WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

Debra Liu, DVM Elise Boller, DVM, DACVECC	**Date Submitted for review:** June 9th, 2011

2. Clinical question:

MON02" In dogs and cats with suspected cardiac arrest (P), is the evaluation of $ETCO_2$ (I) vs. assessment for other signs of life (e.g. pupil size, agonal breathing, femoral pulse) (C) a reliable tool for diagnosis of cardiac arrest?(O)

3. Conflict of interest specific to this question:

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? None

4. Search strategy (including electronic databases searched):

4a. Databases

1) MEDLINE via PUBMED (performed on April 17th 2011)

- Clinical Queries: Category→Diagnosis; SCOPE→Broad
- Keywords: cardiopulmonary arrest end tidal carbon dioxide
- Activated limits: Animals, Humans, English
- Yield: 37 items → ***3 relevant items***

2) CAB abstract (1910-2011 Week 14) (performed on April 17th 2011)

- Basic search
- Keywords: end tidal carbon dioxide cardiopulmonary arrest detection clinical aspects
- No inclusion of related terms
- Activated limits: Abstract, English, Time (1950 to current)
- Additional limits: Journal, Journal article, Journal issue
- Yield: 387 items → ***2 relevant items***

4b. Other sources

1) GOOGLE SCHOLAR (performed on April 17th 2011)

- Keywords: EtCO2 end tidal carbon dioxide cardiopulmonary arrest diagnosis resuscitation
- Yield 1950 items → ***10 relevant items***

2) All references of identified articles above were checked: ***12 relevant items***

3) All references of the following relevant review articles were checked:

American Heart Association: Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science 2010;122 (18;S3)

- ***0 relevant article***

Plunkett SJ, McMichael M. Cardiopulmonary resuscitation in small animal medicine: an update. J Vet Intern Med 2008;22(1):9-25

- ***4 relevant articles***

Cole SG, Otto CM, et al. Cardiopulmonary cerebral resuscitation in small animals – a clinical practice review (Part 1). J Vet Emerg Crit Care 2002; 12(4):261-267.

- ***0 relevant articles***

Cole SG, Otto CM, et al. Cardiopulmonary cerebral resuscitation in small animals – a clinical practice review. Part II J Vet Emerg Crit Care 2003; 13(1):13-23.

- ***0 relevant articles***

Marks S, Haldane S, et al. Cardiopulmonary cerebral resuscitation: emergency drugs and postresuscitative care. Comp Contin Educ Pract Vet 2004;26(10): 791-799

- ***0 relevant article***

Holowaychuk M, Martin L. An In-depth look: misconceptions about emergency and critical care: cardiopulmonary cerebral resuscitation, fluid therapy, shock, and trauma. Comp Contin Educ Pract Vet 2006; 420-433

- ***0 relevant article***

Haldane S, Marks SL. Cardiopulmonary resuscitation: techniques Comp Contin Educ Pract Vet 2004;26(10): 780-790

- ***1 relevant articles***

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

Inclusion criteria

Peer reviewed journal articles, clinical research

Exclusion criteria

Review, editorials, case reports

4d. Number of articles/sources meeting criteria for further review: 32

5. Summary of evidence

Evidence Supporting Clinical Question

Good						
Fair			Blumenthal & Voorhees 1997– A Sanders et al. 1985a - B Sanders et al. 1985b – B Kern et al. 1989-B		Hofmeister et al. 2009– E	Dubin et al. 2000- A Isserles & Breen 1991- A Seliskar, Nemec & Butinar 2006 – F *Falk, Rackow & Weil 1988– A, G* *Sehra, Underwood & Checchia 2003– A* *Pokorna et al. 2010– E* *Idris et al. 1994b – A* *Gudipati et al. 1988– A, E* *Weil et al. 1985-A* *Ornato, Garnett & Glauser 1990– A* *Gazmuri et al. 1989– A* *Xie et al. 2004– B, C, D* *Lewis et al. 1992- A* *Trevino et al. 1985– A, E*
			Dohi, Takeshima & Matsumiya 1987- A			*Shibutani et al. 1994- A*

Poor						*Lepilin et al. 1987– A, E* *Garnett et al. 1987- E* *Steedman & Robertson 1990– E*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A: Cardiac output
B: Coronary perfusion pressure
C: Stroke Volume
D: Aortic pressure
E: Return of spontaneous circulation
F: Hypovolemia
G: Systemic oxygen extraction
Italics = Non-target species studies

Evidence Neutral to Clinical question

Good						
Fair			Morimoto et al. 1993- A			*Idris et al. 1994a – A, B*
Poor						
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A: Cardiac output
B: Minute ventilation

Evidence Opposing Clinical Question

Good						
Fair			Bhende, Karasic & Menegazzi 1995- A Bhende, Karasic & Karasic 1996- A			*Grmec, Lah & Tusek-Bunc 2003- A* *Berg et al. 1996- A* *Courtney, Watts & Kline 2002– B* Reindl & Matis 1998- C
Poor						
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A: End tidal CO2 during asphyxial arrest
B: End tidal CO2 during massive pulmonary embolism
C: End tidal CO2 correlation with the severity of embolaemia

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:
The correlation of end-tidal carbon dioxide ($ETCO_2$) with cardiac output in low cardiac output states has been shown in many animal and human studies (Blumenthal & Voorhees 1997, Falk, Rackow & Weil 1988, Idris et al. 1994b). In a canine model of cardiac arrest, $ETCO_2$ was documented to quantitatively reflect cardiac output when ventilation was held constant. At the onset of cardiac arrest, $ETCO_2$ fell immediately to near zero. During cardiopulmonary resuscitation, $ETCO_2$ increased in correspondence to chest compressions. A sudden, large rise of $ETCO_2$ occurred at the return of spontaneous circulation (Blumenthal & Voorhees 1997). In porcine cardiac arrest models, the linear relationship of $ETCO_2$ and cardiac output was consistently observed (Idris et al. 1994b, Gudipati et al. 1988, Weil et al. 1985, Gazmuri et al. 1989). Falk and his colleagues documented similar clinical observations of $ETCO_2$ changes during cardiopulmonary resuscitation of 13 cardiac arrest patients and found that $ETCO_2$ is inversely correlated to systemic oxygen extraction as well (Falk, Rackow & Weil 1988). Additionally, $ETCO_2$ correlates with coronary perfusion pressure during cardiopulmonary resuscitation (Sanders et al. 1985a, Sanders et al. 1985b, Kern et al. 1989). Therefore, $ETCO_2$ has been used to detect circulatory arrest as an index of cardiac output and to monitor cardiopulmonary resuscitation efficacy.

There are limitations to the usefulness of $ETCO_2$ to diagnose cardiopulmonary arrest, however. First, the presence and severity of pulmonary embolism have been correlated to the decrease of $ETCO_2$ level in dogs undergoing total hip replacement surgery and in experimental rodent cardiac arrest models (Reindl & Matis 1998, Courtney, Watts & Kline 2002). Secondly, in a canine asphyxial arrest model, the initial mean $ETCO_2$ (35mmHg) was found to be higher than the pre-arrest mean $ETCO_2$ level (31.9 mmHg). Subsequent $ETCO_2$ values were lower during cardiopulmonary resuscitation (mean $ETCO_2$ was 12.4 mmHg during resuscitation) until the return of spontaneous circulation. At the return of spontaneous circulation, the mean $ETCO_2$ was 27 mmHg) (Bhende, Karasic & Karasic 1996). Opposite changes in the initial $ETCO_2$ was also observed clinically in patients of asphyxial cardiac arrest (mean initial $ETCO_2$ was 66.4 mmHg) versus patients of primary cardiac arrest (the intial $ETCO_2$ was 16.5 mmHg) (Grmec, Lah & Tusek-Bunc 2003). Studies of the porcine arrest model further validated similar data (Berg et al. 1996).

In summary, $ETCO_2$ is a useful monitoring tool for intubated animals under constant ventilation as an index of pulmonary blood flow/cardiac output. In conjunction with physical examination findings, it may aid in early detection of primary cardiac arrest in these animals. For animals intubated after the arrest, the value of initial $ETCO_2$ may not be reliable to correlate with cardiac output, particulary in the setting of asphyxial arrest. Therefore, evidence suggests that $ETCO_2$ cannot be used as the sole or superior modality to diagnose cardiopulmonary arrest in comparison to physical examination findings.

