MODELS TO STUDY THE RELATION BETWEEN OXYGEN CONSUMPTION AND OXYGEN DELIVERY DURING AN ACUTE REDUCTION IN BLOOD FLOW: COMPARISON OF BALLOON FILLING IN THE INFERIOR VENA CAVA, TAMPONADE, AND HEMORRHAGE

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ABSTRACT—Different animal models have been used to study the relationship between oxygen consumption (VO₂) and oxygen delivery (DO₂) and each of them has its own specificity. The present study compared the models of balloon inflation in the inferior vena cava (BALL), tamponade (TAMP), and hemorrhage (HEM) to acutely reduce blood flow in pentobarbital-anesthetized dogs. The order of the procedures was randomized first, but HEM was irreversible so that HEM was applied as the third procedure (n = 10) or as a unique procedure (n = 4). Critical DO₂ (DO₂ crit) was determined as the intercept of two best fitted lines of regression of VO₂ against DO₂, but similar results were obtained when it was calculated from blood lactate or from arterio-venous differences in pH (AVPΔH) or PaO₂ (VAPPaO₂). At DO₂ crit, VO₂ was 6.6 ± 0.7 mL/min·kg in BALL, 6.2 ± 0.6 mL/min·kg in TAMP and 6.0 ± 0.7 mL/min·kg in HEM (p < .05 vs. BALL). DO₂ crit was significantly greater with BALL (14.3 ± 2.3 mL/min·kg) than with TAMP (10.2 ± 1.7 mL/min·kg, p < .01 vs. BALL) or HEM (9.1 ± 1.4 mL/min·kg, p < .01 vs. BALL). Also, critical oxygen extraction (EO₂ crit) was significantly lower with BALL (64.5 ± 4.8%) than with TAMP (62.1 ± 11.5%, p < .01 vs. BALL) or HEM (66.8 ± 11.4%, p < .01 vs. BALL, p < .05 vs. TAMP). The earlier onset of tissue hypoxia with BALL was probably related to the blood flow redistribution induced by this model. Study of the pressure/flow relationship revealed that the vascular responsiveness was significantly decreased in HEM compared to TAMP. The lack of reversibility of HEM could account, at least in part, for the decreased vascular reactivity when blood volume is reduced.

INTRODUCTION

Experimental studies have shown that oxygen consumption (VO₂) remains relatively stable when oxygen delivery (DO₂) is reduced within a wide range of DO₂ values but becomes dependent on DO₂ when DO₂ falls below a critical value called DO₂ crit (1-19). Below DO₂ crit, blood lactate levels and arterio-venous PaCO₂ gradients markedly increase indicating the development of anaerobic metabolism and cellular acidosis resulting from tissue hypoxia (1, 3, 4, 7, 8, 11-19).

Different animal models have been used to reproduce some pathological alterations associated with sepsis (4, 8, 9, 16, 18) and acute respiratory failure (2) or to study the effects of various interventions on the VO₂/DO₂ relationship (5, 8, 18, 19). These different models may be characterized by different DO₂ crit values. Evaluation of these differences may help to select the most appropriate model to address specific questions in future studies. It may also help to interpret the results of studies using various models. For example, halothane was found to increase DO₂ crit in a hemorrhagic shock model (8) but to decrease DO₂ crit in a model of balloon inflation (5).

