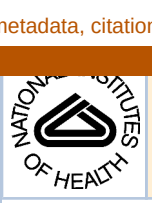

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Dynamic Changes of Left Ventricular Performance and Left Atrial Volume Induced by the Mueller Maneuver in Healthy Young Adults and Implications for Obstructive Sleep Apnea, Atrial Fibrillation and Heart Failure

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Abstract

Using the Mueller maneuver (MM) to simulate obstructive sleep apnea (OSA), we sought to investigate the acute changes in left sided heart morphology and function that develop with apneas occurring during sleep. Strong evidence supports a relationship between OSA and both atrial fibrillation (AF) and heart failure (HF). However, the acute effects of airway obstruction on cardiac structure and function have not been well defined. In addition, it is unclear how OSA might contribute to the development of AF and HF. We utilized echocardiography in healthy young adults to measure various parameters of cardiac structure and function. Subjects were studied at baseline, during and immediately after performance of the MM, and after a 10 minute recovery. Continuous heart rate, blood pressure and pulse oximetry measurements were made. During the MM, left atrial (LA) volume index markedly decreased. Left ventricular (LV) end systolic dimension increased in association with a decrement in LV ejection fraction. On release of the maneuver, there was a compensatory increase in blood flow to the left side of the heart with stroke volume, ejection fraction and cardiac output exceeding baseline. After 10 minutes of recovery all parameters had returned to baseline. In conclusion, sudden imposition of severe negative intrathoracic pressure leads to an abrupt decrease in LA volume and a decrease in LV systolic performance. These changes reflect an increase in LV afterload. Repeated swings in afterload burden and chamber volumes may have implications for future development of AF and HF.

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Keywords

obstructive sleep apnea; Mueller maneuver; echocardiography; atrial fibrillation; heart failure

INTRODUCTION

How obstructive sleep apnea (OSA) might cause or contribute to atrial fibrillation (AF) and heart failure (HF) is not fully understood. It may involve the cumulative effects of repeated obstructive apneas over time. However, co-morbid conditions could also be involved. It is generally accepted that OSA causes chronically elevated sympathetic activity[1] and hypertension.[2] It is hypothesized that these then cause or contribute to ventricular dysfunction.[3–5] This thinking has been challenged by studies demonstrating structural and functional cardiac changes, such as left ventricular (LV) hypertrophy, altered myocardial performance and increased left atrial (LA) volume[6–8] even in the absence of hypertension. Thus, it is not clear whether these changes are a direct consequence of OSA, or due to OSA-related co-morbidities. In this study we sought to determine the acute changes in hemodynamics and left sided heart morphology and function that occur in response to the Mueller maneuver (MM) in healthy, young, normal weight subjects and postulate how these effects might contribute to the development of AF and HF. The MM involves voluntary forced inspiration against a fixed resistance and has been used to simulate the airway obstruction that occurs in OSA.[9–11]

METHODS

We recruited healthy young adults with a normal body mass index (18.5 – 24.9 kg/m^2) and normal sinus rhythm. Exclusion criteria included a history of OSA or use of continuous positive airway pressure, structural heart disease or myocardial ischemia, hypertension (blood pressure ≥140/90 mmHg on any of 3 different measurements), diabetes mellitus or fasting glucose ≥126 mg/dl, asthma, chronic obstructive pulmonary disease, metabolic syndrome and the use of cardioactive medications. Pregnancy tests were performed in all female subjects prior to study. This research was approved by the Institutional Review Board of the Mayo Clinic, Rochester, Minnesota and written consent was obtained from all participants before enrollment.

Previous studies have confirmed that the Muller maneuver closely simulates the changes in intrathoracic pressure produced during sleep in subjects with OSA.[1,10] Briefly, subjects were studied in the left lateral decubitus position. A nose clip and a mouthpiece were placed before each maneuver; the mouthpiece incorporating a small air leak through a 21-gauge needle to prevent complete closure of the glottis during the MM. During the maneuver, mouth pressure was visually monitored by each subject to maintain a target intrathoracic pressure of −40mmHg (−54.4 cm H2O, −5.333 kPa) and the pressure values were digitally recorded on-line. Subjects performed 12 MMs, each lasting 12 seconds, and each separated by a 3 minute rest period. (All subjects were able to achieve these goals).