7. Conclusion
The correlation of cardiac output and $ETCO_2$ during cardiopulmonary arrest has been demonstrated in animal models and human clinical studies (Blumenthal & Voorhees 1997, Falk, Rackow & Weil 1988, Idris et al. 1994b;LOE 3 & 6). Different causes of cardiopulmonary arrest (asphyxial versus primary cardiac) however may alter the initial $ETCO_2$ level at the beginning of cardiopulmonary resuscitation (Bhende, Karasic & Karasic 1996, Grmec, Lah & Tusek-Bunc 2003, Berg et al. 1996; LOE 3 and 6). The presence of massive pulmonary embolism may also affect $ETCO_2$ level proportionally to its severity (Reindl & Matis 1998, Courtney, Watts & Kline 2002; LOE 6). Level 1 or 2 clinical studies of target species are lacking. Based on the available evidence, a sudden decrease of $ETCO_2$ to near zero in intubated, constantly ventilated animals is a reliable indicator of cardiac arrest or massive life-threatening pulmonary embolism. For awake animals, the value of initial $ETCO_2$ value obtained immediately after intubation depends more on concurrent physical examination findings and it may help in differentiating causes of arrest.

8. Acknowledgement

9. Citation list

Berg, RA, Henry, C, Otto, CW, Sanders, AB, Kern, KB, Hilwig, RW & Ewy, GA 1996, 'Initial end-tidal CO2 is markedly elevated during cardiopulmonary resuscitation after asphyxial cardiac arrest', *Pediatr Emerg Care*, vol. 12, no. 4, pp. 245-8.

LOE: 6. Quality: Fair. Direction: Opposing.

Notes: This study used an experimental model of non-target species (pigs) to demonstrate the difference in initial EtCO2 for asphyxial versus primary cardiac arrest.

Abstract

OBJECTIVES:

To compare the initial end-tidal CO2 (PetCO2) during cardiopulmonary resuscitation in asphyxial versus ventricular fibrillatory cardiac arrest.

DESIGN:

A cohort study.

SETTING:

University research laboratory.

SUBJECTS:

Forty domestic piglets.

INTERVENTIONS:

Asphyxial cardiac arrest was produced by clamping the endotracheal tube in 20 piglets and was continued for 10 minutes after loss of aortic pulsations occurred. Ventricular fibrillation (VF) was induced by applying 60 Hz of alternating current via a pacing wire to the myocardium of the other 20 piglets, and continued for a 15-minute downtime. Cardiopulmonary resuscitation (CPR) was then provided to each group for two minutes, followed by standard advanced cardiac life support protocols.

MEASUREMENTS AND MAIN RESULTS:

All piglets were instrumented for continuous monitoring of PetCO2, electrocardiogram, central venous pressure, and aortic pressure. PetCO2 of the first breath of CPR was 91 +/- 20 mmHg in the asphyxial group versus 34 +/- 14 mmHg in the VF group ($P < 0.001$). The asphyxial group continued to exhibit significantly greater PetCO2 for the first five breaths of resuscitation, after which there were no differences. The coronary perfusion pressures during the first breaths of CPR did not differ between the two groups. High initial PetCO2 did not correlate with return of spontaneous circulation.

CONCLUSIONS:

End-tidal CO2 during the first five breaths of CPR is much higher after an asphyxial cardiac arrest than VF. In each case, the initial PetCO2 appears to reflect alveolar CO2 prior to CPR. After one minute of CPR, PetCO2 is useful in monitoring the effectiveness of CPR

Bhende, MS, Karasic, DG & Karasic, RB 1996, 'End-tidal carbon dioxide changes during cardiopulmonary resuscitation after experimental asphyxial cardiac arrest', *Am J Emerg Med*, vol. 14, no. 4, pp. 349-50.

LOE: 3. Quality: Fair. Direction: Opposing.

Notes: This study used an experimental canine asphyxial arrest model to demonstrate the increase in initial EtCO2. The main limitation is the lack of primary cardiac arrest cohort for comparison.

Abstract

A study was undertaken to determine the pattern of end-tidal carbon dioxide (ETCO2) changes during asphyxia-induced cardiac arrest in a pediatric canine model. Eleven intubated, anesthetized, paralyzed dogs

(mean age, 4.1 mo; mean weight, 5.5 kg) were used. Asphyxia was induced by clamping the endotracheal tube (ETT) and discontinuing ventilation. Cardiac arrest ensued a few minutes later, after which closed-chest cardiopulmonary resuscitation (CPR) and ventilation were initiated. The ETCO2 level was recorded at baseline and every minute during CPR. Mean baseline ETCO2 was 31.9 mm Hg. The initial ETCO2 immediately after unclamping the ETT (mean, 35 mm Hg) was higher than subsequent values (mean, 12.4 mm Hg; P < .001). There was a sudden increase in ETCO2 to a mean of 27.0 mm Hg at or just before return of spontaneous circulation (ROSC) in all 11 cases (P < .01). During CPR, ETCO2 levels were initially high, decreased to low levels, and increased again at ROSC. This pattern, not previously described, is different from that observed in animal and adult cardiac arrest caused by ventricular fibrillation, during which ETCO2 decreases to almost zero after the onset of arrest, begins to increase after the onset of effective CPR, and increases to normal levels at ROSC. In this model of asphyxial arrest, continued cardiac output prior to arrest allows continued delivery Of CO2 to the lungs, resulting in higher alveolar CO2; this, in turn, is reflected as increased ETCO2 once ventilation is resumed during CPR. Further study is needed to determine whether the pattern Of ETCO2 changes can be used prospectively to define the etiology of cardiac arrest.

Bhende, MS, Karasic, DG & Menegazzi, JJ 1995, 'Evaluation of an end-tidal CO2 detector during cardiopulmonary resuscitation in a canine model for pediatric cardiac arrest', *Pediatr Emerg Care*, vol. 11, no. 6, pp. 365-8.

LOE: 3. Quality: Fair. Direction: Opposing.

Notes: This study demonstrated EtCO2 changes during cardiopulmonary resuscitation in a canine asphyxial arrest model. The initial EtCO2 level post-arrest is higher than the pre-arrest level.

Abstract

Our objective was to evaluate a colorimetric end-tidal CO2 detector in a canine model for pediatric cardiac arrest. In a prospective unblinded study, cardiac arrest was induced in 11 anesthetized and paralyzed puppies, weighing 5.0 to 6.1 kg, by clamping the endotracheal tube (ETT) and discontinuing mechanical ventilation. During cardiopulmonary resuscitation (CPR), the detector and the capnometer were connected between the ETT and ventilator tubing. Color shades on the detector ranged from 1 (purple) to 6 (yellow) corresponding to increasing concentrations of CO2. End-tidal CO2 concentrations as indicated by detector color and capnometric reading were monitored and recorded throughout the study. The results showed that there was a significant correlation between the detector color score and capnometric readings (P < 0.001). A sudden rise in end-tidal CO2 indicated by both the capnometer and the detector occurred at return of spontaneous circulation (ROSC) in seven or < 1 minute before ROSC in four animals. This association was significant (P = 0.0009). We conclude that these results demonstrate that, in a canine model for pediatric cardiac arrest, the detector readings correlate with capnometry during CPR and indicate ROSC.

Blumenthal, SR & Voorhees, WD 1997, 'The relationship between airway carbon dioxide excretion and cardiac output during cardiopulmonary resuscitation', *Resuscitation*, vol. 34, no. 3, pp. 263-70.

LOE: 3. Quality: Fair. Direction: Supportive.

Notes: This study demonstrated the EtCO2 changes during cardiopulmonary resuscitation in a canine ventricular fibrillation arrest model. The initial EtCO2 level post-arrest is higher than the pre-arrest level.

Abstract

There is currently no practical method for determining cardiopulmonary resuscitation (CPR) efficacy in the field. We investigated the relationship between the volume of carbon dioxide (CO2) excreted in the airway (CO2EX) when tidal volume and respiratory rate are controlled, and cardiac output (CO), an indicator of CPR efficacy, to determine the potential of CO2EX as a practical noninvasive field monitor of CPR efficacy. Thirteen mongrel dogs were anesthetized, instrumented and ventilated 13 times/min at a fixed tidal volume with an infrared airway CO2 sensor. CO2EX = (PCO2/bar. press) x (tidal vol) x (breaths/min), and expressed in ml/min per kg. Sequences of control, CPR with 3-4 different compression forces, and recovery

measurements were recorded 10-15 times/animal. CO2EX and CO fell simultaneously with ventricular fibrillation. CPR immediately increased CO2EX and CO. Both changed consistently and in the same direction as compression force. Return of spontaneous circulation immediately increased CO2EX and CO above controls, with a gradual return to control levels. CO2EX was always below 8 ml-CO2/min/kg during CPR and above this during spontaneous circulation. With alveolar ventilation controlled, CO2 movement is regulated by CO, CO distribution and CO2 stores shifts. Normally, CO accounts for 15% of CO2EX variability. In this study CO accounted for > or = 65% of CO2EX variability during CPR, indicating CO2EX changes were primarily due to CO changes. When ventilation is controlled, CO2EX during CPR reliably tracks changes in CO. Therefore, CO2EX may provide a practical noninvasive method of determining CPR efficacy as the CPR is being performed.