The various methods that have been used to acutely decrease cardiac output may have different effects on venous pressures and on blood flow redistribution. Acute hemorrhage (4, 7, 8, 12, 17) is characterized by a marked decrease in both arterial and venous pressures, while tamponade (6, 10, 14-16, 18, 19) is associated with a marked increase in venous pressures. In previous experimental studies, DO₂ crit ranged from 6.4 to 8.0 mL/min·kg during hemorrhage (4, 7, 8, 12) and from 9 to 10.5 mL/min·kg during tamponade (6, 15, 16, 18, 19). To conclude from this that DO₂ crit is lower during hemorrhage than during tamponade would be inappropriate, because the two models have not been directly compared. Cain et al. (20) observed a steeper slope in the total body VO₂/DO₂ relationship during tamponade than during hemorrhage, suggesting greater oxygen extraction capabilities in the former model but DO₂ crit was not determined in that study. Application of positive end-expiratory pressure (2) or filling of a balloon in the right atrium (3, 9) or both the superior and inferior vena cava (2) induce similar peripheral vascular effects as in tamponade. The inflation of a balloon only in the inferior vena cava (5, 11) is a relatively simple, easily reversible model, but its effects may not be equally distributed throughout the body. In particular, the venous pressure is expected to increase selectively in the body regions drained by the inferior vena cava. Regional differences in venous pressures may account for some blood flow redistribution resulting in a higher DO₂ crit in this model. In a previous study, we found a DO₂ crit value of 18.4 mL/min·kg in

The laboratory animals involved in this study were handled in accordance with the National Institutes of Health Guidelines for the Use of Experimental Animals.

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pentobarbital anesthetized dogs (11). Another study reported a value as high as 19.8 mL/min kg in conscious dogs (5).

The present study compared the effects of hemorrhage (HEM), tamponade (TAMP), and balloon filling in the inferior vena cava (BALL) on DO₂erm in anesthetized dogs. The three procedures were applied in the same animals. We hypothesized that DO₂erm would be either lower in HEM than in TAMP or similar in these two models but in any case lower in these two models than in BALL.

MATERIALS AND METHODS

Animal preparation

14 healthy mongrel dogs (27.4 ± 2.8 kg) were anesthetized with intravenous pentobarbital sodium (25 mg/kg loading dose followed by 1 mg/kg every hour) and paralyzed with pancuronium bromide (4 mg loading dose followed by 1 mg every hour). After endotracheal intubation, each dog was mechanically ventilated with air on control mode (Elema B; Siemens, Solna, Sweden). Respiratory rate was set at 12/min, and tidal volume was adjusted to obtain an arterial PCO₂ between 28 and 36 mmHg at baseline. The ventilator conditions were not changed until the end of the study.

A pulmonary artery catheter (Swan-Ganz model 93A-131-7F; Baxter Healthcare, Irvine, CA) was inserted into a pulmonary artery through a sheath (CC-35CB-SLE; Baxter) placed in the right jugular vein. One catheter (C6 G; Baxter Dickinson, Rutherford, NJ) was inserted in a femoral vein for drug administration, and another identical catheter was inserted via a femoral artery into the distal aorta for blood sampling and pressure monitoring. A Foley catheter (#14) was inserted into the inferior vena cava via a femoral vein with the balloon placed above the origin of the renal veins (11); the correct position was confirmed later during a laparotomy.

A sphenectomy was performed through the left hypochondrium, using the following procedure: ligation of the sphenic artery, maximal splenic contraction by topical application of diluted epinephrine, ligation of the splenic veins, and removal of the spleen.

Through the fifth intercostal space a left thoracotomy was performed to insert a catheter (Intracath 16 G; Deseret Med Inc., Sandy, UT) into the pericardial space (15, 16, 18, 19). The catheter was secured with purse strings, and glue was applied to the suture so that leak could be observed. The chest was closed after insertion of a chest tube (Argyle catheter A75; 28cc-40 cm, Curoc, Tallmore, Ireland) into the pleural space. During the entire surgical procedure, hydroxyethyl starch (Plasmalast, Fresenius, Germany) was perfused at a rate of 4 mL/kg/h. Cefazolin (1 g) was also administered intravenously at induction.

Experimental design

Body temperature was kept constant throughout the study by the use of a warming blanket. Hemocarat was also maintained constant around 30% as it is a common value in critical ill patients. To achieve this, normovolemic hemorrhage was initially performed by blood replacement with hydroxyethyl starch until hemocarat reached 30-33%. Red blood cells were collected in citrated bags, rapidly centrifuged and kept at room temperature. Reinfusion was performed as needed to maintain hemocarat between 27 and 33% throughout the experiment.

