Study objectives: To determine whether generation of negative intrathoracic pressure during apnea would cause more pronounced and sustained reductions in cardiac output in patients with congestive heart failure (CHF) than in healthy subjects.

Design: Physiologic intervention study.

Setting: Cardiorespiratory physiology laboratory.

Participants: Nine patients with CHF and nine healthy control subjects matched for age and sex.

Interventions: Patients with CHF and healthy subjects generated −30 cm H2O of intrathoracic pressure during 15-s Mueller maneuvers (MMs) to simulate the acute hemodynamic effects and aftereffects of obstructive apneas.

Results: In both groups, MMs caused an immediate rise in left ventricular transmural pressure during systole (LVPtmsys) (p < 0.05), but in CHF patients, this immediate increase was followed by a significant drop in LVPtmsys (p < 0.05), associated with significantly greater reductions in systolic BP and cardiac index than in healthy subjects (25 ± 3 mm Hg vs −11 ± 2 mm Hg [p < 0.05] and −0.53 ± 0.11 L/min/m² vs −0.15 ± 0.11 L/min/m² [p < 0.05], respectively). Healthy subjects recovered promptly, but in CHF patients, these adverse hemodynamic effects were sustained following release of the MM.

Conclusions: CHF patients experience more pronounced and sustained reductions in BP and cardiac output both during and following the MM than do healthy subjects. These findings suggest the potential for adverse hemodynamic effects and aftereffects of negative intrathoracic pressure generation during obstructive sleep apnea in patients with CHF.

Key words: cardiopulmonary interactions; heart failure; obstructive sleep apnea

Abbreviations: CHF = congestive heart failure; CI = cardiac index; LV = left ventricular; LVPtmsys = left ventricular transmural pressure during systole; MM = Mueller maneuver; OSA = obstructive sleep apnea; SVI = stroke volume index

Obstructive sleep apnea (OSA) has adverse, yet reversible effects on left ventricular (LV) ejection fraction in patients with coexisting congestive heart failure (CHF). A unique feature of OSA that compromises LV systolic function is the generation of negative intrathoracic pressure during periods of apnea. Among animals and patients with normal cardiac function, OSA causes acute falls in cardiac output proportional to the fall in intrathoracic pressure. The same is true during the Mueller-maneuver (MM), which simulates the effects of obstructive apnea. Similar hemodynamic changes during sleep could precipitate acute cardiac decompensation and impair coronary and cerebral perfusion.

Increases in LV afterload cause greater reductions in cardiac output in subjects with impaired LV function than in those with normal LV function. Data also suggest that patients with CHF are more...
prone to reduced LV diastolic filling in the presence of right ventricular distension, as might occur during OSA.\textsuperscript{3,15} Therefore, negative intrathoracic pressure should cause greater decreases in cardiac output during obstructive apneas in patients with CHF than in subjects with normal cardiac function. We have previously shown, in patients with CHF, that the MM causes an abrupt increase in LV afterload and a fall in cardiac output proportional to the negative intrathoracic pressure generated.\textsuperscript{16} However, hemodynamic responses in patients with CHF were neither compared to those in healthy subjects, nor examined following release of the MM.

In a small study\textsuperscript{2} in CHF patients with OSA, nocturnal continuous positive airway pressure abolished apneas and caused marked improvement in LV ejection fraction measured in the daytime. These results suggest that deleterious effects of OSA on the failing heart are sustained well into the postapneic period. Since there is a high prevalence of OSA among patients with CHF,\textsuperscript{17,18} it is important to establish whether these mechanical events can have adverse cardiovascular consequences during and after the apneic period. We therefore hypothesized that CHF patients would experience greater reductions in cardiac output in response to generation of negative intrathoracic pressure during apnea, and that these would persist longer following its release than in healthy subjects. Because differences between patients in variables that we could not control, such as the magnitude and duration of negative intrathoracic pressure, hypoxia, and arousals,\textsuperscript{3,16,19–24} precluded the testing of this hypothesis in OSA patients during sleep, we simulated the effects of negative intrathoracic pressure during obstructive apneas by having subjects perform the MM to a target negative pressure over a fixed time period while awake.

