Stability of arterial to end-tidal carbon dioxide gradients during postoperative cardiorespiratory support

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The changes in the arterial to end-tidal carbon dioxide gradient, $P(a-ET)CO_2$, were studied in postoperative cardiac surgery patients from the time of admission to the intensive care unit, during changing cardiorespiratory support, up to the time of tracheal extubation. Individual factors evaluated for their effects on $P(a-ET)CO_2$ included rate of mechanical ventilation, infusion of vasoactive agents (nitroglycerin, nitroprusside, dopamine, dobutamine, and metaraminol), and associated changes in haemodynamic pathophysiology (cardiac index, pulmonary artery pressure, pulmonary vascular resistance index, systemic vascular resistance index, and pulmonary capillary wedge pressure). After approval by the Clinical Investigation Committee, 59 patients, age 63 ± 9 (41 to 75) yr, were studied and 382 individual gradient determinations made. Mean $P(a-ET)CO_2$ was 5.47 ± 5.21 mmHg, with the mean $PaCO_2$, 36.51 ± 5.89 mmHg and mean $ETCO_2$, 31.04 ± 6.44 mmHg. For the population as a whole, the correlation between $PaCO_2$ and $ETCO_2$ determined by regression analysis was maintained ($R = 0.644$, $P < 0.001$). Comparison of the individual and population correlation coefficients by Student's t tests showed no significant difference, but a normal population distribution of the gradients ($P < 0.05$). None of the variables assessed could be determined to influence $P(a-ET)CO_2$ significantly. For many of the individual patients, however, the

relationship between $PaCO_2$ and $ETCO_2$ did not maintain a significant correlation throughout the study period. In the postoperative cardiac surgery patient population $P(a-ET)CO_2$ follows a normal distribution and $PaCO_2$ and $ETCO_2$ maintain a statistically significant correlation. However, when evaluating individual patients, this relationship has wide variability.

Les changements de gradient du CO_2 artériel et en fin d'expiration $P(a-ET)CO_2$ ont été étudiés en postop de chirurgie cardiaque chez les patients à partir du temps de l'admission aux soins intensifs, durant les changements du support cardiorespiratoire, jusqu'au temps de l'extubation endotrachéale. Les facteurs individuels évalués pour leurs effets sur la $P(a-ET)CO_2$ ont inclut la fréquence de la ventilation mécanique, la perfusion d'agents vasoactifs (nitroglycérine, nitroprussiate, dopamine, dobutamine, et métariminol), et les changements pathophysiologiques hémodynamiques (index cardiaque, pression de l'artère pulmonaire, résistance indexée des vaisseaux pulmonaires, résistance indexée des vaisseaux systémiques, et la pression artérielle capillaire pulmonaire bloquée). Après acceptation par le Comité d'Investigation Clinique, 59 patients âgés de 63 ± 9 (41 à 75) ans, ont été étudiés et 382 gradients individuels ont été déterminés. La $P(a-ET)CO_2$ moyenne était $5,47 \pm 5,21$ mmHg, avec une $PaCO_2$ moyenne de $36,51 \pm 5,89$ mmHg et une $ETCO_2$ moyenne de $31,04 \pm 6,44$ mmHg. Pour la population entière, la corrélation entre la $PaCO_2$ et la $ETCO_2$ déterminée par analyse de régression était maintenue ($R = 0,644$, $P < 0,001$). Les comparaisons individuelles et les coefficients de corrélation de la population étudiées par le Student's t test n'ont pas montré de différence significative, mais une distribution normale de la population des gradients ($P < 0,05$). Aucune des variables étudiée n'a démontré un rôle significatif dans l'influence sur la $P(a-ET)CO_2$. Cependant pour plusieurs patients la relation entre la $PaCO_2$ et la $ETCO_2$ n'a pas maintenue une corrélation significative tout au long de l'étude. En période postopératoire de chirurgie cardiaque, la $P(a-ET)CO_2$ suit une courbe normale de distribution et la $PaCO_2$ et la $ETCO_2$ ont maintenu une corrélation statistiquement significative. Cependant, quand on évalue les patients individuellement, cette relation présente une variabilité assez étendue.