After baseline measurements, fluid loading was performed with 10 mL/kg of saline in 10 min to prevent any fluid deficit. After a 10 min pause, the dogs were successively submitted to BALL, TAMP, and HEM. A 20 min interval was observed between two successive interventions. Initially, the order of the three interventions was randomized, but the first experiments revealed that the HEM procedure could not be reversed. Hence, only BALL and TAMP were randomized in subsequent experiments, while hemorrhage was applied either alone (n = 4) or as the third intervention (n = 10).

During BALL, the balloon was progressively filled with 1 mL increments until mean arterial pressure reached 40 mmHg (N = 3) or failed to decrease further (N = 7). Then the balloon was progressively deflated.

During TAMP, the pericardium was filled with aliquots progressively reduced from 15 mL (initially) to 5 mL of saline. When mean arterial pressure had decreased to 40 mmHg, the pericardium was progressively emptied by 20 mL aliquots.

During HEM, blood was withdrawn by aliquots progressively reduced from 150 mL (initially) to 10 mL. When mean arterial pressure had decreased to 40 mmHg, blood was reinfused by 50 mL aliquots.

In case of survival at the end of the experiment, the dog was euthanized with a pentobarbital overdose.

Measurements were usually obtained every 10 min, but only when VO₂ had been stable for at least 3 min to ensure steady state conditions.

Measurements and calculations

Heart rate, arterial pressure, pulmonary artery pressure, end tidal CO₂ (PET CO₂) and expired O₂ fraction (FEO₂) were continuously monitored (Siemens; Siemens, Erlangen, Germany) and recorded on paper (2600 S recorder; Gould, Cleveland, OH). The zero pressure was set at mid-chest level. At each point, cardiac output was determined by the thermodilution technique and indexed to the body weight. Aliquots of 5 mL of iced DSW were injected during expiration until three measurements within 10% of each other were obtained. Immediately thereafter, arterial and mixed venous blood samples were analyzed for blood gases (ABL3; Radiometer, Copenhagen, Denmark), oxygen saturations (Hemoximeter Osm 3; Radiometer) and hemocarat (centrifugation). Red blood cell count was also determined every hour so that hemoglobin levels could be derived from the hemocarat and the mean corpuscular volume. Arterial lactate was determined by an enzymatic method (analyzer model 640, Kontron Instruments, Basel, Switzerland).

Exhaled gases were collected in a mixing chamber for sampling. FETCO₂ was determined by a semi-rapid analyzer with zinc oxide cell (model 200D PK; Morgan, Clatham, UK). PET CO₂ was determined by an infrared cell (capnometer 4721 A; Hewlett-Packard, Waltham, MA). Inspiratory volume (Ve) was measured by a spirometer (Haloscale Wright Respirator, Edintron, London, UK) and corrected for STPD conditions.

VO₂, DO₂, oxygen extraction (EO₂) and systemic vascular resistance (SVR) were calculated by the following formulas:

\[
VO₂/kg = \frac{Ve/weight \times (FiO₂ \times (1 - FICO₂) - FICO₂) \times (1 - FiO₂)}{DO₂/kg = CI \times (1.39 \times Hb \times SaO₂ + .0031 \times PaCO₂)} 
\]

\[
EO₂ = \frac{VO₂}{DO₂}
\]

\[
SVR = \frac{(MAP - RAP)}{79.9} \times CO
\]

where MAP represents mean arterial pressure, RAP the right atrial pressure, CO the cardiac output, and CI the cardiac index, respectively.

Data analysis

For each intervention, DO₂erm was determined as the intercept of the two best fitted lines of regression of VO₂ (21), lactate (4, 8, 15), and arterio-venous difference in Pco₂ and pH (12, 15) against DO₂. Only data obtained during the decrease in DO₂ were analyzed. Paired sets of linear regression were calculated for all possible combinations of points separated in low (supply-dependent) and high (supply-independent) DO₂ groups. The pair of regressions with the lowest sum of the standard errors of estimate was taken as the best fitted lines.

