MYOCARDIAL OXYGENATION DURING ACUTE NORMOVOLEMIC HEMODILUTION: IMPACT OF HYPOCAPNIC ALKALOSIS

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Abstract

Background: Increases in myocardial blood flow preserve myocardial oxygenation during moderate acute normovolemic hemodilution. Hypocapnic alkalosis (HA) is known to cause coronary vasoconstriction and increase hemoglobin-oxygen affinity. We evaluated whether these effects would compromise myocardial oxygenation during hemodilution.

Methods: Eighteen anesthetized dogs were studied. Myocardial blood flow (MBF) was measured with radioactive microspheres. Arterial and coronary sinus samples were analyzed for oxygen content and plasma lactate. Myocardial oxygen supply, oxygen uptake, and lactate uptake were calculated. HA (PaCO₂, 23±2 (SD); pH, 7.56±0.03) was induced by removal of dead space tubing at baseline (n=8) and during hemodilution (n = 10), with hematocrit at 43 ± 4% and 19 ± 2 %, respectively.

Results: Hemodilution during normocapnia caused decreases in arterial oxygen content (19.9 ± 2.4 to 9.3 ± 1.2 ml/100; P < 0.05) and the coronary arteriovenous O₂ difference (13.0 ± 3.0 to 6.4 ± 0.9 ml/100ml; P < 0.05). MBF increased (52 ± 12 to 111 ± 36 ml/min/100g; P < 0.05) to maintain myocardial oxygen supply and oxygen uptake. Myocardial lactate uptake increased (31 ± 19 to 68 ± 35 µeq/min/100g; P < 0.05). At normal hematocrit, HA decreased MBF (57 ± 18 to 45 ± 10 ml/min/100; P < 0.05), implying vasoconstriction, accompanied by decreased myocardial oxygen supply. These myocardial effects of HA were not apparent during hemodilution. HA did not alter myocardial lactate uptake during hemodilution.

Conclusion: When HA was induced during hemodilution, its ability to cause coronary vasoconstriction was lost, and myocardial oxygenation remained well preserved.

Keywords: anemia; carbon dioxide; coronary circulation; dog; myocardial blood flow: myocardial oxygen uptake; radioactive microspheres.
Introduction

The increased frequency of complex surgical procedures with extensive blood loss, the risk of transmission of blood-borne antigens during donor blood transfusion, the high cost of transfusion therapy, and shortages at blood banks have led to the implementation of more restrictive transfusion triggers\(^1,2\). This has increased the number of hemodiluted patients in the perioperative period.

Under baseline conditions, the left ventricle extracts approximately 70-75% of delivered oxygen, resulting in a limited oxygen extraction reserve\(^3\). Consequently, in situations of low hemoglobin, the myocardium must rely primarily on increases in blood flow to offset the induced decreases in arterial oxygen content. Experimentally, this compensatory mechanism is adequate for maintaining myocardial oxygenation as long as hematocrit ≥ 10%, as evidenced by stable indices of global cardiac performance, e.g., aortic pressure and pulmonary capillary wedge pressure, an unchanged value for coronary sinus PO\(_2\) (an estimate of myocardial PO\(_2\))\(^4\), and continued lactate extraction suggesting absence of anaerobic metabolism and of myocardial ischemia\(^5,6\).

Intentional (i.e., to reduce intracranial pressure in head trauma) or unintentional (e.g., excessive mechanical ventilation) hypocapnic alkalosis is common perioperatively and in critically ill patients\(^7,8\). Studies in anesthetized dogs\(^9-12\) and conscious humans\(^13,14\) have demonstrated that hypocapnic alkalosis can cause coronary vasoconstriction and a decrease in myocardial blood flow. This decrease in myocardial blood flow was accompanied by an increase in oxygen extraction, suggesting that it is due, at least in part, to direct coronary vasoconstriction\(^15\). Hypocapnic alkalosis also causes a leftward shift of the oxyhemoglobin dissociation curve, increasing hemoglobin oxygen affinity, and thus impairing diffusion of oxygen into the tissue\(^16\).

Although compensatory coronary vascular responses may maintain myocardial oxygenation during hemodilution under normocapnic conditions, these responses could be compromised when hypocapnic alkalosis is co-existent. The current canine study tested the hypothesis that hypocapnic alkalosis impairs the maintenance of myocardial oxygenation under hemodiluted conditions.