**Materials and Methods**

**Subjects**

We studied nine men with the following: (1) CHF of at least 6-months duration secondary to ischemic (n = 3) or idiopathic dilated cardiomyopathy (n = 6); (2) a resting LV ejection fraction of ≤ 45% as measured by \( ^{99} \text{Tc} \) equilibrium radionuclide angiocardiography; (3) chronic exertional dyspnea despite medical therapy; and (4) sinus rhythm. Patients suffering from angina or a myocardial infarction within 3 months of the study and patients with primary valvular heart disease were excluded. Nine healthy men who were not receiving any medications and who were free of cardiovascular and respiratory disease were also studied. The protocol was approved by the local institutional ethics committee, and participants provided written informed consent beforehand.

**Arterial and Esophageal Pressures and Respiratory Measurements**

Finger BP was measured beat by beat using the digital volume clamp method (Finapres: Ohmeda 2300; Englewood, CO) with the arm and hand resting horizontally at heart level throughout the study. As an index of intrathoracic pressure, esophageal pressure was measured using a balloon catheter system attached to a pressure transducer (Validyne Engineering, MP 45 ± 50 cm H\textsubscript{2}O; Northridge, CA).\textsuperscript{23,24} Thoracoabdominal movements and tidal volume were quantitated by a respiratory inductance plethysmograph (Respirtrace; Ambulatory Monitoring; White Plains, NY) calibrated in the direct-current mode against a spirometer.\textsuperscript{27–29} Oxymoglobin saturation was monitored continuously with an ear pulse oximeter (Oxyshuttle; Sensoromedics; Anaheim, CA). The R-R interval was determined from a precordial ECG lead. Signals were recorded continuously onto a strip chart recorder (Model 2800S; Gould; Cleveland, OH).

**Stroke Volume and Cardiac Output**

Maximum instantaneous flow velocity in the ascending aorta was measured from the suprasternal notch with subjects in the supine position, using continuous-wave echocardiographic Doppler technique (Ultrasound 8; Advanced Technology Laboratories; Bothell, WA) as previously described.\textsuperscript{26} Stroke volume was calculated as the product of the mean time-velocity integral (stroke distance) and the cross-sectional area of the aortic annulus (A) calculated as A = \( \pi D/2 \)^2, where D is the diameter of the aortic annulus obtained from a prior parasternal long-axis view at baseline. Echocardiographic Doppler estimates of stroke volume have been validated under experimental conditions similar to those described herein, and have been shown to accurately reflect changes in stroke volume.\textsuperscript{21,30} Cardiac output was calculated from the product of heart rate and stroke volume from which stroke volume index (SVI) and cardiac index (CI) were calculated. Because alterations in thoracic configuration during the MM might affect measures of flow velocity from the suprasternal notch, we performed initial validation experiments in seven healthy subjects and three CHF patients. Time-velocity integrals were acquired by Doppler echocardiography from the suprasternal notch and the right carotid artery, an extrathoracic site that would not be affected by alterations in thoracic configuration during the MM. Measurements were made from each site during tidal breathing and two 15-s MMs (see below). In these 10 subjects, there were no significant differences in relative reductions in time-velocity integrals from baseline, between the suprasternal window and the carotid artery whether averaged over the first 5 s (mean ± SE, –23 ± 3% vs –17 ± 3%) or the last 5 s of the MM (–25 ± 5% vs –15 ± 5%). Thus, the magnitude of changes in time-velocity integrals measured from the suprasternal notch parallel those measured from the right carotid artery.\textsuperscript{16}

**Protocol**

Diuretic treatments were withheld the morning of each study. Baseline measurements were recorded during quiet breathing while in the supine position prior to each MM. Subjects wore a nose clip and a mouthpiece with a small air leak through a 21-gauge needle to prevent closure of the glottis during the MM. Mouth pressure was visually monitored by each subject to maintain the target intrathoracic pressure of − 30 cm H\textsubscript{2}O. All healthy subjects and CHF patients performed several practice MMs before data collection began. In preliminary studies, we found that 15 s was the longest period CHF patients could sustain
an MM without discomfort or oxyhemoglobin desaturation. Subjects performed two 15-s MMs separated by a 3-min rest period.

