Intermittent manual lung hyperinflation (MHI) is used in the respiratory care of critically ill patients who are mechanically ventilated to mobilize and facilitate removal of bronchial secretions and to assist alveolar recruitment.1-6 Patients with septic shock who are mechanically ventilated are at risk of developing pulmonary complications and may benefit from MHI.7

Changes in intrathoracic pressure (ITP) can affect cardiac performance, and continuous positive pressure ventilation is associated with a reduction in left ventricular (LV) preload and cardiac output (CO).8-11 Substantial positive ITP is...
generated by MHI, and large ITP changes, such as those that occur in acute pulmonary disease, were suggested to compromise cardiac performance.\textsuperscript{4,8,9,12} In patients who have undergone coronary artery bypass graft surgery, MHI increased ITP but did not impair ventricular performance,\textsuperscript{13} and lung hyperinflation breaths were reported to increase CO.\textsuperscript{14} However, hemodynamic instability reflected by dependency on administration of vasoactive agents as a common property in septic shock\textsuperscript{15-17} is perceived as a contraindication to MHI.\textsuperscript{18}

The aim of the study was to investigate the occurrence of hemodynamic changes induced by MHI with emphasis on LV output and to assess whether these changes are adverse enough to warrant prohibition of MHI as a routine procedure in the care of patients with septic shock. The present study evaluated the hemodynamic effects of MHI procedures as routinely performed by the ICU nursing staff in mechanically ventilated patients with septic shock.

**MATERIAL AND METHODS**

**Patients**

Thirteen consecutive patients (9 men, 4 women; age, 55 ± 13 years) with septic shock and mechanical ventilation were studied. Septic shock was defined according to the standard criteria of Bone et al.\textsuperscript{19} Informed consent was obtained from the patients’ next-of-kin, and the study design was reviewed and approved by the ethics committee of the participating hospitals.

Exclusion criteria included patient age younger than 19 years or older than 75 years; pregnancy; chronic heart failure (NYHA class III-IV); acute myocardial infarction within 3 months before the study; no invasive arterial or pulmonary artery catheter in situ; life expectancy of less than 24 hours; or enrollment in a previous investigation during the present stay in the intensive care unit.

In this experimental prospective study, patients were treated by their attending physician according to the guidelines of the participating hospitals, which included adequate volume resuscitation (pulmonary artery occlusion pressure [PAOP] >14 mm Hg) and inotropic and vasopressor medication. Patients received broad-spectrum antibiotic coverage, and the antibiotic regimen was adjusted according to the culture results.

**Measurements**

Radial or femoral artery pressure, pulmonary artery pressure (PAP), PAOP, and an electrocardio-
gram were continuously recorded with a standard Hewlett-Packard model 78342A monitor (Hewlett-Packard Company, Medical Products Group, Andover, Mass.). Pressures were measured with the patient in the supine position after calibration and zeroing to the midaxillary level. The resonance frequency of the catheter manometer systems was checked before the start of the protocol and was >15 Hz for intra-arterial pressure and >8 Hz for PAP.

Beat-by-beat changes in LV stroke volume and CO were computed with the Modelflow method. The method uses a nonlinear, three-element model of the aortic input impedance\textsuperscript{20} to compute an aortic flow waveform from arterial pressure, and it has been described in detail previously.\textsuperscript{21,22} The 3 elements of the model represent the major properties of the aorta and arterial system: aortic characteristic impedance, arterial compliance, and peripheral vascular resistance.\textsuperscript{23} The major determinants of the systolic inflow are the aortic characteristic impedance and arterial compliance. These elements are dependent on the elastic properties of the aorta. The third element, peripheral vascular resistance, is not a major determinant of systolic inflow.\textsuperscript{21} It is time-varying and calculated for each heart beat as the quotient of measured arterial pressure and computed Modelflow cardiac output. Integrating the computed aortic flow waveform per beat provides LV stroke volume. CO was computed by multiplying stroke volume and instantaneous heart rate.

Before the start of the study Modelflow CO was calibrated against bolus thermodilution CO. Bolus thermodilution CO was measured with a Baxter COM-2 or SAT-2 device (Baxter Edwards Critical Care, Irvine, Calif.), with the Jansen technique of phase-controlled injections, equally spread over the ventilatory cycle.\textsuperscript{24} The respiratory signal of the ventilator provided the time pulses to trigger injections of 10 mL ice-cooled 5% glucose solution with a computer-controlled injectate pump.

