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Effects of Increasing FiO_2 on Venous Saturation During Cardiopulmonary Bypass in the Swine Model

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Abstract: Adequacy of perfusion during cardiopulmonary bypass (CPB) is dependent on nutrient delivery and waste removal from the tissue. A recent study showed that over 75% of cardiopulmonary bypass procedures are completed using continuous venous saturation (SvO_2) monitoring. The purpose of this study was to determine the effect of changing FiO_2concentration on SvO_2. A total of eight mixed gender 45-kg swine were placed on CPB under moderate hypothermic conditions. Animals were divided evenly into two groups: Experimental, where FiO_2 was increased to 100% and blood flow decreased to an SvO_2 level of prechange in FiO_2, and Control, where the same condition was created except no change in blood flow. Variables measured include hemodynamic, blood gas, intramyocardial pH, and lactic acid concentrations. In the experimental group, percentage change of blood flow was decreased from baseline 28.4% ± 12.5% ($p < .005$) as well as percentage change of oxygen delivery 23.9% ± 14.7% ($p < .005$). Systemic venous saturation percentage change was increased in both the experimental 14.4% ± 6.8% ($p < .05$) and control 11.2% ± 7.1% ($p < .05$) groups. Jugular venous saturation percentage change was decreased in the experimental group 7.8% ± 6.34% ($p < .02$), but not in the control animals. Myocardial venous saturation percentage change decreased in the experimental group to 3.73% ± 8.34% ($p < .004$). Experimental manipulation, however, did not significantly change jugular lactic acid concentrations or intramyocardial pH values. In conclusion, these results suggest that decreased blood flow adjusting for increased SvO_2associated with high PaO_2 did not result in significant reduction of adequacy of perfusion markers for organs studied. **Keywords:** venous saturation, oxygen delivery, adequacy of perfusion, oxygen content. *JECT. 2002;34:118–124*

The mixed venous saturation is used to assess supply and demand economics of oxygenation status in critical care situations (1). However, Swan et al. indicated that the use of venous oxygen saturation as a guide to the adequacy of perfusion has proved unreliable (2). In a recent survey by Mejak et al., it was reported that 79% of all American centers performing cardiac surgery, 75.2% used an in-line venous hemoglobin saturation monitor (3). This survey indicates that the majority of perfusionists practicing in America today consider venous saturation as an important variable to monitor during CPB.

During CPB, adequacy of perfusion is dependent on the delivery of nutrients to the tissue and the removal of waste products. Oxygen is used for aerobic cellular energy production to sustain cellular homeostasis. Oxygen delivery (DO_2) is defined as the cardiac output multiplied by the arterial content of oxygen. When DO_2 is pathologically reduced to levels unable to sustain aerobic metabolism, an oxygen deficit is encountered. Oxygen consumption (VO_2) is initially maintained by a progressive increase in oxygen extraction ratio; however, once the diffusion reserve is exceeded, oxygen consumption begins to decrease (4).

Inadequate levels of oxygen for oxidative phosphorylation causes the cell to switch from aerobic energy production to anaerobic energy production to maintain homeostasis. This process leads to increased amounts of lactate production. Lactate has been identified as a good indicator of both oxygenation difficulties and overall oxygenation (5). Increased lactate production results in an acidosis created by increased hydrogen-ion concentrations, impairing mitochondrial function (6).

Schlichting and Lyberg reported that hypoxia adversely affects cellular immune functions by significantly augmenting the cytotoxic activity of both T lymphocytes and lymphokine-activated killer cells (7). Hypoxia also stimulated peripheral blood monocytes to produce and secrete interleukin-1β and tumor necrosis factor-α. Hypoxia has been shown to initiate an uncontrolled activation of endogenous inflammatory cells to release mediators that

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may contribute to the development of adult respiratory distress syndrome or multiple organ dysfunction syndrome (7). A delay in the diagnosis of reduced tissue perfusion permits a potentially reversible state to become irreversible.

The effects of decreased oxygen delivery are well documented. All these factors demonstrate the importance of having an indication of adequate perfusion during CPB. Mixed venous saturation has been suggested as an indicator for global adequacy of perfusion. However, the question of whether venous saturation is any indication of the adequacy of perfusion in specific organs remains to be answered. Therefore, the purpose of this study was to quantify the effect of increasing PaO_2 using FiO_2 on mixed venous saturation values under varying flow conditions during CPB.

