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End-tidal CO₂ pressure determinants during hemorrhagic shock

Received: 20 October 1999
Final revision received: 21 June 2000
Accepted: 6 July 2000
Published online: 18 October 2000
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Supported in part by a grant from JAEJ Electrónica

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Abstract *Objectives:* To examine the relationship between end-tidal CO₂ (PETCO₂) and its physiological determinants, pulmonary blood flow (cardiac output, CO) and CO₂ production (VCO₂), 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 PETCO₂ with a capnograph, pulmonary artery blood flow with an electromagnetic flow probe, arterial oxygen saturation (SaO₂) with a fiberoptic catheter, and oxygen consumption (VO₂) and VCO₂ by expired gases analysis. Oxygen delivery (DO₂) was continuously calculated from pulmonary blood flow and SaO₂. We studied the correlation of PETCO₂ with CO and VCO₂ in each individual experi-

ment. We also calculated the critical point in the relationships PETCO₂/DO₂ and VO₂/DO₂ by the polynomial method. As expected, PETCO₂ was correlated with CO. The best fit was logarithmic in all experiments (median $r^2 = 0.90$), showing that PETCO₂ decrease is greater in lowest flow states. PETCO₂ was correlated with VCO₂, but the best fit was linear (median $r^2 = 0.77$). Critical DO₂ for PETCO₂ and VO₂ was 8.0 ± 3.3 and 6.3 ± 2.5 ml · min⁻¹ · kg⁻¹, respectively (NS).

Conclusions: Our data reconfirm the relationship between PETCO₂ and CO during hemorrhagic shock. The relatively greater decrease in PETCO₂ at lowest CO levels could represent diminished CO₂ production during the period of VO₂ supply dependency.

Key words Capnography · End-tidal CO₂ pressure · CO₂ production · Cardiac output · Hemorrhagic shock

Introduction

Alveolar CO₂ and end-tidal CO₂ are normally determined by CO₂ production (VCO₂), alveolar ventilation, pulmonary perfusion, and V/Q matching [1]. Despite this some investigators [2, 3, 4] suggest that in low-flow states end-tidal CO₂ pressure (PETCO₂) depends primarily on blood flow. In recent years there has been a growing experimental and clinical body of evidence

demonstrating that PETCO₂ monitoring is a useful and simple method of tracking cardiac output (CO) during cardiopulmonary resuscitation [5, 6, 7, 8]. Additionally, investigators have confirmed that PETCO₂ 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 PETCO₂ 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 PETCO₂ could also be ascribed to decreased metabolic production of CO₂. 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, FIO₂ of 0.21, a respiratory rate adjusted to an initial PETCO₂ 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). PETCO₂ was continuously measured at the tip of the endotracheal tube with a previously calibrated capnograph (Tonocap, Datex Instrumentarium, Helsinki, Finland). Minute-to-minute oxygen consumption (VO₂) and CO₂ elimination (VCO₂) were measured with a metabolic cart (Deltatrac, Datex Instrumentarium) [14]. Oxygen delivery (DO₂) was continuously calculated as the product of pulmonary blood flow and arterial oxygen content (CaO₂). CaO₂ was estimated as hemoglobin \times arterial O₂ saturation \times 1.34 + 0.0031 \times arterial PO₂. The aortic fiberoptic catheter constantly displayed arterial oxygen saturation, and PaO₂ 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. CaO₂ was corrected with

each new hemoglobin value. Pulmonary blood flow, PETCO₂, and oxygen saturation were continuously acquired with a personal computer through a digital-analogical converter.