Courtney, DM, Watts, JA & Kline, JA 2002, 'End tidal CO(2) is reduced during hypotension and cardiac arrest in a rat model of massive pulmonary embolism', *Resuscitation*, vol. 53, no. 1, pp. 83-91.

LOE: 6. Quality: Fair. Direction: Opposing.

Notes: This study compared the difference in EtCO2 changes among arrhythmic cardiac arrest, hemorrhagic shock cardiac arrest, and cardiac arrest from massive pulmonary embolism. Massive pulmonary embolism produced significantly lower EtCO2 than other two causes of cardiac arrest. Rat models are used.

Abstract

BACKGROUND:
We investigated the effect of massive pulmonary embolism (MPE) on end tidal CO(2) (etCO(2)) and tested two hypotheses: (1) that etCO(2) can distinguish massive PE from hemorrhagic shock and (2) that PE with cardiac arrest reduces etCO(2) during resuscitation to a greater extent than arrhythmic cardiac arrest.

METHODS:
Anesthetized, mechanically ventilated rats (N=10 per group), were subjected to either graded PE (latex microspheres), or graded hemorrhagic shock to produce a final mean arterial blood pressure, (MAP) of 40 mmHg; a third group was subjected to surgical/anesthetic control conditions. Cardiac arrest was induced by the following methods: intravenous injection of a large bolus of microspheres in the PE group, aortic puncture in the hemorrhage group, and intravenous tetrodotoxin (TTX) to produce arrhythmic cardiac arrest in the control group.

RESULTS:
At a MAP of 40 mmHg, etCO(2) was significantly decreased in the PE group (18.3+/-1.9 torr) compared with both the hemorrhage (24.3+/-1.3) and the control group (35.0+/-1.3 torr; ANOVA P<0.001). The decreased etCO(2) occurred coincident with an increase in alveolar dead space fraction in the PE group. In the first minute of ventilation after cardiac arrest, the etCO(2) was significantly decreased in the PE group (6.5+/-0.9) versus both hemorrhage (16.5+/-1.1) and TTX (34.2+/-2.4 torr).

CONCLUSIONS:
Massive PE with shock decreases the etCO(2) and increases the dead space fraction to a greater extent than hemorrhagic shock at the same MAP. Cardiac arrest from PE is associated with extremely low etCO(2) readings during CPR.

Dohi, S, Takeshima, R & Matsumiya, N 1987, 'Carbon dioxide elimination during circulatory arrest', *Crit Care Med*, vol. 15, no. 10, pp. 944-6.

LOE: 3. Quality: Poor. Direction: Supportive.

Notes: This studies demonstrated the pattern of carbon dioxide elimination during cardiac arrest in dogs. End tidal CO2 decreases immediately after cardiac arrest occurred.

Abstract

To learn modes of CO2 elimination during cardiac arrest, we continuously measured end-tidal CO2 concentration (ETCO2) in acutely arrested dogs with constant ventilation. A decrease in peak ETCO2 during cardiac arrest in each dog showed a washout biexponential function when graphed on semilog paper. The average half-times of each compartment were 19.2 +/- 3.1 (SD) sec for the fast compartment and 108.1 +/- 23.8 sec for the slow compartment; the fast compartment of the CO2 elimination curve suggested that CO2 was eliminated from the functional residual capacity, while the slow compartment indicated CO2 elimination from the pulmonary capillary blood and tissue stores. Neither pretreatment with sodium bicarbonate (1 mEq/kg iv) nor a 5-min cardiorespiratory arrest altered the mode of CO2 elimination. The ETCO2 also reflected the potential effects of external cardiac compressions on pulmonary blood flow, as previously reported. Besides mixed venous blood CO2 flowing back to the lungs by cardiac compressions, it should be noted that both alveoli and pulmonary capillary blood CO2 are also reflected in the ETCO2 during the first minute of CPR.

Dubin, A, Murias, G, Estenssoro, E, Canales, H, Sottile, P, Badie, J, Baran, M, Rossi, S, Laporte, M, Palizas, F, Giampieri, J, Mediavilla, D, Vacca, E & Botta, D 2000, 'End-tidal CO2 pressure determinants during hemorrhagic shock', *Intensive Care Med*, vol. 26, no. 11, pp. 1619-23.

LOE: 6. Quality: Fair. Direction: Supportive.

Notes: This study demonstrated the correlation between EtCO2 and cardiac output in a canine hemorrhagic shock model.

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 experiment. 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 r2 = 0.90), showing that PETCO2 decrease is greater in lowest flow states. PETCO2 was correlated with VCO2, but the best fit was linear (median r2 = 0.77). Critical DO2 for PETCO2 and VO2 was 8.0 +/- 3.3 and 6.3 +/- 2.5 ml x 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.

Falk, JL, Rackow, EC & Weil, MH 1988, 'End-tidal carbon dioxide concentration during cardiopulmonary resuscitation', *N Engl J Med*, vol. 318, no. 10, pp. 607-11.

LOE: 6. Quality: Fair. Direction: Supportive.

Notes: This study demonstrated the changes in EtCO2 during difference phases of cardiopulmonary resuscitation of clinical patients. An inverse relationship between EtCO2 and systemic oxygen extraction was also documented in support for the positive correlation between EtCO2 and cardiac output.
Abstract
We prospectively measured the end-tidal carbon dioxide concentration during 13 episodes of cardiac arrest in 10 critically ill patients receiving mechanical ventilation, to evaluate its usefulness as an indicator of circulatory status during cardiac arrest and resuscitation. The end-tidal carbon dioxide concentration decreased from a mean (+/- SD) of 1.4 +/- 0.9 to 0.4 +/- 0.4 percent after the onset of cardiac arrest. During precordial compression, it increased to 1.0 +/- 0.5 percent. The decreases in the end-tidal carbon dioxide concentration were associated with increases in systemic oxygen extraction (r = 0.79). Spontaneous circulation was restored on seven occasions. This was heralded by a rapid increase in the end-tidal carbon dioxide concentration, from 1.3 +/- 0.5 percent to an overshoot value of 3.7 +/- 2.1 percent, within approximately 30 seconds. The concentration then declined to a stable value of 2.4 +/- 1.8 percent four minutes after resuscitation. However, it remained 0.7 +/- 0.4 percent in six patients in whom resuscitative efforts failed to restore spontaneous circulation. These observations are consistent with experimental studies of cardiopulmonary resuscitation in pigs, in which the end-tidal carbon dioxide concentration varied directly with the cardiac output produced by precordial compression. We therefore propose that measurement of the end-tidal carbon dioxide concentration may be a practical, non-invasive method for monitoring blood flow generated by precordial compression during cardiopulmonary resuscitation and an almost immediate indicator of successful resuscitation.

Garnett, AR, Ornato, JP, Gonzalez, ER & Johnson, EB 1987, 'End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation', *Jama*, vol. 257, no. 4, pp. 512-5.
LOE: 6. Quality: Poor. Direction: Supportive.
Notes: This study documents the increase in EtCO2 at the return of spontaneousl circultion in humans.
Abstract
The end-tidal carbon dioxide (CO2) concentration has been found to correlate with cardiac output during and after cardiopulmonary resuscitation (CPR) in animal models. We monitored end-tidal CO2 values continuously during cardiac resuscitation in 23 humans while ventilation was held constant with a computer-controlled CPR Thumper. This report focuses on ten of the 23 patients who experienced return of spontaneous circulation (ROSC) during monitoring. There was no significant difference in the end-tidal CO2 value of patients without ROSC (1.8% +/- 0.9%) and the end-tidal CO2 value of patients before ROSC in patients who had ROSC (1.7% +/- 0.6%). The end-tidal CO2 concentration increased immediately in all patients who had ROSC, from 1.7% +/- 0.6% to 4.6% +/- 1.4%, then gradually returned to a new baseline (3.1% +/- 0.9%). Change in the end-tidal CO2 value was often the first clinical indicator that ROSC had occurred. Our findings suggest that end-tidal CO2 monitoring may provide clinically useful information that can be used to guide therapy during CPR.