MATERIALS AND METHODS

All animals used in this study received humane care in compliance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985). A total of eight mixed gender porcine subjects, approximately 45 kg, were used for this investigation. Animals were identified as either control (CG, $N = 4$) or experimental (EG, $N = 4$).

All animals were placed on CPB. Each animal was maintained within normal physiologic ranges of all hemodynamic parameters, with the exception of PaO_2 in both groups. An in-line blood gas monitor (CDI 500, Terumo Sarns, Ann Arbor, MI) was used to continuously monitor the arterial and venous blood gases. Jugular venous blood gases were monitored using additional in-line blood gas monitors (CDI 400 & 100, Terumo Sarns, Ann Arbor, MI). A five-lead electrocardiogram (ECG) was monitored continuously. Mean arterial blood pressure was maintained pre-CPB at 70 to 90 mmHg via adjustment of vasoactive substances. During CPB, mean arterial pressure was maintained at 60–80 mmHg with flow rate adjustment described below.

Anesthetic Management

A mixture of intramuscular ketamine (20 mg/kg) and xylazine (2 mg/kg) was used to anesthetize each animal. An endotracheal tube (6.5 Fr) was used to intubate the animals. The tidal volume was equivalent to 10–15 mL/kg body weight at a rate of 15–20 breaths per minute. Electrocardiogram was used to monitor each animal's heart rate continuously. Each animal was intermittently dosed with pentothal (100 mcg/kg body weight) and pavulon (50 mcg/kg body weight). Bretylium (3 mg/kg), was given before opening the chest through a midline sternotomy to reduce ventricular arrhythmias.

Perfusion Management

A standard CPB circuit was utilized. The circuit consisted of a soft-shell venous reservoir (COBE Cardiovascular, Arada, CO), a cardiotomy reservoir (COBE Cardiovascular, Arada, CO), a centrifugal pump (Medtronic, Brooklyn Park, MN), a hollow fiber membrane oxygenator (Optima, COBE Cardiovascular, Arada, CO), a 40-micron arterial line filter (Sentry, COBE Cardiovascular, Arada, CO), and polyvinylchloride tubing. CDI 500 shunt sensors were inserted into the purge line off the arterial line filter and a bypass line off the venous line. In addition, a CDI 500 H/S cuvette was placed in the venous line. A CDI 400 cuvette and a CDI 100 H/S cuvette were inserted into the jugular venous line.

The circuit was primed with 1300 mL of plasmalyte-A (a balanced electrolyte solution), 50 mL of 8.4% sodium bicarbonate (1 mEq/mL), and 2500 IU of bovine lung heparin. Arterial, venous, and rectal temperatures were monitored throughout each trial of the experiment. All animals were cooled to a rectal temperature of 34°C and remained there for the duration of the treatment. Thereafter, weaning was begun, and the animals were separated from CPB when the rectal temperature had risen to 36°C. After the experiment ended, protamine sulfate (1 mg/100 IU of total heparin) was given to reverse the effects of heparin. Each animal was euthanized by a simultaneous dose of barbiturate (1 mg/kg) and potassium chloride (20 mEq) injected into the aortic root.

Test Preparation

In both groups, fraction of inspired oxygen (FiO_2) was increased from a baseline of 0.70 up to 1.00 with a concomitant rise in PaO_2 to greater than 600 mmHg. Data were recorded from the in-line monitors at every 50 mmHg increase in PaO_2, beginning at 200 mmHg. Three constant SvO_2 values over a 5-min period were used as the marker for maximum increase in SvO_2 by increasing FiO_2. In the control group, FiO_2 was then turned back down until the SvO_2 matched the baseline value. In the experimental group, pump flows were reduced to decrease SvO_2 to the baseline value.

Surgical Management

A median sternotomy was performed to expose the heart, followed by dissection of the great vessels for cannulation. Anticoagulation was achieved via a bolus dose of 400 IU/kg of bovine lung heparin. Kaolin activated clotting times (ACT) were performed, and anticoagulation was accepted at greater than 480 sec. A double purse string suture was placed in the aorta to secure a 7.0-mm

arterial cannula (Texas Medical Products, Houston, TX). A single purse string suture was placed in the right atrial appendage to secure a dual stage 32/40 Fr cannula (Research Medical Inc., Midvale, UT). The right internal jugular vein was cannulated using a 16 Fr cannula (Research Medical Inc., Midvale, UT) and secured into place with a purse string suture. A 16-gauge, micro pH electrode (Orion Research Inc., Boston, MA) was inserted into the myocardium in the lateral free wall of the left ventricle.

