Sensitivity of End-tidal Nitrogen in Venous Air Embolism Detection in Dogs

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Embodied nitrogen appears in alveolar gas during clinical and experimental venous air embolism (VAE). Since early detection of VAE is believed to reduce morbidity and mortality, this study was done to compare the sensitivity of end-tidal nitrogen (ETN₂) monitoring with other detection methods in current clinical use—precordial Doppler (PD), end-tidal CO₂ (ETCO₂), and pulmonary artery pressure (PAP). Ten mongrel dogs (10–17 kg) were anesthetized, placed in the supine position, immobilized, and ventilated (FIO₂ 1.0; PACO₂ 35–40 mmHg). Anesthesia and muscle relaxation were maintained with constant infusions of thiamyal and pancuronium. Maintenance fluids were administered at 5 ml · kg⁻¹ · h⁻¹. Mean arterial pressure (MAP), PAP, and ETN₂ and ETCO₂ (Medspec II® mass spectrometer) were displayed on a strip chart recorder. The dogs were divided into two equal groups and given either a step-wise sequence of 1-min air infusions (0.1–1.5 ml · kg⁻¹ · min⁻¹) or 5-s bolus air injections (0.25–1.0 ml · kg⁻¹). Changes in PD sounds occurred in all animals at all air doses. Changes in cardiovascular variables and Pao₂ were minimal. The threshold dose for ETCO₂ and ETN₂ to reach significance was 0.1 and 0.25 ml · kg⁻¹, respectively, while PAP increases were significant at >0.5 ml · kg⁻¹ air doses. The time to maximum change (Δmax) ETN₂ was 30–90 s earlier than Δmax ETCO₂ (P < 0.05) and 6–105 s earlier than Δmax PAP. The Δmax for all variables was dose related and statistically significant except for the smallest infusion VAE, where only ETCO₂ was significantly changed. At 0.5 ml · kg⁻¹ and greater air doses, increases in ETN₂ after bolus VAE were double those following infusion of the same amount of air. The magnitude of the changes in ETCO₂ and PAP were comparable following bolus and infusion VAE. It is concluded that changes in ETN₂ following low-dose infusion VAE are less sensitive than changes in ETCO₂, while during the bolus doses studied, they are equally sensitive. Changes in ETN₂ and ETCO₂ are more sensitive than changes in PAP during bolus and infusion VAE. Continuous mass spectrometry monitoring of ETN₂ may not provide early warning of air entry after small emboli, however, when a significant increase in ETN₂ occurs following VAE, it precedes changes in ETCO₂ and PAP. (Key words: Embolism: air. Gases: nitrogen, end-tidal. Monitoring: mass spectrometer.)

Many surgeons continue to perform surgery with patients in the seated position or in positions in which the surgical incision is greater than 5–10 cm above heart level.¹² Although some authors report no venous air embolism episodes,³ others have encountered significant emboli.⁴ Early detection and treatment of venous air embolism (VAE) is considered essential, since this reduces the potential for significant cardiovascular compromise.⁴ Perhaps of more concern is arterial air embolism (AAE) via a patent foramen ovale or pulmonary A-V communications.⁵⁶ AAE is undetectable clinically except when air bubbles appear in the arteries in the operative field or when sophisticated monitoring such as 2-D echocardiography is used.⁷ Since the neurologic and cardiovascular sequelae of AAE are potentially catastrophic, early detection of venous air entry is considered essential to eliminate, as soon as possible, potentially harmful increases in right atrial pressure.⁸⁹

Experimental and clinical observations¹⁰¹¹ (Severinghaus, personal communication) have demonstrated an increase in alveolar nitrogen concentration during venous air embolism but its sensitivity relative to other currently available detection methods has not been evaluated. This study was undertaken to compare the sensitivity of end-tidal nitrogen (ETN₂) measured by mass spectrometry with other currently available detection methods (precordial Doppler, end-tidal CO₂, mean pulmonary artery pressure) during graded infusion and bolus venous air emboli.