Gazmuri, RJ, von Planta, M, Weil, MH & Rackow, EC 1989, 'Arterial PCO2 as an indicator of systemic perfusion during cardiopulmonary resuscitation', *Crit Care Med*, vol. 17, no. 3, pp. 237-40.
LOE: 6. Quality: Fair. Direction: Supportive.
Notes: This study used an experimental porcine cardiac arrest model to demonstrate the correlation among EtCO2, cardiac output/pulmonary blood flow, and coronary perfusion pressure.
Abstract
End-tidal PCO2 (PetCO2) is a quantitative indicator of pulmonary blood flow generated by precordial compression and therefore predicts resuscitability during CPR. A striking increase in PetCO2 follows return of spontaneous circulation. Since PaCO2 is closely related to alveolar PCO2 (PACO2) and therefore PetCO2, we hypothesized that PaCO2 may itself serve as an indicator of the blood flow generated during CPR. In a porcine model of cardiac arrest, PaCO2 during precordial compression was highly correlated with PetCO2 (r = .89), cardiac output (r = .72), and coronary perfusion pressure (CPP) (r = .74). In 14 successfully resuscitated

animals, PaCO2, PetCO2, and CPP during precordial compression were significantly higher than in nine nonresuscitated animals. After restoration of spontaneous circulation, there was a marked increase in PaCO2 to levels exceeding control values, which corresponded to the sharp increase in PetCO2 that is characteristic of successful resuscitation. We therefore confirm that both PetCO2 and PaCO2 correspond to the pulmonary blood flow and therefore cardiac output which is generated by precordial compression during CPR. Moreover, both serve as prognosticators of cardiac resuscitability and early indicators that spontaneous circulation has been restored.

Grmec, S, Lah, K & Tusek-Bunc, K 2003, 'Difference in end-tidal CO2 between asphyxia cardiac arrest and ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest in the prehospital setting', *Crit Care*, vol. 7, no. 6, pp. R139-44.

LOE: 6. Quality: Fair. Direction: Opposing.

Notes: This study demonstrated the difference of the initial EtCO2 between patients with primary cardiac arrest versus asphyxial arrest.

Abstract

INTRODUCTION:

There has been increased interest in the use of capnometry in recent years. During cardiopulmonary resuscitation (CPR), the partial pressure of end-tidal carbon dioxide (PetCO2) correlates with cardiac output and, consequently, it has a prognostic value in CPR. This study was undertaken to compare the initial PetCO2 and the PetCO2 after 1 min during CPR in asphyxial cardiac arrest versus primary cardiac arrest.

METHODS:

The prospective observational study included two groups of patients: cardiac arrest due to asphyxia with initial rhythm asystole or pulseless electrical activity, and cardiac arrest due to acute myocardial infarction or malignant arrhythmias with initial rhythm ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). The PetCO2 was measured for both groups immediately after intubation and then repeatedly every minute, both for patients with and without return of spontaneous circulation (ROSC).

RESULTS:

We analyzed 44 patients with asphyxial cardiac arrest and 141 patients with primary cardiac arrest. The first group showed no significant difference in the initial value of the PetCO2, even when we compared those with and without ROSC. There was a significant difference in the PetCO2 after 1 min of CPR between those patients with ROSC and those without ROSC. The mean value for all patients was significantly higher in the group with asphyxial arrest. In the group with VF/VT arrest there was a significant difference in the initial PetCO2 between patients without and with ROSC. In all patients with ROSC the initial PetCO2 was higher than 10 mmHg.

CONCLUSIONS:

The initial PetCO2 is significantly higher in asphyxial arrest than in VT/VF cardiac arrest. Regarding asphyxial arrest there is also no difference in values of initial PetCO2 between patients with and without ROSC. On the contrary, there is a significant difference in values of the initial PetCO2 in the VF/VT cardiac arrest between patients with and without ROSC. This difference could prove to be useful as one of the methods in prehospital diagnostic procedures and attendance of cardiac arrest. For this reason we should always include other clinical and laboratory tests.

Gudipati, CV, Weil, MH, Bisera, J, Deshmukh, HG & Rackow, EC 1988, 'Expired carbon dioxide: a noninvasive monitor of cardiopulmonary resuscitation', *Circulation*, vol. 77, no. 1, pp. 234-9.

LOE: 6. Quality: Fair. Direction: Supportive.

Notes: This study demonstrated changes in EtCO2 during cardioplmonary resuscitation of a porcine ventricular fibrillation arrest model. End tidal CO2 is higher in animals that achieved return of spontaneous circulation.

Abstract
End-tidal CO2 concentration (ETCO2) may serve as a simple noninvasive measurement of the blood flow generated by precordial compression during cardiopulmonary resuscitation (CPR). In a mechanically ventilated porcine preparation of ventricular fibrillation, onset of fibrillation was associated with a rapid decrease in ETCO2 from 4.0 +/- 0.2% to less than 0.7 +/- 0.2%. With precordial compression, it increased to 1.9 +/- 0.3%. Animals that were successfully defibrillated after 12 min of CPR demonstrated an immediate increase in ETCO2. The ETCO2 increased from 1.9 +/- 0.3% to 4.9 +/- 0.3% over an interval of between 30 and 60 sec. These changes in ETCO2 were closely related to proportionally similar decreases and increases in cardiac output (CO), and a close correlation between ETCO2 and CO was demonstrated (r = .92). A similar highly significant correlation between ETCO2 and CO was also demonstrated during open-chest cardiac massage (r = .95). ETCO2 therefore serves as a noninvasive measure of pulmonary blood flow and therefore CO. In 17 successfully resuscitated animals. ETCO2 during precordial compression averaged 1.7 +/- 0.2%, whereas it was only 0.5 +/- 0.1% in five animals in whom resuscitation procedures were unsuccessful (p less than .001). Accordingly, ETCO2 prognosticates outcome during CPR and immediately identifies restoration of spontaneous circulation.

Hofmeister, EH, Brainard, BM, Egger, CM & Kang, S 2009, 'Prognostic indicators for dogs and cats with cardiopulmonary arrest treated by cardiopulmonary cerebral resuscitation at a university teaching hospital', *J Am Vet Med Assoc*, vol. 235, no. 1, pp. 50-7.

LOE: 5. Quality: Fair. Direction: Supportive.

Notes: Prospective observational clinical study of target species (dogs and cats). End tidal CO2 was used to diagnosed cardiopulmonary arrest in some animals clinically. End tidal CO2 may be used to prognosticate for return of spontaneous circulation.

Abstract
OBJECTIVE:
To determine the association among signalment, health status, other clinical variables, and treatments and events during cardiopulmonary cerebral resuscitation (CPCR) with the return of spontaneous circulation (ROSC) for animals with cardiopulmonary arrest (CPA) in a veterinary teaching hospital.

DESIGN:
Cross-sectional study.

ANIMALS:
161 dogs and 43 cats with CPA.

PROCEDURES:
Data were gathered during a 60-month period on animals that had CPA and underwent CPCR. Logistic regression was used to evaluate effects of multiple predictors for ROSC.

RESULTS:
56 (35%) dogs and 19 (44%) cats had successful CPCR. Twelve (6%) animals (9 dogs and 3 cats) were discharged from the hospital. Successfully resuscitated dogs were significantly more likely to have been treated with mannitol, lidocaine, fluids, dopamine, corticosteroids, or vasopressin; had CPA while anesthetized; received chest compressions while positioned in lateral recumbency; and had a suspected cause of CPA other than hemorrhage or anemia, shock, hypoxemia, multiple organ dysfunction syndrome, cerebral trauma, malignant arrhythmia, or an anaphylactoid reaction and were less likely to have been treated with multiple doses of epinephrine, had a longer duration of CPA, or had multiple disease conditions, compared with findings in dogs that were not successfully resuscitated. Successfully resuscitated cats were significantly more likely to have had more people participate in CPCR and less likely to have had shock as the suspected cause of CPA, compared with findings in cats that were not successfully resuscitated.

CONCLUSIONS AND CLINICAL RELEVANCE:
The prognosis was grave for animals with CPA, except for those that had CPA while anesthetized.

Idris, AH, Staples, ED, O'Brien, DJ, Melker, RJ, Rush, WJ, Del Duca, KD & Falk, JL 1994a, 'Effect of ventilation on acid-base balance and oxygenation in low blood-flow states', *Crit Care Med*, vol. 22, no. 11, pp. 1827-34.
LOE: 6. Quality: Fair. Direction: Neutral.
Notes: This study demonstrated that both ventilation and cardiac output influences EtCO2 in low blood-flow states.
Abstract
OBJECTIVES:
To investigate how minute ventilation affects the partial pressure of end-tidal CO2 and arterial and mixed venous pH, PCO2, PO2, and the concentration of bicarbonate during low blood-flow states. We tested the null hypothesis that acid-base conditions during low rates of blood flow are not significantly different when minute ventilation is doubled or halved.

DESIGN:
Prospective, experimental, animal study.