Key words

ANAESTHESIA: cardiac;
CARBON DIOXIDE: monitoring, tension, arterial, gradients, end-tidal;
MONITORING: carbon dioxide;
VENTILATION: carbon dioxide tension.

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Continuous measurement of end-tidal carbon dioxide (ETCO₂) by mass spectrometry or infrared capnometry is routinely utilized to monitor intraoperative and postoperative mechanically ventilated patients.¹ Without arterial blood gas sampling, ETCO₂ is used to reflect arterial carbon dioxide (PaCO₂) levels.² If the relationship between these two measurements of ventilatory adequacy, as expressed by the arterial to end-tidal carbon dioxide gradient, or P(a-ET)CO₂, maintains a close correlation, then ETCO₂ can be reliably used to follow respiratory acid-base status and help decrease the frequency and expense of arterial blood gas sampling during the acute postoperative period and weaning from mechanical ventilation.

The P(a-ET)CO₂ is primarily a reflection of respiratory deadspace, increasing as deadspace increases. Acute increases in deadspace, such as those secondary to pulmonary embolism, widen this gradient.³ It also reflects, although to a lesser degree, venous admixture or shunting. Increased ventilation-perfusion inhomogeneity in the lungs also alters this relationship in a similar manner.⁴ In order to determine the consistency of the P(a-ET)CO₂ during the period following surgery from admission to the intensive care unit up to discontinuation of mechanical ventilation, arterial and end-tidal carbon dioxide partial pressures were sampled from postoperative cardiac surgery patients and compared over a wide range of cardiorespiratory support during this period of acute and often multiple pathophysiological changes.

Methods

After approval of the Clinical Investigations Committee, 59 (46 male and 13 female) postoperative cardiac surgery patients were evaluated. Their mean age was 63 ± 9 yr, range 41 to 75 yr. Patients had had coronary artery bypass grafting ($n = 45$), valve replacements ($n = 8$), both coronary artery bypass grafting and valve replacement ($n = 2$), cardiac transplantation ($n = 2$), or atrial septal defect repairs ($n = 2$). No patients had obstructive lung disease requiring preoperative bronchodilator therapy. Although some patients had left ventricular dysfunction, pulmonary capillary wedge pressures were normal preoperatively. One patient did have pulmonary hypertension.

Upon arrival in the intensive care unit, all patients were still paralyzed, anaesthetized and their lungs were mechanically ventilated. Throughout the study period, core temperatures ranged from 34.5 to 37.5° C. The initial comparison was made with the admission arterial blood gas measurement. Patients were monitored by electrocardiogram and radial and pulmonary artery catheters for pressure measurements. Pulmonary artery pressures ((PAP), $n = 340$), pulmonary capillary wedge pressures

((PCWP), $n = 287$), and thermodilution cardiac outputs (CO) were measured as medically indicated with a maximum sampling interval of four hours. Cardiac index ((CI), $n = 46$), systemic vascular resistance index ((SVRI), $n = 46$), and pulmonary vascular resistance index ((PVRI), $n = 45$) were calculated after each cardiac output. The P(a-ET)CO₂ values were also compared during administration of different concentrations of inspired oxygen ((FiO₂), $n = 367$) rates of mechanical ventilation ($n = 352$), and infusion rates of nitroprusside ($n = 63$), nitroglycerin ($n = 212$), dopamine ($n = 141$), dobutamine ($n = 41$), and metaraminol ($n = 37$). (See Table.) The final gradient determination was made during full spontaneous ventilation prior to extubation.