Systemic vascular resistance was expressed as mean arterial pressure divided by CO. Index values for LV stroke volume, CO, and systemic vascular resistance were calculated from body surface area\textsuperscript{25} and variables obtained and expressed as SVI (mL · m\textsuperscript{-2}), cardiac index (l · min\textsuperscript{-1} · m\textsuperscript{-2}), and systemic vascular resistance index (dyne · s · cm\textsuperscript{-5} · m\textsuperscript{2}).

A calibrated pressure transducer connected to the Hewlett-Packard model 78342A monitor and a Fleish head pneumotachograph were placed between the endotracheal tube and the Y-piece of the ventilator circuit, or the manual rebreathing bag, to measure airway pressure and inspiratory and expiratory airway flow. The pneumotachygraph
Interruption is sensitive to movement, and technically satisfactory simultaneous recordings of airway flow and pressure during the MHI procedure were obtained in 5 of the 13 patients; therefore tidal lung volume could be derived from the airway flow signal by integration of the area under a single expiratory flow waveform.

**Manual lung hyperinflation and endotracheal suction procedure**

The nursing staff performed the MHI procedure as part of daily care under normoxic conditions (arterial oxygen saturation = 96%) (Table I). A Mapleson C breathing system with a 2.3 L manual rebreathing bag (RüsC, Kernen-Rommelshausen, Germany) was connected to the tube. The operator subjectively assessed the lung compliance for several breaths and adjusted the pressure relief valve to prevent rigorous inflation of the lungs, and then MHI breaths were delivered for as long as the operator found indicated. No attempt was made to control the number of breaths delivered or the duration of MHI. We used the technique of Clement and Hubsch,26 modified by King and Morrel,18 which involves a deep inspiration, short inspiratory hold phase, and then a rapid release of the insufflation pressure with an unobstructed expiration.27 In all patients studied, endotracheal suction was considered clinically indicated to remove bronchial secretions during the MHI procedure. To minimize additional confounding effects on cardiovascular variables, cleaning of the airways by suctioning during the MHI was performed once or twice and for short episodes only.28,29 In addition, the tracheal catheter was introduced into the tubing system through a valve thereby counteracting dissipation of airway pressure. At the end of the hyperinflation procedure, the endotracheal tube was clamped during reconnection to the ventilator to avoid airway collapse. Except for blood pressure and heart rate signals, the operators were blinded to the additional study measurements. The infusion rates of vasoactive agents, sedatives and fluids, and ventilatory settings were kept constant during this episode.

**Signal processing and analysis**

From 5 minutes before to 15 minutes after the MHI procedure, the analogue signals (radial or femoral arterial pressures, PAP, electrocardiogram, airway pressure, and airway flow) were sampled continuously with a computer-based system. All signals to and from the computer were routed through an interface providing electrical isolation A/D converted at 100 Hz (RTI 815, Analog Devices, Norwood, Mass.) and recorded on a polygraph (Graphtec, Tokyo, Japan) for direct inspection. From the continuous hemodynamic recordings, 15-second average values were taken 5 min before MHI, just before MHI, during the last 15 seconds of