Experimental procedure

After basal hemodynamic and oxygen transport measurements were 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 PETCO₂ and pulmonary blood flow values were averaged for 1-min periods, and correlations with simultaneously gathered VCO₂ values were examined. In each experiment, the relationships of PETCO₂ to CO and to VCO₂ 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 DO₂ points for PETCO₂/DO₂ and VO₂/DO₂ 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. PETCO₂ 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 PETCO₂ decrease is accentuated with low flow values. PETCO₂ was also correlated with VCO₂, 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 PETCO₂ with CO and VCO₂ in a typical experiment. Figure 2 shows changes in PETCO₂, VO₂, and VCO₂ related to changes in DO₂ during bleeding (mean \pm SEM). Mean critical DO₂ for PETCO₂ and VO₂ were 8.0 ± 3.3 and 6.3 ± 2.5 ml \cdot min⁻¹ \cdot kg⁻¹, respectively (NS).

Discussion

In steady-state conditions alveolar CO₂ elimination, and therefore PETCO₂, depend on CO₂ 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 PETCO₂ reflects an alteration in the third variable. Using this relationship, investigators have demonstrated that PETCO₂ effectively tracks hemodynamic changes in experimental and clinical settings of

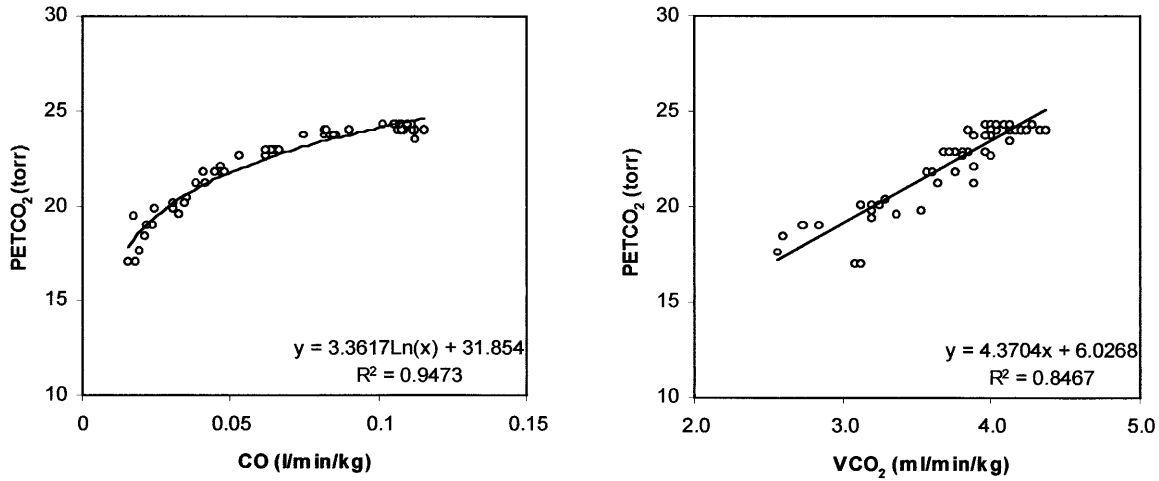


Fig.1 Relationships of end-tidal CO₂ pressure (*PETCO₂*) with CO and CO₂ production (*VCO₂*) in a typical experiment

no-flow or low-flow conditions [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. For example, during cardiac arrest *PETCO₂* falls close to zero [5, 6, 7, 8, 9, 10, 11, 12]. When cardiopulmonary resuscitation starts, *PETCO₂* 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 *PETCO₂*/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 *PETCO₂* 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 *PETCO₂* 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 *PETCO₂* and *VCO₂* with CO; ratios between the proportional decrease in *PETCO₂* and *VCO₂* to the proportional decrease in CO were 1:3.

However, other investigators have reported other findings on the *PETCO₂*/CO relationship. Morimoto et al. [19] during cardiopulmonary resuscitation in dogs found a 37% decrease in *PETCO₂*, 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 *PETCO₂*/CO relationship; this implies that the greatest *PETCO₂* 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.

