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

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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. A decreased afterload, as produced by administration of amyl nitrite, or nitroglycerin or by the Valsalva maneuver, significantly increases the left ventricular outflow obstruction. Conversely, an increase in left ventricular afterload by vasoactive agents such as methoxamine, phenylephrine, angiotensin, and norepinephrine decreases the pressure gradient in muscular subaortic stenosis as well as the associated mitral regurgitation. 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.

Recent work by Permut and associates 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. If Permut'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...
in the pressure gradient in patients with muscular sub-
aortic stenosis during these respiratory maneuvers.

Methods

The study population consisted of nine patients with muscular subaortic stenosis — five males and four females, mean age 43.7 years (range 17-62 years). Five patients had a left ventricular outflow tract gradient at rest, whereas four patients had latent (i.e., provokable) left ventricular outflow tract obstruction. In all patients, propranolol was discontinued at least 48 hours before the study.

Each patient was taught to perform a Müller maneuver at constant pressure with an open glottis. Movement and tension of the thoracic and abdominal musculature were closely observed to ensure a proper maneuver. In three patients, changes in intrathoracic pressure were inferred from changes in airway opening pressure during a no-flow, open-glottis strain maneuver of negative intrathoracic pressure (Müller maneuver). Changes in airway opening pressure were measured with a Boehringer inspiratory meter calibrated to a water manometer to within ± 0.5 cm of water, or directly to a Statham P23Db transducer.

All intracardiac pressures were recorded relative to atmospheric pressure. Intracardiac pressures were recorded with a transseptal catheter in the left ventricular inflow tract and a retrograde catheter in the aortic root. Using previously described techniques, care was taken to ensure that intraventricular pressures were not affected by catheter entrapment. The ECG, intracardiac pressures and airway opening pressures were recorded simultaneously.

Baseline recordings were made during quiet, supine respiration at a normal respiratory rate and a tidal volume of approximately 400 ml. At least two complete respiratory cycles were recorded. At the end of normal end-tidal expiration, the exit valve was occluded and the patient was asked to "pull" to deflect the force meter maximally. After several seconds of sustained negative intrathoracic pressure, the occlusion was released and the subject was allowed to breathe spontaneously.

In the four patients with latent left ventricular outflow tract obstruction, a left ventricular outflow tract gradient was provoked with isoproterenol or amyl nitrite before each respiratory maneuver was attempted. In each case, the left ventricular outflow tract gradient returned to the provoked gradient after each respiratory maneuver.

The left ventricular ejection time was measured in each patient in the control state and during each maneuver. The left ventricular ejection time was measured from the onset of the aortic pressure rise to the dicrotic notch. Each ejection time was corrected for heart rate by dividing by the square root of the cycle length.

The five patients with a resting left ventricular outflow tract gradient underwent echocardiographic examination in the supine position to ascertain the effect of the Müller maneuver on the systolic anterior motion of the anterior mitral leaflet. Echocardiograms were obtained using a Smith-Kline Ekoline 20A ultrasonoscope and 2.25-MHz transducer that had a 13-mm diameter and a beam collimation depth of 5 cm. The echocardiograms were recorded using an Irex Continent 101 and were performed in the control state and during the Müller maneuver with the ultrasonic beam focused on the anterior mitral leaflet. Transducer position was maintained constant throughout the control phase, during the Müller maneuver and after release.

The same five patients with muscular subaortic stenosis and a resting left ventricular outflow tract gradient were examined at the bedside for variations in intensity of the systolic murmur during quiet respiration and during the Müller maneuver. Two patients had phonocardiograms performed in the control state, during the Müller maneuver and after release.

All data are expressed as mean ± SEM. The paired t test was used for statistical analysis.

Results

Hemodynamic Studies

Deep inspiration consistently decreased the left ventricular outflow tract gradient in each patient (figs. 1 and 2). The left ventricular outflow tract gradient decreased from 60 ± 11 to 34 ± 6 mm Hg on deep inspiration (p < 0.01) (fig. 2). There was no significant change in heart rate (78 ± 3 to 76 ± 2 beats/min, p > 0.05).