Methods

Ten mongrel dogs (10–17 kg) were anesthetized with intravenous pentobarbital 30 mg · kg⁻¹ and intubated. Ventilation was maintained with a volume-cycled ventilator (Engstrom 312®) at an FIO₂ of 1.0 (hospital grade oxygen, 0.04% N₂ contamination) to maintain PACO₂ between 35–40 mmHg, verified before each air injection. The animals were supine for the study. Anesthesia was maintained with a constant infusion of thiamyal 1–3 mg · kg⁻¹ · h⁻¹ and pancuronium 0.1 mg · kg⁻¹ · h⁻¹ was administered to produce immobilization. Maintenance fluids were administered at 5 ml · kg⁻¹ · h⁻¹.

Direct blood pressure measurements and blood gas samples were obtained from a femoral arterial catheter. A pulmonary artery catheter was inserted via a femoral vein to the wedge position and the balloon deflated. The Doppler was positioned over the shaved precordium so that a rapid injection of 10 ml of saline through the central venous port of the pulmonary artery catheter produced characteristic sounds. A separate forelimb vein was used for air injection. Denitrogenation was carried out for 1 h.

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before beginning air injections; $\text{ET}_N_2$ was below 0.5% and stable.

Mean arterial pressure (MAP), pulmonary artery pressure (PAP), $\text{ET}_N_2$, and $\text{ET}_{CO_2}$ (Medspec II Mass Spectrometer$^9$) were displayed continuously on a strip recorder. Temperature was maintained between 36–37°C. The vascular pressure transducers were calibrated to atmospheric pressure and to a 50 mmHg equivalent water column. The mass spectrometer was calibrated with three gas combinations: room air; 100% oxygen; and 3.5% $N_2$, 5.5% $CO_2$, 91% $O_2$ (factory analyzed ± 0.03%). The mass spectrometer sensitivity for $N_2$ and $CO_2$ was 0.01% and 0.1%, respectively. Calibration was verified at the end of the experiment and was stable.

The dogs were divided into two equal groups and given either a step-wise sequence of 1-min air infusions (0.1, 0.25, 0.5, 1.0, 1.5 ml·kg$^{-1}$·min$^{-1}$) or 5-s bolus air injections (0.25, 0.5, 0.75, 1.0 ml·kg$^{-1}$) via a Harvard$^6$ syringe infusion pump or by hand, respectively. In preliminary studies, these doses were found to cause minimal alterations in systemic cardiovascular variables. Baseline measurements were taken before each air injection, and 20–30 min were allowed for return of all parameters to baseline.

Following each air embolus, the time and magnitude of the peak changes in $\text{ET}_N_2$, $\text{ET}_{CO_2}$, and PAP were observed. Arterial $P_{CO_2}$ and $P_{O_2}$ were measured at the time of maximal depression of $\text{ET}_{CO_2}$. Changes in MAP and PAP were measured at end-expiration. Intrapulmonary shunt and cardiac output were not measured, since aspiration of venous blood or air or injection of fluid into the right heart may have affected end-tidal gas measurements or pulmonary distribution of air bubbles. No attempt was made to quantitate the volume of nitrogen excreted after each VAE.

Changes in end-tidal values after venous air embolism were considered significant if they exceeded baseline values by three standard deviations (SD). A change in pulmonary artery pressure was considered significant if it exceeded the baseline value by 25%. The Wilcoxon paired sample rank sum test and the $t$ test for paired differences (baseline vs. peak change) were applied in data analysis.

### Results

Changes in precordial Doppler sounds indicating VAE occurred in all animals at all air doses. All animals had less than a 10% change in MAP with the exception of two animals in whom MAP decreased 25% and 27% during infusion of 0.25 and 1 ml·kg$^{-1}$·min$^{-1}$, respectively. The arterial oxygen tension did not decrease more than 10 mmHg in any animal at the time of maximum depression of $\text{ET}_{CO_2}$ concentration. The pooled standard deviation (SD) of the baseline end-tidal nitrogen and carbon dioxide values before infusion VAE was 0.0086% and 0.079%, respectively, and 0.0074% and 0.092%, respectively, before bolus VAE.

