ventricle were generated and corrected for background activity. A representative cardiac cycle was derived from the time-activity curves of four to six beats. Global ejection fraction (EF) was determined by the summed end-diastolic counts minus the summed end-systolic counts divided by the summed end-diastolic counts. Validation of EF determination with this technique has been reported. Further computer processing yielded images of end-diastolic and end-systolic cavity perimeters. Accounting for variability of operator injection time and circulation time we assumed that the data represent cardiac cycles at 10–15 seconds into the Mueller maneuvers. The computer-generated end-diastolic and end-systolic perimeters were used for evaluation of regional myocardial shortening by the hemiaxis method. There is good correlation between radionuclide and contrast ventriculographic techniques for assessing changes in regional wall motion. For the hemiaxis method, a line connecting the midpoint of the aortic valve plane and the LV apex was drawn. Hemiaxes were drawn bisecting the long axis at right angles. Each hemiaxis was measured and its fractional change from end-diastole (end-diastolic minus end-systolic length divided by end-diastolic length) was recorded to ascertain the amount of regional shortening. Five hemiaxes were thus ascertained and numbered: 1 — apex-base; 2 — posterobasal; 3 — septal; 4 — low posterolateral wall; 5 — high posterolateral wall. Figure 1 illustrates the hemiaxes.

We have reported data for normal young volunteers on changes in end-diastolic volume, end-systolic volume, stroke volume and EF during the Mueller maneuver. We did not analyze regional wall motion at that time. For the present study, we retrospectively analyzed regional wall motion abnormalities by the hemiaxis method in the 12 of the original 14 volunteers in whom the images were considered technically adequate for analysis.

Heart rate was determined from the time-activity curves. Blood pressure was measured by standard sphygmomanometry in five of the 14 patients with CAD and four of the five non-CAD patients.

Statistical significance was determined by paired t-test variates unless otherwise specified. All results are expressed as mean ± SEM.

### Table 1. **Clinical Profile—Coronary Artery Disease Patients**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>CAD, S/P MVR, CHF</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>CAD, COPD</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>CAD, COPD, documented inferior wall MI 3 weeks before study</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>CAD, documented inferior wall MI 4 years before study</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>CAD, hypertension, diabetes, COPD</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>CAD, documented anteroseptal MI several years previously, diabetes</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>CAD, post-coronary artery bypass graft (3 vessels)</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>CAD, unstable angina</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>CAD, type IV hyperlipidemia, old anteroseptal MI, bypass graft to RCA 3 years previously</td>
</tr>
<tr>
<td>10</td>
<td>74</td>
<td>CAD, COPD</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>CAD, 2 MIs in past (documented), COPD, diabetes, CHF</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>CAD, 3 documented MIs</td>
</tr>
<tr>
<td>13</td>
<td>73</td>
<td>CAD, inferior wall MI documented 6 years previously, rheumatoid arthritis</td>
</tr>
<tr>
<td>14</td>
<td>64</td>
<td>CAD, aortic stenosis (mild) cardiomyopathy</td>
</tr>
</tbody>
</table>

**Abbreviations:** CAD = coronary artery disease; S/P = status post; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; MI = myocardial infarct; MVR = mitral valve regurgitation; RCA = right coronary artery.

### Table 2. **Clinical Profile—Patients Without Coronary Artery Disease**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>51</td>
<td>Asthma, Meniere's disease</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>COPD/asthma, steroid dependency</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>Ankylosing spondylitis with restrictive lung disease, cor pulmonale</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>Alcoholic cardiomyopathy, asthma</td>
</tr>
<tr>
<td>19</td>
<td>51</td>
<td>Asthma</td>
</tr>
</tbody>
</table>

**Abbreviation:** COPD = chronic obstructive pulmonary disease.
Table 3. Hemodynamic Data

<table>
<thead>
<tr>
<th>Subjects</th>
<th>EF</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>M</td>
</tr>
<tr>
<td>No CAD (n = 5)</td>
<td>0.53 ± 0.06</td>
<td>0.51 ± 0.07</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CAD (n = 14)</td>
<td>0.37 ± 0.03</td>
<td>0.33 ± 0.03</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Previously studied normals* (n = 12)</td>
<td>0.58 ± 0.02</td>
<td>0.50 ± 0.09</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. The p value indicates the difference between control and Mueller.