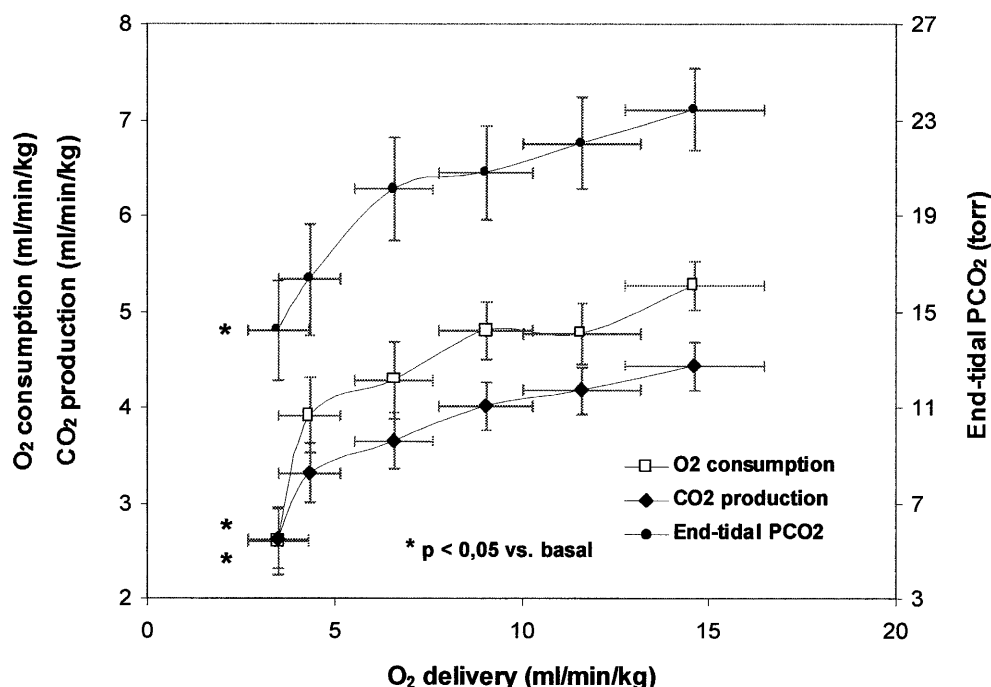
Our results could be explained at least by three factors. First, we studied not only the steep and plateau portions of the curve but its whole range, from mild decreases in CO, as Shibutani et al. [17] did, to deep shock. Next, we took a different approach to data analysis, comparing linear to logarithmic 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, *DO₂* oxygen delivery, *VO₂* oxygen consumption, *Pa-ETCO₂* arterial minus end-tidal PCO₂, *Pv-aCO₂* mixed venous minus arterial PCO₂)

	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-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-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 CO₂ pressure (*PET-CO₂*), CO₂ production (*VCO₂*), and O₂ consumption (*VO₂*) with O₂ 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 CO₂ stores.

In conclusion, with an improved methodology, our results reaffirm the logarithmic relationship between CO and PETCO₂. Although not confirmed in this study, the greatest reduction in PETCO₂ 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 PETCO₂ for tracking changes in pulmonary blood flow and for warning of ongoing anaerobic metabolism.

Acknowledgements We are indebted to Dr. Eduardo De Vito for his critical commentary on the manuscript.