During the initial postoperative period, inotropic and vasopressor drugs were used to maintain a mean systemic blood pressure of 80 mmHg and a CI of $2.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^2$. Nitroglycerin was used to treat myocardial ischaemia and, along with nitroprusside, to help decrease systemic and pulmonary vascular resistance. Each patient was mechanically ventilated with a volume ventilator (tidal volume, $10\text{--}15 \text{ ml} \cdot \text{kg}^{-1}$) at a rate necessary to maintain a PaCO₂ of 32–40 mmHg. A positive end-expiratory pressure of $5 \text{ cm} \cdot \text{H}_2\text{O}^{-1}$ was maintained up to discontinuation of mechanical ventilation. The drugs utilized and their infusion rates, as well as ventilator settings, were adjusted as medically necessary, based upon each patient's physiological condition. Patients were followed from admission into the intensive care unit until establishment of full, adequate spontaneous ventilation with continuous positive airway pressure of $5 \text{ cm} \cdot \text{H}_2\text{O}^{-1}$, which was followed by extubation.

A total of 382 comparisons of PaCO₂ and ETCO₂ were made. Hewlett Packard 78520A infrared capnometers measured the ETCO₂ of each patient with a four-second sampling period for each measurement. The capnometer was calibrated according to established protocol utilizing two reference cells and calibration buttons present on each unit. There is automatic compensation for humidity while the airway adapter is heated to eliminate condensation. A continuous breath-by-breath capnograph was displayed on the monitor screen. Arterial blood as drawn for blood gas analysis according to established protocol every four hours or as medically indicated and measured by a self-calibrating Corning 168 pH/Blood gas Analyzer. The PaCO₂ values were referred to a temperature of 37° C.

The collected data are expressed as mean $\pm$ standard deviation. Statistical analysis was performed utilizing multiple regression analysis and Student's *t* tests, where applicable. A *P* value < 0.05 was considered significant. Multiple regression analysis was performed to correlate the PaCO₂ and ETCO₂ values of each individual patient as well as the total study population. The correlation

FIGURE 1 Correlation between arterial and end-tidal carbon dioxide during postoperative cardiorespiratory support.

coefficient of each patient was compared to that of the study population by Student's *t* tests.

Results

The relationship between PaCO_2 and ETCO_2 was assessed during widely varying conditions of cardiorespiratory support in postoperative cardiac patients. From the 382 total gradient determinations, PaCO_2 was 36.5 ± 5.9 mmHg and ETCO_2 was 31.0 ± 6.4 mmHg. Mean P(a-ET)CO_2 was 5.5 ± 5.2 mmHg, ranging from -8 to $+21.9$ mmHg. Of note was the presence of negative gradients, which made up 31, or 8.1 per cent, of total measurements and the presence of particularly high gradients, which made up 39, or 10.2 per cent. The number of gradient determinations per individual patient varied from a minimum of two in one patient to a maximum of 31.

For the whole population, the PaCO_2 and ETCO_2 measurements maintained a significant correlation ($R = 0.644$, $P < 0.001$) throughout the study period (Figure 1). The P(a-ET)CO_2 did vary from patient to patient (Figure 2). When individual patient data were analyzed many patients did not have a statistically significant correlation between the PaCO_2 and ETCO_2 measurements. The *P* values for individual patients varied from 0.0001 to 0.9. Comparison of the mean of the individual patient correlation coefficients with the correlation coefficient of the study population demonstrated a normal distribution with gradients representative of the same population ($P < 0.05$).

The infusion rates of dopamine, dobutamine, nitroglycerin, nitroprusside, and metaraminol as well as the rate of mechanical ventilation, and FiO_2 during the postoperative period varied between individual patients as

FIGURE 2 Measured values for P(a-ET)CO_2 .

dictated by their physical condition. None of the individual respiratory (FiO_2 and ventilator rate), haemodynamic factors (CI, PAP, PCWP, PVRI, or SVRI), or pharmacological factors (vasodilator, inotropic, or vasopressor agents) that were assessed resulted in a significant change in P(a-ET)CO_2 (Figures 3 and 4).