* Abbreviations: C = control; M = Mueller; EF = ejection fraction; HR = heart rate; CAD = coronary artery disease.

Results

Table 3 gives the hemodynamic data on the patients with and without CAD. In the non-CAD patients and in the previously studied normal subjects, EF did not change significantly during the Mueller maneuver. In patients with CAD, mean baseline EF was lower and decreased significantly with the Mueller maneuver. Heart rate did not change in any group. The mean systolic blood pressure of the nine patients measured was 144 ± 6 mm Hg and mean diastolic pressure was 84 ± 4 mm Hg. These did not change significantly during the Mueller maneuver.

With respect to the analysis of the LV hemiaxes, in the normal volunteers and in the patients without CAD, no statistically significant difference was noted in the fractional shortening of any of the five hemiaxes studied. In the patients with CAD, axis 1 (apex-base) (control 0.14 ± 0.02, Mueller 0.07 ± 0.02; p < 0.005) and hemiaxis 4 (low posterolateral wall) (control 0.37 ± 0.04, Mueller 0.29 ± 0.03; p < 0.005) showed decreases with the Mueller maneuver. The location of the diminished fractional shortening as determined by the hemiaxes did not correlate well with the apparent anatomic location of previous MIs as determined by ECG. Of note is the difference between the normal subjects and non-CAD patients vs the CAD patients on the other. None of the normal subjects or non-CAD patients had or developed akinesis, as defined by fraction of shortening = 0, in any hemiaxis studied. In contrast, some CAD patients had akinesis during control measurements and, in nine of the 14 patients, akinesis developed in at least one additional segment during the Mueller maneuver (table 4), a difference that was statistically significant (p < 0.001, by chi-square analysis). Figure 2 shows ventriculograms from patient 3, who developed a decreased EF, cavitary enlargement, and apical akinesis during the Mueller maneuver. This patient had had a well-documented inferior wall MI.

Discussion

The response to the Mueller maneuver of the non-CAD group resembled that of the normal volunteers in that EF did not change significantly. The decrease in EF was, however, significant in the patients with CAD. Taken as a whole, these data are compatible with the hypothesis that the Mueller maneuver impairs LV ejection. Blood pressure did not change and pleural pressure decreased by 20-30 cm H$_2$O (15-22 torr), so arterial transmural pressure can be considered to have increased by 15-22 torr. This indicated that LV transmural pressure during ejection was increased, which would have acted to impede LV emptying.

The clearest difference in the response to the Mueller maneuver between the CAD patients on the one hand, and the non-CAD patients and normal subjects on the other, was the development of akinesis in at least one region of the left ventricle in nine of the 14 CAD patients. Experimental data indicate that...
myocardial ischemia rapidly results in localized abnormalities of myocardial contraction.\textsuperscript{21-26} An increase in aortic and LV transmural pressure, coupled with cardiac dilatation, could have led to increased myocardial tension development and increased myocardial oxygen demand. In the presence of CAD, when oxygen supply is marginal, this would have led to myocardial ischemia and decreased regional contractile function. Alternatively, the development of asynergy may relate to latent mechanical abnormalities in the myocardium, such as loss of muscle fibers or scarring in an area of old infarction. Such areas may have been uncovered by the pressure load imposed on the LV during the Mueller maneuver.\textsuperscript{25}

Other interventions that increase LV afterload are also associated with impaired LV performance. For instance, angiotensin infusion caused decreased EF in both normal subjects and patients with CAD.\textsuperscript{26} Furthermore, although isometric handgrip exercise is associated with an elevation of arterial pressure in both normal subjects and in patients with CAD, only patients with CAD develop regional wall motion changes.\textsuperscript{13, 14, 27} In this latter maneuver, however, an increase in heart rate associated with sympathetic stimulation\textsuperscript{28} may also contribute to regional ischemia. These methods of increasing myocardial afterload have been used as stress tests of ventricular function in patients with CAD. The Mueller maneuver could also serve as a stress test to detect CAD, because the responses to the Mueller maneuver were similar to those seen with other methods of increasing afterload. The clinical efficacy of the Mueller maneuver in this regard has not been determined. If the predictive accuracy of the Mueller maneuver were comparable to that of other tests (e.g., handgrip), it could be advantageous, because it is of short duration, easily reversible and involves minimal instrumentation and patient risk.