Data Collection

Data collection times for both groups were as follows: prebypass, baseline on CPB, and after F_iO_2 was increased to 1.00. In addition, a final sample was taken in the control group after $F_iO_2$was turned down, and the venous saturation returned to baseline values. In the experimental group, the final sample was taken after flows were reduced, and the venous saturation returned to baseline values.

The following data were measured: arterial pH (pH_a), venous pH (pH_v), arterial partial pressure of oxygen (PaO_2), venous partial pressure of oxygen (PvO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), venous partial pressure of carbon dioxide ($PvCO_2$), arterial hemoglobin–oxygen saturation (SaO_2), venous hemoglobin–oxygen saturation (SvO_2), hematocrit (Hct), hemoglobin (Hgb), temperature (arterial, venous, and rectal), mean arterial pressure (MAP), arterial and venous lactate concentration.

Data from the jugular vein included: pH (pH_{jv}), partial pressure of oxygen ($Pjv O_2$), partial pressure of carbon dioxide ($P_{jv}CO_2$), lactate concentration, and hemoglobin–oxygen saturation ($S_{jv}O_2$). The following data were measured from the myocardium: pH (pH_m), partial pressure of oxygen (PmO_2), partial pressure of carbon dioxide ($PmCO_2$), lactate concentration, and hemoglobin–oxygen saturation (SmO_2). Intercellular pH of the heart (pH_{ih}) was also measured.

The previous measurements were used to calculate the following: arterial oxygen content (CaO_2), systemic venous oxygen content (CvO_2), oxygen delivery (DO_2), systemic oxygen consumption (VO_2). These variables were calculated as follows:

$$C_xO_2\ (\text{mL } O_2/\text{dL}) = ([\text{Hgb}] \times 1.36 \times S_xO_2) + (P_xO_2 \times 0.003)$$

$$DO_2\ (\text{mL } O_2/\text{dL}) = CaO_2 \times \text{Pump Flow Rate} \times 10$$

$$VO_2\ (\text{mL } O_2/\text{dL}) = \text{Pump Flow Rate} \times 10 \times (CaO_2 - CvO_2)$$

Statistical Analysis

Data were analyzed using a one-way analysis of variance. Fisher's protected least significant post hoc analysis was completed on significant factors when achieved. Statistical significance was accepted at a $p < .05$. All data are expressed as mean ± standard deviation of the mean (SD).

RESULTS

In the experimental group (Figure 1), to maintain a constant SvO_2 with increased FiO_2, flow rate decreased by 28.4 ± 12.5% ($p < .005$). PO_2 % change for both control and experimental groups are shown in Figures 1 and 2, respectively. In the control group, both systemic arterial and venous values were decreased from baseline ($p < .003$). In the experimental group, percentage change of PO_2 was significantly decreased from baseline in systemic

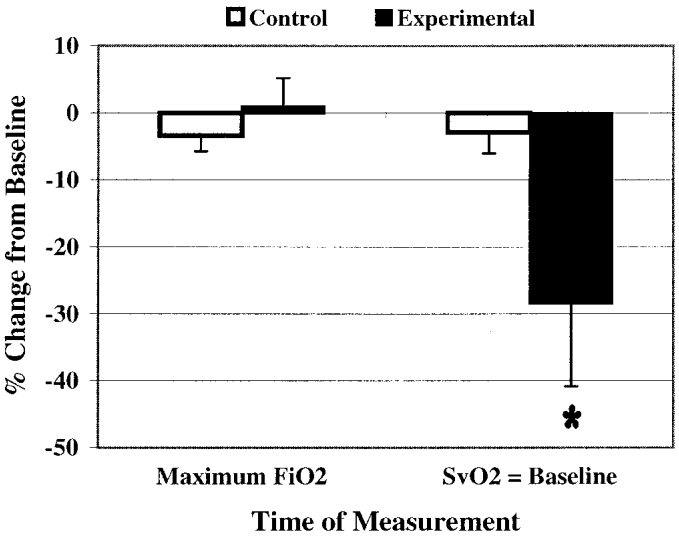

Figure 1. Change in flow from baseline. *$p < .005$ vs. maximum FiO_2 value in the experimental group.