<table>
<thead>
<tr>
<th>No.</th>
<th>I:E</th>
<th>f (min⁻¹)</th>
<th>Vt (mL)</th>
<th>Fio₂ (% O₂)</th>
<th>Pao₂ (mm Hg)</th>
<th>SaO₂ (%)</th>
<th>Peak P (cm H₂O)</th>
<th>PEEP (cm H₂O)</th>
<th>Ventilator type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>1:1</td>
<td>25</td>
<td>840</td>
<td>99</td>
<td>98</td>
<td>96</td>
<td>51</td>
<td>7 Evita 4*</td>
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<td>2</td>
<td>1:1</td>
<td>1:1</td>
<td>16</td>
<td>700</td>
<td>99</td>
<td>103</td>
<td>97</td>
<td>43</td>
<td>18 Servo 900 C†</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>1:2</td>
<td>10</td>
<td>710</td>
<td>41</td>
<td>119</td>
<td>100</td>
<td>25</td>
<td>7 Evita 4</td>
</tr>
<tr>
<td>4</td>
<td>1:1</td>
<td>1:1</td>
<td>16</td>
<td>610</td>
<td>40</td>
<td>119</td>
<td>99</td>
<td>33</td>
<td>13 Evita 4</td>
</tr>
<tr>
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<td>1:2</td>
<td>9</td>
<td>520</td>
<td>50</td>
<td>99</td>
<td>97</td>
<td>22</td>
<td>7 Evita 4</td>
</tr>
<tr>
<td>6</td>
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<td>1:2</td>
<td>20</td>
<td>470</td>
<td>41</td>
<td>125</td>
<td>99</td>
<td>40</td>
<td>8 Servo 900 C</td>
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<td>1:2</td>
<td>12</td>
<td>430</td>
<td>40</td>
<td>88</td>
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<td>154</td>
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<td>10 Servo 900 C</td>
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<tr>
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<td>2:1</td>
<td>20</td>
<td>510</td>
<td>80</td>
<td>130</td>
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<td>15</td>
<td>680</td>
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<td>158</td>
<td>98</td>
<td>26</td>
<td>12 Evita 4</td>
</tr>
<tr>
<td>11</td>
<td>2:1</td>
<td>2:1</td>
<td>16</td>
<td>710</td>
<td>60</td>
<td>149</td>
<td>100</td>
<td>32</td>
<td>12 Servo 900 C</td>
</tr>
<tr>
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<td>1:2</td>
<td>1:2</td>
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<td>470</td>
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<td>140</td>
<td>98</td>
<td>32</td>
<td>10 Servo 900 C</td>
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<tr>
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<td>1:2</td>
<td>1:2</td>
<td>14</td>
<td>690</td>
<td>46</td>
<td>111</td>
<td>97</td>
<td>31</td>
<td>5 Evita 4</td>
</tr>
</tbody>
</table>

I:E, Inspiration-expiration ratio; f, ventilatory frequency; Vt, preset tidal volume; Fio₂, inspiratory oxygen concentration; Pao₂, arterial oxygen tension; SaO₂, oxygen saturation; Peak P, peak airway pressure.

*Evita 4, Dräger, Lübeck, Germany.
†Servo 900 C, Siemens-Elema, Solna, Sweden.
MHI, and 5 minutes and 15 minutes after MHI. Percentage changes were calculated in reference to the 15-second average value just before MHI (ie, baseline value). Myocardial function before the MHI procedure was assessed by calculating LV stroke work index from systemic flow and arterial and pulmonary occlusion wedge pressure. Stroke work index equals $0.0136 \times SVI \times (MAP - PAOP)$.

Table II
Clinical characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Underlying disease</th>
<th>Blood culture</th>
<th>Inotropics (µg/kg/min)</th>
<th>Timing* (days)</th>
<th>Final outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>30</td>
<td>Pneumonia</td>
<td>Pseudomonas aeruginosa</td>
<td>Dop: 13 N: 0.14</td>
<td>1</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>52</td>
<td>Pneumonia</td>
<td>Pneumococcus</td>
<td>Dop: 32 N: 3.2/E: 0.12</td>
<td>1</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>47</td>
<td>Pneumonia</td>
<td>Negative</td>
<td>Dop: 9.5 N: 0.02</td>
<td>4</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>58</td>
<td>Pneumonia</td>
<td>Pneumococcus</td>
<td>Dop: 4 N: 0.02</td>
<td>3</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>69</td>
<td>Pneumonia</td>
<td>Staphylococcus aureus</td>
<td>Dop: 7.2 Dob: 12 N: 0.1</td>
<td>5</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>70</td>
<td>Pseudomembranous colitis</td>
<td>Negative</td>
<td>Dop: 8.2 N: 0.9</td>
<td>6</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>52</td>
<td>Ischemic colitis</td>
<td>Negative</td>
<td>Dop: 15 N: 0.9</td>
<td>3</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>75</td>
<td>Peritonitis</td>
<td>Enterococcus</td>
<td>Dop: 13 N: 0.3</td>
<td>6</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>56</td>
<td>Pneumonia</td>
<td>Negative</td>
<td>Dop: 10 N: 0.2</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>31</td>
<td>Unknown</td>
<td>Staphylococcus aureus</td>
<td>Dop: 5 N: 0.4</td>
<td>1</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>55</td>
<td>Peritonitis</td>
<td>Negative</td>
<td>Dop: 10 N: 0.1</td>
<td>2</td>
<td>Died</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>58</td>
<td>Pneumonia</td>
<td>Klebsiella pneumoniae</td>
<td>Dop: 4 N: 0.04</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>57</td>
<td>Unknown</td>
<td>Negative</td>
<td>Dop: 14 N: 0.5</td>
<td>6</td>
<td>Died</td>
</tr>
</tbody>
</table>