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Effect of Negative Intrathoracic Pressure on Left Ventricular Outflow Tract Obstruction in Muscular Subaortic Stenosis

ANDREW J. BUDA, M.D., GARRY W. MACKENZIE, M.D., AND E. DOUGLAS WIGLE, M.D.

SUMMARY To study the effect of respiration and negative intrathoracic pressure on the left ventricular outflow tract gradient in patients with muscular subaortic stenosis, we studied nine patients using various respiratory maneuvers at the time of cardiac catheterization. Deep inspiration decreased the left ventricular outflow tract gradient from 60 ± 11 to 34 ± 6 mm Hg (p < 0.01) and decreased the left ventricular ejection time (corrected for heart rate) from 0.42 ± 0.01 to 0.38 ± 0.01 second (p < 0.001). The Müller maneuver decreased the left ventricular outflow tract gradient from 69 ± 13 to 7 ± 3 mm Hg (p < 0.001) and decreased the corrected left ventricular ejection time from 0.42 ± 0.02 to 0.34 ± 0.01 second (p < 0.01). In keeping with this amelioration of left ventricular outflow tract obstruction, echocardiography showed a reduction or abolition of the systolic anterior motion of the anterior mitral leaflet, and auscultatory and phonocardiographic studies revealed a decrease or abolition of the apical systolic murmur. These findings indicate that negative intrathoracic pressure reduced the left ventricular outflow tract gradient in muscular subaortic stenosis. We believe that negative intrathoracic pressure produced these changes by increasing left ventricular afterload through an increase in left ventricular transmural pressure, resulting in a decrease in the left ventricular outflow tract obstruction. These observations provide an explanation for the decrease in pressure gradient that occurs on inspiration in patients with muscular subaortic stenosis.

CHANGES in left ventricular afterload can have a dramatic effect on the pressure gradient in patients with muscular subaortic stenosis.1-8 A decreased afterload, as produced by administration of amyl nitrite1,4 or nitroglycerin2 or by the Valsalva maneuver,2 significantly increases the left ventricular outflow obstruction. Conversely, an increase in left ventricular afterload by vasoactive agents such as methoxamine,8 phenylephrine,8 angiotensin,4 and norepinephrine,8 decreases the pressure gradient in muscular subaortic stenosis1,8 as well as the associated mitral regurgitation.7 Previous studies have suggested that such changes in ventricular afterload alter the degree of left ventricular outflow obstruction in muscular subaortic stenosis by altering ejection velocity and, hence, the degree to which the anterior mitral leaflet is drawn into the outflow tract by the Venturi mechanism.8

Recent work by Permutt and associates9-12 has suggested that inspiration and the Müller maneuver increase left ventricular afterload by increasing the negativity of intrathoracic pressure, which increases the left ventricular transmural pressure. They suggested that in situations in which major changes were occurring in intrathoracic pressure, left ventricular transmural pressure (i.e., left ventricular pressure minus intrathoracic pressure) was a better reflection of left ventricular afterload than was the aortic or left ventricular systolic pressure.

Because pharmacologic or physiologic increases in left ventricular afterload decreased or abolished the pressure gradient in muscular subaortic stenosis, these patients represented a unique opportunity to test the hypothesis that increases in the negativity of intrathoracic pressure increased left ventricular afterload by increasing left ventricular transmural pressure.9-13 If Permutt's hypothesis is true, inspiration and the Müller maneuver should decrease the pressure gradient in muscular subaortic stenosis, as does the pharmacologic increase in afterload.

In this report, we document the changes that occur
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