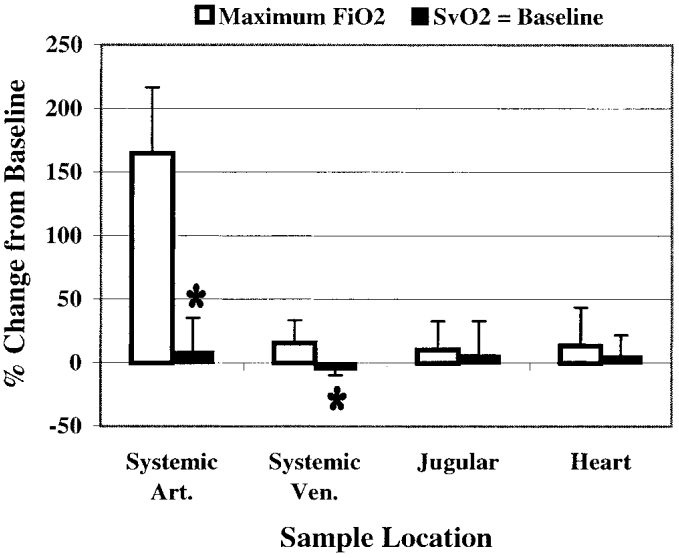

Figure 2. Control group: change in PO_2 from baseline. *$p < .003$ vs. maximum FiO_2 value.

venous –3.62 ± 7.03%, jugular –17.67 ± 11.11%, and cardiac values –7.29 ± 10.05%.

Arterial and venous oxygen content percentage change from baseline are shown in Figure 3 and 4. CaO_2 was significantly decreased in the control group ($p < .02$); whereas, CvO_2 decreased in the experimental group ($p < .005$). Percentage change of oxygen delivery (Figure 5) in the experimental group decreased from baseline 23.90 ± 14.66% ($p < .0001$). In the same figure, VO_2 was also decreased significantly in the experimental group.

Changes in saturation levels are shown in Figure 6. Systemic venous saturation percentage change was increased in both the experimental 14.37 ± 6.79% ($p < .05$) and control 11.24 ± 7.06% ($p < .05$) groups. Jugular venous saturation percentage change decreased in the experimental group 3.73 ± 8.34% ($p < .004$).

Significant increases in pH values were only observed in the control group ($p < .05$) shown in Figure 7. Intramyocardial pH % change (Figure 8) was increased in the control group to 1.74 ± 0.13% ($p < .04$). No significant changes were observed in either group for lactic acid concentrations (Figure 9).

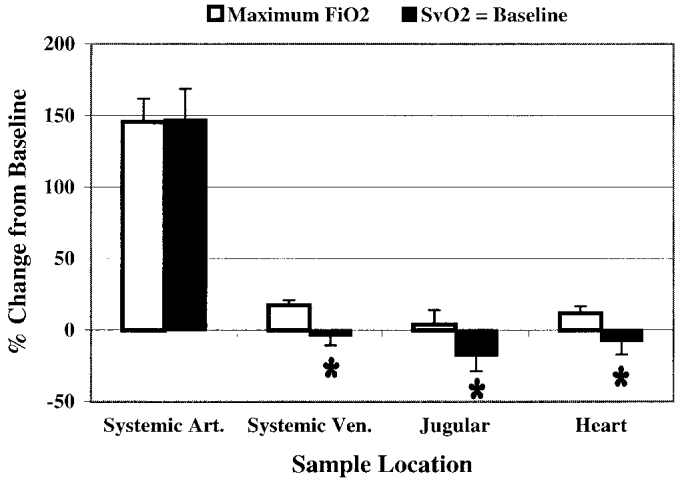

Figure 3. Experimental group: change in PO_2 from baseline. *$p < .05$ vs. maximum FiO_2 value.

DISCUSSION

Providing adequate perfusion during CPB is something every perfusionist strives for. There are many different indications for adequacy of perfusion, but often all these parameters cannot be measured. Base deficit, blood lactate concentrations, arterial–venous oxygen content difference, mixed venous oxygen saturation, oxygen delivery, oxygen consumption, oxygen extraction, and intramucosal pH have all been used (7). Decreased oxygen to the tissue can lead to anaerobic metabolism. During anaerobic metabolism, pyruvate is converted to lactate, plasma lactate concentration is, therefore, used by many as a marker of anaerobic metabolism (8). Swan et al. reported that a rise in blood lactic acid in excess of 1 μm/mL is a true indicator of the development of a clinically important level of acidosis (2).