The P(a-ET)CO_2 varied both for and between individual patients. A positive correlation existed between PaCO_2 and ETCO_2 for the patient population studied as a whole. The variation was typical of a normal population distribution. However, the lack of a demonstrable positive correlation for each individual limits the clinical relevance of this finding. The individual variations seen in P(a-ET)CO_2 make careful interpretation necessary and periodic comparison to arterial blood gas analysis necessary.

Discussion

The gradient between arterial and end-tidal carbon dioxide partial pressures, P(a-ET)CO_2 , was found to maintain a positive relationship in the total population of postoperative cardiac surgery patients during different degrees of cardiorespiratory support. Although the range of P(a-ET)CO_2 values exhibited both by and between individuals was relatively wide, it was typical for a single population distribution. Practically, a single PaCO_2 and ETCO_2 comparison for determination of gradient may not yield a consistent relationship and individual patients must still be observed closely and arterial blood gas analyses sampled as clinically indicated.

A consistent P(a-ET)CO_2 for an individual patient would allow measured ETCO_2 to be reliably utilized as a monitor of PaO_2 . It could be used as a sensitive reflection of respiratory acid-base balance and adequacy of ventilation. Although PaCO_2 is the best approximation of

FIGURE 3 Relationship between P(a-ET)CO₂ and inspired oxygen, IMV rate, cardiac index, vascular resistance, and infusion rates of dopamine, nitroglycerin and nitroprusside.

alveolar CO₂, end-tidal gas analysis allows breath-by-breath determinations and is both continuous and individually less expensive. The ET-CO₂ has also been shown to vary inversely with alveolar ventilation.³ It is this relationship that results in the P(a-ET)CO₂ increasing as respiratory deadspace (primarily alveolar deadspace) increases and to a lesser degree with increased intrapulmonary shunting.^{4,5} Niehoff *et al.* found that capnometry combined with pulse oximetry allowed weaning from mechanical ventilation to occur with fewer arterial blood gas determinations; however, capnometry was relatively insensitive to hypercapnia.⁶ The reliability of ET-CO₂ to reflect PaCO₂ accurately on a consistent basis has been questioned.

The mean P(a-ET)CO₂ of 5.47 ± 5.21 mmHg is similar to clinical gradient values previously reported. However, most earlier determinations of P(a-ET)CO₂ were made in normal volunteers under controlled conditions or in

FIGURE 4 Relationship of P(a-ET)CO₂ to mean PAP.

patients under relatively static conditions rather during a period of changing pathophysiology and medical intervention. Collier *et al.* determined the $P(a-ET)CO_2$ to be -0.9 ± 1.8 mmHg in healthy, awake volunteers.³ During stable general anaesthesia, $PaCO_2$ and $ETCO_2$ correlated significantly ($P < 0.0001$) with the mean $P(a-ET)CO_2$ being 0.8 mmHg in patients with normal pulmonary function and 3.3 mmHg in those with lung disease.⁷ Older age, higher systolic blood pressure, and higher ASA physical status were associated with larger gradients. This is also in agreement with the 3.6 mmHg gradient determined by Takki *et al.* in 24 stable patients.⁸ In more clinically relevant situations, a $P(a-ET)CO_2$ of 5.9 ± 2.7 mmHg increased slightly during deliberate hypotension with pentolinium and head-up tilt.⁹ The patient population assessed in the present study exhibited a similar difference between arterial and end-tidal measurements of carbon dioxide to patient populations previously studied, although the $P(a-ET)CO_2$ was greater than those previously reported for healthy volunteers.