To assess cardiovascular reactivity in TAMP and HEM, individual pressure/flow relations were analyzed from the relation between mean arterial pressure – right arterial pressure and cardiac index. As this relationship is sigmoidal, we excluded data points obtained on the independent part, so that a linear regression could be calculated.

Data were analyzed for differences by a two-way analysis of variance for repeated measurements (group and time) followed by post-hoc Newman-Keuls analysis (CRUNCH 3; Crunch Software Corporation, Oakland, CA). Statistical significance was determined at the 0.05 level. All data are presented as mean ± SD.

RESULTS

General effects of the three interventions

At baseline, there was no significant difference among the three procedures in any of the determined parameters (Table
Also, the order of the three interventions had no significant influence on any of these parameters. Hemoglobin levels remained stable during BALL and TAMP, but decreased during HEM, especially below $DO_{2\text{crit}}$ ($p < .01$).

At $DO_{2\text{crit}}$ mean arterial pressure had decreased during TAMP and especially during HEM but not during BALL ($p < .01$). Cardiac index was significantly lower during TAMP and HEM than during BALL. Systemic vascular resistance increased more during TAMP and BALL than during HEM. The mean arterial pressure minus right arterial pressure/cardiac index relationship had a steeper slope during TAMP than during HEM (941 ± 398 vs. 608 ± 291 mmHg-min·kg⁻¹·l⁻¹, $p < .05$) (Fig. 1).

$P_{aco_2}$ remained stable during the three interventions. A lower $P_{vco_2}$ reflected a higher oxygen extraction in TAMP and HEM than in BALL. Arterial and mixed-venous pH remained unchanged during BALL and TAMP but decreased during HEM. Arteriovenous differences in pH and $P_{aco_2}$ increased more during TAMP and HEM than in BALL.

At the lowest $DO_2$, as expected, the pulmonary artery occluded pressure and right atrial pressure were higher in TAMP than in BALL and HEM and the hemoglobin levels were lower in HEM. If anything, alterations were more profound in TAMP than in HEM, as indicated by a greater increase in VAPCO₂ and lactate.

**Effects on $DO_{2\text{crit}}$**

An example of individual VO₂/DO₂ relationships in three representative dogs is shown in Fig. 2. VO₂ at $DO_{2\text{crit}}$ was significantly higher in BALL than in HEM but similar in TAMP and HEM (Table 1). $DO_{2\text{crit}}$ was significantly higher during BALL (14.3 ± 2.3 mL/min·kg⁻¹) than during TAMP (10.2 ± 1.7 mL/min·kg⁻¹) or HEM (9.1 ± 1.4 mL/min·kg⁻¹). $DO_{2\text{crit}}$ was slightly higher during HEM than during TAMP, but the difference did not reach statistical significance. Similar results were obtained when $DO_{2\text{crit}}$ was related to lactate, VAPCO₂, or AVpH (Table 2).

$EO_{2\text{crit}}$ was significantly greater during TAMP or HEM than during BALL, and it was greater during HEM than during TAMP (Table 1). The slope of the dependent part of the VO₂/DO₂ relationship was steeper during TAMP (38.3%) and HEM (40.1%) than during BALL (17.9%, $p < .01$), reflecting the lower extraction capabilities during BALL (Fig. 3).

**DISCUSSION**

**Validity of the methods**

This study compared the effects of tamponade, hemorrhage, and balloon filling in the inferior vena cava on the VO₂/DO₂ relationship in the anesthetized dog. Whenever possible, the three interventions were applied successively in the same animal to limit the influence of random variation of $DO_{2\text{crit}}$ between subjects. All parameters, including arterial lactate levels, had returned to baseline between each successive intervention. From baseline to $DO_{2\text{crit}}$ there was no significant difference in arterial pH or in hematocrit levels that may have influenced $DO_{2\text{crit}}$ (17, 20). The order of interventions had no influence on $DO_{2\text{crit}}$ or any other parameter. During the entire
Fig. 1. Individual relationships between mean arterial pressure minus right arterial pressure and cardiac index during tamponade and hemorrhage in two representative animals.