Corresponding to the decrease in left ventricular outflow tract gradient on inspiration, the left ventricular ejection time corrected for heart rate decreased from 0.42 ± 0.01 to 0.38 ± 0.01 second (p < 0.001) (fig. 3).

The Müller maneuver produced an immediate decrease in the left ventricular outflow tract gradient in each patient (figs. 4 and 5). In five patients, the gradient was completely abolished. With the Müller maneuver, the left ventricular outflow tract gradient decreased during inspiration. LV = left ventricular; Ao = aortic.
The effect of deep inspiration on the left ventricular outflow tract (LVOT) gradient in the nine patients with muscular subaortic stenosis.}

decreased from 69 ± 13 to 7 ± 3 mm Hg (p < 0.001) (fig. 5). During the maneuver, there was no significant change in heart rate (109 ± 9 to 106 ± 9 beats/min, p < 0.05).

Corresponding to the decrease in the left ventricular outflow tract gradient during the Müller maneuver, the corrected left ventricular ejection time decreased from 0.42 ± 0.02 to 0.34 ± 0.01 second (p < 0.01) (fig. 6).

Simultaneous left ventricular (LV) inflow and aortic (Ao) pressure tracings showing the effect of the Müller maneuver on the left ventricular outflow tract gradient in a patient with muscular subaortic stenosis. The calibration of the LV and Ao pressures is on the left and the calibration of the airway (Air.) opening pressure (negative intrathoracic pressure) generated by the Müller maneuver is on the right. The onset and offset of the Müller maneuver are indicated by the arrows. Because of the length of the tubing measuring the airway opening pressure (negative intrathoracic pressure), there is a delay in the onset and offset of this pressure decline in these recordings. The LV outflow tract gradient decreased immediately with application of the Müller maneuver. This reduction in outflow tract gradient persisted throughout the Müller maneuver; however, the gradient increased in two postextrasystolic beats but failed to reach control values.

The effect of deep inspiration on the left ventricular ejection time in the nine patients with muscular subaortic stenosis. ETc = ejection time (corrected for heart rate).
Auscultatory murmur was noted in each of the five patients with a reduction of the murmur during inspiration and an increase in the murmur during expiration. The Müller maneuver produced marked reduction in the intensity of the murmur in each patient (fig. 9).

**Discussion**

Traditional teaching has suggested that respiration affects cardiac hemodynamics as a result of shifts of blood volumes during the respiratory cycle. Thus, on inspiration, the drop in intrathoracic pressure increases right ventricular filling and, by the Frank-Starling mechanism, the right ventricular stroke volume. In addition, inspiration is said to produce pooling of blood in the lungs, thereby decreasing left ventricular filling and, subsequently, the left ventricular stroke volume. Conversely, on expiration, the relative increase in intrathoracic pressure decreases right ventricular filling and right ventricular stroke volume; the pulmonary blood volume also decreases, increasing venous return to the left ventricle and increasing left ventricular stroke volume. This volume hypothesis of cardiac hemodynamics during respiration is generally well accepted and has been supported by several investigators. However, it does not explain all effects of respiration on cardiovascular dynamics. Shaw et al. showed that inspiration may decrease the left ventricular outflow tract obstruction in patients with muscular subaortic stenosis, a phenomenon that has not been adequately explained, because the volume hypothesis would suggest that the gradient should increase on inspiration due to a diminished left ventricular volume. The present study confirms the inspiratory decrease in the obstructive pressure gradient in muscular subaortic stenosis.
which is incompatible with the volume hypothesis and emphasizes the need for an alternative explanation.

Recently, Schrijen et al.9 offered an explanation that resolves this paradox. They found that the left ventricular end-diastolic transmural pressure (i.e., the left ventricular diastolic pressure relative to the pleural pressure) did not decrease during inspiration. They argued that such a finding is incompatible with the classic volume hypothesis of hemodynamic changes during respiration, because one would expect a decrease in the transmural left ventricular end-diastolic pressure as blood was pooled in the lungs during inspiration. Further, Summer et al.,11 using chronically implanted endocardial ultrasound probes in dogs, found that left ventricular end-diastolic and end-systolic volumes increased with inspiration and, to a greater extent, with the Müller maneuver. On the basis of these observations, Permutt and his associates8–11 offered an alternative explanation to clarify the hemodynamic alterations during respiration. These investigators have suggested that changes in transmural left ventricular pressure more accurately reflect left ventricular afterload than does systolic aortic pressure alone during dynamic alterations in pleural pressure. Accordingly, these authors provide evidence that inspiration increases left ventricular afterload whereas expiration decreases it through the changes effected in the left ventricular transmural pressure by alterations in intrathoracic pressure induced by respiratory maneuvers.8–13