Dob, Dobutamine; Dop, dopamine; E, epinephrine; N, norepinephrine.

*Timing indicates the timing of the procedure in days after the diagnosis of septic shock was made.

Table III
Average hemodynamic effects of intermittent MHI*

<table>
<thead>
<tr>
<th></th>
<th>-5 min</th>
<th>Baseline</th>
<th>During MHI</th>
<th>5 min</th>
<th>15 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>85 ± 18</td>
<td>84 ± 17</td>
<td>90 ± 18</td>
<td>81 ± 14†</td>
<td>84 ± 17</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>30 ± 6</td>
<td>30 ± 6</td>
<td>30 ± 6</td>
<td>29 ± 5</td>
<td>30 ± 6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>99 ± 23</td>
<td>99 ± 23</td>
<td>98 ± 23</td>
<td>99 ± 24</td>
<td>100 ± 22</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>45 ± 18</td>
<td>44 ± 17</td>
<td>46 ± 16</td>
<td>44 ± 16</td>
<td>46 ± 16</td>
</tr>
<tr>
<td>Cl (L · min⁻¹ · m⁻²)</td>
<td>4.2 ± 1.6</td>
<td>4.2 ± 1.6</td>
<td>4.4 ± 1.3</td>
<td>4.2 ± 1.4</td>
<td>4.4 ± 1.7</td>
</tr>
<tr>
<td>SVRI (dyne · cm⁻⁵ · m²)</td>
<td>588 ± 298</td>
<td>588 ± 284</td>
<td>582 ± 230</td>
<td>545 ± 240</td>
<td>579 ± 310</td>
</tr>
</tbody>
</table>

MAP, Mean arterial pressure; MPAP, mean pulmonary artery pressure; HR, heart rate; CI, cardiac index; SVRI, systemic vascular resistance index.

*Values presented as mean ± SD.
†P <0.05, during MHI vs 5 min after MHI.
Statistical analysis

Values are expressed as mean ± SD. Spearman rank correlation was used to assess the association between the duration of the MHI procedure and, respectively, the tidal lung volume and the magnitude of the hemodynamic changes. Repeated measures analysis of variance on ranks was used to detect changes in the course of the procedure. Differences between groups were assessed by the Mann-Whitney rank sum test. A P value of less than .05 was considered to indicate a significant difference.

RESULTS

Clinical characteristics of the patients investigated are given in Table II. Seven patients had positive blood cultures. Overall hospital mortality was 46%. Average time between the diagnosis of septic shock and the study procedure was 1 to 7 days. Ventilatory data before the MHI procedure are given in Table I. All patients received pressure controlled ventilation with positive end-expiratory pressure (PEEP) ranging from 5 to 18 cm H2O (except patient no. 5 treated with pressure support ventilation). Patients were sedated with opiates and benzodiazepines. In patient no. 1, muscle relaxation was induced by a continuous infusion of vecuronium (4 mg/h), and in this patient, PAP monitoring was not available as a result of catheter occlusion during the MHI procedure.

The duration of the MHI procedure was 288 ± 205 seconds (mean ± SD). The procedure was performed at a rate of 16 ± 5 breaths per minute with an inspiratory:expiratory ratio < 1 in 10 of 13 patients. Peak inspiratory pressure generated by MHI was 72 ± 17 cm H2O and varied from 140% to 288% of the ventilator delivered peak inspiratory pressure.

