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Introduction

Intermittent increases in internal or airway resistance are frequent occurrences in the critically ill, for instance in patients incurring upper airway obstruction during sedation or owing to comorbidities such as sleep apnea. Further, increased airway resistance may be encountered when small-diameter endotracheal tubes are utilized or if kinking of tubes or respirator hoses occurs [1,2]. Airway obstruction can lead to inadequate gas exchange due to restriction in flow and result in hypoxemia, hypercapnia, and respiratory fatigue in spontaneously breathing patients. However, how changes in airway resistance affect hemodynamic parameters is less well studied. It has been suggested that spontaneous breathing efforts against increased airway impedance lead to periodic shifts in intrathoracic pressure, which can invoke complex hemodynamic alterations [3]. During maximum inspiration against a completely obstructed airway (Mueller maneuver), a net decrease in cardiac index was observed in previous studies, likely as a result of decreased atrial filling, and of increased afterload due to transmural pressure [4,5]. However, the usefulness of the Mueller maneuver for simulation of the situations mentioned above is limited, predominantly due to its “all-or-nothing” characteristic. Available data on quantitative changes of hemodynamic parameters during airway obstruction of progressively increasing magnitude are scarce. Obtaining those parameters was traditionally associated with high levels of complexity and invasiveness. Utilizing a novel, validated non-invasive device based on bioelectrical impedance [6], we sought to identify short-term dynamic effects of incremental upper airway obstruction on Stroke Volume (SV), Heart Rate (HR), Cardiac Index (CI), Blood Pressure (BP) and other physiologic parameters in healthy volunteers. Unlike previous studies that applied the Mueller maneuver as a model for forced inspiration against upper airway obstruction, we utilized tubes with known length and diameters as defined external airway resistors. Thus, our study applies a dynamic model of in- and expiration against resistance rather than static inspiration.

Materials and Methods

IRB approval

This study was reviewed and approved by the Hospital for Special Surgery Institutional Review Board (IRB number 2012-007). Informed consent was obtained from all eligible participants prior to enrollment into the study.
Enrollment process

Healthy volunteers were recruited and screened for exclusion criteria of a history of any cardiovascular and/or pulmonary disease, history of intrathoracic surgery or pathology, bronchoscopy, cardiac catheterization, major ENT surgery or other airway pathology, history of obstructive sleep apnea, known excessive snoring, and known excessive daytime sleepiness.

Study procedure

Participants were asked to assume supine position. All were connected to the Non-Invasive Cardiac Output Monitor device (Cheetah Medical Inc., Vancouver, WA), which continuously records left-ventricular Stroke Volume (SV), Heart Rate (HR), Cardiac Index (CI) and arterial oxygen saturation (SpO₂) and intermittently records brachial blood pressure (BP). The device uses the principal of bioreactance to derive stroke volume as a function of changes in thoracic impedance and conductance [7]. Four 2-pole leads were attached to the subjects’ backs to obtain bioreactance measurements. Readings acquired using bioreactance in general and the NICOM device in particular have been proven accurate and reliable by validation against both traditional (thermodilution) and semi-invasive methods (pulse curve analysis) [6,8]. After an equilibration period of 10 minutes a nose clip was applied, participants were asked to breathe through a flexible, leak-free mouthpiece, which was attached to spirometry and end-tidal CO₂ (EtCO₂) recording equipment (Datex-Ohmeda, Madison, WI). Baseline data was collected for 10 minutes. Subsequently, subjects were asked to breathe through a number of endotracheal tubes (ETT; Covidien, Mansfield, MA) with decreasing internal diameter (ID: 8, 6, 5, 4, 3 mm), serving as external airway resistors. Each level was maintained for two minutes. The mouthpiece was attached to the proximal end of the tube, while the distal end was connected to the spirometry device. Subjects were asked to briefly hold their breath when changing to the next tube size. After a pause of 15 minutes, breathing cycles were repeated a second time for each volunteer for control purposes.

Power analysis

Assuming a 10% decrease from an average baseline cardiac index of 4.0 l/min at maximum airway resistance with a variance of 0.75 l/min, as observed in preliminary experiments, our estimated required sample size was 14 subjects, with a two-sided alpha level of 0.05 and a power of 0.80.

Data recording and statistical analysis

Continuously recorded data (SV, HR, CI) was averaged to 30-second epochs by the NICOM device, resulting in a total of four readings for every two-minute period during each level of airway resistance. Simultaneously, spirometry data (Tidal Volume (TV), Respiratory Rate (RR), end-expiratory CO₂ tension (EtCO₂)) and other available parameters (BP, SpO₂) were averaged for each 30-second epoch. All available readings from both rounds of measures were tabulated and averaged per subject for each level. Continuous values are expressed as means ± standard deviation. Normality of the data was assessed using the Shapiro-Wilk W test. Differences in hemodynamic (SV, HR, CI) as well as in respiratory parameters (MV, RR, EtCO₂) between baseline and individual levels of airway resistance were tested for significance using Repeated Measures Analysis of Variance (rm-ANOVA). The increase in external airway resistance was calculated for every level according to Hagen-Poiseuille’s law (\( \Delta R = \frac{8n\mu l}{\pi r^4} \)), where \( \Delta R \) is the difference in resistance, \( n \) is viscosity (estimated at 18 sym·10⁻⁶ Pa·s), \( l \) is length of the ET tube, \( r \) is radius of the ET tube. Baseline
This table details changes in non-invasive blood pressure, respiratory rate, minute volume and end-tidal CO2 across different levels of external airway resistance.

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>#8</th>
<th>#6</th>
<th>#5</th>
<th>#4</th>
<th>#3</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sys/dias/map ± SD</td>
<td>115/73/87 ± 12/12/11</td>
<td>121/67/88 ± 22/14/13</td>
<td>114/71/87 ± 9/7/6</td>
<td>114/73/87 ± 15/6/8</td>
<td>115/71/86 ± 15/8/8</td>
<td>110/69/84 ± 7/8 5</td>
</tr>
<tr>
<td>Respiratory Rate (breaths/min, mean ± SD)</td>
<td>11.14 ± 1.57</td>
<td>10.86 ± 1.61</td>
<td>10.79 ± 1.58</td>
<td>11.15 ± 1.95</td>
<td>11.08 ± 2.11</td>
<td>11.27 ± 2.05</td>
</tr>
<tr>
<td>Minute Volume (l/min, mean ± SD)</td>
<td>4.80 ± 0.32</td>
<td>5.70 ± 1.70</td>
<td>5.51 ± 1.10</td>
<td>5.70 ± 1.30</td>
<td>4.78 ± 1.07</td>
<td>4.22 ± 0.61</td>
</tr>
<tr>
<td>End-Tidal CO2 (mmHg, mean ± SD)</td>
<td>40.00 ± 3.63</td>
<td>40.86 ± 3.06</td>
<td>40.71 ± 3.06</td>
<td>41.00 ± 3.46</td>
<td>41.00 ± 4.28</td>
<td>42.18 ± 4.02</td>
</tr>
</tbody>
</table>

This table details changes in non-invasive blood pressure, respiratory rate, minute volume and end-tidal CO2 across different levels of external airway resistance.

**Table 1:** Blood pressure and respiratory parameters during different levels of airway resistance.

External airway resistance (when subjects were breathing through the spirometry device only) was defined as zero. Subsequently, Pearson correlation coefficients were calculated to assess the correlation between overall external airway resistance and SV, HR and CI at each time point.

**Results**

14 subjects were enrolled (9 female, 5 male; mean age 27.8 ± 4.1 years, mean body mass index 26.1 ± 3.6 kg/m²) in the study. No adverse events attributable to the study protocol occurred. Figures 1-3 detail of a restricted breathing cycle. In contrast to this, respiratory efforts are detectable during Mueller maneuvers, indicating a linear relation between decreases in respiratory rate and increases in cardiac index.