Fig. 2. Individual VO2, DO2 relationships in three representative dogs. X axis = DO2 mL/min/kg; y axis = VO2 mL/min/kg.

Table 2. DO2crit determined by VO2, lactate, AVPCO2 and AVPH

<table>
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<tr>
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<th>TAMPA</th>
<th>HEM</th>
<th>BALL</th>
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</thead>
<tbody>
<tr>
<td>VO2</td>
<td>10.2 ± 1.7</td>
<td>9.1 ± 1.4</td>
<td>14.3 ± 2.3</td>
</tr>
<tr>
<td>Lactate</td>
<td>9.5 ± 1.8*</td>
<td>8.4 ± 1.0*</td>
<td>13.9 ± 1.3*</td>
</tr>
<tr>
<td>AVPCO2</td>
<td>10.3 ± 2.2</td>
<td>9.3 ± 1.8</td>
<td>14.5 ± 1.7</td>
</tr>
<tr>
<td>AVPH</td>
<td>18.8 ± 2.2</td>
<td>9.4 ± 1.7</td>
<td>13.9 ± 2.1</td>
</tr>
</tbody>
</table>

*p < .01 vs. BALL; p = NS TAMPA vs. HEM; DO2 is expressed in mL/min/kg

experiment, the temperature, the respiratory conditions, and the degree of anesthesia were constant, so we can assume that the oxygen demand remained stable. Hence every effort was made to prevent any influence of one intervention on the following one.

We determined DO2crit as the intercept of two best fitted regression lines between VO2 and DO2 (21), between DO2 and lactate (4, 7, 8) and between DO2 and AVPH and AVPCO2 differences (12, 15). It might seem hazardous to calculate DO2crit from AVPH and AVPCO2 differences, because those parameters should increase progressively during a reduction in cardiac output due to the respiratory impairment of CO2 elimination. However, recent studies (12, 15) demonstrated a brisk increase in AVPH and AVPCO2 below DO2crit, in relation to the development of cellular acidosis. We observed that calculation of DO2crit from VO2, lactate, AVPH, and AVPCO2 yielded similar results.

Balloon filling

DO2crit was significantly higher and EO2crit significantly lower during BALL than during TAMPA or HEM. These differences in DO2crit were also found when DO2 was plotted against lactate even though the lactate levels were lower during BALL than during the other procedures. The highest DO2crit was commensurate with less severe hypotension during this procedure.

A high DO2crit during progressive obstruction of the inferior vena cava has been reported in two previous studies (5, 11). During the constriction of the inferior vena cava by the application of a ring in conscious dogs, Rock et al. found a DO2crit of 19.8 mL/min/kg (5). During balloon filling in the inferior vena cava in pentobarbital-anesthetized dogs, we obtained a DO2crit of 18.4 mL/min/kg (11). This higher DO2crit in BALL than in other models is probably due to blood flow redistribution within and among the different organs. Occlusion of the inferior vena cava selectively increases outflow pressure in the lower body muscles and kidneys, so that capillary shunts may open in these regions. In addition, redistribution of blood flow to the splanchic area and the upper part of the body may result in a relative “overperfusion” of these regions. These effects may explain our failure to show an influence of endotoxin on DO2crit in this model (11) in contrast to other models (4, 10, 16). They may also account for differences in studies on the effects of some drugs on DO2crit. Anesthesia with halothane was found to decrease DO2crit from 19.8 to 10.5 mL/min/kg in a model of constriction of inferior vena cava (5) but to increase DO2crit from 7.3 to 9.6 and 13.0 mL/min/kg in a model of hemorrhage (8). Conceivably, the potent vasodilating effects of halothane may improve the blood flow distribution during inferior vena cava constriction but may alter oxygen extraction.
during hemorrhage. Therefore, interruption of blood flow in the inferior vena cava, although attractive for its easy reversibility, seems to have serious limitations for the study of the VO\textsubscript{2}/DO\textsubscript{2} relationship.