Methods

The study was conducted after approval from the Institutional Animal Research Committee of the University of Illinois at Chicago. Experiments were performed on 18 adult, healthy, mongrel dogs of either sex (weight range 21-24 kg). Anesthesia was induced with an intravenous bolus injection of thiopental (30 mg/kg). After tracheal intubation, anesthesia was maintained by controlled ventilation with 0.9 % (1 MAC) halothane in oxygen using a semi-closed circular system. Initially, dead space tubing (volume of 300 ml) was added to the endotracheal tube with tidal volume and ventilator rate adjusted to establish PaCO\(_2\) at a physiological value (approximately 40 mmHg). This volume of dead space was demonstrated in preliminary studies to reduce arterial PCO\(_2\) by approximately 50 % when removed. Values for PO\(_2\), PCO\(_2\), and pH in arterial blood samples were obtained electrometrically (model 413, Instrumentation Laboratories, Lexington, MA). Sodium bicarbonate solution was given as necessary to correct metabolic acidosis. Hematocrit of blood samples was determined volumetrically. Core body temperature was monitored and maintained at 38° C with a heating pad, warmed intravenous fluids, and warming lights.

Polyethylene cannulas were inserted into 1) the thoracic aorta for monitoring arterial blood pressure and for obtaining samples of arterial blood for analysis, 2) the right femoral vein for IV injections, and 3) the left femoral vein and left femoral artery for isovolemic exchange of whole blood with 5 % dextran solution. A left thoracotomy was performed in the fourth intercostal space and the pericardium was incised to expose the heart. A small polyethylene catheter was inserted into the left atrium via the left atrial appendage for injecting radioactive microspheres. Heparin, 300 U/kg, was administered IV post-surgically to prevent coagulation in exchange circuits. Arterial pressure was measured with a Statham transducer (model P23ID, Gould, Cleveland, Ohio), averaged electronically, and recorded (model 2800S, Gould, Cleveland, Ohio). A non-cannulating electromagnetic flow transducer was
Myocardial oxygenation in Hypocapnia and Hemodilution

placed around the ascending aorta to measure cardiac output (less coronary blood flow).

Hypocapnic alkalosis was demonstrated in our preliminary studies and in previously published reports^9,10^ to cause a decrease in arterial pressure. Hypotension can influence myocardial blood flow by reducing perfusion pressure and by altering determinants of cardiac work demand, i.e., afterload and heart rate^15^. To avoid this potentially confounding variable, a controlled pressure reservoir was used^17^. Translocation of blood from the reservoir to the animal’s circulation stabilized arterial pressure during hypocapnic alkalosis.

**Experimental Measurements**

**Regional myocardial blood flow.** Regional myocardial blood flow was measured with the radioactive microsphere technique, as described in detail previously^6^. This technique is based on the principle that microspheres injected into the left atrium are well mixed in the left ventricular output, that they distribute to body tissues in proportion to flow rate, and that they remain permanently entrapped^18^. After the final injection of microspheres, the heart was stopped with potassium chloride and excised, and full thickness myocardial samples were obtained from the left and right ventricular free walls. The samples from the left ventricular wall were cut into thirds transmurally and those from the right ventricular wall into halves to yield regional myocardial samples. A value for regional myocardial blood flow (ml/min/100g) was determined for each tissue sample by comparing its radioactivity, assessed with a gamma scintillation counter, to that in a reference arterial blood sample withdrawn at a known rate at the time of microsphere injection. A value for mean transmural blood flow was calculated in each ventricular wall by averaging the values for regional myocardial blood flow. An endocardial-to-epicardial flow ratio was calculated by dividing the value for myocardial blood flow in the subendocardial sample by that in the subepicardial sample.

**Myocardial oxygen uptake.** A polyethylene cannula was positioned in the coronary sinus through the right jugular vein and the right atrium for collecting samples of venous effluent from the left ventricle. One milliliter blood samples were collected anaerobically from the aorta and the coronary sinus to determine the left coronary arteriovenous oxygen difference. Myocardial oxygen extraction (EO₂; %) was determined by dividing the arteriovenous oxygen difference by the oxygen content of the aortic blood.

Myocardial oxygen uptake (MVO₂; ml/min/100g) for the left ventricle was calculated from the Fick equation: MVO₂ = MBF x [(a - v) O₂ difference/100], where MBF is mean transmural myocardial blood flow for the left ventricle (ml/min/100g) and the (a-v) O₂ difference is the coronary arteriovenous oxygen difference (ml/100 ml). Oxygen supply to the left and right ventricles was calculated by multiplying the values for arterial oxygen content and the respective myocardial blood flow. Systemic oxygen supply was calculated by multiplying the values for arterial oxygen content and cardiac output.