**Discussion**

Increases in airway resistance were associated with significant hemodynamic alterations. While no significant changes in blood pressure, arterial oxygen saturation and spirometry parameters were detectable, SV, HR and CI decreased significantly during the Mueller maneuver. The association between respiratory and cardiac parameters was assessed using Pearson correlations. Strong inverse Pearson correlations were detectable between changes in airway resistance and cardiac index, SV, HR and CI, with a significant decrease in cardiac index during the Mueller maneuver.

Our findings have immediate clinical significance for a number of different patient populations. Spontaneously breathing patients in the intensive care unit are known to frequently sustain increases in upper airway resistance, allowing for repetitive assessment of associated changes on a continuous scale. Moreover, it takes the expirational component of the breathing cycle into account, which is particularly important in patients suffering from partial occlusion. The latter situation is of high clinical relevance in the intensive care unit.

malformations, muscular hypoactivity, obesity and nicotine or alcohol abuse [12]. During obstructive episodes, intermittent arterial oxygen desaturation and changes in respiratory parameters are recorded. However, mechanisms underlying the development of long-term cardiorespiratory complications of OSAS are not fully understood [13-15]. In a perioperative setting, patients with a concomitant diagnosis of OSAS are more likely to incur severe cardio-respiratory complications [16]. Our data suggest that the effect of increases in upper airway resistance on hemodynamics must necessarily be taken into consideration, even if the airway obstruction is only of partial nature.

Our study is limited by a number of factors. Firstly, as we only enrolled healthy volunteers, we were not able to study the influence of increasing airway resistance in settings of preexisting heart conditions. This is important, as 1) ischemic heart disease or heart failure have been reported to aggravate detriments to cardiac performance exerted by intrathoracic pressure shifts [5] and 2) these comorbidities are common in critically ill patients [17]. Thus, our findings likely underestimate the full extent of hemodynamic disturbances in patients with reduced cardiac capacity. Secondly, concerns about the longitudinal validity of bioimpedance-based cardiac output measurements have been raised previously, as readings have been found to vary in relation to external factors like fluid status and posture. However, the individual reading cycles were comparatively short for every subject and conditions were kept unchanged as much as possible. Moreover, a recent study by Aron et al. measured cardiac output during Mueller maneuver using a bioimpedance-based approach similar to ours, and the authors found a good reproducibility of findings over several days [18]. Finally, as we elected to only use non-invasive measurements for this study, we do not have continuous data on blood pressure and thus cannot reliably assess associations of resistance or cardiac output with blood pressure.

In conclusion, increases in airway resistance were continuously associated with significant hemodynamic alterations in healthy volunteers. When applied to a population with limited cardiovascular reserve this phenomenon could potentially contribute to a larger degree to acute circulatory disturbances. Our study expands the current knowledge by adding a dynamic component to the breathing maneuver, while using a novel technique to quantitatively assess cardiac capacity. Secondly, concerns about the longitudinal validity of bioimpedance-based cardiac output measurements have been raised previously, as readings have been found to vary in relation to external factors like fluid status and posture. However, the individual reading cycles were comparatively short for every subject and conditions were kept unchanged as much as possible. Moreover, a recent study by Aron et al. measured cardiac output during Mueller maneuver using a bioimpedance-based approach similar to ours, and the authors found a good reproducibility of findings over several days [18]. Finally, as we elected to only use non-invasive measurements for this study, we do not have continuous data on blood pressure and thus cannot reliably assess associations of resistance or cardiac output with blood pressure.

Disclosures
Conflict of interest
No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. All authors declare that no conflict of interest arises from participation in this study.

Previous abstract presentation
Parts of the data this manuscript is based on were presented as an abstract at the annual meeting of the Society of Anesthesia and Sleep Medicine (SASM) in Washington, DC, on October 12, 2012.

Attribute to/Work Performed
Department of Anesthesiology, Hospital for Special Surgery, Weill Medical College of Cornell University.

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