Our findings are compatible with the suggestions that inspiration and the Müller maneuver increase left ventricular afterload in patients with muscular subaortic stenosis. As with pharmacologic increase of afterload in this condition, inspiration and the Müller maneuver decreased or abolished the pressure gradient, and concomitantly decreased left ventricular ejection time, presumably by increasing the negative intrathoracic pressure and increasing left ventricular transmural pressure (left ventricular afterload).22

Based on this study,22 further studies were undertaken to further test the hypothesis that negative intrathoracic pressure increases left ventricular afterload.23 In this study, using patients with intramyocardial markers, the Müller maneuver depressed left ventricular function when heart rate was unchanged, preload was elevated and arterial pressure was decreased, suggesting that negative intrapleural pressure increased left ventricular afterload.

The left ventricular outflow tract gradient in muscular subaortic stenosis may also be decreased by increasing left ventricular volume, increasing volume flow across the outflow tract, or decreasing left ventricular contractility. We cannot entirely exclude these alternate explanations for the decrease in the pressure
gradient that we observed, because volume, flow and contractility were not directly assessed. However, in our studies, the decrease in the left ventricular outflow tract gradient occurred immediately during the Müller maneuver. This sudden decrease with the first cardiac cycle argues against shifts of intrathoracic blood volume, which are associated with a lag period of a few seconds. Moreover, the production of very negative intrapleural pressures has only a small effect on increasing venous return because of the collapse of the large veins as they enter the thorax. This would limit both right and left ventricular filling during the Müller maneuver. There was no significant change in heart rate during inspiration or the Müller maneuver, suggesting that changes in autonomic tone with resultant changes in contractility were not operative in the change in the left ventricular outflow tract gradient.

To exclude the possibility of alteration in catheter position as the cause of changes in left ventricular outflow tract gradient during inspiration and the Müller maneuver, care was taken to exclude catheter entrapment, and the left ventricular ejection time was measured in each patient during the control state and during each respiratory maneuver. With each maneuver in each of our patients there was a significant decrease of the left ventricular ejection time that was directly related to the decrease in the left ventricular outflow tract gradient. We have shown that changes in left ventricular ejection time are directly related to changes in the left ventricular outflow tract gradient in patients with muscular subaortic stenosis. Therefore, the changes in left ventricular ejection time are in keeping with an actual decrease in the obstruction during inspiration and the Müller maneuver.

Echocardiography also suggested a decrease in left ventricular outflow tract obstruction during the Müller maneuver. Systolic anterior motion of the anterior mitral leaflet, which by opposing with the ventricular septum is believed to cause the left ventricular outflow tract obstruction in muscular subaortic stenosis, decreased or disappeared during the Müller maneuver.

Auscultation and phonocardiography showed that changes in left ventricular outflow tract gradient during respiration may be suspected by changes in the intensity of the systolic murmur in many patients with muscular subaortic stenosis. In all patients, inspiration decreased and expiration increased the intensity of the apical systolic murmur. During the Müller maneuver, the murmur was reduced or abolished in these patients. Therefore, a diagnosis of muscular subaortic stenosis should be suspected when the apical systolic murmur decreases during inspiration or is abolished during the Müller maneuver.

In conclusion, large negative intrathoracic pressures can virtually abolish the left ventricular outflow tract gradient in patients with muscular subaortic stenosis. These changes cannot be explained on the basis of changes in left ventricular volume. Rather, negative intrathoracic pressure produces an increase in left ventricular transmural pressure and left ventricular afterload. This afterload effect, as with pharmacologic afterloading in muscular subaortic stenosis, decreases the left ventricular outflow tract obstruction in these patients. The results of this investigation are compatible with the hypothesis that an increase in negative intrathoracic pressure causes increased left ventricular afterload by increasing left ventricular transmural pressure.

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