Pump flow is often directly associated with adequate perfusion. However, Cook et al. showed that cerebral oxygenation was well maintained at lower than conventional pump flow levels during CPB (9). In addition, Sungurtekin and associates showed that over the typical range of flows in adult CPB, pump flow does not have an effect on cerebral perfusion independent of its effect on mean arterial pressure (10). Sungurtekin indicated that pressure is a better predictor of adequate perfusion than flow. In our

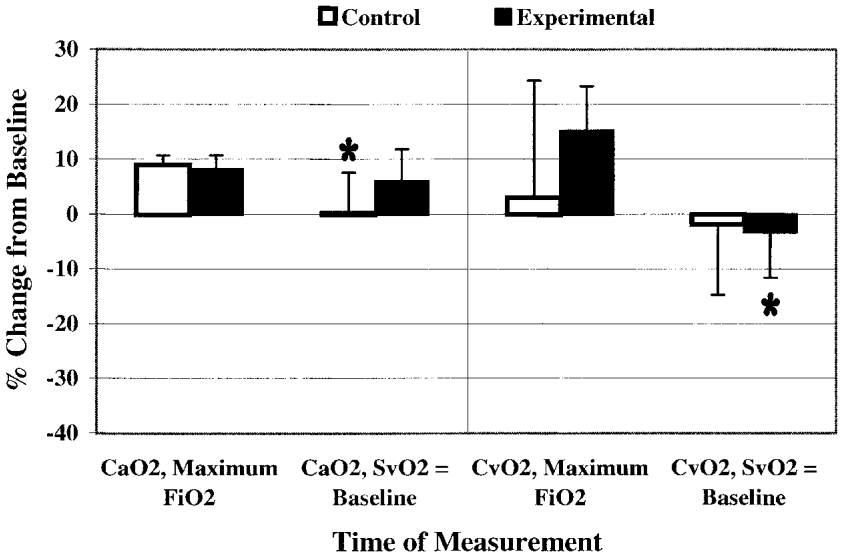

Figure 4. Change in CaO_2 CvO_2 fom baseline. *$p < .02$ vs. maximum FiO_2 value in control group; $p < .05$ vs. experimental group.

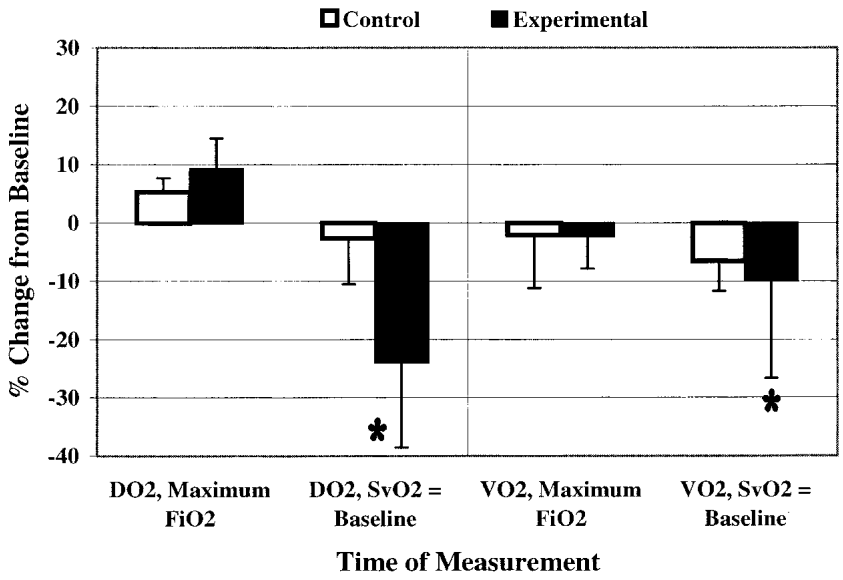

Figure 5. Change in DO_2 and VO_2 from baseline. *p < .0001 vs. maximum FiO_2 value in experimental group; p < 0.1 in experimental group.