A complete two-dimensional and Doppler echocardiographic study was performed according to a pre-specified protocol and following the standards of the American Society of Echocardiography.[12] All echocardiographic data were recorded and stored on the hard drive of the echocardiographic machine (Siemens Sequoia C512, Mountain View CA), and copied to compact discs for further off-line analysis. Measurements were performed at baseline, during the MM, immediately after termination, and 10 minutes after the last MM (recovery). When making measurements, the investigators were blinded to patient data and phase of the study. The final value for each measure was the average of values obtained from 3 cardiac cycles at each time-point of the study.

Standard parasternal, apical and subcostal views were obtained. Off-line analysis included measurement of LV end-systolic and end-diastolic dimensions, posterior and septal wall thickness, and calculation of LV ejection fraction, stroke volume and cardiac output using the modified Quinones method.[12] LV filling patterns were determined by pulsed-wave Doppler from the four-chamber view.[13] Mitral inflow patterns were analyzed for early (E wave) and late (A wave) diastolic velocities and the E/A ratio.[14] The integral of transmitral diastolic flow velocity over time (velocity-time integral) was measured to assess changes in blood flow through the mitral valve. Using pulsed-wave tissue Doppler imaging, early diastolic velocity (e') of the septal portion of the mitral annulus was measured from the apical 4-chamber view. The E/e' ratio was calculated to estimate LV filling pressure.[15] LA size was measured just prior to mitral valve opening and LA volume was calculated using the area-length method using the apical 4-chamber and 2-chamber views.[16,17] LA volume was then indexed to body surface area.

We measured R-R intervals as well as systolic and diastolic blood pressure, before, during and after the MM. Baseline measurements were recorded during quiet breathing with the subject supine for 5 minutes. Repeat measurements were made 1 minute prior to each maneuver. R-R intervals were obtained from continuous electrocardiogram recordings (ECG/Biotach SC; Gould Instrument Systems, Inc.). Noninvasive blood pressure measurements were continuously recorded using a Portapres Model-2 instrument (TPD Biomedical Instrumentation Amsterdam, The Netherlands) and the data were verified by sphygmomanometer (Dinamap MPSTM, Johnson & Johnson). Analogue signals were digitized by 16-bit A/D converter with a sampling frequency of 400Hz and recorded by an acquisition system (PowerLab/16SP, Chart v3.6.3/s; AD Instruments Ltd., Castle Hill, Australia). Mean R-R, systolic and diastolic blood pressure values were calculated using custom made ANNAlab ScopeWin ANS software. For the heart rate and blood pressure analyses, several intervals of interest were established: the 10 sec interval preceding the MM, a 12 sec interval during the MM, and four consecutive 5 sec intervals after termination of the MM. Suboptimal MMs (noisy electrocardiogram recording, blood pressure artifact, poorly performed MM) were excluded from further analysis. Data from five randomly selected maneuvers per subject were then analyzed and averaged. The within subject data variability did not exceed 15%.

We also measured oxygen saturation by pulse oximetry (Nellcor Incorporated) while breathing effort was monitored using a respiratory band (Gould Instrument Systems, Inc) and the "negative" pressure signal from MM device (Gould Transducer, Gould Instrument Systems, Inc).

Values are expressed as mean ± SD for continuous variables and as numbers and percentages for categorical variables. One way analysis of variance was performed to reveal any significant difference between groups (p-value <0.05). To compare responses to the MM with baseline measurements and values at other time intervals, Student's paired t-tests with Bonferroni adjustment for multiple comparisons were used ($p < 0.01$). Data were analyzed using JMP software (SAS Institute Inc., Cary, North Carolina).