Although changing respiratory rates and inspired oxygen concentrations, as well as withdrawal of positive pressure breaths, can change intrapulmonary ventilation-perfusion relationships, a correlation could not be demonstrated with $P(a-ET)CO_2$ in the patients assessed in this study. Previous studies (with measured gradients of 4.24 ± 4.42 , and 4.6 ± 2.5 mmHg) reported greater $P(a-ET)CO_2$ values with spontaneous than controlled ventilation, but no relationship between gradients and either $PaCO_2$ or tidal volume.¹⁰⁻¹² However, intrapulmonary shunting is greater at higher respiratory rates, both in absolute terms and in relation to cardiac output. A high FiO_2 can result in absorption atelectasis and be associated with oxygen-dependant redistribution of perfusion.¹³ Although high respiratory rates can result in increased anatomical deadspace, alveolar deadspace is not dependant on respiratory rate.¹⁴ The variations in alveolar deadspace volume do not correlate with the variations in lung volume. However, we did not assess the effect of actual respiratory rate, combining mechanical and spontaneous breaths or the tidal volumes generated. We found that $P(a-ET)CO_2$ was not effected during the weaning period when ventilator delivered breaths (beginning at rates up to $18 \cdot \text{min}^{-1}$ in the SIMV mode) were decreased to full spontaneous ventilation with 5 cm H_2O CPAP.

We also found that changes of $P(a-ET)CO_2$ could not be correlated with the values for the different haemodynamic measurements made. Previously, Askrog reported that the mean pulmonary artery pressure was inversely related to the $P(a-ET)CO_2$.¹⁵ This relationship was felt to be the result of increased pulmonary perfusion secondary to increased pulmonary artery pressures causing decreased alveolar deadspace. We could not demon-

TABLE Factors most commonly assessed for their influence on $P(a-ET)CO_2$

Factors	Range
<i>Respiratory</i>	
FiO_2	0.4–1.0
Ventilator rate	0–18 breaths per minute
<i>Haemodynamic</i>	
CI	$1.7\text{--}4.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^2$
SVRI	$14.9\text{--}44.4 \text{ mmHg} \cdot \text{L}^{-1} \cdot \text{min}^{-1} \cdot \text{m}^2$
PVRI	$0.4\text{--}7.2 \text{ mmHg} \cdot \text{L}^{-1} \cdot \text{min}^{-1} \cdot \text{m}^2$
PAP	7–40 mmHg
PCWP	6–30 mmHg
<i>Pharmacologic</i>	
Nitroprusside	$0.17\text{--}7.8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$
Nitroglycerin	$23\text{--}150 \mu\text{g} \cdot \text{min}^{-1}$
Dopamine	$1\text{--}10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$

strate a similar relationship over a wide range of pulmonary artery pressures. A wide range of the measurements indicative of cardiac function and physiological conditions (Table) expected to effect ventilation-perfusion relationships and alveolar dead-space or intrapulmonary shunt was found. For example, the increased cardiac outputs found may have also increased intrapulmonary shunting and by increasing pulmonary perfusion decreased alveolar deadspace.¹⁶ Despite findings such as this, we could not establish a relationship between haemodynamic indices and $P(a-ET)CO_2$.

A relationship between $P(a-ET)CO_2$ and the pharmacological agents used to maintain clinically acceptable cardiovascular physiological states was also absent although many of these agents directly or indirectly alter respiratory deadspace or shunt fraction. Nitroglycerin and nitroprusside both increase shunting, alter pulmonary perfusion and decrease hypoxic pulmonary vasoconstriction.¹⁷⁻¹⁹ Dobutamine and possibly dopamine may also inhibit normal hypoxic pulmonary vasoconstriction.^{20,21} It must be noted that many of these patients were receiving more than one vasoactive agent simultaneously and the effects of drug interactions, either by altering the expected response to one agent or by a combination of effects creating a totally different response in deadspace or shunting, could not be assessed.