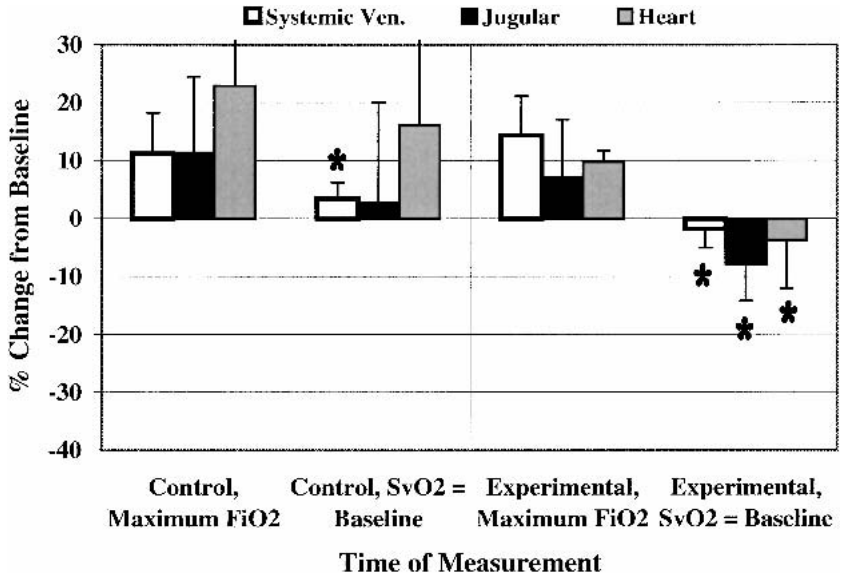

Figure 6. Change in SO2 from bseline. *p < .05 vs. FiO_2 value from same sample location and same group.

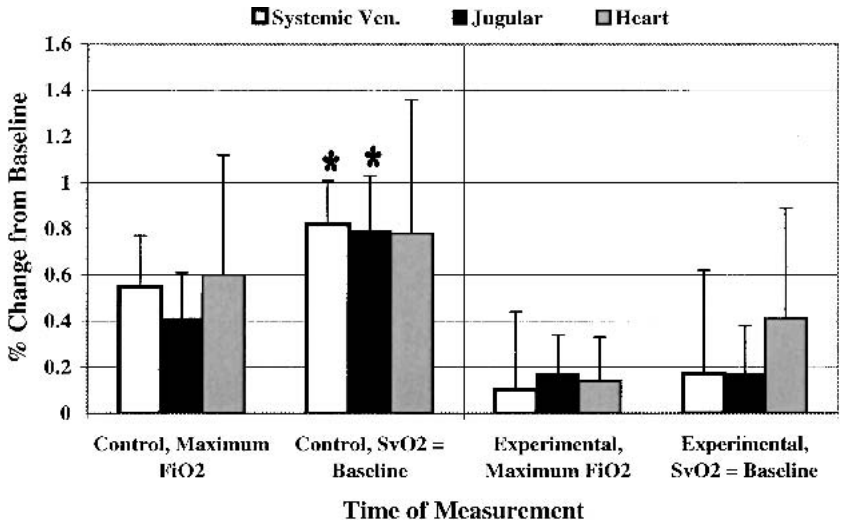

Figure 7. Change in pH from baseline. *p < .05 vs. FiO_2 value from same sample location in control group.

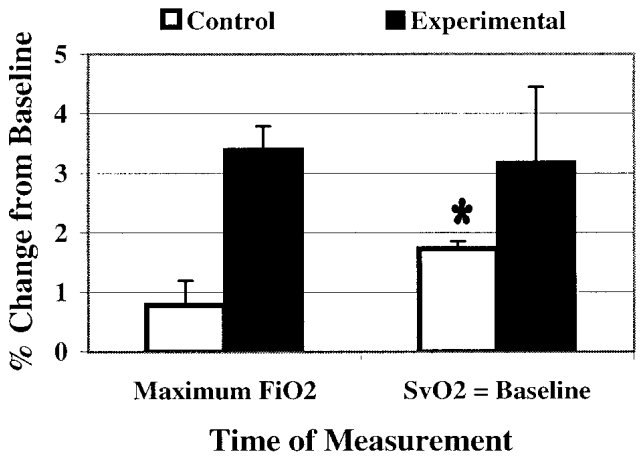

Figure 8. Change in intramyocardial pH from baseline. *$p < .04$ vs. FiO_2 value in the control group.

study, flow, oxygen delivery, and oxygen consumption were all significantly decreased in the experimental group.