RESULTS

Twenty-four healthy subjects (9 female) with a normal body mass index (23.4 ± 3.1 kg/m^2), normal blood pressure and heart rate and normal sinus rhythm were enrolled into the study. Four subjects were excluded from the echocardiographic analysis due to suboptimal image quality at baseline or during the MM. The remaining 20 subjects (8 women), mean age 32 ± 4 years, were studied according to the outlined protocol and their data were analyzed.

The LV echocardiographic measurements are shown in Table 1. LA volume index changed significantly in association with the MM (Figure 1). During the maneuver atrial volume markedly decreased ($p<0.0001$), followed by an increase immediately after release (slightly exceeding the baseline value [NS]). During the MM, markers of LV systolic performance (ejection fraction, stroke volume index, and cardiac index) decreased significantly from baseline values. Immediately after termination of the MM, these measures increased in a compensatory fashion, intermittently exceeding baseline values. By recovery (10 min after the MM) all measurements had returned to baseline. Changes in LV dimensions are shown in Table 1. The end systolic LV dimension, but not the diastolic dimension, increased significantly ($p<0.0001$) during the MM, while both dimensions decreased significantly after termination ($p=0.005$ and <0.0001, respectively).

Changes in LV diastolic function Doppler measures were less pronounced. Early diastolic velocity (E) was not influenced by the MM but late diastolic velocity (A) significantly increased immediately after termination. This resulted in a transient significant decrease of E/A ratio after termination of the MM ($p=0.005$). Mitral annular early diastolic velocity (e') was slightly reduced during the MM followed by an increase (nearly reaching statistical significance) immediately after release of the MM. E/e' ratio did not change significantly during the study. The velocity-time integral of the transmitral diastolic flow showed a significant reduction during the MM ($p<0.0001$), followed by an increase immediately after the release (temporarily exceeding the baseline value [NS]).

Figure 2 shows a typical recording of heart rate and blood pressure during a MM. Overall, heart rate changed significantly (ANOVA, $p<0.001$, values not shown) with a gradual increase throughout the MM and a further significant increase during the first 5 seconds after MM termination. This was followed by a return to baseline. Systolic and diastolic blood pressure decreased during the MM and increased immediately after termination with significant change in the systolic values (ANOVA, $p<0.05$, values not shown). There was a delay in the heart rate response compared to the blood pressure response (Figure 2).

DISCUSSION

High negative intrathoracic pressure is the defining feature of obstructive apnea.[18] To assess the cardiovascular effects of such apneas, we used Doppler echocardiography in subjects performing the MM. This maneuver causes an abrupt drop in intrathoracic pressure as well as sympathetic activation and produces hemodynamic changes similar to those occurring in OSA.[1,19,20] By employing the MM in healthy subjects we were able to study the effects of airway obstruction without the confounding influences of hypoxemia and sleep arousals that occur in OSA, or the confounding co-morbidities often present in OSA patients.[21,22]

The important new finding of this study is that LA volume decreases and LV end systolic volume increases acutely in response to high negative intrathoracic pressure. LV end diastolic volume did not change. The net effect was a fall in stroke volume, ejection fraction and cardiac output. Upon release of the maneuver there was a rise in mitral A wave velocity and a significant increase in LA volume. Ejection fraction, stroke volume and cardiac output also rose, exceeding baseline values. These results suggest that 1) the MM adversely impacts LV systolic function and 2) blood flow into the LA decreases during the maneuver, with a compensatory increase upon its release. Given that the entire thorax is exposed to the high negative pressure, these findings require careful explanation.

Previous studies in animals and humans have noted decreased LV systolic function during the MM.[23–25] It has been proposed that the high negative intrathoracic pressure imposes an afterload burden on the LV with resultant systolic dysfunction.[23] In essence, during vigorous

inspiratory effort, the LV must pump blood from the lower pressure thorax into the higher pressure extrathoracic compartment. The lower the pleural pressure, the larger the gradient between the intra- and extra-thoracic vascular beds and the greater the afterload. To the best of our knowledge, this is the first echocardiographic study to confirm these findings.

Finally, cyclic changes in LA volume might explain the observed increase in overnight atrial natriuretic peptide (ANP) levels in untreated OSA patients.[26] It has previously been shown that ANP secretion is stimulated by passive atrial stretch during blood volume expansion and by increased atrial pressure during accentuated atrial contraction.[27]

In this study we used the MM as a surrogate of OSA. This maneuver only partially simulates the pathophysiology of true OSA. While altering hemodynamics and stimulating catecholamine release, it does not produce the profound hypoxemia that is frequently present with spontaneous apneas during sleep. In addition, the arousals that characterize true OSA and the systemic inflammation observed in sleep apneics are not reproduced by the MM. On the other hand, use of the maneuver eliminated these variables as potential confounders, and their possible additive or synergistic effects, allowing us to better define the hemodynamic effects of forced inspiration against a fixed obstruction. We did not measure intracardiac pressure changes but these measurements have been well described in animals and humans and our data are consistent with previous findings.

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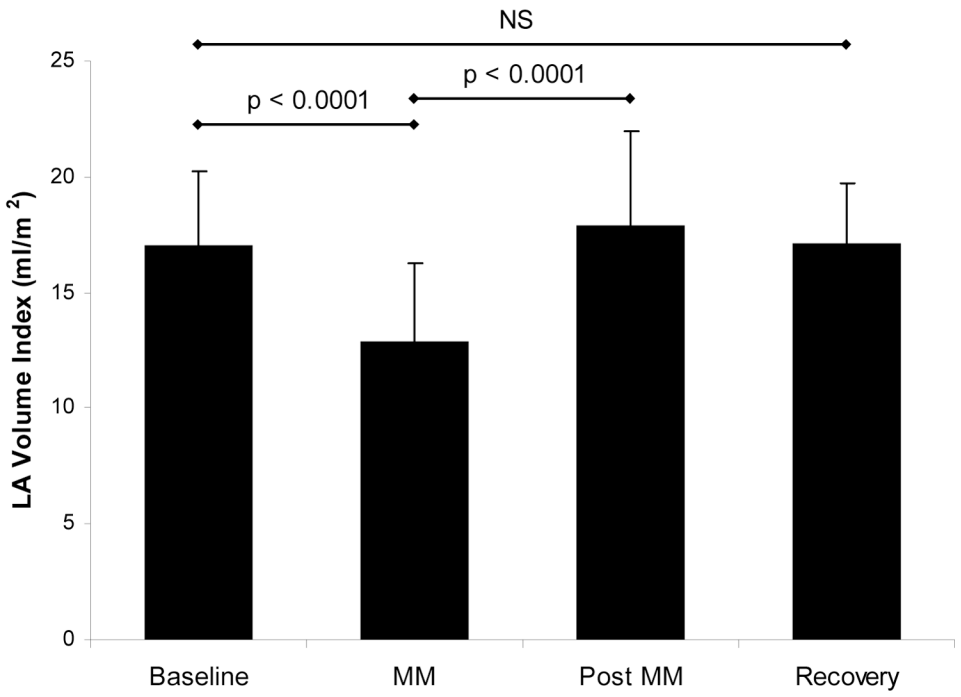

Figure 1. Changes in LA Volume Index

LA volume index (ml/m^2) changes significantly during the Mueller maneuver (p value for trend = 0.0002). During the maneuver there was a significant decrease compared to baseline, p<0.0001. After release, there was a transient increase, p<0.0001. LA volume index in recovery was not different from baseline, p = NS. Data show mean values ± SD.

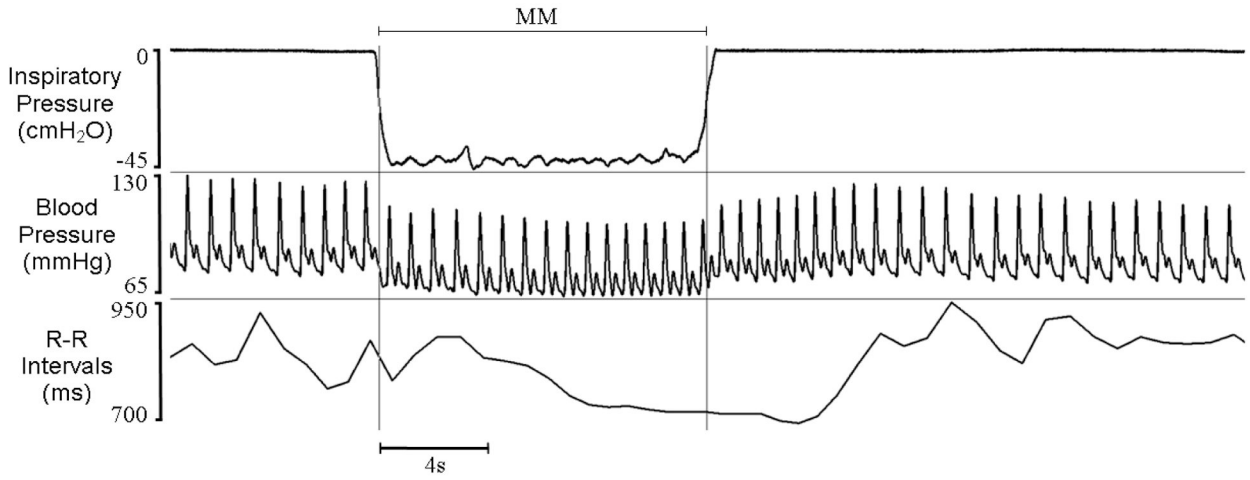

Figure 2. Blood Pressure and R-R Changes during the Mueller Maneuver

Recordings of inspiratory pressure, blood pressure and R-R interval with forced inspiration against airway obstruction during a Mueller maneuver (MM). Blood pressure decreases during the MM and briskly increases after termination of the maneuver, reaching the baseline value within several seconds. R-R interval gradually decreases during the MM with an even more pronounced shortening (increased heart rate) after the maneuver and a slightly delayed recovery to baseline.

Table 1

Changes in Left-Sided Echocardiographic Measures Induced by the Mueller Maneuver (MM)

Variable	Baseline (a)	During MM (b)	Post MM (c)	Recovery (d)	p (a–b)	p (b–c)	p (a–d)
Ejection Fraction (%)	61.4 ± 5.5	51.7 ± 6.1	67.2 ± 6.2	61.9 ± 4.5	<0.0001	<0.0001	NS
Stroke Volume Index (mL/m^2)	41.3 ± 6.1	29.5 ± 6.5	43.2 ± 6.7	39.6 ± 5.5	<0.0001	<0.0001	NS
Cardiac Index (L/min/m^2)	2.6 ± 0.4	2.0 ± 0.4	3.3 ± 0.5	2.5 ± 0.3	<0.0001	<0.0001	NS
LV Systolic Dimension (mm)	29.1 ± 3.2	32.7 ± 3.4	26.1 ± 3.2	29.1 ± 2.9	<0.0001	<0.0001	NS
LV Diastolic Dimension (mm)	47.1 ± 3.5	47.1 ± 4.2	45.8 ± 3.7	47.3 ± 3.3	NS	0.05	NS
LA Volume Index (mL/m^2)	17.05 ± 3.2	12.9 ± 3.4	17.9 ± 4.1	17.1 ± 2.6	<0.0001	<0.0001	NS
e’ (m/s)	0.18 ± 0.05	0.17 ± 0.03	0.19 ± 0.04	0.17 ± 0.03	NS	0.02	NS
E wave (m/s)	0.86 ± 0.11	0.84 ± 0.23	0.85 ± 0.18	0.85 ± 0.14	NS	NS	NS
A wave (m/s)	0.46 ± 0.06	0.46 ± 0.1	0.60 ± 0.1	0.46 ± 0.07	NS	<0.0001	NS
E/e’ ratio	5.1 ± 1.2	5.3 ± 1.2	4.9 ± 1.3	5.2 ± 1.0	NS	0.06	NS
E/A ratio	1.9 ± 0.3	1.9 ± 0.6	1.5 ± 0.3	1.9 ±0.4	NS	0.002	NS
Mitral Valve Velocity Time Integral (cm)	16.9	14.2	18.5	17.3	<0.0001	<0.0001	NS