When evaluating the $P(a-ET)CO_2$ after cardiac surgery, the potential changes caused by the surgical procedure or cardiopulmonary bypass must be considered. Pulmonary artery manipulation and associated changes in pulmonary perfusion do alter $P(a-ET)CO_2$.²² Likewise, the gradient has been documented to increase from 4.57 ± 2.86 pre-bypass to 11.48 ± 3.46 measured 30 min after cardiopulmonary bypass.²³ In these previous studies measure-

ments were not extended into the postoperative period. However, the P(a-ET)CO₂ was no greater on the first arterial blood gas sampling on arrival in the intensive care unit. It appears that the effects of pulmonary artery manipulation and bypass itself act over relatively short time periods.

The P(a-ET)CO₂ values measured ranged from -8 to +22 mmHg. Of the gradients recorded, 31 (or 8.1 per cent) were negative. Both Raemer *et al.* and Jones *et al.* previously reported negative gradients, with the PaCO₂ as much as 12 mmHg less than the ETCO₂.^{12,24} Shankar *et al.* found that the P(a-ET)CO₂ was negative in 50 per cent of an obstetrical patient population undergoing Caesarean section with halothane-nitrous oxide general anaesthesia.²⁵ During general anaesthesia the usual cause of a PaCO₂ exceeding the ETCO₂ is rebreathing of expired carbon dioxide. However, a negative gradient can also occur with slow, large tidal volume respirations. The positive slope of the expired carbon dioxide results in the peak expired value exceeding the temporal mean alveolar concentration, represented by the PaCO₂. In situations where deadspace and ventilation-perfusion mismatching are minimal, alveolar carbon dioxide (as reflected by ETCO₂) may also exceed arterial levels. Thus, the presence of a negative P(a-ET)CO₂, although the meaning is not totally clear, may represent normal respiratory physiological variations. Error in measurement is an unlikely possibility in these patients. The increased frequency of large gradients, compared with previous studies, reflects the different patient population studied.

There are a number of limitations in this type of clinical study. The effects of individual drugs and therapies cannot be totally separated from the other therapeutic manoeuvres that an individual patient is receiving at the same time. For example, although a low cardiac output may have been present and increased deadspace expected, simultaneous administration of nitroglycerin or nitroprusside may have helped increase pulmonary perfusion, at the same time increasing intrapulmonary shunting. The number of gradient determinations was not the same in each patient. This reflected the different physical status of patients and variations in the required duration of ventilatory support. Individual patients varied in their preoperative physical and, more specifically, their cardiac and pulmonary condition. Preoperative pulmonary function testing was not done. The gradients were not compared for smokers and nonsmokers. There was no clinically significant pulmonary disease present interfering with normal activity or requiring medication preoperatively. However, preoperative P(a-ET)CO₂ was not assessed. Conditions were not controlled, but could not be in an evolving acute postoperative situation. Some of these difficulties could be overcome by studying a larger, less

acutely ill population in which there are fewer simultaneous therapeutic interventions.

The correlation between the partial pressure of carbon dioxide in arterial blood and in end-tidal gases maintained a positive, statistically significant relationship when a population of postoperative cardiac surgery patients was assessed. This relationship held across the population despite widely varied cardiorespiratory support. The lack of a demonstrable positive correlation between PaCO₂ and ETCO₂ for each individual limits the clinical relevance of the positive relationship found for the patient population as a whole. Although changes in PaCO₂ are reflected by changes in ETCO₂, the relationship varies and is influenced by individual and interacting factors that make correlation variable. Differences in P(a-ET)CO₂ induced by changes in ventilatory mechanics or regional lung physiology may be eliminated by analysis of the expired CO₂ waveform and utilizing the ETCO₂ value determined at the plateau of the capnograph, which is more indicative of alveolar ventilation.

Individual cardiorespiratory changes and drug administration could not be shown to have a specific, measured influence on P(a-ET)CO₂. The interaction of multiple mechanical and pharmacological factors and their combined influence on pathophysiology cannot be eliminated. The individual variations demonstrated in P(a-ET)CO₂ in postoperative cardiac patients make periodic assessments of ventilatory adequacy by arterial blood gas measurements necessary.

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