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ORIGINAL

End-tidal CO_2 pressure determinants during hemorrhagic shock

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Abstract *Objectives:* To examine the relationship between end-tidal CO_2 ($PETCO_2$) and its physiological determinants, pulmonary blood flow (cardiac output, CO) and CO_2 production (VCO_2), in a model of hemorrhagic shock during fixed minute ventilation.
Design and setting: Prospective, observational study in a research laboratory at a university center.
Subjects and interventions: Six anesthetized, intubated, and mechanically ventilated mongrel dogs. Progressive stepwise bleeding.
Measurements and results: We continuously measured $PETCO_2$ with a capnograph, pulmonary artery blood flow with an electromagnetic flow probe, arterial oxygen saturation (SaO_2) with a fiberoptic catheter, and oxygen consumption (VO_2) and VCO_2 by expired gases analysis. Oxygen delivery (DO_2) was continuously calculated from pulmonary blood flow and SaO_2. We studied the correlation of $PETCO_2$ with CO and VCO_2 in each individual experiment. We also calculated the critical point in the relationships $PETCO_2$/DO_2 and VO_2/DO_2 by the polynomial method. As expected, $PETCO_2$ was correlated with CO. The best fit was logarithmic in all experiments (median $r^2 = 0.90$), showing that $PETCO_2$ decrease is greater in lowest flow states. $PETCO_2$ was correlated with VCO_2, but the best fit was linear (median $r^2 = 0.77$). Critical DO_2 for $PETCO_2$ and VO_2 was 8.0 ± 3.3 and 6.3 ± 2.5 ml · min^{-1} · kg^{-1}, respectively (NS).
Conclusions: Our data reconfirm the relationship between $PETCO_2$ and CO during hemorrhagic shock. The relatively greater decrease in $PETCO_2$ at lowest CO levels could represent diminished CO_2 production during the period of VO_2 supply dependency.

Key words Capnography · End-tidal CO_2 pressure · CO_2 production · Cardiac output · Hemorrhagic shock

Introduction

Alveolar CO_2 and end-tidal CO_2 are normally determined by CO_2 production (VCO_2), alveolar ventilation, pulmonary perfusion, and V/Q matching [1]. Despite this some investigators [2, 3, 4] suggest that in low-flow states end-tidal CO_2 pressure ($PETCO_2$) depends primarily on blood flow. In recent years there has been a growing experimental and clinical body of evidence demonstrating that $PETCO_2$ monitoring is a useful and simple method of tracking cardiac output (CO) during cardiopulmonary resuscitation [5, 6, 7, 8]. Additionally, investigators have confirmed that $PETCO_2$ can be used as a prognostic tool in cardiac arrest [2, 9, 10, 11, 12]. We have also shown its value in other low-flow states such as hemorrhagic shock [13]. To better characterize this relationship we studied $PETCO_2$ and its physiological determinants during fixed minute ventilation in a

model of hemorrhagic shock. We hypothesized that during critical reductions in CO the fall in $PETCO_2$ could also be ascribed to decreased metabolic production of CO_2. In addition to, previous studies have measured CO by thermodilution, a method that lacks accuracy in low-flow conditions. We sought to improve this drawback by the use of an electromagnetic flow probe.

Materials and methods

This study was approved by the local Animal Care Committee. Care of the studied animals was in accordance with National Institutes of Health guidelines.

Animal preparation

Six mongrel dogs weighing 27.3 ± 5.9 kg were anesthetized with 30 mg/kg sodium pentobarbital, with supplemental doses as needed. They were intubated and ventilated in supine position, with a volume-cycled ventilator (Harvard Apparatus Dual Phase Control Respirator Pump Ventilator, model 613 A, Harvard Apparatus, Southnatick, Mass., USA), with a tidal volume of 15 ml/kg, FIO_2 of 0.21, a respiratory rate adjusted to an initial $PETCO_2$ of 30 torr, and I/E ratio of 0.3. This pattern was kept constant throughout the experiment. Neuromuscular blockade was provided with pancuronium bromide (0.06 mg/kg). Catheters (Oximetrix Flow-directed thermodilution fiberoptic pulmonary artery catheter model P 7110, Abbott Critical Care Systems, Mountain View, Calif., USA) were placed in the pulmonary artery through the right jugular vein and in the abdominal aorta through the right femoral artery to continuously measure oxygen saturations and to extract blood samples. We also cannulated the left femoral artery and vein to bleed the dogs and to measure mean arterial pressure and to administer fluids and drugs, respectively. After performing a medial sternotomy the main pulmonary artery was carefully dissected and a 14- or 16-mm electromagnetic flow probe (Flo-probe Blood Flowmeter Transducer, Gould-Statham Instruments, Oxnard, Calif., USA) was placed around it.

