The Influence of High-Frequency Jet Ventilation With Varying Cardiac-Cycle Specific Synchronization on Cardiac Output in ARDS*

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**Background:** Previous studies have shown “beat-to-beat” variation in systemic BP with high-frequency jet ventilation (HFJV). However, it is not clear if such changes are paralleled by changes in cardiac output.

**Objective:** To characterize the effect of HFJV near or equal to the heart rate (HR) on beat-to-beat cardiac output in an adult human subject with ARDS.

**Design:** Case study.

**Setting:** ICU, university teaching hospital.

**Patients:** One patient with end-stage liver disease complicated by sepsis, severe pancreatitis, ARDS, and multisystem organ failure.

**Methods:** The patient was intubated, sedated, paralyzed, and ventilated with controlled mechanical ventilation (CMV). Ventilatory mode was then switched to HFJV at fixed frequencies (f) near but not equal to the HR (f=100, 110, and 120 beats/min; HR=108/min). HFJV was then synchronized to the ECG such that f and HR were equal. Continuous cardiac output (COc) was monitored during change of ventilator mode from CMV to fixed-rate HFJV to synchronized HFJV, then followed through progressive delays in jet triggering within the cardiac cycle during the synchronous HFJV mode. COc was monitored by arterial pulse-contour analysis, allowing assessment of beat-to-beat changes in cardiac output.

**Measurements and main results:** A cyclic variation in COc equal to the beat frequency difference between f and HR was observed (harmonic interaction) during fixed-rate HFJV. This COc oscillation was abolished during synchronous HFJV. COc was significantly greater during systolic synchronous HFJV as compared to diastolic synchronous HFJV or fixed-rate HFJV (10.1 to 9.0 [p<0.05] and to 8.6 [p<0.05] L/min, systolic synchronous to diastolic synchronous and to fixed-rate HFJV, respectively).

**Conclusions:** This study demonstrates instantaneous variations in cardiac output in a human subject with fixed rates of HFJV near to the HR in humans. These variations are abolished by synchronous HFJV but cardiac output was dependent on the timing of the HFJV inspiration in relation to the cardiac cycle. COc is a potentially valuable method to monitor sudden changes in cardiac output and facilitate attempts to maximize cardiac output during synchronized HFJV.

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**Key words:** ARDS; cardiac synchronization; continuous cardiac output monitor; high-frequency jet ventilation; sepsis

**Abbreviations:** CMV=controlled mechanical ventilation; COc=continuous cardiac output; f=frequency; FIO2=fraction of inspired oxygen; HFJV=high-frequency jet ventilation; HR=heart rate; ITP=intrathoracic pressure; Paw=airway pressure; PEEP=positive end-expiratory pressure; PIP=peak inspiratory pressure

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Positive pressure ventilation may significantly influence cardiovascular homeostasis by altering intrathoracic pressure (ITP). Although subjects with normal ventricular function usually demonstrate either minimal changes in cardiac output or decrement in proportion to the increase in ITP, cardiac output may increase in heart failure states. Although these interactions have been demonstrated dynamically in instrumented canine models, to our knowledge, the
effects of ITP on cardiac output in humans have been described only during steady-state conditions. Since numerous factors (such as changes in sympathetic tone, intravascular volume shifts, contractility, and selective changes in venous return and left ventricular afterload) may summate to create this steady-state response, the actual effect of increases in ITP on left ventricular function may be difficult to ascertain. Accordingly, we studied the effects of changes in ITP on continuously monitored cardiac output in one subject in whom ITP was varied using high-frequency jet ventilation (HFJV).

This approach has not been systematically employed in patients with sepsis and ARDS. Furthermore, in previous human studies, only thermodilution cardiac output monitoring has been used to monitor synchronous HFJV. In view of the potentially deleterious effects of HFJV if not timed accurately to the cardiac cycle, we monitored the cardiac output with a continuous-pulse contour method, recently validated by our group. We report on the hemodynamic effects of this management strategy, as well as confirmation of certain cardiopulmonary interactions in humans.