SETTING:
University hospital laboratory.

SUBJECTS:
Domestic swine.

INTERVENTIONS:
We studied ten anesthetized and mechanically ventilated swine (weight, 43 to 102 kg) in a new model of controlled systemic and pulmonary blood flow in which each animal was maintained on ventricular assist devices. After electrical induction of ventricular fibrillation, ventricular assist device blood flow was decreased in steps. At each decrease, control minute ventilation, two times the control minute ventilation (hyperventilation), and one-half the control minute ventilation (hypoventilation) were administered; each ventilatory change was maintained for 6 mins.

MEASUREMENTS AND MAIN RESULTS:
Aortic, pulmonary arterial and central venous pressures, ventricular assist device blood flow, and end-tidal CO2 were recorded continuously. Acid-base conditions were studied at three different mean blood flow rates: 49%, 30%, and 12% of baseline prearrest cardiac index. Arterial pH and PaO2 and mixed venous pH varied directly ($p < .003$) with minute ventilation, while PaCO2 and mixed venous PCO2, and end-tidal CO2 varied inversely ($p < .0001$) with minute ventilation. Mixed venous PO2 was not significantly related to minute ventilation ($p = .6$). PaCO2 and arterial bicarbonate; mixed venous pH, mixed venous PO2, and mixed venous bicarbonate, and end-tidal CO2 varied directly ($p < .001$) with blood flow, while mixed venous PCO2 varied inversely with blood flow ($p < .05$). Arterial pH was not significantly related to blood flow ($p = .3$). When minute ventilation changed from hyperventilation to hypoventilation at a mean blood flow rate of 49%, mean arterial pH decreased 0.22 +/- 0.06 ($p < .05$), mean PaCO2 increased 28 +/- 6 torr (3.7 +/- 0.8 kPa) ($p < .05$), and mean PaO2 decreased 99 +/- 77 torr (13.2 +/- 10 kPa); mean mixed venous pH decreased 0.11 +/- 0.02, mean mixed venous PCO2 increased 16 +/- 2.2 torr (2.1 +/- 0.3 kPa) ($p < .05$), and mean mixed venous PO2 did not change; mean end-tidal CO2 increased 18 +/- 2 torr (2.4 +/- 0.3 kPa) ($p < .05$). The effect of changes in minute ventilation on blood gases and end-tidal CO2 was similar for mean blood flow rates of 30% and 12% of baseline cardiac index.

CONCLUSIONS:

During low rates of blood flow similar to those rates found in shock and cardiopulmonary resuscitation, alterations in minute ventilation significantly influenced end-tidal CO2 and both arterial and mixed venous pH and PCO2. These findings may have clinical importance in improving the treatment of shock and cardiac arrest.

Idris, AH, Staples, ED, O'Brien, DJ, Melker, RJ, Rush, WJ, Del Duca, KD & Falk, JL 1994b, 'End-tidal carbon dioxide during extremely low cardiac output', *Ann Emerg Med*, vol. 23, no. 3, pp. 568-72.

LOE: 6. Quality: Fair. Direction: Supportive.

Notes: This study demonstrated the close correlation of EtCO2 with cardiac output at low cardiac-output state in an experimental porcine model. Minute ventilation was kept constant.

Abstract

STUDY OBJECTIVE:

A number of studies have shown that expired CO2 concentration is closely related to cardiac output, but that cardiac output was not controlled as an independent variable. In addition, the partial pressure of end-tidal CO2 (PETCO2) during extremely low cardiac output has not been reported. The objective of the present study was to measure PETCO2 during well-controlled, very low blood flow rates under conditions of constant minute ventilation.

DESIGN:

Ten anesthetized, intubated, and mechanically ventilated swine (weight, 43 to 102 kg) were placed on two ventricular assist devices in order to control cardiac output. Minute ventilation was measured and kept constant. Ventricular assist device output (measured with an ultrasonic flow probe); PETCO2; and aortic, pulmonary artery, and central venous pressures were recorded continuously.

INTERVENTIONS:

After electrical induction of ventricular fibrillation, pump output was decreased in steps.

MEASUREMENTS AND MAIN RESULTS:

Cardiac index ranged from 0 to 5,371 mL/min/m2; 59% of PETCO2 measurements were made at cardiac indexes of less than 1,313 mL/min/m2 (30 mL/min/kg). The relationship of PETCO2 levels to cardiac index was determined with linear regression analysis; $P < .05$ was statistically significant. PETCO2 correlated significantly with cardiac index ($P < .0001$). The best-fit line by least-squares analysis produced the equation: PETCO2 = 4.98 + 0.012 [cardiac index] ($r2 = .82$).

CONCLUSION:

Under conditions of constant minute ventilation, PETCO2 correlated closely with cardiac index over a large range of blood flow rates, including extremely low rates.

Isserles, SA & Breen, PH 1991, 'Can changes in end-tidal PCO2 measure changes in cardiac output?' *Anesth Analg*, vol. 73, no. 6, pp. 808-14.

LOE: 6. Quality: Fair. Direction: Supportive.

Notes: This study demonstrated the correlation between cardiac output and EtCO2 in experimental canine models.

Abstract

In recent studies of cardiopulmonary resuscitation, an increase in end-tidal carbon dioxide tension (PETCO2) signifies an increase in cardiac output (QT) as spontaneous circulation resumes. We hypothesized that changes in QT might generally be measured by changes in PETCO2. In five pentobarbital-anesthetized dogs, we inflated percutaneously inserted vena cava balloons to impede venous return and to decrease QT (measured by pulmonary thermodulation). The PECTCO2 was measured at the airway opening by sidestream infrared capnometry. In 32 vena cava balloon inflation sequences during constant ventilation in five dogs, the percent

decrease in PETCO2 directly correlated with the percent decrease in QT (slope = 0.73, R2 = 0.89, P less than 0.001). During decreased QT, reduced CO2 delivery to the lungs decreased alveolar PCO2 to cause part of the decrease in PETCO2. The remaining reduction in PETCO2 resulted from the increase in alveolar dead space (in turn due to lower pulmonary perfusion pressures during reduced QT), which diluted the CO2 from perfused alveolar spaces to further reduce PETCO2. During a sustained reduction in QT, increasing CO2 accumulation in the peripheral tissues and in venous blood began to restore CO2 delivery to the lung and PETCO2 toward baseline levels. Reciprocal changes occurred during increases in QT when the vena cava balloons were deflated. The linear relationship between changes in PETCO2 and QT in animals supports a decision to perform clinical studies necessary to determine whether a change in PETCO2 will be useful as a noninvasive, continuous monitor of a change in QT during anesthesia or intensive care.

Kern, KB, Sanders, AB, Voorhees, WD, Babbs, CF, Tacker, WA & Ewy, GA 1989, 'Changes in expired end-tidal carbon dioxide during cardiopulmonary resuscitation in dogs: a prognostic guide for resuscitation efforts', *J Am Coll Cardiol*, vol. 13, no. 5, pp. 1184-9.

LOE: 3. Quality: Fair. Direction: Supportive.

Notes: This study demonstrated correlation between EtCO2 and coronary pefusion pressure. End tidal CO2 fell right after the cardiac arrest. The differences of EtCO2 and coronary perfusion pressure between dogs that achieved return of spontaneous circulation and those that did not were observed.

Abstract

Expired end-tidal carbon dioxide (PCO2) measurements made during cardiopulmonary resuscitation have correlated with cardiac output and coronary perfusion pressure when wide ranges of blood flow are included. The utility of such measurements for predicting resuscitation outcome during the low flow state associated with closed chest cardiopulmonary resuscitation remains uncertain. Expired end-tidal PCO2 and coronary perfusion pressures were measured in 15 mongrel dogs undergoing 15 min of closed chest cardiopulmonary resuscitation after a 3 min period of untreated ventricular fibrillation. In six successfully resuscitated dogs, the mean expired end-tidal PCO2 was significantly higher than that in nine nonresuscitated dogs only after 14 min of cardiopulmonary resuscitation (6.2 +/- 1.2 versus 3.4 +/- 0.8 mm Hg; p less than 0.05). No differences in expired end-tidal PCO2 values were found at 2, 7 or 12 min of cardiopulmonary resuscitation. A significant decline in end-tidal PCO2 levels during the resuscitation effort was seen in the nonresuscitated group (from 6.3 +/- 0.8 to 3.4 +/- 0.8 mm Hg; p less than 0.05); the successfully resuscitated group had constant PCO2 levels throughout the 15 min of cardiac arrest (from 6.8 +/- 1.1 to 6.2 +/- 1.2 mm Hg). Changes in expired PCO2 levels during cardiopulmonary resuscitation may be a useful noninvasive predictor of successful resuscitation and survival from cardiac arrest.