Effects on airway volume, flow, and pressure

Ventilatory tidal volume increased from 499 ± 176 mL (mean ± SD) before MHI to 587 ± 82 mL 5 minutes after MHI (P < .05) with a return to baseline values within 15 minutes after the procedure. There was no relation between the changes in tidal volume and the duration of the MHI procedure. Airway pressure-flow relations are given in Fig 1.

Hemodynamic effects

MHI did not induce statistically significant hemodynamic changes in the patients (Table III). To assess the direction and magnitude of the changes in LV output in individual patients, patients were separated into those who increased (SVI increase) versus those who decreased (SVI decrease) their SVI during hyperinflation (Fig 2). SVI increased in 9 (69%) patients (37 ± 15 to 41 ± 17 mL · m⁻²; P < .05) (Table IV) and decreased in 4 (31%) patients (60 ± 10 to 50 ± 14 mL · m⁻²; not significant). A typical example of the increase in SVI induced by the MHI procedure is given in Fig 3.
The 2 groups did not differ in mean age, medical condition, primary origin and severity of disease, duration of the septic shock phase before the study, hospital mortality, duration of the MHI procedure, changes in tidal volume, or level of peak inspiratory pressure generated by MHI ($SVI_{\text{increase}}$, 72 ± 20 cm H$_2$O vs $SVI_{\text{decrease}}$, 73 ± 10 cm H$_2$O). No relation was found between magnitude or direction of the hemodynamic changes and the duration of the MHI procedure. There were no differences between SVI groups in baseline values of heart rate, mean arterial pressure, MPAP (Table IV), and PAOP ($SVI_{\text{decrease}}$, 18 ± 3 mm Hg vs $SVI_{\text{increase}}$, 16 ± 2 mm Hg). However, baseline values of SVI and cardiac index were higher and values of systemic vascular resistance index were lower in $SVI_{\text{decrease}}$ ($P < .05$) (Table IV). In
addition, LV stroke work index was higher in SVI\textsubscript{decrease} (52 ± 9 vs SVI\textsubscript{increase}, 34 ± 8; P < .05).

**Cardiopulmonary interaction**

Two representative examples of cardiopulmonary interaction during MHI are given in Fig 4. In general, phasic MHI-related increments in mean inspiratory airway pressure were concordant to changes in MPAP ($r^2 = 0.67$). MPAP increased 0.6 mm Hg per cm H\textsubscript{2}O mean inspiratory pressure on average. The magnitude of the increments in MPAP was not reflected in magnitude of SVI ($r^2 = 0.06$). However, the magnitude of changes in inspiratory pressure was related moderately to the magnitude of changes in SVI ($r^2 = 0.35$).

**DISCUSSION**

This study shows that intermittent MHI in patients with septic shock induced relatively small hemodynamic changes and generated a significant though temporary increase in tidal volume.

**Manual lung hyperinflation**

The MHI procedure consists of deliberate induction of phasic increments in ITP and is aimed to facilitate subsequent removal of excess bronchial secretions and recruitment of atelectatic alveoli in patients who are mechanically ventilated. Delivery of hyperinflation breaths results in increased airway pressure and was reported to have hemodynamic consequences. In an inquiring survey on the application of MHI as a respiratory care technique in intensive care departments, hemodynamic instability was perceived as a contraindication to MHI by 85% of the respondents. The potential risk of inducing pulmonary barotrauma with positive pressure ventilation is well recognized, and ventilatory strategies that limit plateau pressures have been proposed to prevent or lessen the development of ventilation-associated lung injury.

In the present study, the MHI breaths were delivered for a limited period of time and none of the patients revealed clinical signs or chest radiograph manifestations indicative of barotrauma throughout their intensive care stay. The highest level of peak inspiratory pressure generated by MHI in this study was lower than those reported in patients who had undergone coronary artery bypass graft surgery and conformed to data from Singer et al, who observed a highest peak inspiratory pressure generated by MHI of 82 cm H\textsubscript{2}O with percentage changes in peak inspiratory pressure ranging from –30% to 250%. Ventilation-induced variation in arterial pulse pressure has been demonstrated to be related to the effects of