Data Analysis

Baseline data in the two groups were compared by unpaired t tests. LV systolic transmural pressure (LVPtmsys), an index of LV afterload, was calculated as the differences between esophageal pressure measured synchronously with systolic BP. Data collection began during the baseline control period prior to each MM, and continued throughout and for 25 s after the release of each MM. Beat-by-beat measurements were obtained for these variables for each individual. Baseline values were averaged over the 5 s immediately before the onset of the MM. Mean values for the first and last 5 s of each MM and for 5-s periods immediately, 10 s, and 20 s after release of the MM were also obtained and were averaged for the two MMs performed by each subject. Mean changes from baseline at each of these points for each variable were calculated and compared within and between the two groups by two-way analysis of variance for repeated measures, corrected for multiple comparisons by Student-Newman-Keuls test. A p value of < 0.05 was considered statistically significant. All data are expressed as mean ± SE.

Results

Characteristics of the Subjects

Mean age, body mass index, and values of physiologic variables were similar in the two groups (Table 1). The CHF patients had severe LV systolic dysfunction as indicated by a mean LV ejection fraction of 19 ± 5%. Five CHF patients were in New York Heart Association class II, and four patients were in class III. All patients with CHF were receiving appropriate medical therapy for CHF, which included diuretics in nine patients, digoxin and angiotensin-converting enzyme inhibitors in eight patients, hydralazine and nitrates in three patients, and β-blockers in two patients.

Responses During MMs

Figure 1 shows a representative recording of tidal

Table 1—Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy Subjects</th>
<th>CHF Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>46.3 ± 3.2</td>
<td>52.2 ± 4.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.4 ± 1.7</td>
<td>28.6 ± 1.7</td>
</tr>
<tr>
<td>Systolic esophageal pressure, cm H₂O</td>
<td>-3.3 ± 0.3</td>
<td>-2.5 ± 0.2</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>133.4 ± 6.2</td>
<td>120.9 ± 6.5</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>85.5 ± 7.2</td>
<td>69.5 ± 3.3</td>
</tr>
<tr>
<td>LVPtmsys, mm Hg</td>
<td>131.7 ± 5.1</td>
<td>122.7 ± 6.5</td>
</tr>
<tr>
<td>R-R interval, s</td>
<td>0.91 ± 0.05</td>
<td>0.94 ± 0.05</td>
</tr>
<tr>
<td>SVI, mL/m²</td>
<td>29.5 ± 2.0</td>
<td>26.7 ± 3.3</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.1 ± 0.2</td>
<td>1.9 ± 0.2</td>
</tr>
</tbody>
</table>

*There were no significant differences in any of these variables between the healthy subjects and CHF patients.

Figure 1. A representative recording of tidal volume (VT), esophageal pressure (Pes) and BP from one patient with CHF before, during, and after a 15-s MM. Note that BP falls immediately at the onset of negative esophageal pressure generation and falls progressively throughout the MM. In addition, BP remains depressed in the immediate post-MM period. Note also that esophageal pressure increases above baseline following release of the MM in association with a reduction in end-expiratory lung volume.
experienced an immediate increase in LVPtmsys over the first 5 s. However, by the last 5 s, LVPtmsys decreased significantly more than in healthy subjects ($25 \pm 6 \text{ mmHg s}^{-1}$ vs $1 \pm 0.05$) and fell significantly below the baseline level due to the progressive fall in systolic BP.