Measurements and calculations

Pulmonary blood flow was continuously measured with an electromagnetic flow transducer (Spectramed Blood Flowmeter model SP 2202 B, Spectramed, Oxnard, Calif., USA). $PETCO_2$ was continuously measured at the tip of the endotracheal tube with a previously calibrated capnograph (Tonocap, Datex Instrumentarium, Helsinski, Finland). Minute-to-minute oxygen consumption (VO_2) and CO_2 elimination (VCO_2) were measured with a metabolic cart (Deltatrac, Datex Instrumentarium) [14]. Oxygen delivery (DO_2) was continuously calculated as the product of pulmonary blood flow and arterial oxygen content (CaO_2). CaO_2 was estimated as hemoglobin × arterial O_2 saturation × 1.34 + 0.0031 × arterial PO_2. The aortic fiberoptic catheter constantly displayed arterial oxygen saturation, and PaO_2 was calculated from it with the aid of the oxyhemoglobin dissociation curve. Fiberoptic catheter oxygen saturation was calibrated with a simultaneous blood sample measured in a co-oximeter (OSM 3, Radiometer, Copenhagen, Denmark). After each bleeding step arterial and mixed venous samples were extracted to measure gases (ABL 30, Radiometer), oxygen saturations, and hemoglobin. CaO_2 was corrected with each new hemoglobin value. Pulmonary blood flow, $PETCO_2$, and oxygen saturation were continuously acquired with a personal computer through a digital-analogical converter.

Experimental procedure

After basal hemodynamic and oxygen transport measurements we performed consecutive bleeding of 6 ml/kg with 10 min between them. The experiment continued until a circulatory crisis of rapidly falling arterial blood pressure occurred. Core temperature was monitored by the pulmonary catheter and was kept constant with a heating lamp throughout the experiment. At the end of the protocol dogs were killed with an intravenous KCl bolus.

Data analysis

Digitally acquired $PETCO_2$ and pulmonary blood flow values were averaged for 1-min periods, and correlations with simultaneously gathered VCO_2 values were examined. In each experiment, the relationships of $PETCO_2$ to CO and to VCO_2 were tested for linear as well as for logarithmic fit, using the method of least square regression. We chose the function that showed the best determination coefficient (the best r^2). Additionally, we compared linear against logarithmic fits using a nonparametric test (Wilcoxon signed rank test). Critical DO_2 points for $PETCO_2/DO_2$ and VO_2/DO_2 relationships were calculated by the polynomial method [15] and compared by a *t* test.

Results

Table 1 displays hemodynamic and metabolic data at baseline and at each bleeding step. $PETCO_2$ was correlated with CO. In all experiments the logarithmic fit was better than the linear [median $r^2 = 0.90$ (range = 0.63–0.95) vs. 0.82 (range = 0.49–0.89), $p < 0.02$], which suggests that $PETCO_2$ decrease is accentuated with low flow values. $PETCO_2$ was also correlated with VCO_2, but the best fit was linear [median $r^2 = 0.77$ (range = 0.59–0.85) vs. 0.74 (range = 0.60–0.83), $p < 0.05$]. Figure 1 shows the relationships of $PETCO_2$ with CO and VCO_2 in a typical experiment. Figure 2 shows changes in $PETCO_2$, VO_2, and VCO_2 related to changes in DO_2 during bleeding (mean ± SEM). Mean critical DO_2 for $PETCO_2$ and VO_2 were 8.0 ± 3.3 and 6.3 ± 2.5 ml · $min^{-1} \cdot kg^{-1}$, respectively (NS).