**Experimental Protocol**

The dogs were divided into two groups. In the Control Group (n = 8), after baseline hemodynamic measurements were obtained, hypocapnic alkalosis was induced by removal of the dead space tubing. This approach avoided the hemodynamic instabilities, e.g., reductions in cardiac output and systemic arterial pressure, which characterize increases in mechanical ventilation^19^. After approximately 30 min, when PaCO₂ stabilized at a minimal level (approximately 20 mmHg), hemodynamic measurements were repeated. In the Hemodilution Group (n = 10), after baseline measurements, isovolemic hemodilution was produced by removing blood from the left femoral artery at a
rate of 20 ml/min while replacing it with 5% dextran (molecular weight 40,000; Baxter, McGaw Park, IL) pumped into the left femoral vein at the same rate. The total volume exchanged was 45 ml/kg, which reduced hematocrit by approximately one-half. The preparation was permitted to stabilize for 15 min after completion of fluid exchange before measurements of myocardial blood flow and related variables were repeated. Hypocapnic alkalosis was then induced in a manner identical to the Control Group (by removal of the dead space tubing), and final hemodynamic measurements were obtained.

Statistical Analysis

A power analysis was performed a priori using the change in myocardial blood flow (mean difference of 62 with a SD of 8 ml/min/100g) during acute normovolemic hemodilution of the same degree in halothane-anesthetized dogs. These results indicated that a sample size of 6 would provide 100% power at a two-sided 0.01 significance level.

Data are presented as mean ± SD. The metabolic and hemodynamic findings were evaluated using the Student’s t test for paired samples (Control Group) or a one-way analysis of variance for repeated measures and the Student’s t test with a Bonferroni correction based on all possible comparisons for post hoc analysis (Hemodilution Group). A P< 0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS, Inc., Chicago, IL).

Results

In the Control Group (hematocrit at baseline), removal of the dead space tubing caused a reduction in arterial PCO₂ (41±2 to 23±2 mmHg) and an increase in arterial pH (7.38±0.02 to 7.56±0.03) (Table 1). Hypocapnic alkalosis decreased myocardial blood flow by approximately 20% in both the left and right ventricles (Tables 2 and 3). The endocardial-to-epicardial flow ratio remained equal to unity. In both ventricles, the increase in myocardial blood flow was sufficient to offset the reduction in arterial oxygen content and to maintain oxygen supply constant (Tables 2 and 3). In the left ventricle, oxygen uptake was unchanged, despite a marked reduction in the arteriovenous oxygen difference (Table 2). Percent oxygen extraction and coronary sinus PO₂ and SO₂ were not affected. Although percent lactate extraction decreased during

In the Hemodilution Group, hemodilution (hematocrit, 19±2%) with normocapnia (Table 1) caused an approximately 100% increase in myocardial blood flow in both the left and right ventricles (Tables 2 and 3). The endocardial-to-epicardial flow ratio remained equal to unity. In both ventricles, the increase in myocardial blood flow was sufficient to offset the reduction in arterial oxygen content and to maintain oxygen supply constant (Tables 2 and 3). In the left ventricle, oxygen uptake was unchanged, despite a marked reduction in the arteriovenous oxygen difference (Table 2). Percent oxygen extraction and coronary sinus PO₂ and SO₂ were not affected. Although percent lactate extraction decreased during
Table 1
Arterial blood composition and systemic hemodynamic variables during hypocapnic alkalosis (HA) alone and combined with hemodilution (HD)