**Materials and Methods**

**Ventilation Techniques**

Conventional intermittent positive-pressure ventilation was delivered at a tidal volume of 7 mL/kg and a frequency (f) of 25 breaths/min (7200 Series Ventilator; Puritan-Bennett; Carlsbad, Calif). HFJV was delivered via a swivel adapter (Portex) connected to the proximal end of the endotracheal tube at a driving pressure of 35 psi and a 40% inspiratory time (model AMS 1000 Universal Jet Ventilator; Acutronics; Pittsburgh). Injected and entrained gases were humidified and f was set at fixed rates of 100, 110, and 120 breaths/min. Positive end-expiratory pressure (PEEP) and fraction of inspired oxygen (FIO2) were titrated to maintain arterial saturation >90% but fixed shortly before and throughout synchronization. When synchronization of the jet ventilator was initiated, the R wave of ECG lead II was used as a trigger and a variable delay circuit inserted so that the exact positioning of the jet pulse within the cardiac cycle could be adjusted by delaying the trigger in 10% increments from 0 to 90% of the R-R interval of the subsequent heart beat as previously described. Thus, the HFJV was not only synchronized to the heart rate (HR) but the overlap of the airway pressure wave generated by the jet ventilator could be aligned with cardiac systole (systolic synchronous HFJV) or diastole (diastolic synchronous HFJV) depending on the percent delay.

**Cardiac Output Monitoring**

The associated hemodynamic response to these ventilatory maneuvers was monitored by thermodilution cardiac output and continuous mixed venous and arterial saturations during steady-state conditions. Additionally, a continuous cardiac output (COc) device (TNO-European Path, US License; Baxter Healthcare Corp; Irvine, Calif) was attached to the existing patient monitoring system to assess the "heart-to-beat" response to changes in ventilatory therapy.

The COc method has been validated previously in healthy volunteers and in critically ill persons requiring active resuscitation. Comparing COc to dye-dilution cardiac output in 20 healthy volunteers, Wesseling et al demonstrated high correlation (R2=0.79) with 0.04 L/min difference in mean measurements and a root mean square error of 0.96 L/min. Lidsky et al compared COc to thermodilution cardiac output in 23 critically ill patients with cardiac outputs ranging from 2.1 to 15.8 L/min. In this study, the correlation was again high (R2=0.9) while bias was −0.05 L/min and the precision was 1 L/min. The COc device utilizes the analog output of the arterial BP waveform and an algorithm to calculate the area under the systolic portion of the arterial pulse contour to estimate left ventricular stroke volume (Fig 1). This area is directly proportional to the stroke volume when central aortic impedance is fixed. Although aortic input impedance can vary over time, beat-to-beat changes in COc reflect only instantaneous changes in left ventricular stroke volume because the time constant for vascular smooth muscle changes greatly exceeds the R-R interval. The three major variables affecting central aortic impedance over time are age, HR, and mean arterial pressure. These relationships have been defined and are utilized by the COc monitor to continuously adjust central aortic impedance.

Initial COc, and therefore central aortic impedance, is defined by calibration with a series of four thermodilution cardiac outputs performed by mechanical injection of 10-mL aliquots of DSW at room temperature using a computer-directed pneumatic pump capable of spacing the injections equally throughout the respiratory cycle. This computer-timed thermodilution technique has been shown previously to derive estimates of cardiac output within 5% of simultaneously measured aortic flow probe derived data.

The COc device was used to confirm results obtained with thermodilution and to monitor beat-to-beat changes during transition from conventional positive-pressure ventilation to HFJV, from HFJV to synchronous HFJV, and, finally, as the jet trigger of synchronous HFJV was progressively delayed through the cardiac cycle. A minimum of 30 COc measurements were recorded in each HFJV mode (fixed rate and synchronous HFJV at each 10% increment in delay).

**Figure 1. Pulse contour method for the calculation of cardiac output.** Illustration of the COc pulse contour formula. PAO(t)=aortic pressure wave; T=duration of R-R interval; PED=end-diastolic aortic pressure. Area A is proportional to stroke volume. Adapted from Wesseling KH et al.
Data Analysis

To detect differences in cardiac output between different HFJV modes, we compared the series of COc measurements generated in each HFJV mode by t test, and analysis of variance for repeated measures over time, with Scheffe’s analysis where means were statistically different. Thus, differences in cardiac output were inferred when there were statistically significant differences in mean COc data. The change in variability between fixed rate and synchronous HFJV was assessed by comparing the coefficient of variation (variation in amplitude divided by mean value) of the COc data obtained during the different HFJV modes. COc data are expressed as mean±1 SD and significance is presumed at p<0.05.