Discussion

In steady-state conditions alveolar CO_2 elimination, and therefore $PETCO_2$, depend on CO_2 production and on alveolar ventilation and pulmonary perfusion, that is to say, CO. If any two of these variables are held constant, any change in $PETCO_2$ reflects an alteration in the third variable. Using this relationship, investigators have demonstrated that $PETCO_2$ effectively tracks hemodynamic changes in experimental and clinical settings of

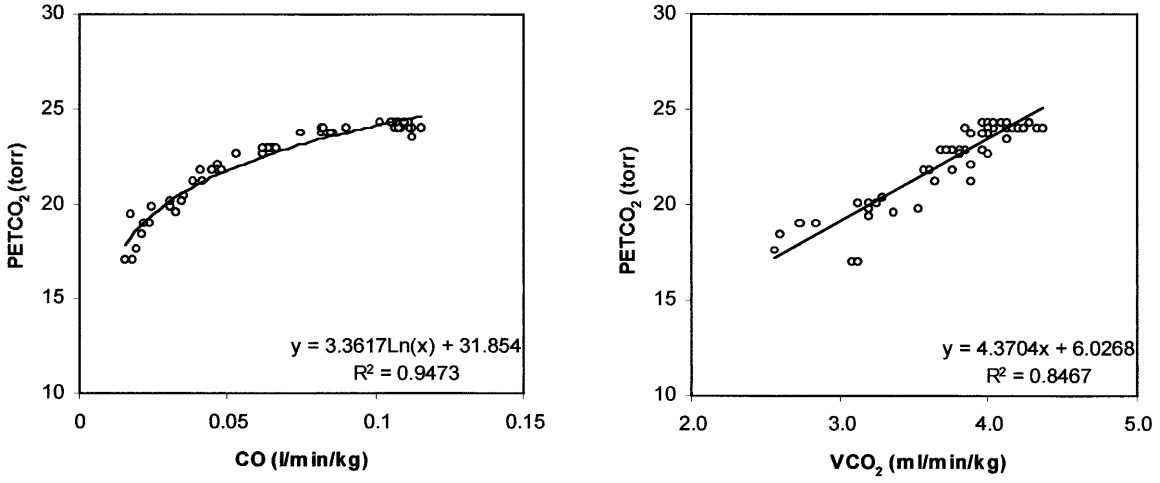

Fig. 1 Relationships of end-tidal CO_2 pressure ($PETCO_2$) with CO and CO_2 production (VCO_2) in a typical experiment

no-flow or low-flow conditions [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. For example, during cardiac arrest $PETCO_2$ falls close to zero [5, 6, 7, 8, 9, 10, 11, 12]. When cardiopulmonary resuscitation starts, $PETCO_2$ increases and is correlated to pulmonary blood flow [5, 6, 7]. Other investigators extended these findings to low-flow conditions such as hemorrhagic [13, 16], anesthetic [17], and obstructive shock [18].

The $PETCO_2$/CO relationship has been described as linear. Weil et al. [5] and Gazmuri et al. [7] have described a strong linear correlation between CO and $PETCO_2$ after the induction of ventricular fibrillation in minipigs. Isserles and Breen [18] induced an acute decrease in CO in dogs and found that the proportional decrease in $PETCO_2$ was directly correlated with the decrease in CO. Lastly, in anesthetized patients undergoing aortic aneurismal surgery with constant ventilation Shibutani et al. [17] described a linear correlation of both $PETCO_2$ and VCO_2 with CO; ratios between the proportional decrease in $PETCO_2$ and VCO_2 to the proportional decrease in CO were 1:3.

However, other investigators have reported other findings on the $PETCO_2$/CO relationship. Morimoto et al. [19] during cardiopulmonary resuscitation in dogs found a 37% decrease in $PETCO_2$, corresponding to a 77% reduction in CO, which would result in a greater ratio (approximately 1:2). In a model of hemorrhagic shock in dogs we have previously shown that a logarithmic function better fits the $PETCO_2$/CO relationship; this implies that the greatest $PETCO_2$ decrements occur with the lowest blood flows [13]. Ornato et al. [16] obtained similar results to ours in a design of stepwise reductions in CO in sheep.