Table 1 is the summary of significant responses to five infusion emboli in five dogs and four bolus emboli in five dogs. The threshold dose for $\text{ET}_{CO_2}$ and $\text{ET}_N_2$ to reach significance was 0.1 and 0.25 ml·kg$^{-1}$, respectively, after bolus and infusion emboli, while PAP increases were significant at 0.5 ml·kg$^{-1}$ and greater air doses.

The maximum change (Δmax) from preembolism control values for all variables was dose related and statistically significant (table 2) except for the smallest infusion VAE, where $\text{ET}_N_2$ and PAP did not change significantly. At 0.5 ml·kg$^{-1}$ and greater air doses, increases in $\text{ET}_N_2$ after bolus VAE were approximately double those following infusion of the same amount of air. The magnitude of the changes in $\text{ET}_{CO_2}$ and PAP was approximately the same following comparable infusion and bolus air doses.

The time to Δmax $\text{ET}_N_2$ was earlier than Δmax $\text{ET}_{CO_2}$ during all air infusions above 0.25 ml·kg$^{-1}$·min$^{-1}$ and during all bolus VAE doses ($P < 0.05$) (table 3). At infusion doses above 0.25 ml·kg$^{-1}$·min$^{-1}$, Δmax $\text{ET}_N_2$ preceded Δmax $\text{ET}_{CO_2}$ by 92–36 s, and the difference in time to Δmax decreased with increasing air doses. After all bolus VAE doses, the difference in time to Δmax in $\text{ET}_{CO_2}$ compared with Δmax $\text{ET}_N_2$ was approximately 60 s ($\text{ET}_N_2$ earlier). The time to maximum change in PAP ranged from 40 to 140 s and was intermediate when compared with $\text{ET}_N_2$ and $\text{ET}_{CO_2}$ at 0.5 ml·kg$^{-1}$ and greater air doses.

Figure 1 represents the response of one dog to air infusions from 0.1 to 1.5 ml·kg$^{-1}$·min$^{-1}$. As the dose in-
increased above 0.25 ml·kg⁻¹·min⁻¹, \( ET_{N_2} \) concentration increased earlier during the 1-min infusion and was diagnostically sooner than changes in \( ET_{CO_2} \) and PA pressure. The time to return to baseline of all variables after infusion VAE was between 1.5 and 32 min and was dose related.

Figure 2 shows the response in one animal to four bolus venous air emboli from 0.25 to 1 ml·kg⁻¹. Changes in end-tidal gases and PAP are very abrupt. During low-dose embolism (0.25 ml·kg⁻¹), \( ET_{N_2} \) increases without accompanying decreases in \( ET_{CO_2} \) or increases in PAP. At doses of 0.5 ml·kg⁻¹ and greater, the change in all variables is very rapid (\( ET_{N_2} \) still earlier). The time to return to baseline of all variables after bolus VAE was 3–30 min.

\( ET_{N_2} \) often decreased below preembolism values coincident with the maximum decrease in \( ET_{CO_2} \) concentration. All animals survived the experiment and returned to normal function. Since the animals were not killed, there was no definitive proof that cardiopulmonary abnormalities were absent.

### Discussion

Increases in end-tidal nitrogen concentration following infusion venous air embolism are less sensitive than decreases in end-tidal \( CO_2 \), while during the bolus doses given in this study, they are equally abrupt. Changes in \( ET_{N_2} \) and \( ET_{CO_2} \) are more sensitive than changes in PAP during bolus and infusion VAE. When \( ET_{N_2} \) increases following VAE, it is diagnostic sooner than decreases in \( ET_{CO_2} \). Mass spectrometers now in clinical use have a nitrogen sensitivity of 0.1%, not 0.01%, as used in this study. Monitoring \( ET_{N_2} \) may not provide early warning of air entry and pulmonary excretion after small emboli. Studies are currently underway to test this clinically.

In the present study, the maximum changes in \( ET_{N_2} \) and \( ET_{CO_2} \) were often more diagnostic than changes in PAP, particularly during low-dose bolus or infusion VAE. This fact may allow the substitution of a noninvasive monitor for an invasive one without sacrificing sensitivity.