Lepilin, MG, Vasilyev, AV, Bildinov, OA & Rostovtseva, NA 1987, 'End-tidal carbon dioxide as a noninvasive monitor of circulatory status during cardiopulmonary resuscitation: a preliminary clinical study', *Crit Care Med*, vol. 15, no. 10, pp. 958-9.

LOE: 6. Quality: Poor. Direction: Supportive.

Notes: This study demonstrated the correlation between EtCO2 and cardiac output in a small number of human cardiac arrest patients.

Abstract

In four postoperative cardiac patients during controlled ventilation, acute circulatory failure was associated with decreases in end-tidal CO2 (PetCO2) and cardiac index. Closed cardiac compression caused an increase in both PetCO2 and cardiac index, with complete restoration to baseline values after successful CPR. Our data indicate that PetCO2 measurements during controlled ventilation in acute circulatory failure patients may be used as an indirect noninvasive tool to monitor the patient's hemodynamic status during CPR.

Lewis, LM, Stothert, J, Standeven, J, Chandel, B, Kurtz, M & Fortney, J 1992, 'Correlation of end-tidal CO2 to cerebral perfusion during CPR', *Ann Emerg Med*, vol. 21, no. 9, pp. 1131-4.
LOE: 6. Quality: Fair. Direction: Supportive.
Notes: This study demonstrated the correlation between EtCO2 and cardiac output during cardiopulmonary resuscitation. The correlation between EtCO2 and cerebral perfusion pressure only present when cardiac output and cerebral perfusion pressure correlated as well.
Abstract
STUDY OBJECTIVE:
A number of studies have demonstrated a correlation between end-tidal carbon dioxide (ETCO2), cardiac output, and return of spontaneous circulation in experimental animals and in patients undergoing closed-chest CPR. Our study attempted to correlate ETCO2 to cerebral blood flow during cardiac arrest.

DESIGN:
Sixteen piglets were anesthetized, intubated, and instrumented for cerebral blood flow studies. An ultrasonic flow probe was placed on both internal carotid arteries for continuous flow measurements. The animal was fibrillated, and closed-chest CPR was begun. Continuous ETCO2 measurements were obtained and compared with simultaneous internal carotid, cardiac output, and cerebral blood flow measurements.

MEASUREMENTS AND MAIN RESULTS:
Correlations between ETCO2 and carotid and cerebral blood flow were determined using Pearson's method. The correlation between ETCO2 and total internal carotid flow was .58 (P = .01, Bonferroni's adjusted P = .30). Correlation between ETCO2 and cerebral blood flow was .64 (P = .01, Bonferroni's adjusted P = .09). A partial correlation coefficient for ETCO2 versus cardiac output was .70, whereas it was only .30 for ETCO2 versus cerebral blood flow.

CONCLUSION:
Partial correlation coefficients suggest that ETCO2 correlates with cerebral blood flow when changes in cerebral blood flow parallel changes in cardiac output.

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*, vol. 21, no. 10, pp. 1572-6.
LOE: 3. Quality: Fair. Direction: Neutral.
Notes: This study demonstrated that small increase in EtCO2 occurred during cardiopulmonary resuscitation when cardiac output is held constant. Possible theory proposed for such as increase include changes in pulmonary capillary blood flow and tissue CO2 production.
Abstract
OBJECTIVES:
To evaluate a) whether end-tidal CO2 values change under constant cardiac output during cardiopulmonary resuscitation (CPR), and b) what factors are responsible for the change.

DESIGN:
A cohort study.

SETTING:
University research laboratory.

SUBJECTS:
Nine mongrel dogs.

INTERVENTIONS:

Ventricular fibrillation was electrically induced. After 2 mins, open-chest cardiac massage was initiated to maintain cardiac output at 0.2 L/min (23% of baseline cardiac output) by the measurement of blood flow with an electromagnetic flow probe on the ascending aorta. The cardiac massage was kept constant until 50 mins after the induction of ventricular fibrillation.

MEASUREMENTS AND MAIN RESULTS:
Before and during ventricular fibrillation, end-tidal CO2, minute volume of alveolar ventilation, and CO2 excretion were continuously monitored. Blood gases and oxygen saturation values were also measured in arterial and the mixed venous blood samples. CO2 content was calculated. After induction of ventricular fibrillation, end-tidal CO2 decreased and thereafter continued to increase until the end of the experiment. Two mechanisms may have contributed to the early reduction in end-tidal CO2. One mechanism is a further decrease in CO2 excretion compared with the reduction in alveolar ventilation and the other is an increase in alveolar deadspace (estimated from the increase in the difference between PaCO2 and end-tidal CO2). The subsequent increase in end-tidal CO2 was mainly due to a change in CO2 excretion. There are two hypotheses concerning the subsequent increase in CO2 excretion: the increase in pulmonary capillary blood flow (estimated from the change in the arteriovenous CO2 content gradient) and the increase in CO2 production itself.

CONCLUSIONS:
End-tidal CO2 changes under constant cardiac output during CPR. When end-tidal CO2 is used to estimate the effectiveness of the cardiac massage, this type of change must be recognized.

Ornato, JP, Garnett, AR & Glauser, FL 1990, 'Relationship between cardiac output and the end-tidal carbon dioxide tension', *Ann Emerg Med*, vol. 19, no. 10, pp. 1104-6.
LOE: 6. Quality: Fair. Direction: Supportive.
Notes: This study used hemorrhagic shock sheep model to demonstrate the correlation between EtCO2 and cardiac output.
Abstract
STUDY OBJECTIVE:
To further define the relationship between cardiac output (CO) and end-tidal carbon dioxide tension (ETCO2) at various levels of systemic flow.

DESIGN:
Prospective, controlled laboratory investigation.

SETTING:
Animal laboratory.

TYPE OF PARTICIPANTS:
Fourteen anesthetized, intubated sheep weighing 23 to 47 kg.

INTERVENTIONS:
One hundred seventy-two simultaneous measurements of thermodilution CO and ETCO2 were made during controlled arterial hemorrhage. After a 30-minute baseline control period, CO was sampled from approximately 0.6 to more than 8.0 L/min during a 60- to 90-minute period of controlled hemorrhage.

MEASUREMENTS:
Thermodilution CO; arterial pressure using fluid-filled plastic 14-gauge catheters; ETCO2 using an infrared analyzer.

MAIN RESULTS:

A plot of CO versus ETCO2 suggested that the relationship was logarithmic rather than linear. Linear regression showed that ETCO2 was significantly related (r = .91; P less than .001) to a logarithmic transformation of the CO.

CONCLUSIONS:
The relationship between CO and ETCO2 is logarithmic. Decreased presentation of CO2 to the lungs is the major, rate-limiting determinant of the ETCO2 during low flow. As the CO increases during resuscitation from shock or cardiac arrest, respiration becomes the rate-limiting controller of the ETCO2 (after the tissue washout of CO2 has occurred). Under such conditions, the ETCO2 provides useful information about the adequacy of ventilation provided that there is little ventilation/perfusion mismatch.

Pokorna, M, Necas, E, Kratochvil, J, Skripsky, R, Andrlik, M & Franek, O, 2010, 'A sudden increase in partial pressure end-tidal carbon dioxide (P(ET)CO(2)) at the moment of return of spontaneous circulation', *J Emerg Med*, vol. 38, no. 5, pp. 614-21.
LOE: 6. Quality: Fair. Direction: Supportive.
Notes: During advanced life support, a sudden increase of EtCO2 greater than 10mmHg indicates return of spontaneous circulation in humans.
Abstract
BACKGROUND:
Previous studies established that a level of partial pressure end-tidal carbon dioxide (P(ET)CO(2)) of 10 mm Hg divided patients undergoing advanced life support (ALS) into those likely to be resuscitated (values > 10 mm Hg) and those likely to die during ALS (values < 10 mm Hg). Objective: The study tested the significance of a sudden increase in the P(ET)CO(2) in signaling the return of spontaneous circulation (ROSC) during ALS.

MATERIAL AND METHODS:
P(ET)CO(2) values were continuously recorded during ALS in out-of-hospital patients with cardiac arrest. Constant ventilation was maintained by an automatic device. There were 108 patients, representing two extreme outcomes of ALS, who were subdivided into two groups. The first group included 59 patients with a single ROSC followed by a stable spontaneous circulation. The second group included 49 patients with no signs of ROSC. Results: ROSC was associated with a sudden increase in P(ET)CO(2) that remained significantly higher than before ROSC. P(ET)CO(2) did not rise during the entire ALS in the second group of patients without ROSC and was lower than in the first group of patients.