Case Report

A 42-year-old white man with end-stage liver disease secondary to cirrhosis developed severe sepsis, pancreatitis, and ARDS. He was orotracheally intubated, mechanically ventilated, sedated, and given muscle relaxants in attempts to improve oxygenation. FIO2 was titrated to 1.0 and PEEP was titrated to 12.5 cm H2O. Further increases in PEEP were limited by rising airway pressures and worsening hypotension. Because of high peak inspiratory pressures (PIP) (60 cm H2O) and worsening gas exchange despite maximal conventional ventilatory support, a trial of fixed HFJV was instituted (model AMS 1000 jet ventilator). Gas exchange and ventilating pressures (both PIP and mean airway pressure [Paw]) improved such that the clinical team elected to maintain the patient on a regimen of HFJV (Table 1, columns 2 to 5 [day 1]).

The following day, however, cardiovascular insufficiency developed as evidenced by systemic hypotension, poor capillary refill, decreased mental status, oliguria, and increased arterial blood lactate level from 3 to 8 mmol/L. Hypotension worsened despite large doses of vasopressors (norepinephrine, 0.86 μg/kg/min) and continued fluid resuscitation. Attempts by the clinical team to revert back to controlled mechanical ventilation (CMV) were unsuccessful due to immediate and profound hypotension and hypoxia. This was attributed to high PIP with CMV (data not shown) and it was decided by the attending physician to leave the patient on the regimen of HFJV and attempt a trial of synchronous HFJV to augment cardiac output (Table 1, columns 5 to 7 [day 2]). Despite transient improvements in COc, the patient’s septic shock and cardiovascular insufficiency persisted and he died 2 days later.

Results

Figure 2 displays COc trend recordings while the patient was receiving HFJV at three different frequencies close to the HR and during synchronous HFJV with 0% delay. During each of the three asynchronous fixed-rate frequencies, there is a phasic variation in COc, referred to as a “beat frequency,”18,19 the periodicity equaling f minus HR. Figure 3 shows a COc trend recording during asynchronous fixed-rate HFJV where the beat frequency is highlighted by a superimposed sine wave generated by a mathematical regression technique. Figure 4 describes the transition from HFJV to synchronous HFJV showing that the beat frequency phenomenon is abolished. During synchronous HFJV, the difference between f and HR is zero. The coefficient of variation for COc during fixed-rate HFJV was 10% and during synchronous HFJV (0% delay) it was 2.8%. The coefficient of variation remained low (mean, 3.0%; range, 1.9 to 4.7%) throughout all percent delay series of synchronous HFJV.

Figures 5 and 6 display the effect on COc of progressive delays in the jet trigger while in the synchronous mode. When compared to 0% delay, all percent delays, with the exception of 10%, produced significantly different cardiac outputs (p<0.05). Figure 5 illustrates that the maximal depression of cardiac output occurred between 20% and 50% delays. As illustrated by Figure 6 (which shows the

Table 1—Hemodynamic and Blood Gas Variations With Changing Modes of Ventilation*

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Fixed-Rate HFJV</th>
<th>Day 2</th>
<th>Synch HFJV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 h Pre-HFJV</td>
<td>0.7</td>
<td>Pre-HFJV</td>
<td>1.0</td>
<td></td>
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<tr>
<td>6 h Post-CMV</td>
<td>0.85</td>
<td></td>
<td>1.00</td>
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<tr>
<td>PaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HFJV</td>
<td>103</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>PEEP</td>
<td>95</td>
<td>82</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>74</td>
<td>76</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>37</td>
<td>39</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>PIP</td>
<td>56</td>
<td>60</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Mean Paw</td>
<td>27</td>
<td>29</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>PCWP</td>
<td>20</td>
<td>18</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>SvO2</td>
<td>79</td>
<td></td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>16.1</td>
<td></td>
<td>9.7</td>
<td></td>
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<tr>
<td>Norepinephrine, μg/kg/min</td>
<td>0.18</td>
<td>0.28</td>
<td>0.28</td>
<td>8.6±0.3</td>
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<tr>
<td></td>
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<td></td>
<td>10.1±0.2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>9.0±0.4</td>
</tr>
</tbody>
</table>

*SvO2 = arterial oxygen saturation; synch = synchronized; PCWP = pulmonary capillary wedge pressure; SvO2 = mixed venous oxygen saturation; CO = cardiac output.

*p<0.05 (compared to fixed rate and synch with 40% delay measurements).
relationship of airway pressure to the cardiac cycle at 0% and 40% delays), these delays represent conditions in which PIP occurs in diastole whereas 0% delay is associated with PIP occurring in systole.