<table>
<thead>
<tr>
<th>Arterial Blood Variables</th>
<th>Control Group</th>
<th>Hemodilution Group</th>
<th>HD</th>
<th>HD during HD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE</strong></td>
<td><strong>HA</strong></td>
<td><strong>BASELINE</strong></td>
<td><strong>HD</strong></td>
<td><strong>HA during HD</strong></td>
</tr>
<tr>
<td><strong>PCO$_2$, mmHg</strong></td>
<td>41 ± 2</td>
<td>23 ± 2</td>
<td>*</td>
<td>39 ± 2</td>
</tr>
<tr>
<td><strong>PO$_2$, mmHg</strong></td>
<td>348 ± 148</td>
<td>329 ± 165</td>
<td></td>
<td>378 ± 151</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.38 ± 0.02</td>
<td>7.56 ± 0.03</td>
<td>*</td>
<td>7.39 ± 0.02</td>
</tr>
<tr>
<td><strong>O$_2$ saturation, %</strong></td>
<td>95.3 ± 3.3</td>
<td>95.2 ± 3.3</td>
<td></td>
<td>97.4 ± 1.1</td>
</tr>
<tr>
<td><strong>Hematocrit, %</strong></td>
<td>43 ± 4</td>
<td>42 ± 4</td>
<td></td>
<td>43 ± 5</td>
</tr>
<tr>
<td><strong>Hemoglobin, g/100ml</strong></td>
<td>14.5 ± 1.3</td>
<td>14.5 ± 1.5</td>
<td></td>
<td>14.6 ± 2.0</td>
</tr>
<tr>
<td><strong>O$_2$ content, ml/100ml</strong></td>
<td>19.2 ± 1.8</td>
<td>19.0 ± 2.0</td>
<td></td>
<td>19.9 ± 2.4</td>
</tr>
<tr>
<td><strong>Plasma lactate, mEq/L</strong></td>
<td>1.5 ± 0.7</td>
<td>3.1 ± 1.5</td>
<td>*</td>
<td>2.3 ± 0.7</td>
</tr>
</tbody>
</table>

**Hemodynamic Variables**

| **MAP, mmHg** | 85 ± 17 | 80 ± 15 | | 87 ± 17 | 84 ± 14 | 80 ± 14 | |
| **Heart rate, beats/min** | 139 ± 29 | 148 ± 26 | | 138 ± 14 | 148 ± 25 | 152 ± 31 | |
| **Cardiac output, ml/min** | 1232 ± 501 | 1194 ± 416 | | 1245 ± 234 | 1674 ± 532 | 1948 ± 738 | *† |
| **O$_2$ supply, ml/min** | 234 ± 89 | 227 ± 90 | | 250 ± 62 | 160 ± 66 | * | 190 ± 85 | * |

Values are Mean ± SD. P < 0.05, * vs. BASELINE, † vs. HD. Abbreviations: PCO$_2$, carbon dioxide tension; PO$_2$, oxygen tension; MAP, mean arterial pressure.

Table 2
Left ventricular oxygen supply and demand variables during hypocapnic alkalosis (HA) alone and combined with hemodilution (HD)

<table>
<thead>
<tr>
<th>Coronary sinus values</th>
<th>Control Group</th>
<th>Hemodilution Group</th>
<th>HD</th>
<th>HD during HD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE</strong></td>
<td><strong>HA</strong></td>
<td><strong>BASELINE</strong></td>
<td><strong>HD</strong></td>
<td><strong>HA during HD</strong></td>
</tr>
<tr>
<td><strong>Blood flow, ml/min/100g</strong></td>
<td>57 ± 18</td>
<td>45 ± 10</td>
<td>*</td>
<td>52 ± 12</td>
</tr>
<tr>
<td><strong>Endo/Epi ratio</strong></td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.1</td>
<td></td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td><strong>O$_2$ supply, ml/min/100g</strong></td>
<td>11.5 ± 3.8</td>
<td>9.1 ± 2.4</td>
<td>*</td>
<td>11.1 ± 3.1</td>
</tr>
<tr>
<td><strong>O$_2$ uptake, ml/min/100g</strong></td>
<td>7.7 ± 2.7</td>
<td>6.6 ± 2.0</td>
<td>*</td>
<td>6.8 ± 2.1</td>
</tr>
<tr>
<td><strong>(a-v) O$_2$ diff., ml/100ml</strong></td>
<td>13.6 ± 2.1</td>
<td>14.6 ± 2.3</td>
<td>*</td>
<td>13.0 ± 3.0</td>
</tr>
<tr>
<td><strong>O$_2$ extraction, %</strong></td>
<td>67 ± 8</td>
<td>72 ± 7</td>
<td>*</td>
<td>61 ± 10</td>
</tr>
<tr>
<td><strong>Coronary sinus values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PO$_2$, mmHg</strong></td>
<td>32 ± 6</td>
<td>25 ± 5</td>
<td>*</td>
<td>31 ± 6</td>
</tr>
<tr>
<td><strong>PCO$_2$, mmHg</strong></td>
<td>55 ± 4</td>
<td>37 ± 4</td>
<td>*</td>
<td>54 ± 5</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.32 ± 0.01</td>
<td>7.47 ± 0.05</td>
<td>*</td>
<td>7.31 ± 0.03</td>
</tr>
<tr>
<td><strong>O$_2$ saturation, %</strong></td>
<td>33 ± 8</td>
<td>30 ± 7</td>
<td>*</td>
<td>39 ± 10</td>
</tr>
<tr>
<td><strong>O$_2$ content, ml/100ml</strong></td>
<td>6.6 ± 1.7</td>
<td>5.8 ± 1.5</td>
<td>*</td>
<td>8.0 ± 1.6</td>
</tr>
</tbody>
</table>