CONCLUSIONS:
In constantly ventilated patients, P(ET)CO(2) is significantly higher (about 10 mm Hg) after ROSC than before ROSC. A sudden increase in P(ET)CO(2) exceeding 10 mm Hg may indicate ROSC. Consequently, the rule of 10 mm Hg may be extended to include a sudden increase in continuously recorded P(ET)CO(2) by more than 10 mm Hg as an indicator of the possibility of ROSC.

Reindl, S & Matis, U 1998, 'Detection of embolic events by capnography and trans-oesophageal echocardiography during total hip replacement'. *Vet Comp Orthop Traumatol*, vol.11, no. 2, pp.68-75.
LOE: 6. Quality: Fair. Direction: Opposing.
Notes: This study documented the correlation between the changes in EtCO2 and the severity of embolaemia in dogs undergoing total hip replacement surgery.

Abstract
Trans-oesophageal echocardiography and continuous monitoring of the partial pressure of carbon dioxide at end expiration ($P_{ET}CO_2$) were performed in 63 dogs during total hip replacement and in 3 dogs during femoral stem revision. The $P_{ET}CO_2$ usually did not change during insertion of the acetabular prosthesis, but in 17.5% of the cases, it decreased by more than 10 mmHg after insertion of the femoral prosthesis. In all of the cases,

trans-oesophageal echocardiography revealed echogenic structures in the right side of the heart, immediately after insertion of the acetabular and of the femoral prostheses. These appeared as either numerous pinpoint echoes, which passed through the right side of the heart in a "snow flurry" like fashion, or more echogenic particles. The embolaemia, seen ultrasonographically, was categorized into one of six grades of severity. Statistical analysis showed significant positive correlations between the severity of the embolaemia and the extent of the decrease in $P_{ET}CO_2$ (rs = 0.405; P = 0.001; n = 60), and between the severity of the embolaemia and the duration of the decrease in $P_{ET}CO_2$ before it returned to baseline values (rs = 0.345; P = 0.007; n = 60). Trans-oesophageal echocardiography demonstrated that embolaemia was induced during cemented prosthesis insertion. It was proposed that an increase in intramedullary pressure, during insertion, forces bone marrow into the venous circulation. Bone marrow itself can constitute an embolus, but also it may activate intravascular coagulation, thus leading to thromboembolism, in addition to bone marrow embolism. Elongated particulate emboli, up to several centimetres in length, were seen on ultrasonogrammes and were thought to be, at least in part, products of intravascular coagulation. A significant decrease in the platelet concentration in peripheral venous blood, after insertion of the femoral prosthesis, was also indicative of intravascular coagulation. The extent of the impairment of gas exchange was documented by means of capnography. The significant positive correlation between the embolaemia, seen via ultrasonography, and the decrease in $P_{ET}CO_2$ strongly suggest a causal relationship between the two variables. The rapid recovery, that occurred in most patients, is attributed to the enormous lytic ability of pulmonary tissue. Prophylactic measures include the maintenance of normovolaemia during the operations, thorough lavage of the intramedullary cavity before prosthesis insertion and steps to prevent an increase in intramedullary pressure during implantation.

Sanders, AB, Atlas, M, Ewy, GA, Kern, KB & Bragg, S 1985a, 'Expired PCO2 as an index of coronary perfusion pressure', *Am J Emerg Med*, vol. 3, no. 2, pp. 147-9.
LOE: 3. Quality: Fair. Direction: Supportive.
Notes: This study demonstrated the correlation between EtCO2 and coronary perfusion pressure in experimental canine cardiac arrest model.

Abstract
Presently, there is no reliable noninvasive method of assessing the adequacy of cardiopulmonary resuscitation (CPR). Studies of animals have shown that during prolonged arrest the coronary perfusion pressure (CPP) is correlated with successful resuscitation. During previous studies it appeared that expired PCO2 correlated with CPP. To investigate this relationship, eight mongrel dogs (mean weight, 22.7 +/- 5.8 kg) were anesthetized with pentobarbital. Catheters were placed in the thoracic aorta and right atrium of each dog. Each animal was electrically fibrillated, and CPR was started using mechanical resuscitator. The PCO2 was determined at end expiration using a Hewlett Packard 47210A Capnometer with the electrode attached to the endotracheal tube. After 10, 15, 20, or 25 minutes of ventricular fibrillation and closed-chest massage, a thoracotomy was performed, and internal massage was begun. Coronary perfusion pressure was calculated at least each minute and correlated with the PCO2 values. A correlation coefficient of 0.78 was calculated based on 368 data points for eight dogs (P less than 0.01). The results of this study indicate that expired PCO2 is positively correlated with CPP in the canine model of CPR. Inasmuch as CPP correlates with survival in prolonged CPR, the noninvasive measurement of PCO2 may be a useful method of assessing the adequacy of CPR.

Sanders, AB, Ewy, GA, Bragg, S, Atlas, M & Kern, KB 1985b, 'Expired PCO2 as a prognostic indicator of successful resuscitation from cardiac arrest', *Ann Emerg Med*, vol. 14, no. 10, pp. 948-52.
LOE: 3. Quality: Fair. Direction: Supportive.
Notes: Canine cardiac arrest model was used in this study. Dogs that received higher chest compression force had higher EtCO2 and were more likely to achieve return of spontaneous circulation. This study also demonstrated the correlation between EtCO2 and coronary perfusion pressure.

Abstract
We performed a study to determine if the measurement of expired PCO2 during CPR for cardiac arrest could be used as a prognostic indicator of successful resuscitation. Twelve mongrel dogs were fibrillated electrically, and external chest massage and assisted ventilation were applied for 15 minutes. Expired PCO2 and aortic and right atrial pressures were monitored each minute of arrest. Coronary perfusion pressure (CPP) was calculated by subtracting the right atrial from the aortic diastolic pressure. Half the dogs received high-force chest compression (80 lb) and half received low-force chest compression (40 lb). The six dogs that received high-force compression were resuscitated successfully. The expired PCO2 was significantly higher in the successfully resuscitated dogs (expired PCO2 = 9.6 +/- 3.2 mm Hg) when compared to those dogs that died (expired PCO2 = 3.2 +/- 1.1 mm Hg, P less than .01). Expired PCO2 was highly correlated (r = 0.91, P less than .01) with the CPPs. The measurement of expired PCO2 during attempted CPR may be useful as a noninvasive indicator of CPP and adequate technique. Further studies on the use of this technique as an assessment criterion are warranted.

Sehra, R, Underwood, K & Checchia, P 2003, 'End tidal CO2 is a quantitative measure of cardiac arrest', *Pacing Clin Electrophysiol*, vol. 26, no. 1 Pt 2, pp. 515-7.
LOE: 6. Quality: Fair. Direction: Supportive.
Notes: This study demonstrated changes in EtCO2 correlating to cardiac output during episdoes of ventricular fibrillation in human patients receiving defibrillator implant.
Abstract
PURPOSE OF THE STUDY:
Predictors of severity of cardiac arrest or efficacy of cardiopulmonary resuscitation are few. Respiratory end tidal CO2 (ETCO) is a marker of pulmonary blood flow and, possibly, cardiac arrest. The purpose of this study was to evaluate ETCO as a quantitative marker of cardiac arrest in a human model of ventricular fibrillation (VF).

METHODS:
Thirty-one cardiac arrest/VF episodes (mean BP < 40 mmHg) in 8 men and 3 women mean age = 42 +/- 24 years, mean left ventricular ejection fraction = 39%) undergoing defibrillator (ICD) implant for ventricular tachycardia or previous cardiac arrest were evaluated with continuous ETCO monitoring during defibrillation threshold testing. All patients but one were intubated.

RESULTS:
Significant differences (P < 0.001) were noted between ETCO values prior (mean 37.2 +/- 6.8 mmHg) versus during VF (mean 27.1 +/- 5.9 mmHg), and during VF versus return of spontaneous circulation (mean 36.6 +/- 6.6 mmHg). ETCO decreased by 23% +/- 8% from pre-VF to during VF. It increased by 37% +/- 16% during VF to return of spontaneous circulation. These changes were significantly different (P < 0.001).

CONCLUSION:
Significant changes in ETCO were measured during VF arrest. ETCO can predict acute cardiac arrest in a quantitative manner.