SVI dropped transiently during the first 5 s of the MM in healthy subjects, and then recovered to the baseline value by the last 5 s, even though LVPtmsys, a determinant of LV afterload, remained elevated throughout (Fig 3). However, in CHF patients, SVI also fell during the first 5 s, but by the end of the MM, it fell by more than twice as much as in the healthy subjects ($-8.5 \pm 1.8 \text{ mL/m}^2$ vs $-4.1 \pm 2.1 \text{ mL/m}^2$; $p < 0.05$). This occurred even though LVPtmsys had actually fallen below initial baseline values at this point.

The pattern of the chronotropic response to the MM was similar in the two groups (Fig 4). In the healthy subjects, R-R intervals tended to fall during the first and final 5 s of the MM, but these reductions were not significant. In the CHF patients, R-R intervals fell significantly below baseline in the first and final 5 s of the MM.

In healthy subjects, CI fell significantly below baseline only during the initial 5 s of MM, but recovered toward baseline by the last 5 s (Fig 4). In contrast, during the MM, the CHF patients experienced an initial reduction in CI followed by further reductions that were three times greater than observed in the healthy subjects ($-0.53 \pm 0.11 \text{ L/min/m}^2$ vs $-0.15 \pm 0.11 \text{ L/min/m}^2$; $p < 0.05$).

**Responses Following Release of the MM**

Following release of the MM, systolic esophageal pressure rose above the baseline value in both groups (Fig 1, 2). This increase occurred immediately in the CHF patients but was delayed in the healthy subjects. Systolic BP recovered to baseline immediately following release of the MM in healthy subjects (Fig 2), but remained significantly below baseline among CHF patients. This reduction in systolic BP was greater than in the healthy subjects ($-15 \pm 4 \text{ mmHg vs } -4 \pm 3 \text{ mmHg}$; $p < 0.05$). Immediately following release of the MM, diastolic BP remained at the baseline level in healthy subjects and recovered to the baseline level in the CHF patients.
In the immediate period following the MM, LVPtmsys, the index of afterload, returned abruptly to its baseline level in the healthy subjects (Fig 3). In contrast, LVPtmsys remained significantly below baseline in the immediate and 10-s post-MM periods in the CHF patients. The LVPtmsys in the immediate post-MM period was significantly lower in the CHF than in the healthy subjects (2196 mmHg vs 23.9±3 mm Hg; p<0.05).

SVI remained at the baseline level throughout the post-MM period in healthy subjects (Fig 3). In contrast, in CHF patients, the decrease in SVI that occurred during the MM was sustained into the immediate post-MM interval, even though LVPtmsys, or afterload, was significantly reduced from baseline values at this time. SVI then recovered to baseline by the 10-s post-MM interval. R-R intervals were significantly reduced only immediately following release of the MM in the healthy subjects and then returned to baseline at the 10-s post-MM interval (Fig 4). In patients with CHF, significant reductions in R-R intervals were also present immediately following release of the MM, but were sustained throughout the post-MM period. Whereas CI was maintained at the baseline level throughout the post-MM period in healthy subjects (Fig 4), in patients with CHF, reductions in CI were sustained into the immediate post-MM period. At this time, the reduction in CI was significantly greater than in healthy subjects (−0.31 ± 0.11 L/min/m² vs 0.05 ± 0.09 L/min/m²; p<0.05.).

**DISCUSSION**

Since generation of negative intrathoracic pressure against the occluded airway is a unique feature of OSA that could have adverse effects on cardiac function, we designed these experiments to focus specifically on this particular pathophysiologic aspect of OSA independent of potential confounding hemodynamic influences of hypoxia or arousals from sleep. To do so necessitated studying subjects while awake so that we could assess and compare responses to a stimulus of constant length and magnitude in healthy subjects and CHF patients.