The difference in time to maximum change in \( ET_{N_2} \) and \( ET_{CO_2} \) decreased with larger infusion but not bolus VAE. In the clinical situation, rapid changes in \( ET_{N_2} \) and \( CO_2 \) may herald the onset of a large embolus and should prompt rapid reactions on the part of the anesthesiologist and surgeon. During steady state anesthesia, the variations in \( ET_{N_2} \) and \( ET_{CO_2} \) are very small, as shown by the small standard deviation of the baseline end-tidal values in this study. This suggests that audible alert and alarm limits can be set to detect significant changes once steady state conditions are reached. An increase in \( ET_{N_2} \) of 0.1% or a decrease in \( ET_{CO_2} \) of 0.22% (or 2 mmHg) are presumed to be reasonable limits.

The difference between a bolus and an infusion air embolus is a relative one. Bolus or large infusion emboli may be more likely to cause acute increases in right atrial pressure and lead to either an air lock at the right heart

### Table 2. Maximum Change (mean ± SD) from Preembolism Control Values Following Infusion (I) and Bolus (B) Venous Air Embolism

<table>
<thead>
<tr>
<th>Air</th>
<th>ml·kg⁻¹·min⁻¹</th>
<th>0.1</th>
<th>0.25</th>
<th>0.50</th>
<th>—</th>
<th>1.0</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>0.25</td>
<td>0.25</td>
<td></td>
<td></td>
<td>—</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>( \Delta ET_{N_2} )</td>
<td>I 0.02 ± 0.03</td>
<td>0.05 ± 0.02*</td>
<td>0.05 ± 0.03*</td>
<td>—</td>
<td>0.20 ± 0.04*</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>—</td>
<td>0.04 ± 0.02*</td>
<td>0.14 ± 0.10*</td>
<td>0.16 ± 0.09*</td>
<td>0.26 ± 0.20*</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>( \Delta ET_{CO_2} )</td>
<td>I 0.22 ± 0.14*</td>
<td>0.66 ± 0.18*</td>
<td>—</td>
<td>1.9 ± 0.29*</td>
<td>2.0 ± 0.27†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>—</td>
<td>0.52 ± 0.16*</td>
<td>1.0 ± 0.24†</td>
<td>1.6 ± 0.35*</td>
<td>1.7 ± 0.57†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta PAP ) (mmHg)</td>
<td>I 0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>4.3 ± 2.0*</td>
<td>9.5 ± 5.5*</td>
<td>16 ± 4.5†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>—</td>
<td>2.8 ± 1.3*</td>
<td>5.4 ± 3.7*</td>
<td>14.6 ± 7.9*</td>
<td>—</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* \( P < 0.05 \).
† \( P < 0.001 \).

\( = \) no data.

### Table 3. Time to Maximum Change (mean ± SD) in Seconds Following Infusion (I) and Bolus (B) Venous Air Embolism

<table>
<thead>
<tr>
<th>Air</th>
<th>ml·kg⁻¹·min⁻¹</th>
<th>0.1</th>
<th>0.25</th>
<th>0.50</th>
<th>—</th>
<th>1.0</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>—</td>
<td>0.25</td>
<td>0.50</td>
<td>0.75</td>
<td>—</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>( \Delta ET_{N_2} )</td>
<td>I 121 ± 81</td>
<td>85 ± 50</td>
<td>66 ± 9</td>
<td>75 ± 23</td>
<td>78 ± 24</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>—</td>
<td>39 ± 4</td>
<td>37 ± 14</td>
<td>35 ± 3</td>
<td>32 ± 8</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>( \Delta ET_{CO_2} )</td>
<td>I 123 ± 70</td>
<td>178 ± 34</td>
<td>171 ± 30</td>
<td>145 ± 28</td>
<td>114 ± 19</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>—</td>
<td>106 ± 39</td>
<td>103 ± 37</td>
<td>99 ± 32</td>
<td>95 ± 56</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>( \Delta PAP ) (mmHg)</td>
<td>I —</td>
<td>—</td>
<td>86 ± 49</td>
<td>—</td>
<td>122 ± 67</td>
<td>108 ± 12</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>—</td>
<td>144 ± 120</td>
<td>43 ± 27</td>
<td>42 ± 20</td>
<td>57 ± 34</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