Our results could be explained at least by three factors. First, we studied not only the steep and plateau portions of the curve but its whole range, from mild decreases in CO, as Shibutani et al. [17] did, to deep shock. Next, we took a different approach to data analysis, comparing linear to logarithmic fit and choosing the best determination coefficient (r^2). Finally, continuous

Table 1 Hemodynamic and metabolic parameters at baseline and progressive stepwise bleeding (*CO* cardiac output, DO_2 oxygen delivery, VO_2 oxygen consumption, $Pa\text{-}ETCO_2$ arterial minus end-tidal PCO_2, $Pv\text{-}aCO_2$ mixed venous minus arterial PCO_2)

	Basal	Bleeding # 1	Bleeding # 2	Bleeding # 3	Bleeding # 4	Bleeding # 5
Arterial pH	7.36 ± 0.04	7.35 ± 0.05	7.33 ± 0.06	7.31 ± 0.06	7.27 ± 0.09*	7.18 ± 0.12*
Arterial PCO_2 (torr)	27 ± 1	30 ± 4	28 ± 4	27 ± 5	24 ± 5	24 ± 3
Arterial PO_2 (torr)	72 ± 15	70 ± 9	68 ± 11	72 ± 21	77 ± 26	74 ± 25
End-tidal PCO_2 (torr)	23 ± 4	22 ± 4	21 ± 4	20 ± 5	16 ± 5	14 ± 5*
CO (1 min^{-1} kg^{-1})	0.099 ± 0.015	0.077 ± 0.007*	0.060 ± 0.007**	0.045 ± 0.005[4]*	0.032 ± 0.005[4]*	0.028 ± 0.012[4]*
DO_2 (1 min^{-1} kg^{-1})	14.6 ± 4.2	11.6 ± 3.5	9.0 ± 2.8	6.6 ± 2.3**	4.3 ± 1.9**	3.5 ± 1.8**
VO_2 (1 min^{-1} kg^{-1})	5.3 ± 0.6	4.8 ± 0.7	4.8 ± 0.7	4.3 ± 0.9	3.9 ± 0.9	2.6 ± 0.8**
VCO_2 (1 min^{-1} kg^{-1})	4.4 ± 0.5	4.2 ± 0.6	4.0 ± 0.6	3.6 ± 0.7	3.3 ± 0.7	2.6 ± 0.7**
Respiratory quotient	0.84 ± 0.07	0.88 ± 0.10	0.84 ± 0.06	0.86 ± 0.07	0.86 ± 0.06	1.02 ± 0.07*
$Pa\text{-}ETCO_2$ (torr)	3.0 ± 1.3	6.7 ± 3.7	6.5 ± 2.2*	8.3 ± 3.2*	9.2 ± 3.4**	10.5 ± 3.5**
$Pv\text{-}aCO_2$ (torr)	5.7 ± 3.7	5.0 ± 2.2	7.8 ± 0.8	11.2 ± 9.0	22.3 ± 10.7*	27.7 ± 13.7*

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; [4]*$P < 0.0001$ vs. basal (by repeated measures of analysis of variance followed by *t* test with Bonferroni correction)

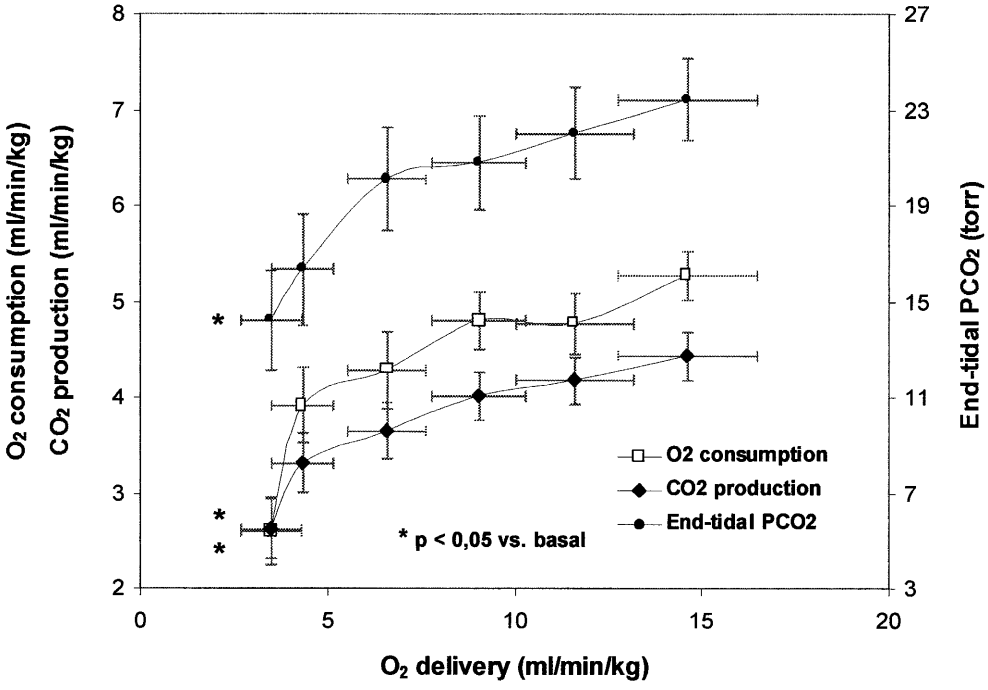

Fig. 2 Relationship between end-tidal CO_2 pressure (*PET-CO_2*), CO_2 production (*VCO_2*), and O_2 consumption (VO_2) with O_2 delivery. Data are shown as mean ± SEM