Our data demonstrate three important differences in the hemodynamic responses to an MM between subjects with normal and impaired ventricular function. First, for the same negative intrathoracic pressure generated, there were greater reductions in stroke volume and cardiac output in patients with CHF than in healthy subjects. Second, in contrast to healthy subjects, in CHF patients these reductions in stroke volume and cardiac output were sustained after cessation of the MM, despite a greater reduc-
Finally, the hemodynamic effects of the MM differed significantly over its course between healthy subjects and CHF patients. BP and LVPtmsys decreased significantly over the duration of the MM in CHF patients but not in healthy subjects. These findings indicate that negative intrathoracic pressure generated during apnea causes more pronounced and prolonged hemodynamic impairment in treated CHF patients than in healthy subjects.

Responses During MMs

We observed significant reductions in systolic BP during MMs in both groups and in diastolic BP in the CHF patients. By the end of the MM, systolic BP had fallen more than twice as much, and cardiac output three times more in CHF patients than in healthy subjects. As a measure of LV afterload, we used LVPtmsys. Changes in intrathoracic pressure accurately reflect changes in pericardial pressure for systolic events during the MM in both humans and animals. In the healthy subjects, LVPtmsys remained elevated throughout the MM. In contrast, following an initial increase in LVPtmsys in the patients with CHF, it decreased to below the baseline value over the final 5 s of the MM, indicating a reduction in LV afterload. This was in keeping with the decline in systolic BP. These findings indicate that changes in LVPtmsys during MM in CHF patients are time dependent and must be taken into account when interpreting cardiac output responses to upper-airway occlusion.

A striking finding of our study was the divergence of the stroke volume and cardiac output responses between the two groups during the MM. In both the healthy and CHF subjects, SVI and CI decreased during the initial part of the MM. Therefore, the increase in LVPtmsys, due to the fall in intrathoracic pressure, observed at this point suggests that increased LV afterload is an important cause of initial reductions in SVI and CI in subjects with both normal and impaired LV function, just as in unanesthetized dogs with experimental OSA. In healthy subjects, SVI and CI returned to baseline by the end of the MM, despite the concomitant increase in LV afterload. In patients with CHF, however, SVI and CI fell more than twice as much at the end of the MM as in healthy subjects. This hemodynamic compromise occurred despite the simultaneous decrease in LV afterload, which should have allowed CI to increase, or at least prevented it from falling further. Taken together, these data indicate that CHF patients were less able to maintain cardiac output or defend against a fall in BP over the course of the MM than healthy subjects.

The mechanism(s) responsible for the progressive
decrease in stroke volume during the final 5 s of the MM in the CHF patients cannot be determined from the present study. It cannot be attributed to increased LV afterload since LV Ptpmsys had fallen below baseline at this point. One possible mechanism is a reduction in LV preload. This could result from leftward interventricular septal shift due to increased venous return causing reduced LV filling.\textsuperscript{5,34,35} Atherton et al\textsuperscript{14} observed, in a subset of patients with severe CHF, that right ventricular distension was limiting LV filling. Generation of exaggerated negative intrathoracic pressure with consequent further distension of the right ventricle in similar patients could further restrict LV filling by further displacing the interventricular septum to the left.\textsuperscript{15,16} Patients with CHF might be particularly susceptible to such an effect.\textsuperscript{16,36} Our findings over the last 5 s of the MM in the CHF patients might be explained by this mechanism. However, recent data in unanesthetized, intact dogs with experimentally induced OSA indicated that as stroke volume fell during obstructive apneas, LV end-diastolic volume actually increased. Therefore, in that model, reductions in stroke volume could not be attributed to decreases in LV filling. Unfortunately, because chest wall distortion precluded reliable measurements of changes in LV end-diastolic dimensions from normal breathing to MMs by echocardiography in our experiments, we could not resolve this issue. Therefore, we cannot exclude a reduction in LV preload as a factor contributing to the reduced SVI observed during these MMs. Decreased LV filling by increased pooling of blood in the pulmonary circulation is not relevant to the MM because increased pooling occurs secondary to restriction to LV filling by high left atrial pressures, and cannot be its cause. Another possible explanation for reductions in stroke volume in the CHF patients, suggested by the progressive reductions in both systolic BP and LV Ptpmsys during MMs, is a reduction in myocardial contractility due to concurrent drops in diastolic BP and coronary artery perfusion with ischemia.\textsuperscript{7,37,38}