The question remains on whether oxygen consumption is a good predictor of adequacy of perfusion. Engoren et al. found no association between oxygen consumption and lactic acid levels, even at levels of oxygen consumption that are considered delivery dependent (11). In addition, Alston et al. showed that at low flow rates, oxygen consumption is directly related to flow. However, Alston showed no significant increase in base excess or lactate results at the lower flow rates (12).

Another common indicator for adequacy of perfusion is venous saturation values. In our study, venous saturation was maintained using flow in the control group and using increased partial pressure of oxygen on the experimental group. The fact that the same value can be obtained by two very different means lends support to the notion that this is not a reliable indication of perfusion. Croughwell and colleagues showed that systemic venous saturation is a poor indicator of cerebral saturation. In addition, there is a poor association of jugular and systemic pump venous saturations, and this underscores our inability to evaluate adequacy of cerebral perfusion (13).

In the experimental group, FiO_2 was increased to 100% oxygen and PaO_2 levels were allowed to rise to supersystemic levels. During periods of low flow, it seems that increasing the fraction of inspired oxygen will increase adequacy of perfusion. However, this subject is also in debate. Joachimsson et al. showed that hyperoxemia increased global oxygen delivery and oxygen saturation during CPB. However, they state that under both normal and disease states, hyperoxemia actually disturbs capillary flow and can impair tissue oxygenation (14). In our experimental group, jugular venous saturation percentage change and myocardial venous percentage change did significantly decrease, indicating that adequate perfusion was not provided. However, the majority of adequate perfusion indicators did not decrease in the experimental group.

Finally, lactic acid levels have been proposed as a good indicator of adequate perfusion. Demers and colleagues found that systemic microvascular control may become disordered in CPB resulting in peripheral arteriovenous shunting and a rise in lactate levels despite apparent adequate oxygen supply. Increased levels of lactate led to a significantly higher postoperative morbidity and mortality (15). Munoz et al. also show that an intraoperative increment in lactate levels is an early and specific indicator of patients at high risk for morbidity and mortality (16). Our study showed no significant differences in lactic acid levels in the experimental group. However, these changes may have been significant with a larger population of animals; one possible limitation of this study. In the future, repeating this study under normothermic conditions would be beneficial. Normothermia may elicit greater differences in the metabolic state of the subjects and find significance

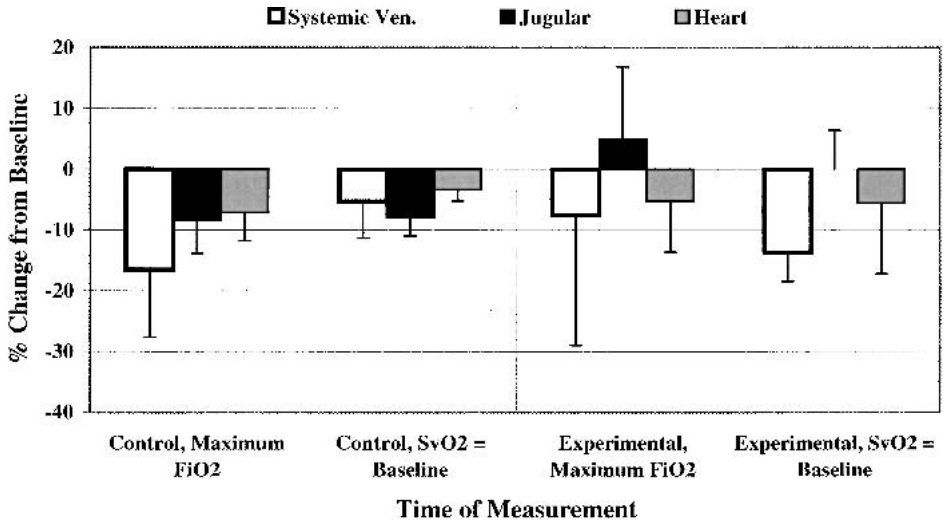

Figure 9. Change in lactic acid from baseline.

where this study did not. In conclusion, these findings suggest that in the swine model, decreased blood flow adjusting for increased SvO_2 associated with high PaO_2 did not result in a significant decrease in adequacy of perfusion indicators within organs measured.

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