digitalized data might improve the description of a mathematical function. To our knowledge, this is the first shock study evaluating $PETCO_2$/CO relationship in which CO is measured with an electromagnetic flow probe. Accuracy in low CO ranges may certainly be greater than with the thermodilution method [20].

As expected, $PETCO_2$ and VCO_2 were linearly correlated. VCO_2 depends on two different factors: pulmonary excretion and metabolic production of CO_2. In low flow and constant ventilation conditions, VCO_2 falls secondary to decreased delivery of CO_2 to the lungs and to pulmonary blood flow heterogeneity, with subsequent increase in alveolar deadspace. Although precise patterns of perfusion can be defined only by the multiple inert gases technique, an increased arterial-end-tidal PCO_2 gradient (Pa-$ETCO_2$) might reflect high V/Q relationships frequently noted in this setting [21]. Accordingly, in this study Pa-$ETCO_2$ rose significantly after the last bleeding period (from 3 ± 1 to 11 ± 4 torr). Determination of CO_2 production, the other variable that affects VCO_2 and $PETCO_2$, is more elusive. Metabolic carts do not report the extent to which the measured reduction in VCO_2 is due to a fall in excretion or in production. Some investigators have questioned whether reductions in CO_2 production in cardiac arrest and shock might affect VCO_2 [17, 18]. Weil et al. [22, 23] showed that VCO_2 nearly fell to zero after induction of ventricular fibrillation in pigs, and that it increased parallel to CO with the start of chest wall compression. When normal heart rhythm was restored, there was a great elevation in CO and an overshoot in VCO_2, in accordance with a fall in the venoarterial PCO_2 gradient. Relman [24] concludes that the findings of Weil et al. not only show a reduction in pulmonary CO_2 excretion but suggest a net reduction in CO_2 production as well, because VCO_2 overshoot after rhythm restoration was lower than cumulative reduction in CO_2 excretion during ventricular fibrillation. In cardiac arrest studies CO certainly decreases below the level that supports critical oxygen delivery to tissues (DO_{2crit}) [25], hence oxygen consumption falls and, accordingly, CO_2 production decreases, which leads to diminished $PETCO_2$ and VCO_2. In our study DO_{2crit} was also reached (6.3 ± 2.5). Interestingly, this value did not differ statistically from the DO_2 level below which $PETCO_2$ fell (8.0 ± 3.3). As in the study by Guzman et al. [3], $PETCO_2$ effectively indicated the onset of supply dependency.

The likelihood of changes in CO_2 stores after CO modifications further complicates the analysis [26]. An increase in CO increases CO_2 transport from the tissues to the lung, and tissue CO_2 stores therefore decrease. Conversely, a decrease in CO builds up CO_2 storage [26]. For example, in head-out immersion CO increases by 47 %, and CO_2 stores decrease by 148 ml. CO_2 elimination starts rapidly and recovers after a mean of 79.3 s [27]. Longer stabilization periods have been suggested, particularly during decreases in CO [28]. These calculations demand a breath-to-breath technique to measure VCO_2, and a limitation of this study is that the metabolic cart reports it on minute-to-minute basis. In our experimental design the relatively long periods of 10 min

between each bleeding step should have allowed a steady state, at least in blood CO_2 stores.

In conclusion, with an improved methodology, our results reaffirm the logarithmic relationship between CO and $PETCO_2$. Although not confirmed in this study, the greatest reduction in $PETCO_2$ observed with a critical CO decrease might be attributed not only to a lessening of its excretion but also to a decrease in its production, during the phase of oxygen supply-dependent metabolism. Our data provide a better description of a physiological phenomenon and reinforce previous work on the clinical usefulness of $PETCO_2$ for tracking changes in pulmonary blood flow and for warning of ongoing anaerobic metabolism.

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