Responses Following Release of the MM
Following release of the MM, esophageal pressure during systole rose above baseline values in both groups (Fig 1, 2). This novel observation indicates that the respiratory system contributed to unloading of the left ventricle in the post-MM period by increasing esophageal pressure and reducing LV Ptpmsys through recruitment of expiratory muscles, analogous to the effects of applying continuous positive airway pressure.\textsuperscript{26,39} This response could assist in the recovery of CI in the post-MM period, especially in the CHF patients. The mechanism mediating this response is not known.

In contrast to healthy subjects, in CHF patients, falls in systolic BP and LV Ptpmsys persisted into the post-MM period. Despite this reduction in LV afterload, stroke volume remained depressed. The potential mechanisms responsible for this depression of stroke volume in the immediate post-MM period include reductions in preload and/or myocardial contractility. However, since esophageal pressure became positive following release of the MM and should have reduced rather than increased adverse ventricular interactions, it appears less likely that reduced LV preload played as prominent a role in reducing stroke volume as it might during the MM.\textsuperscript{14,40} This suggests a significant role for reduced contractility, but one we could not directly assess.

In a previous study, MMs were shown to reduce LV ejection fraction more in patients with coronary artery disease than in healthy subjects.\textsuperscript{39} However, in contrast to the present study, most patients in that study did not have CHF, and the time courses of ejection fraction, BP, and LV Ptpmsys responses during and following the MMs were not characterized. Therefore, our study extends the findings of that previous study to heart failure patients and demonstrates that, in contrast to healthy subjects, reductions in stroke volume are progressive over the course of MMs, and are sustained after their release.

We are limited in extrapolating our findings to clinical OSA by several considerations. The MM applied in our protocol differs from obstructive apnea in that negative intrathoracic pressure was sustained rather than intermittent. Nevertheless, its immediate effects on afterload and cardiac output are similar to those of obstructive apneas in both animals and humans with normal LV function.\textsuperscript{6,8,35,41} Therefore, the hemodynamic effects and aftereffects of the MM we observed should be representative of those occurring in response to obstructive apneas. Second, our study did not examine the effects of other features of OSA, such as hypoxia and arousals from sleep. Therefore, further experiments should be performed during sleep in CHF patients to delineate the functional significance of each of these factors. Unlike control subjects, CHF patients were receiving medications with vasodilator properties. Nonetheless, our present findings are relevant to the clinical setting since CHF patients with OSA would be receiving similar medications. Moreover, similar reductions in BP have been described during obstructive apneas in patients with normal cardiac function, as well as in patients with CHF receiving similar vasodilating drugs.\textsuperscript{42,43}

The most impressive finding of our study is that in patients with CHF, generation of $\sim$ 30 cm H\textsubscript{2}O of intrathoracic pressure lasting only 15 s can precipitate marked reductions in BP and stroke volume that
persist beyond the release of the obstruction. Although our experiments do not define the precise mechanism for this sustained hemodynamic impairment, this finding could well have important clinical implications. Since CHF patients with OSA typically experience hundreds of apneas per night accompanied by negative intrathoracic pressure swings, there may be a cumulative adverse effect on the failing myocardium. Our previous observation that abolition of OSA in CHF patients by nocturnal continuous positive airway pressure improves daytime LV function is consistent with this concept. We conclude that negative intrathoracic pressure causes more profound and sustained reductions in stroke volume and cardiac output during the MM and following its release in treated CHF patients than in healthy subjects.

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REFERENCES


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