Seliskar, A, Nemec, A & Butinar, J 2006, 'The relationship between end-tidal CO2, mean arterial blood pressure and neuroendocrine response in canine haemorrhagic shock'. *Acta Veterinaria (Beograd)*, vol. 56, no. 4, pp. 295-304.
LOE: 6. Quality: Fair. Direction: Supportive.
Nots: This study demonstrated the correlation of EtCO2 with cardiac output in a canine hemorrhagic shock model. Mean arterial blood pressure did not correlate with cardiac output as well as EtCO2.
Abstract

The relationship between end-tidal CO2 (ETCO2), mean arterial blood pressure (MAP) and neuroendocrine response was investigated in experimentally induced haemorrhagic shock in six anaesthetized, spontaneously breathing dogs. One third of the calculated whole blood volume, i.e. 30 ml/kg was gradually withdrawn in 32 minutes. After 16 minutes, the blood was transfused to the dogs. Blood samples were taken regularly for plasma adrenaline, noradrenaline, beta-endorphin and serum cortisol levels. MAP and ETCO2 decreased simultaneously during the withdrawal period. MAP increased before resuscitation commenced due to the increased sympathetic response, confirmed by high adrenalin levels. ETCO2 remained low, suggesting that ETCO2 reflects changes in cardiac output earlier during resuscitation when compared to MAP. Adrenaline, noradrenaline, beta-endorphin and cortisol levels increased during haemorrhagic shock and slowly decreased during resuscitation. The results of the study proved a good correlation and clinical relevance of ETCO2 and MAP during development of haemorrhagic shock while the difference between ETCO2 and MAP increased during resuscitation, suggesting the influence of sympathetic response, confirmed by increased levels of adrenaline. According to a proven positive correlation between ETCO2 and cardiac output during haemorrhagic shock, the results suggest that ETCO2 may be used as a better indicator of haemodynamic events when compared to MAP during a resuscitation period in haemorrhagic shock.

Shibutani, K, Muraoka, M, Shirasaki, S, Kubal, K, Sanchala, VT & Gupte, P 1994, 'Do changes in end-tidal PCO2 quantitatively reflect changes in cardiac output?' *Anesth Analg*, vol. 79, no. 5, pp. 829-33.
LOE: 6. Quality: Poor. Direction: Supportive.
Notes: This study demonstrated correlation of EtCO2 and cardiac output in patients undergoing aortic aneurysm surgery.
Abstract
In anesthetized patients, acute decreases in cardiac output (CO) are often reflected as decreases in end-tidal CO2 tension (PETCO2), but the quantitative relationship between the changes in CO and the changes in PETCO2 is uncertain. We hypothesize that a quantitative relationship can be demonstrated if timing of the measurements in each episode of hemodynamic perturbation is standardized. In 24 patients undergoing abdominal aortic aneurysm surgery with constant ventilation, we prospectively performed 33 measurements of CO, PETCO2, and CO2 elimination (VECO2) within 10 min of hemodynamic changes. The percent decrease in PETCO2 directly correlated with the percent decrease in CO (slope = 0.33, r2 = 0.82). Also, the percent decrease in VECO2 correlated with the percent decrease in CO similarly (slope = 0.28, r2 = 0.84). The changes in PETCO2 and VECO2 following hemodynamic perturbation were parallel. This finding suggests that decreases in PETCO2 quantitatively reflect the decreases in CO2 elimination.

Steedman, DJ & Robertson, CE 1990, 'Measurement of end-tidal carbon dioxide concentration during cardiopulmonary resuscitation', *Arch Emerg Med*, vol. 7, no. 3, pp. 129-34.
LOE: 6. Quality: Poor. Direction: Supportive.
Notes: This study documented the observation that EtCO2 increases suddenly at the return of spontanous circulation.
Abstract
End-tidal carbon dioxide concentrations were measured prospectively in 12 cardiac arrest patients undergoing cardiopulmonary resuscitation (CPR) in an accident and emergency department. The end-tidal carbon dioxide (CO2) concentration decreased from a mean (+/- SD) of 4.55 +/- 0.88% 1 min after chest compression and ventilation was established, to values ranging from 2.29 +/- 0.84% at 2 min to 1.56 +/- 0.66% following 8 min of CPR. Spontaneous circulation was restored in five patients. This was accompanied by a rapid rise in end-tidal CO2 which peaked at 2 min (3.7 +/- 1.08%). Changes in end-tidal CO2 values were often the first indication of return of spontaneous cardiac output. There was a significant difference in the end-tidal CO2 in patients undergoing CPR before return of spontaneous circulation (2.63 +/- 0.32%) and patients who failed to develop spontaneous output (1.64 +/- 0.89%) ($p < 0.001$). We conclude that measurement of end-tidal CO2

concentration provides a simple and non-invasive method of measuring blood flow during CPR and can indicate return of spontaneous circulation.

Trevino, RP, Bisera, J, Weil, MH, Rackow, EC & Grundler, WG 1985, 'End-tidal CO2 as a guide to successful cardiopulmonary resuscitation: a preliminary report', *Crit Care Med*, vol. 13, no. 11, pp. 910-1.
LOE: 6. Quality: Fair. Direction: Supportive.
Notes: This study demonstrated changes in EtCO2 during cardiopulmonary resuscitation of a experimental porcine cardiac arrest model.
Abstract
Utilizing a well-established porcine model of cardiac arrest, we found that end-tidal CO2 concentration (ETCO2) strikingly decreased to approximately 24% of control levels, immediately after cardiac arrest and before precordial compression. During precordial compression, ETCO2 progressively increased to 46% of control values in successfully resuscitated animals but only to 26% in animals which failed to respond to resuscitation efforts. After successful resuscitation, ETCO2 rapidly returned to baseline values. These data indicate that ETCO2 may be a useful monitor for assessing the adequacy of CPR.

Weil, MH, Bisera, J, Trevino, RP & Rackow, EC 1985, 'Cardiac output and end-tidal carbon dioxide', *Crit Care Med*, vol. 13, no. 11, pp. 907-9.
LOE: 6. Quality: Fair. Direction: Supportive.
Notes: This study demonstrated the correlation between EtCO2 and cardiac output in an experimental porcine cardiac arrest model.
Abstract
Previous studies demonstrated selective increases in mixed venous carbon dioxide tension (PvCO2) during CPR in a porcine model of cardiac arrest. This was associated with a decrease in end-tidal carbon dioxide concentration (ETCO2), possibly due to a critical reduction in cardiac output and therefore pulmonary blood flow during CPR. We investigated the relationship between ETco2 and cardiac output before cardiac arrest and during CPR. Observations in 19 minipigs confirmed a high linear correlation between ETco2 and cardiac output. We conclude that the increase in Pvco2 and the concurrent decrease in ETco2 reflect a critical reduction in cardiac output, which reduces alveolar blood flow to the extent that carbon dioxide clearance by the lung fails to keep pace with systemic CO2 production.

Xie, J, Weil, MH, Sun, S, Yu, T & Tang, W 2004, 'Spontaneous gasping generates cardiac output during cardiac arrest', *Crit Care Med*, vol. 32, no. 1, pp. 238-40.
LOE: 6. Quality: Fair. Direction: Supportive.
Notes: In this study of porcine cardiac arrest model, changes in EtCO2 correlated to the increase in stroke volume, coronary perfusion pressure and aortic pressure at each spontaneous gasping episodes.
Abstract
OBJECTIVES:
To measure stroke volumes coincident with spontaneous gasping during untreated ventricular fibrillation and to evaluate the effects of gasping.

DESIGN:
Prospective study in laboratory animals.

SETTING:
University-affiliated research institute.

SUBJECTS:
Male Yorkshire-X domestic pigs.

INTERVENTIONS:
Pigs were anesthetized (ketamine, 20 mg/kg intramuscularly and sodium pentobarbital, 30 mg/kg intravenously), intubated, and mechanically ventilated. Ventricular fibrillation was electrically induced and untreated for 7 mins. The right femoral artery and vein were cannulated. A 5.5/7.5-MHz biplanar transesophageal echocardiography transducer was advanced into the esophagus.

MEASUREMENTS AND MAIN RESULTS:
Stroke volumes were measured as the product of the transaortic blood flow velocity and transesophageal echocardiographic measurements of valve area. In addition, left ventricular volumes were echocardiographically estimated at peak inspiration and at peak expiration of each gasp by transesophageal methods. The stroke volume produced by gasping averaged 23 +/- 6 mL, which represented approximately 60% of a precardiac arrest stroke volume (38 +/- 8 mL, $p < .001$). Increases in end-tidal carbon dioxide tension coincident with each gasp were consistent with comparable increases in pulmonary blood flow and therefore stroke volumes. Both were associated with increases in aortic pressure from 20 +/- 3 to 33 +/- 8 mm Hg ($p < .001$) and coronary perfusion pressure from 4 +/- 3 to 13 +/- 7 mm Hg ($p < .001$).

CONCLUSIONS:
Our studies confirm that preterminal gasping during ventricular fibrillation increases both ventilation and forward blood flow.