**Tamponade versus hemorrhage**

An important difference between the two models lies in the venous outflow pressures, which must increase during TAM to but decrease during HEM. The increase in venous outflow pressure in TAM may open shunts within the organs or influence the distribution of blood flow among the organs. Cain et al. observed similar limb VO\textsubscript{2}/DO\textsubscript{2} relationships with TAM and HEM but a steeper slope of the total body VO\textsubscript{2}/DO\textsubscript{2} relationship during TAM (52%) than during HEM (39%) (20). TAM was characterized by higher tissue perfusion pressures and systemic vascular resistance. In other studies, DO\textsubscript{2} crit was somewhat lower in HEM (between 6.8 and 8.1 mL/min·kg (4, 7, 8)) than in TAM (between 9.0 and 10.5 mL/min·kg (6, 14–16, 18, 19)). We also found a slightly lower DO\textsubscript{2} crit during HEM than during TAM, Although these differences were not significant. However, EO\textsubscript{2} crit was significantly higher in HEM than in TAM. These observations are consistent with recent data by Samsel and Schumacker showing that systemic hemorrhage in the dog augments EO\textsubscript{2} crit in intestine during stagnant hypoxia (22).

Furthermore, reversal was easy with TAM, as we previously reported (14), but virtually impossible in HEM, suggesting that a state of irreversible decomposition was obtained in HEM but not in TAM. We can find three explanations for these differences. One is a longer ischemic time in HEM than in TAM, but this was unlikely since the duration of the three interventions was quite similar. A second one is that the hemodynamic and cellular alterations were more profound at the end of the procedure in HEM than in TAM. This also was not supported by the data, because, before the reversal of the intervention, TAM was, if anything, associated with a lower DO\textsubscript{2} and greater alterations in P\textsubscript{PaO\textsubscript{2}}, V\textsubscript{a}PCO\textsubscript{2}, and lactate (Table 1). A third explanation is a difference in vascular reactivity between TAM and HEM. This was indeed supported by the observation that, for any cardiac index, arterial pressure was greater in TAM than in HEM. The steeper slope of the arterial pressure minus right arterial pressure/cardiac index relationship thus indicated a greater vascular reactivity in TAM than in HEM. This increased vascular tone should improve the extraction capabilities when oxygen supply becomes limited (7, 23). Recently, Wang et al. (24) observed a reduced release of endothelium-derived relaxing but also contracting factors during acute hemorrhage in rats. In their study, hypoxic vasodilatation was altered early after hemorrhage and persisted despite fluid resuscitation. Also Zingarelli et al. (25) observed a decreased responsiveness to phenylephrine of aortic rings from rats submitted to hemorrhagic shock, and attributed this phenomenon to the release of tumor necrosis factor \(\alpha\). Thus the maintenance of blood volume may play an important role in the control of vascular tone. These differences in vascular tone also explain the higher arterial pressure at DO\textsubscript{2} crit during TAM than during HEM.

**CONCLUSIONS**

Balloon filling in the inferior vena cava is a relatively simple, easily reversible model to study VO\textsubscript{2}/DO\textsubscript{2} relationship. However, the markedly higher DO\textsubscript{2} crit and lower EO\textsubscript{2} crit in this model cast some doubt upon the generalized applications of the observations made using this model. Although there was no major difference in DO\textsubscript{2} crit between TAM and HEM, TAM was easily reversible, while HEM was not. Hence, the HEM model cannot be used for repeated studies of the VO\textsubscript{2}/DO\textsubscript{2} relation. Differences in vascular reactivity may also influence the response to interventions which may act oppositely on the different models.

**REFERENCES**