References

- West JB (1977) Ventilation-perfusion relationships. *Am Rev Respir Dis* 116: 919–943
- Levine RL, Wayne MA, Miller CC (1997) End-tidal carbon dioxide an outcome of out-of-hospital cardiac arrest. *N Engl J Med* 337: 301–306
- Guzman JA, Lacombe FJ, Najjar A, Kruse JA (1997) End-tidal PCO₂ as a noninvasive indicator of systemic oxygen supply-dependency during hemorrhagic shock and resuscitation. *Shock* 8: 427–431
- Garnett AR, Ornato JP, Gonzalez ER, Johnson EB (1987) End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation. *JAMA* 257: 512–515
- Weil MH, Bisera J, Trevino RP, Rackow EC (1985) Cardiac output and end-tidal carbon dioxide. *Crit Care Med* 13: 907–909
- Gudipati CV, Weil MH, Bisera J, Deshmukh HG, Rackow EC (1988) Expired carbon dioxide: a noninvasive monitor of cardiopulmonary resuscitation. *Circulation* 77: 234–239
- Gazmuri RJ, von Planta M, Weil MH, Rackow EC (1989) Arterial PCO₂ as an indicator of systemic perfusion during cardiopulmonary resuscitation. *Crit Care Med* 17: 237–240
- Falk J, Rackow EC, Weil MH (1988) End-tidal carbon dioxide during cardiopulmonary resuscitation. *N Engl J Med* 318: 607–611
- Sanders AB, Kern KB, Otto CW, Milander MM, Ewy GA (1989) End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation. A prognostic indicator for survival. *JAMA* 262: 1347–1351
- Callahan M, Baron C (1990) Prediction of outcome of cardiopulmonary resuscitation from end-tidal carbon dioxide concentration. *Crit Care Med* 18: 358–362
- Wayne MA, Levine RL, Miller CC (1995) Use of end-tidal carbon dioxide to predict outcome in prehospital cardiac arrest. *Ann Emerg Med* 25: 762–767
- Cantineau JP, Lambert Y, Merckx P, Reynaud P, Porte F, Bertrand C, Duvaldestin P (1996) End-tidal carbon dioxide during cardiopulmonary resuscitation in humans presenting mostly with asystole: a predictor of outcome. *Crit Care Med* 24: 791–796
- Dubin A, Silva C, Calvo G, Valli J, Fariña O, Estenssoro E, Mordujovich P (1990) End-tidal CO₂ pressure in the monitoring of cardiac output during canine hemorrhagic shock. *J Crit Care* 5: 42–46
- Takala J, Keinanen O, Vaisanen P, Kari A (1989) Measurement of gas exchange in intensive care medicine: laboratory and clinical validation of a new device. *Crit Care Med* 17: 1041–1047
- Gutierrez G, Warley AR, Dantzker DR (1986) Oxygen delivery and utilization in hypothermic dogs. *J Appl Physiol* 60: 751–757
- Ornato JP, Garnett AR, Glauser FL (1990) Relationship between cardiac output and end tidal carbon dioxide tension. *Ann Emerg Med* 19: 1104–1106
- Shibutani K, Muraoka M, Shirasaki S, Kubal K, Sanchala V, Gupte P (1994) Do changes in end-tidal PCO₂ quantitatively reflect changes in cardiac output? *Anesth Analg* 79: 829–833
- Isserles SA, Breen PH (1991) Can changes in end-tidal PCO₂ measure changes in cardiac output. *Anesth Analg* 73: 808–814
- Morimoto Y, Kemmotsu O, Murakami F, Yamamura T, Mayumi T (1993) End-tidal CO₂ changes under constant cardiac output during cardiopulmonary resuscitation. *Crit Care Med* 21: 1572–1576
- Van Grondelle A, Ditchey RV, Groves BM, Wagner WW Jr, Reeves JT (1983) Thermodilution method overestimates low cardiac output in humans. *Am J Physiol* 245: 690–692
- Yamanaka MK, Sue DY (1987) Comparison of arterial-end-tidal PCO₂ difference and dead space/tidal volume ratio in respiratory failure. *Chest* 92: 832–835
- Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI (1986) Differences in acid-base status between venous and arterial blood during cardiopulmonary resuscitation. *N Engl J Med* 315: 153–156
- Weil MH, Rackow EC, Falk JL, Griffel MI (1986) Letter. *N Engl J Med* 315: 1617–1618
- Relman AS (1986) Letter. *N Engl J Med* 315: 1618
- Cain SM (1977) Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *J Appl Physiol* 42: 228–234
- Farhi LE, Rahn H (1955) Gas stores of the body and the unsteady state. *J Appl Physiol* 7: 472–4816
- Linér MH (1993) Tissue gas stores of the body and head-out immersion in humans. *J Appl Physiol* 75: 1285–1293
- Farhi LE, Rahn H (1960) Dynamics of changes in carbon dioxide store. *Anesthesiology* 21: 604–614