\( = \) no data; \( — = \) no change.
END-TIDAL NITROGEN AND VENOUS AIR EMBOLISM DETECTION

![Graph showing PaCO₂, ET N₂%, ET CO₂%, and PAP over time with different doses](image)

**Fig. 1.** Characteristic response to infusion venous air embolism. During infusion, ET N₂ is significantly increased during 0.25 ml·Kg⁻¹·min⁻¹ dose at 60 s, while ET CO₂ and PAP are unchanged.

or to a reversal of the gradient between the right and left atria and predispose to arterial air emboli. In addition, air may pass more easily to the systemic arterial circulation through A-V communications in the lung.

Since the changes in end-tidal gas values may be abrupt and unexpected, intermittent monitoring, as with a shared operating room mass spectrometer, may not provide early warning of air entry if sampling is infrequent. The time between data points with the shared system may be as long as 1–2 min if all stations are being monitored.

Steady-state ET N₂ values after 1 h denitrogenation range from 0.3 to 0.5% in the dog. Abrupt increases in end-tidal nitrogen occur with any leaks in the anesthesia circuit or the endotracheal tube cuff, or if the partially paralyzed animal begins breathing out of phase with the ventilator. Presumably, nitrogen entry occurs around the tracheal cuff with the development of negative intrathoracic pressure. These sources of nitrogen entry must be eliminated for ET N₂ to be specific for venous air embolism detection in the clinical setting.

Reduced overall or segmental pulmonary blood flow may account for the observed decrease in ET N₂ below baseline, which persisted until dissipation of the pulmonary vascular air. With air doses causing a decrease in cardiac output, the decrease below baseline may be more severe and protracted. The ability to detect ongoing air entry via ET N₂ monitoring in this circumstance would depend on the volume of air entry, the number of arterioles obstructed, and the continuation of right ventricular function.

This study was done while the animals were breathing 100% oxygen. The nitrogen sensitivity of the mass spectrometer was 0.01%. Air breathing during experimental air embolism has been associated with greater cardiovascular depression than during comparable air embolism in animals breathing 100% oxygen. The high alveolar nitrogen concentration during air breathing would limit the excretion gradient for embolized air and could potentially limit the ability of the mass spectrometers now in clinical use to detect subtle changes in ET N₂. The effect of N₂O breathing on N₂ excretion during VAE has not been tested.
Precordial Doppler monitoring is the most sensitive, qualitative detector of air entry into the superior vena cava and heart, however, it does not allow quantitative measurement of air entry into and dissipation from the lungs. The precordial Doppler sounds are affected by changes in position of the detector or by alterations in cardiac rhythm and systemic blood pressure. Indeed, VAE may occur without changes in Doppler sounds.4,9 Hemodynamically insignificant emboli may continuously interrupt completion of surgery or air entry may not be detected because of improper or undetected change in the position of the precordial probe. In addition, the anesthesiologist may fail to recognize subtle changes in the Doppler sounds.

Increases in PAP and decreases in ET CO2 are reported to be equally sensitive VAE monitors.9 However, the invasive nature of the pulmonary artery catheter and the resistance to air aspiration via the central venous port make it less than the ideal monitor and inferior to the central venous catheter in therapeutic effectiveness. ET CO2 decreases with increased alveolar dead space (hypotension, VAE) but also is affected by changing anesthetic depth or level of alveolar ventilation,13 therefore the specificity of this monitor may be decreased if a VAE precedes the establishment of a new baseline ET CO2 level.

In summary, changes in ET N2 following low-dose infusion VAE are less sensitive than changes in ET CO2, while during bolus VAE they are equally sensitive. Changes in ET N2 precede changes in ET CO2 during bolus VAE and above 0.25 ml·kg⁻¹·min⁻¹ doses during infusion VAE. Both ET N2 and ET CO2 are more sensitive than changes in PAP. It remains to be determined whether shared operating room mass spectrometers are sensitive enough and sample frequently enough to be of value in the early detection of clinical VAE. Individual mass spectrometers would eliminate the potential disadvantages of the shared systems.
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References