Values are Mean ± SD. P < 0.05, * vs. BASELINE, † vs. HD. Abbreviations: (a-v) O$_2$ diff.; arteriovenous oxygen difference; PO$_2$, oxygen tension; PCO$_2$, carbon dioxide tension.
constant, the increase in myocardial blood flow was the result of a decrease in coronary vascular resistance. Two factors can theoretically account for the decrease in coronary vascular resistance: 1) coronary vasodilation in response to reduced arterial oxygen content, and 2) reduced blood viscosity. Hemodilution has been demonstrated to cause a reduction in the coronary vasodilator reserve in both the left and right ventricles, as indicated by diminished reactive hyperemic responses. These findings provided evidence that coronary vasodilation was integral to the hemodilution-related decrease in coronary vascular resistance. The inability of hemodilution to raise peak reactive hyperemic flow argued against an influence for reduced blood viscosity as an explanation for this response.

The increases in myocardial blood flow were proportional to the induced decreases in hemoglobin concentration (and thus arterial oxygen content), which maintained oxygen supply in both ventricles at the baseline level. In the left ventricle (where samples of venous effluent were available), the increases in myocardial blood flow during hemodilution completely offset the decreases in the arteriovenous oxygen difference, and thus maintained oxygen uptake, percent oxygen extraction, coronary sinus oxygen saturation, and coronary sinus PO2 constant. These findings were evidence that local metabolic control mechanisms were effective in matching the extent of coronary vasodilation to the prevailing myocardial oxygen demands. The continued, and, in fact, increased uptake of lactate, was an indication of the increases in myocardial blood flow.

Table 3

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Hemodilution Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE HA</td>
<td>BASELINE HD HA during HD</td>
</tr>
<tr>
<td>Blood flow</td>
<td>40 ± 8 33 ± 6 *</td>
</tr>
<tr>
<td>Endo/Epi ratio</td>
<td>1.0 ± 0.2 1.0 ± 0.1</td>
</tr>
<tr>
<td>O2 Supply</td>
<td>8.2 ± 2.0 6.7 ± 1.5 *</td>
</tr>
</tbody>
</table>

Values are Mean ± SD. * P < 0.05 from BASELINE.
that myocardial oxygenation remained adequate at the mitochondrial level\textsuperscript{3,22}. The increase in lactate uptake during hemodilution presumably reflected its increased delivery at a higher flow rate and the preference of the myocardium for lactate as a substrate for energy metabolism\textsuperscript{23}.

In contrast to findings obtained in the myocardium, the increases in blood flow in the systemic circulation, i.e., cardiac output, during hemodilution were small and insufficient to avert a decline in systemic oxygen supply. Nevertheless, previous studies have demonstrated that systemic oxygen uptake is maintained because of the recruitment of an oxygen extraction reserve, which results in decreases in both mixed venous oxygen saturation and PO\textsubscript{2}\textsuperscript{5}. The reduced values for mixed venous PO\textsubscript{2} during hemodilution reflected decreases in the aggregate PO\textsubscript{2} of the body tissues\textsuperscript{4}. However, arterial lactate concentration remained unchanged, which suggested absence of widespread anaerobic metabolism.

Hypocapnic alkalosis with hematocrit normal caused an approximate 20\%, transmurally-uniform, decrease in myocardial blood flow in both the left and right ventricles, which, in the presence of controlled perfusion pressure, reflected coronary vasoconstriction. These findings are in keeping with data obtained in the dog\textsuperscript{9-12} and conscious man\textsuperscript{13,14}. In the left ventricle the coronary vasoconstriction could be attributed, in part, to the action of local metabolic mechanisms responding to a decrease, albeit modest, in myocardial oxygen uptake\textsuperscript{15}. The latter effect was presumably the result of a decrease in myocardial contractility due to chemoreflex-mediated reduction in sympathetic drive\textsuperscript{24,25}. The predominant coronary vasoconstrictor mechanism operating during hypocapnic alkalosis was a directly induced increase in vasomotor tone. The magnitude of this vasoconstriction was reflected in the degree to which hypocapnic alkalosis caused an imbalance between myocardial oxygen supply and demand, that is, in the increases in oxygen extraction and the resultant decreases in coronary sinus oxygen saturation and PO\textsubscript{2}\textsuperscript{15}. The increased oxygen extraction during hypocapnic alkalosis required a disproportionate reduction in coronary PO\textsubscript{2}, reflecting a leftward shift of the oxyhemoglobin dissociation curve. However, it is important to note that hypocapnic alkalosis did not reduce myocardial lactate uptake or convert it to production, which suggested that intramyocardial PO\textsubscript{2} remained adequate for unimpaired oxidative metabolism\textsuperscript{3,22}.