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Hemodynamic changes by MHI in patients allocated according to their LV stroke volume responses*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-5 min</td>
</tr>
<tr>
<td>SVI\textsubscript{decrease} (n = 4)</td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>77 ± 18</td>
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<tr>
<td>MPAP (mm Hg)</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>99 ± 6</td>
</tr>
<tr>
<td>SVI (mL/m\textsuperscript{2})</td>
<td>61 ± 9‡</td>
</tr>
<tr>
<td>CI (L/min\textsuperscript{-1}· m\textsuperscript{2})</td>
<td>6.0 ± 1.0‡</td>
</tr>
<tr>
<td>SVRI (dyne·cm\textsuperscript{-5}· m\textsuperscript{2})</td>
<td>293 ± 57‡</td>
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<td>SVI\textsubscript{increase} (n = 9)</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>88 ± 17</td>
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<tr>
<td>MPAP (mm Hg)</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>99 ± 28</td>
</tr>
<tr>
<td>SVI (mL/m\textsuperscript{2})</td>
<td>37 ± 16</td>
</tr>
<tr>
<td>CI (L/min\textsuperscript{-1}· m\textsuperscript{2})</td>
<td>3.5 ± 1.1</td>
</tr>
<tr>
<td>SVRI (dyne·cm\textsuperscript{-5}· m\textsuperscript{2})</td>
<td>720 ± 262</td>
</tr>
</tbody>
</table>

*Values presented as mean ± SD. †P < .05 compared with baseline. ‡P < .05: SVI\textsubscript{increase} vs SVI\textsubscript{decrease}.
CI, Cardiac index; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index. SVI\textsubscript{decrease} patients 3, 5, 10, 11 (in Tables I and II).
PEEP,34 supporting that information on arterial flow can be derived from arterial pressure.

One of the beliefs behind MHI is that it may serve as an “alveolar recruitment strategy”; if inspiratory recruitment is combined with sufficient PEEP, alveoli will remain open.35 During general anesthesia the alveolar recruitment strategy has been shown to improve arterial oxygenation, but this has not been investigated in patients with sepsis who are receiving ventilation.36 In case of recruitment of collapsed airways by MHI, one would expect changes in lung mechanics with an increase in tidal lung volume. We found a short lasting increase in tidal lung volume in 5 patients with satisfactory flow recordings and virtually no change in the pressure-flow relationship. These data do not support an important contribution of MHI to additional alveolar recruitment in patients with septic shock and respiratory failure who are receiving ventilation.

Measurement of LV output

Continuous CO measurements with model-simulated CO from radial arterial pressure in open-heart surgical patients follow changes in thermodilution CO in direction and degree, and beat-to-beat changes in stroke volume are equally well-assessed by Modelflow and Doppler ultrasonography.21,37,38 Changes in ITP are expected to modulate aortic impedance by interference with aortic compliance as a model parameter. We have shown that during prolonged orthostatic stress, a condition that induces changes in transmural aortic pressure and impedance,39,40 model-derived stroke volume precisely tracked thermodilution-based estimates.41 The estimate of peripheral vascular resistance included in the model was simulated appropriately during 70° passive head-up tilt for as long as 1 hour, supporting that conditions associated with changes in vascular smooth muscle tone and amplification of reflex vasoconstriction do not significantly affect the capability of beat-to-beat model cardiac stroke volume tracking from arterial pressure.41,42 Also, under the adverse circumstances of low arterial pressure and treatment with catecholamines in severe septic shock, calibrated CO computed from radial or femoral arterial pressure tracks thermodilution-based CO estimates with a limited offset (2% ± 7%) over a wide range (4.2 to 18.2 L/min) for up to 2 days after a single calibration.22

LIMITATIONS

Several limitations may prevent direct generalizations from these data. Notwithstanding efforts to standardize,26 individual differences may have existed in the performance of the MHI procedure. There is no documented evidence that a single technique for MHI is superior, and the effectiveness of MHI as a technique is uncertain.18 Also the variation in MHI technique among different intensive care centers is considerable,18 and the use of MHI and the way it is performed vary between and among countries.27 In patients who had undergone coronary artery bypass graft surgery without respiratory insufficiency, the cardiovascular changes of randomly ventilator-delivered lung hyperinflation breaths at different volumes were not dependent on volume.14 The present study addressed the effects of MHI as delivered in daily practice in critically ill patients with respiratory insufficiency and differences in lung compliance who were mechanically ventilated. In these patients with pressure-controlled ventilation, the tidal volume delivered...
by the ventilator varies with lung compliance. Conversely, with volume-controlled ventilation the variation is in airway pressure. Thus in this category of patients receiving ventilation fixing of either the MHI tidal volume or airway pressure inherently results in differences between patients with respect to transfer of delivered pressure to the airways and the vasculature. This implies that this specific variation in MHI related changes in airway volume and pressure cannot be controlled but checked only. No relation was found between the duration of the MHI procedure and the magnitude of changes in hemodynamic parameters. Moreover, the average level of peak inspiratory pressure generated by the MHI procedure was comparable for both SVI groups, and similar responses were observed when the MHI procedure was repeated in the same patient.

Differences in LV preload should be considered. We recognize that the level of PAOP may not accurately reflect the actual preload to the left ventricle when its compliance is compromised as in patients with sepsis who are mechanically ventilated. Nevertheless, when taking into account that baseline levels of PAOP were sufficiently high and not different between the SVI groups, 16 mm Hg and 18 mm Hg respectively, the influence of differences in LV preload seems less likely in these patients.

**Changes in LV output**

An increase in ITP may induce a fall in LV preload and output attributed to a fall in venous return. Indeed, Singer et al. found a considerable reduction in Doppler ultrasonography aortic blood velocity up to 15 minutes after MHI in a heterogeneous group of critically ill patients. On the other hand, in patients who had undergone coronary artery bypass graft surgery, lung hyperinflation was reported to increase CO.

In this study of patients with sepsis, we also observed a small increase in stroke volume during MHI in 9 of them. These observations are consistent with those from a dog-model study by Robotham et al. who reported an increase in LV stroke volume after intermittently applied positive airway pressure. In a study of dogs subjected to phasic increases in ITP by high-frequency jet ventilation, Pinsky et al. demonstrated that with normal cardiac function, LV stroke volume decreased, but during β-blockade LV stroke volume had become dependent on the level of LV pressure. They suggested the improvement in cardiac function was dependent on adequate filling and decreased afterload of the left ventricle. The effects of elevated ITP in an endotoxin dog model appeared unrelated to the cardiac cycle and were attributed to endotoxin-induced changes in peripheral vasomotor.
motor tone counterbalancing any depressed myocardial contractility. Fessler et al have shown, in dogs, that PEEP did not reduce the pressure gradient for venous return defined as the difference between mean arterial filling and right atrial pressure. A venous pressure gradient in the inferior caval vein across the diaphragm has been proposed as a possible mechanism. Changes in ITP can influence cardiac performance by affecting ventricular loading conditions. Systemic venous return and factors determining LV ejection may vary over the cardiac cycle, and the finding that increments in mean airway and PAPs were not reflected in the magnitude of SVI confirms that MHI may differentially affect LV preload and afterload. Myocardial depression is a well-documented feature of septic shock, and in patients with a compromised cardiac function, an increase in ITP has been shown to improve cardiac performance. This was attributed to a decrease in effective afterload induced by a fall in transmural pressure.

Conversely, the decrement in stroke volume during MHI in patients with a more evident hyperdynamic septic state, as reflected by higher baseline values for cardiac index and LV stroke work index and lower baseline values for systemic vascular resistance index, suggests a predominance of the reduction in preload as the operating mechanism because the afterload is already decreased. This suggests that the nature of the hemodynamic effects induced by MHI is related to the cardiovascular state before the procedure.

The positive ITP generated by MHI is intermittent rather than constant. Preservation of the airway flow-pressure relationship after MHI does not exclude a contribution of entrapped air during MHI with continued elevation of ITP. Consequently, the beneficial influence on afterload may dissipate with the associated reduction in LV preload becoming dominant.

In conclusion, this study shows that the immediate SVI response is complex and dynamic and seems to be the net effect of the balance between changes in LV preload and afterload and in venous return. The hemodynamic effects of intermittent MHI in patients with septic shock are relatively small in magnitude and their direction seems to be related to the cardiovascular state before the hyperinflation. This suggests that these hemodynamic changes do not warrant prohibition of the MHI procedure in patients with septic shock who are mechanically ventilated.

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REFERENCES
Intermittent manual lung hyperinflation