**DISCUSSION**

The oscillatory or beat frequency pattern in BP seen prior to synchronization of ventilation with the HR has been described over a wide range of ITP in humans and in both right and left ventricular flows in animals.\(^{18-21}\) This amplitude modulation is caused by direct summation and subtraction of the airway pressure to the ITP being monitored.\(^ {19}\) More specifically, the swings in ITP directly alter all intrathoracic vascular structures.\(^ {19}\) The beat frequency represents a first-order harmonic interaction between \(f\) and HR. This case study demonstrates that this interaction affects not only vascular pressures but also cardiac output. There is a predictable beat frequency for cardiac output that develops when \(f\) and HR are similar but not identical. During synchronous HFJV, swings in ITP have a constant relationship to the cardiac cycle and thus the beat frequency phenomenon otherwise seen in vascular pressures and cardiac output is abolished. These cardiopulmonary interactions have been shown previously in animal studies\(^ {22,23}\) using aortic flow probes to measure cardiac output and are clearly illustrated in our patient with the use of COc monitoring. This study also confirms in man the observation from earlier animal studies\(^ {22-24}\) that, for similar \(f\) and ventilator settings, the timing of the increases in ITP within the cardiac cycle may have significant effects on steady-state cardiac output.

Sepsis is associated with a form of cardiomyopathy in which contractility is impaired even though cardiac output is usually preserved or supranormal through a combination of compensatory ventricular dilatation and decreases in systemic vascular resistance.\(^ {25,26}\) Furthermore, effective intravascular volume is often reduced due to a variety of processes and therefore cardiac output is potentially dependent on both preload and afterload in these subjects. Additionally, ARDS commonly complicates the course of sepsis, and during positive-pressure ventilation, the associated increases in PIP and mean Paw may cause a further reduction in cardiac output by decreasing venous return as well as inducing pulmonary barotrauma. Accordingly, in these subjects, HFJV is a reasonable therapeutic option for pressure-limited ventilation when cardiopulmonary function is deteriorating.

Based on this case study and our prior animal studies,\(^ {10,22}\) a reasonable approach to optimize ventricular loading conditions in hemodynamically unstable patients with sepsis and with ARDS who are receiving HFJV would be to use synchronized HFJV,
such that PIP occurs in ventricular systole, reducing the afterload during ejection, while trough PIP occurs during diastole. Pinsky et al.\textsuperscript{12,22} demonstrated significant improvements in cardiac output utilizing this method in heart failure patients, as compared with the nonspecific increases in ITP which occur with conventional mechanical ventilation.

High-frequency ventilation is not limited to ventilatory rates equal or close to the HR. High-frequency oscillation can be applied at f equal to two or greater times the basal HR. Assuming that such higher ventilatory frequencies induce hemodynamic interactions by altering either ITP or lung volume, our data suggest that if such higher rates of ventilation are delivered, synchronization with the cardiac cycle ought to be considered.

Finally, although the changes in COc seen between jet triggering at different points in the cardiac cycle may not have been clinically significant in this example, there may be an advantage to monitoring these changes in other patients. For example, where there is a predominance of either afterload-dependent cardiac output, such as in congestive heart failure, or preload dependence, such as hemorrhagic shock, there could be a therapeutic significance to small changes in left ventricular loading conditions.

We hypothesize that the rapid separation of critically ill patients into afterload vs preload dependent subgroups, which has inherent therapeutic implications, may be possible using this physiologic approach of combining synchronous HFJV and COc monitoring to assess the hemodynamic response to cardiac cycle-specific increases in ITP. If, as in our patient, the difference in cardiac output is greatest between systolic and diastolic triggering, then based on animal data using this intervention,\textsuperscript{22} this is evidence for adequate contractility. Thus, therapy aimed at enhancing preload should be beneficial. If, however, there are significant differences within different systolic triggering intervals such that maximal COc occurred at peak arterial pressure, that would then suggest not only that careful titration of percent delay is necessary but that efforts to reduce afterload or improve contractility should be undertaken. Clearly, this hypothesis awaits prospective clinical trials.
Figure 6. COc, airway pressure, and arterial pressure during synchronized HFJV at 0% and 40% delays. COc was measured by pulse contour continuous cardiac output monitor; Pa = arterial pressure.

REFERENCES


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