We observed that the coronary vasoconstrictor effect of hypocapnic alkalosis disappeared during hemodilution. The increase in myocardial blood flow during hemodilution remained intact and able to compensate fully for the reduction in the arteriovenous oxygen difference, and thus to maintain myocardial oxygen uptake. Adequate tissue oxygenation was implied by continued and undiminished lactate uptake. Apparently the local metabolic vasodilating factors operating during hemodilution were sufficiently potent to prevent the coronary vasoconstriction by hypocapnic alkalosis. In contrast to findings during normal hematocrit, a decrease in myocardial uptake (and the accompanying metabolic coronary vasoconstriction) during hypocapnic alkalosis was not observed in the presence of hemodilution. This may be due to the inability of hypocapnic alkalosis to reduce cardiac sympathetic tone when it was at a heightened state during hemodilution\textsuperscript{26}.

Case et al.\textsuperscript{12} showed in anesthetized dogs that extreme hyperventilation (PaCO\textsubscript{2}, 11±1; pHa, 7.74± 0.01 mmHg) with hematocrit normal caused severe coronary vasoconstriction, as reflected in coronary sinus PO\textsubscript{2} values of less than 9 mmHg with a corresponding myocardial oxygen extraction of nearly 90\%. Reductions in coronary sinus PO\textsubscript{2} of this magnitude are associated with insufficient myocardial oxygenation and lactate production\textsuperscript{22}. The findings from Case et al. indicate that extreme hyperventilation may be risky in any patient, regardless of hematocrit.

Several methodological issues warrant address. Since anesthetic drugs may have different effects on baseline vascular tone, vascular reactivity, and the determinants of myocardial oxygen demand, it is conceivable that the responses to hemodilution and/ or hypocapnic alkalosis would differ if an anesthetic other than halothane were used. An F\textsubscript{io2} equal to 1.0 was used to ensure that arterial PO\textsubscript{2} was sufficient to fully saturate hemoglobin. The large variation in the arterial PO\textsubscript{2} values within each condition reflects differences in the physiological status of the lungs of the dogs and the difference in their ability to tolerate
general anesthesia, a thoracotomy, and invasive surgery. However, the average arterial PO$_2$ values were comparable across all treatment conditions. Previous canine studies have demonstrated that hyperoxia can be a coronary vasoconstrictor$^{15}$, which in conscious dogs has been shown to cause an 18% decrease in myocardial blood flow$^{27}$. The influence of this factor should be less in the current study because the increases in arterial PO$_2$ were smaller (approximately 300 vs. 500 mmHg). The induced reduction in hematocrit was to a value equivalent to the suggested “transfusion trigger” of 7g/100 ml and thus approximated the most severe degree of hemodilution likely to be encountered clinically. It is possible that the level of hypocapnic alkalosis that we tested would have been detrimental to myocardial oxygenation if hematocrit were reduced further.

In conclusion, we demonstrated that moderate hypocapnic alkalosis did not compromise myocardial oxygenation either in the absence or presence of hemodilution. The current findings pertain strictly to the specific conditions of this study. An extrapolation to human patients should be made only with caution. It would be inappropriate to apply our findings in the normal canine coronary circulation to the patient who presents with conditions, such as coronary atherosclerosis, which may alter the responsiveness of the coronary circulation to hypocapnic alkalosis and hemodilution.

**Acknowledgment**

The authors thank Dana Villines, MA, for her expert statistical assistance.
References

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Volunteer studies have demonstrated a slight (17%-22%) and transient (<30 minutes) prolongation of the prothrombin time (PT)/activated partial thromboplastin time (APTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on peri- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised in patients on anticoagulation for a pre-existing or corneal condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exceptions of toremifene, fusidic acid, and hormonal contraceptives.

† Train-of-four
² Post-tetanic counts
³ Second twitch

REFERENCES:
1. BRIDION Summary of Product Characteristics (SPC)

Please see summary of product characteristics for full prescribing information.

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References: