



Evaluation of variables to describe the shape of volumetric capnography curves during bronchoconstriction in dogs

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ABSTRACT

The aim of the study was to investigate changes in volumetric capnography (V_C) variables during bronchoconstriction in dogs and compare it with total respiratory resistance (R_L) measured with a Fleisch pneumotachograph. Six dogs were challenged with increasing concentrations of carbachol until obvious signs of bronchoconstriction were seen. All V_C parameters were obtained before, directly after, 10 and 20 min after maximal bronchoconstriction. The slope of phase III (SIII) and airway and alveolar dead space parameters were significantly different from baseline directly after the challenge. The V_C curve obtained a typical shape at the time of maximal bronchoconstriction and a trend to return to baseline shape was seen over time. A significant correlation was found for all aforementioned parameters with R_L . We conclude that the shape of the V_C curve in combination with dead space calculation can be used to verify bronchoconstriction on a breath-to-breath basis.

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1. Introduction

Volumetric capnography (V_C) or the single-breath test of CO_2 is a method used for analysis of dead space values at the bedside in ventilated and spontaneously breathing subjects (Ferrer et al., 1998; Fletcher and Jonson, 1984; Fletcher et al., 1981; Prisk et al., 1994; West et al., 1957). It is a simple automated method to follow dead space changes over time where expiratory partial pressure of CO_2 is plotted against the expired volume.

Different variables of V_C have been used to detect lung pathology. The slope of phase II (SII) and phase III (SIII) of the V_C curve are of particular interest as these variables indicate improvement or aggravation of pulmonary dead space as well as pulmonary ventilation and/or perfusion on a breath-by-breath basis (Blanch et al., 1994; Boehm et al., 2009; Romero et al., 1997; Tusman et al., 2005; Tusman et al., 2004). A combination of SIII and the Bohr dead space has been used to differentiate between asthma and emphysema with the same degree of airway obstruction (Kars et al., 1997). A direct correlation was found between the severity of bronchocon-

striction and changes in SIII (Kars et al., 1997). Romero et al. (2007) found a direct correlation between SII and SIII in awake non-ventilated humans.

The diagnose of bronchoconstriction in spontaneously breathing anaesthetised animals remains challenging.

The aim of the present study was to follow the shape of the V_C curve over a period of severe provoked bronchoconstriction and investigate the usefulness of SII, SIII and dead space parameters to diagnose bronchoconstriction in spontaneously breathing anaesthetised dogs by correlating the derived indices with conventionally used markers of bronchoconstriction namely total pulmonary resistance.

2. Materials and methods

2.1. Animals

The study protocol was approved and discussed by the Institutional Ethics Committee of the Veterinary University Vienna and had governmental approval (GZ-68.205/0142-BrGT/2005). Six male Beagle dogs with a mean body weight of 18.0 ± 0.9 kg and mean age of 1.75 years were included. On the basis of physical examination and complete blood cell counts, all dogs were found to be healthy prior to starting the study. Food was withheld on the day of the trial.

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2.2. Anaesthesia and instrumentation

Anaesthesia was induced with pentobarbital 10 mg kg⁻¹ (Narkodorm, CP Pharma, Burgdorf, Germany) intravenously (IV) after premedication with acepromazine 0.03 mg kg⁻¹ (Vanastress, Vana, Austria) and buprenorphine 0.01 mg kg⁻¹ (Temgesic, AESCA GesmbH, Traiskirchen, Austria) intramuscularly. The dogs were breathing room air throughout carbachol nebulization.

2.3. Measuring Equipment and measured parameters

Respiratory parameters were recorded with two devices: the V_C unit and a Fleisch pneumotachograph.

2.3.1. V_C unit and measured variables

Respiratory parameter and dead space measurements were performed using a V_C unit (Novamatrix Medical Systems, Wallingford, Conn., USA) as described previously (Mosing et al., 2010). The unit consists of a main-stream capnograph (Capnograph 1265, Novamatrix Medical Systems, Wallingford, Conn., USA) using a non-dispersive infrared absorption technique (accuracy ± 2 mm Hg) and a fixed orifice differential pressure flow sensor (Ventrac 1550, Novamatrix Medical Systems, Wallingford, Conn., USA). The V_C curve was recorded on a breath-by-breath basis on a laptop computer using commercially available software (Analysis Plus, Novamatrix Medical Systems, Wallingford, Conn., USA). Before each study period a routine calibration of the V_C device was performed according to the manufacturers instructions. The accuracy of the V_C pneumotachograph was verified with a calibration syringe before and after the study period.

Tidal volume (V_T), minute volume (V_M), alveolar tidal volume ($V_{T_{alv}}$), respiratory rate (f_R) and the end-tidal CO_2 (P_{ETCO_2}) were recorded automatically by the computer software throughout the whole study period and trends over 1 min exported and used for statistical analysis.

All V_C parameters were calculated using Functional Approximation based on the Levenberg–Marquardt Algorithm (FA-LMA) described by Tusman et al. (2009) after exporting the data from the recording software.

The expired CO_2 volume per breath (V_{CO_2}/br) represents the area under the curve and is the integral of the expired CO_2 plotted as the function of expired volume. Slope II and III, angle α and VD_{aw} were calculated by the software as described by Tusman et al. (2009) (Fig. 1). Both slopes were normalized using the mean expired alveolar CO_2 (PAE_{CO_2}). This allows comparison of SII and SIII from breaths with different CO_2 excretion (Tusman et al., 2005).

Physiologic and alveolar dead space parameters were calculated automatically based on the method described by Fowler and the Bohr–Enghoff equation ($Pa_{CO_2} - Pe_{CO_2} / Pa_{CO_2}$, where Pa_{CO_2} is the arterial partial pressure of oxygen and Pe_{CO_2} is the partial pressure of mixed expired CO_2) after the Pa_{CO_2} was entered (Enghoff, 1938; Fowler, 1948). The Pe_{CO_2} was calculated as $Pe_{CO_2} = V_{CO_2} / br \times (PB - PH_2O) / V_T$, where PB is the barometric pressure and PH_2O is the partial pressure of water vapor.

2.3.2. Fleisch pneumotachograph and conventional measurements

A heated No. 2 Fleisch pneumotachograph (FPT) was placed distal to the V_C sensor at each measurement point. The FPT was connected to a differential pressure transducer (DP 45-14, Validyne Engineering, Northridge, CA, US) by two equally long tubes with 4 mm I.D. Volume calibration was performed with a 100 ml syringe, whereas for pressure calibration a water manometer was used.

An oesophageal balloon catheter (balloon length 5 cm) was placed in the thoracic oesophagus and connected to a differential pressure transducer (DP 45-28, Validyne Engineering) to obtain

intrathoracic pressure. The position of the balloon catheter was adjusted to reach maximum pressure variation. Downstream, the transduced signals were amplified using a strain gauge amplifier (Buxco Electronics Inc., Sharon, Connecticut, US), digitised and sampled from the measurement unit. Analysis of the waveforms on a breath-by-breath basis was performed using commercial software (Buxco XA Biosystem, Anesthetized Animal Measurements, Traditional Mechanics, Sharon, Connecticut, US). Total pulmonary resistance (R_L) were calculated from simultaneous airflow and oesophageal pressure measurements by the software.

2.4. Carbachol challenge and measurement periods

After tracheal intubation the V_C unit and the FPT were connected to the endotracheal tube in series and respiratory data were collected over 4 min (time point 1: baseline = T_{BL}). At the same time an arterial blood sample was slowly withdrawn and immediately analyzed (I-Stat, Abbott, Birmingham, UK) and Pa_{CO_2} values were entered into the VC computer. Thereafter the dogs were transferred into an acryl glass chamber and positioned in left lateral recumbency. In this chamber the dogs were exposed to increasing concentrations of aerosolised carbachol (0.25%, 0.5%, 0.75% and 1% in physiologic saline). The solution was aerosolised with a jet nebuliser driven by a compressor producing approximately 8 L/min of aerosol (Pari Master, Pari GmbH, Starnberg, Germany). Each concentration was nebulised for 3 min with at least 20 min between nebulisation periods.

End point for carbachol challenge was a clinically evident bronchoconstriction (laboured inspiration and laboured expiration). At this point the box was opened and the V_C unit and the FPT were reconnected to the ETT in series, an arterial blood sample collected and respiratory data recorded over 4 min (time point 2: clinical reaction = T_{CR}). Data collection and blood gas sampling were repeated 10 (time point 3: T_{CR10}) and 20 (time point 4: T_{CR20}) minutes for 4 min after CR.

Fifteen to 20 breaths were marked retrospectively for FA-LMA analysis, exported to a Matlab program and analyzed off line.

If oxygen partial pressure (Pa_{O_2}) < 9.31 kPa was revealed by arterial blood gas analysis, 100% oxygen was provided to the lungs of the dogs via an anaesthetic circle system. Any undesired effects after carbachol nebulisation were recorded. Heart rate and f_R were recorded at each time point.

2.5. Statistics

Statistical analyzes were performed using MedCalc for Windows, version 10.1.0.0 (MedCalc Software, Mariakerke, Belgium). Data was normally distributed when tested with a d'Agostino-Pearson test. All values are presented as mean (SD). The differences between the time points were compared using one-way ANOVA. A Student Newman Keuls pairwise comparison was performed where appropriate. Overall a $P < 0.05$ was chosen to demonstrate statistical significance.

Pearsons correlation was performed to evaluate the correlation between R_L , and all derived V_C indices.

3. Results

The mean concentration (SD) of carbachol needed to achieve a clinically evident bronchoconstriction was 0.71 (0.25)%.

All measured and calculated V_C data are shown in Table 1. Respiratory parameters and significant differences between values for the four time points are shown in Table 1.

All dogs had a $Pa_{O_2} > 9.31$ kPa at T_{BL} [10.82 (0.62) kPa]. After carbachol challenge (T_{CR}) ABG analysis revealed hypoxemia in all dogs

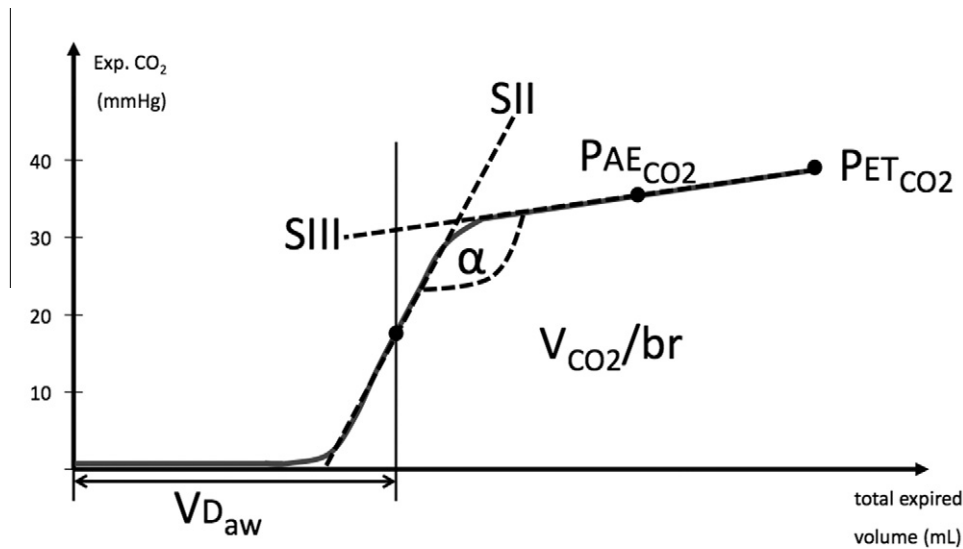


Fig. 1. Graphical illustration of a volumetric capnography curve illustrating the measured indices: slope II (SII), slope III (SIII), alpha angle (α), expired CO₂ volume per breath (V_{CO_2}/br), mean expired alveolar CO₂ (PAE_{CO_2}), end-tidal CO₂ (PET_{CO_2}) and airway dead space (VD_{aw}).

Table 1
Mean and standard deviation for general respiratory and dead space parameters, and values derived from volumetric capnography (V_C) and the Fleisch pneumotachgraph (FPT) as well as P values of the one way ANOVA before bronchoconstriction (T_{BL}), at clinical reaction (T_{CR}), and 10 (T_{CR10}) and 20 (T_{CR20}) minutes after clinical reaction.

		T_{BL}		T_{CR}		T_{CR10}		T_{CR20}		p
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
f_R	br/min	17.8	7.0	23.2	7.5	13.4	5.5	12.8	7.1	0.098
V_M	l/min	3.022	0.8818	5.248	1.440	3.678	1.547	3.322	1.161	0.063
V_T	ml	195	27	223	45	223	68	220	33	0.731
$V_{T_{aliv}}$	ml	128	28	182	39	166	68	160	33	0.319
<i>Dead space parameters</i>										
VD_{phys}	ml	109	10	141	28	137	41	126	18	0.298
VD_{phys}/V_T		0.568	0.046	0.634	0.019	0.610	0.040	0.575	0.054	0.080
VD_{aw}	ml	66.8	15.9	41.72*	5.3	57.3*	7.9	59.9*	7.5	0.008
VD_{aw}/V_T		0.346	0.084	0.194*	0.023	0.274	0.071	0.279	0.053	0.013
VD_{aliv}	ml	43.2	17.1	99.5*	22.9	79.2	40.9	66.1	18.3	0.028
$VD_{aliv}/V_{T_{aliv}}$		0.333	0.090	0.544*	0.019	0.460*	0.081	0.411*	0.068	0.002
<i>V_C derived parameters</i>										
VT_{CO_2}/br	ml	4.36	1.75	5.06	1.08	5.33	2.12	5.72	1.62	0.639
SII	mmHg/ml	0.850	0.299	1.094	0.395	0.813	0.187	0.843	0.121	0.357
SnII	mmHg/ml	0.022	0.013	0.039	0.012	0.025*	0.006	0.024	0.003	0.050
SIII	mmHg/ml	0.068	0.043	0.135*	0.033	0.065*	0.024	0.052*	0.024	0.004
SnIII	mmHg/ml	0.1176	0.146	0.483*	0.101	0.206*	0.077	0.151*	0.075	<0.001
Angle α		139.7	4.2	142.3	11.0	145.2	7.3	143.1	5.4	
PAE_{CO_2}	mmHg	41.7	8.1	27.9*	3.2	32.1* ⁺	1.6	35.3*	3.2	0.002
<i>FPT derived values</i>										
C_{dyn}	ml/cmH ₂ O	137	50	22*	11	85*	20	132*	74	0.004
R_L	cmH ₂ O/ml/s	2.58	0.21	20.58*	4.31	5.78* ⁺	1.38	4.20* ⁺	2.58	<0.001

f_R : respiratory rate, V_M : minute volume, V_T : tidal volume, $V_{T_{aliv}}$: alveolar tidal volume, VD_{phys} : physiologic dead space, VD_{phys}/V_T : physiologic dead space ratio, VD_{aw} : airway dead space, VD_{aw}/V_T : airway dead space ratio, VD_{aliv} : alveolar dead space, $VD_{aliv}/V_{T_{aliv}}$: alveolar dead space ratio, V_{CO_2}/br : expired CO₂ volume per breath, SII: slope phase 2, SnII: normalized slope phase II using the mean expired alveolar CO₂, SIII: slope phase 3, SnIII: normalized slope phase III using the mean expired alveolar CO₂, Angle α : angle between phase II and III, PAE_{CO_2} : mean expired alveolar CO₂, C_{dyn} : dynamic lung compliance, R_L : total pulmonary resistance.

* Significantly ($p < 0.05$) different from T_{BL} .

⁺ Significantly different from T_{CR} .

[6.87 (1.22) kPa]. Therefore the inspired fraction of O₂ was increased to 100% in all dogs. At T_{CR10} oxygen partial pressure was 74.61 (1.96) kPa. In all dogs clinical signs of bronchoconstriction resolved within the first 10 min after maximal bronchoconstriction.

3.1. FPT data

A significant difference was seen for pulmonary resistance from TBL to all other time points ($P < 0.002$; power 0.97). A steep increase was seen between TBL and TCR followed by a slow decrease

over time (Table 1). Values for R_L were not significantly different from T_{BL} at T_{CR10} and T_{CR20} .

3.2. Changes of parameters and "shape" of the V_C curve over time

Values obtained from one dog had to be excluded due to marked cardiovascular signs clinically (drop in fH from 140 to 68 after carbachol challenge) and on the V_C curve (marked drop in V_{CO_2}/br). Statistical evaluation was done on the remaining five dogs.

The shape of the V_C curve changed markedly after carbachol challenge with visible changes in the steepness of SIII, the position of phase II (the phase of the upwards swing of CO_2), and the level of the alpha angle in all five remaining dogs (Fig. 1).

Values for SII showed no significant changes ($P = 0.357$; power 0.95) throughout the time points whereas SIII increased significantly between T_{BL} and T_{CR} , then returned to baseline values at T_{CR10} and T_{CR20} ($P < 0.004$; power 0.96) (Table 1). No significant difference from baseline was found for SIII at T_{CR10} and T_{CR20} .

The normalized value for SnII using the mean expired alveolar CO_2 revealed a significant change between T_{CR} and T_{CR10} , but not any other time points for SnII ($P = 0.050$; power 0.95). A more obvious increase in SnIII compared to SIII was observed as well due to the changes in the mean expired alveolar CO_2 ($P < 0.001$; power 0.97) (Table 1).

A significant change for VD_{aw}/V_T was seen between T_{BL} and T_{CR} ($P = 0.013$; power 0.96). Values for VD_{aw}/V_T returned to baseline at T_{CR10} and T_{CR20} .

The $\text{VD}_{alv}/V_{T_{alv}}$ increased at T_{CR} and T_{CR10} and returned close to baseline at T_{CR20} ($P = 0.002$; power 0.97). No significant change in VD_{phys} or VD_{phys}/V_T was seen over time ($P = 0.080$; power 0.95). The VCO_2/br did not change over time ($P = 0.639$; power 0.95).

3.3. Results for correlation with total airway resistance

The correlation coefficient for the non-invasive parameters VD_{aw}/V_T , SII and SIII were -0.566 , 0.523 and 0.683 , respectively. An increase in the correlation coefficient to R_L was seen after normalization of SII and SIII of 0.716 and 0.776 , respectively. $\text{VD}_{alv}/V_{T_{alv}}$ and VD_{phys}/V_T were showing a correlation coefficient of 0.670 and 0.546 , respectively.

4. Discussion

This study describes the changes in shape of the V_C curve during profound provoked bronchoconstriction in dogs and confirms the finding that slope III of the capnogram in conjunction with VD_{aw}/V_T can be used on breath-by-breath basis to verify bronchoconstriction in spontaneously breathing subjects.

Furthermore the values for the alveolar dead space ratio can be used to confirm the ventilation–perfusion mismatch due to changes in airway caliber. Based on these findings volumetric capnography can be used to diagnose and quantitate bronchoconstriction in spontaneously breathing anaesthetised dogs.

We used the increase in R_L as our default value to detect bronchoconstriction during carbachol challenge and correlate these values with the V_C parameters derived over the same time period. This variable has been used before to characterize bronchoconstriction (Brown et al., 1998; Colebatch et al., 1966; DeKock et al., 1966; Ludwig et al., 1989; Mitzner et al., 1992). By choosing obvious signs of bronchoconstriction in the spontaneously breathing dogs as endpoint of carbachol challenge a direct link between clinical confirmation and derived values exists. The fact that the dogs were breathing spontaneously might have contributed to the high heterogeneity in several values used in this study. However, the aim of this study was to confirm findings in humans that volumetric capnography can be used in spontaneously breathing subjects to measure bronchoconstriction non-invasively on a breath-by-breath basis. This fact can be important during anaesthesia as measurements of dynamic compliance and airway resistance often used to verify bronchoconstriction in a clinical setting are unspecific. Changes in airway resistance can be due to increased secretion, kinks or mucus in the endotracheal tube or simple changes in flow or gas composition (Pilbeam, 2006). A decrease in dynamic compliance more often indicates changes in the lung parenchyma

than diameter of the airways (Pilbeam, 2006). Using volumetric capnography the anaesthetist can distinct between the aforementioned reasons in changes in airway resistance and a ‘true’ reduction in airway diameter and can quickly take action. Furthermore volumetric capnography can be used as a lung function test in sedated dogs to measure airway reactivity after carbachol challenge (Scheffzek et al., 2007).

The most striking change in the shape of the V_C curve after carbachol challenge was the change in SIII indicating a mismatch between ventilation and perfusion (Fig. 2A–E). This lung heterogeneity results in variations in CO_2 concentration in different lung units leading to asynchronous emptying of compartments with different V/Q ratios indicated by an increase in SIII (Fletcher et al., 1981; West et al., 1957). This change became not only obvious in the shape of the V_C curves (Fig. 2A–E) but was statistically significant for the five dogs included into statistical analysis. The shape of the V_C curve of the dog that was excluded from statistical analysis indicated a non-sequential, synchronously emptying of lung units as SIII showed no sloping, but a parallel drop and remained almost horizontal (Fig. 2F).

Changes in the slope of phase II reveal a change in the positioning of the airway–alveolar interface indicating asynchronous emptying (Tusman et al., 2005). However, no significant changes for SII were seen in our study.

Fig. 2 shows that a change in position of phase II was more obvious in our dogs than a change in the steepness of SII during bronchoconstriction. The position of phase II is best described by the evaluation of the airway dead space. The inflection point of the V_C curve, which was used to derive VD_{aw} represents almost the middle of SII. This point migrated closer to the y-axis at T_{CR} in all five dogs (Fig. 2A–E). This is reflected in the marked decrease in airway dead space at T_{CR} . The clinical usefulness of VD_{aw} to diagnose bronchoconstriction has been shown previously (Olsson et al., 1999).

As CO_2 is a gas with high blood solubility and a complex transport mechanism within the blood, pulmonary blood flow influences V_C parameters (Fletcher et al., 1986). Tusman et al. (2005) found a strong influence of pulmonary blood flow (PBF) on SII and SIII.

In an attempt to compensate for different conditions in PBF due to changing physiologic situation after provoked bronchoconstriction during the study period we normalized both slope values by dividing them by PAE_{CO_2} (Blanch et al., 1994; Boehm et al., 2009; Romero et al., 1997; Tusman et al., 2005). In the normalized values an increase in SII between T_{BL} and T_{CR} became more obvious but still not significant. The reason for not finding a significant change was very likely due to the small number of dogs and therefore high standard deviation. This assumption is substantiated by the significant difference between T_{CR} and T_{CR10} for SnII with a very low standard deviation at T_{CR10} . The already significant SIII values became more distinct after normalization with a fourfold increase at T_{CR} compared to baseline values (Table 1).

Bronchoconstriction can be further verified by the calculation of physiologic and alveolar dead space values. Both parameters, especially $\text{VD}_{alv}/V_{T_{alv}}$ showed a parallel pathway with R_L , which might allow quantitation of the bronchoconstriction present. Alveolar dead space has been widely used to quantitate ventilation–perfusion mismatch during mechanical ventilation and to diagnose pulmonary embolism (Eriksson et al., 1989; Olsson et al., 1998; Tusman et al., 2006; Verschuren et al., 2004; Wenzel et al., 1999). Its evaluation during bronchoconstriction is not as popular as it is influenced by several cardiovascular parameters. Intrapulmonary shunt can cause an alveolar dead space like effect, as can changes in cardiac output (Niklason et al., 2008; Tusman et al., 2006). During bronchoconstriction a reduction in pulmonary capillary blood volume secondary to the high intrathoracic pressure might influence the alveolar dead space measurements (Aliverti

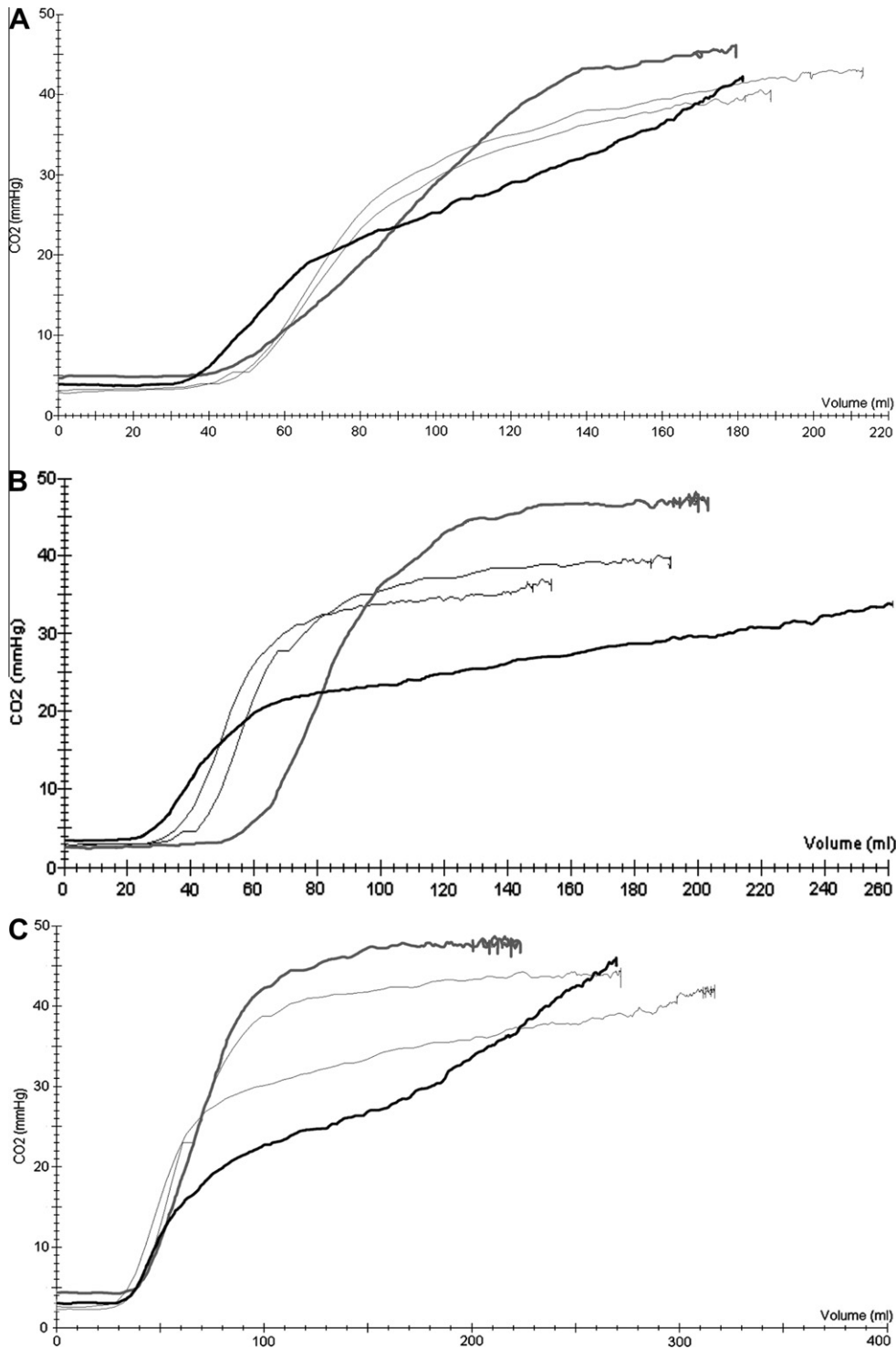


Fig. 2. Representative volumetric capnography curves of six dogs (A–F) before bronchoconstriction (grey solid line), at clinical reaction (black solid line), and 10 and 20 min (thin solid black lines) after clinical reaction. Results of dog F were excluded from the statistical analysis.

et al., 2007). Beside the cardiovascular alterations an increase in ventilation can cause another dead space-like effect as the ratio between ventilation and perfusion is altered (Lumb, 2005). As an increase in minute volume was seen in our dogs this effect could have contributed to the actual increase in VD_{alv} .

Due to the aforementioned influences of the cardiovascular system on V_C parameters, results of one dog were excluded from the analysis (dog F). A severe drop in heart rate from 140 to 68 bpm after carbachol challenge was found in this dog. A marked drop

in V_{CO_2}/br values between T_{BL} and T_{CR} in the excluded dog confirmed our suspicion of marked drop in cardiac output and PBF. The CO_2 elimination per breath is a routine parameter to evaluate cardiac output based on Fick's formula for CO_2 elimination and lung perfusion (Tusman et al., 2005).

Pentobarbital was used as mono-anaesthetic as it has no effect on airway baseline tone and causes no modification in respiratory mechanics or lung morphometry (Correa et al., 2001; Fletcher et al., 1968). Additionally carbachol was nebulised in a chamber

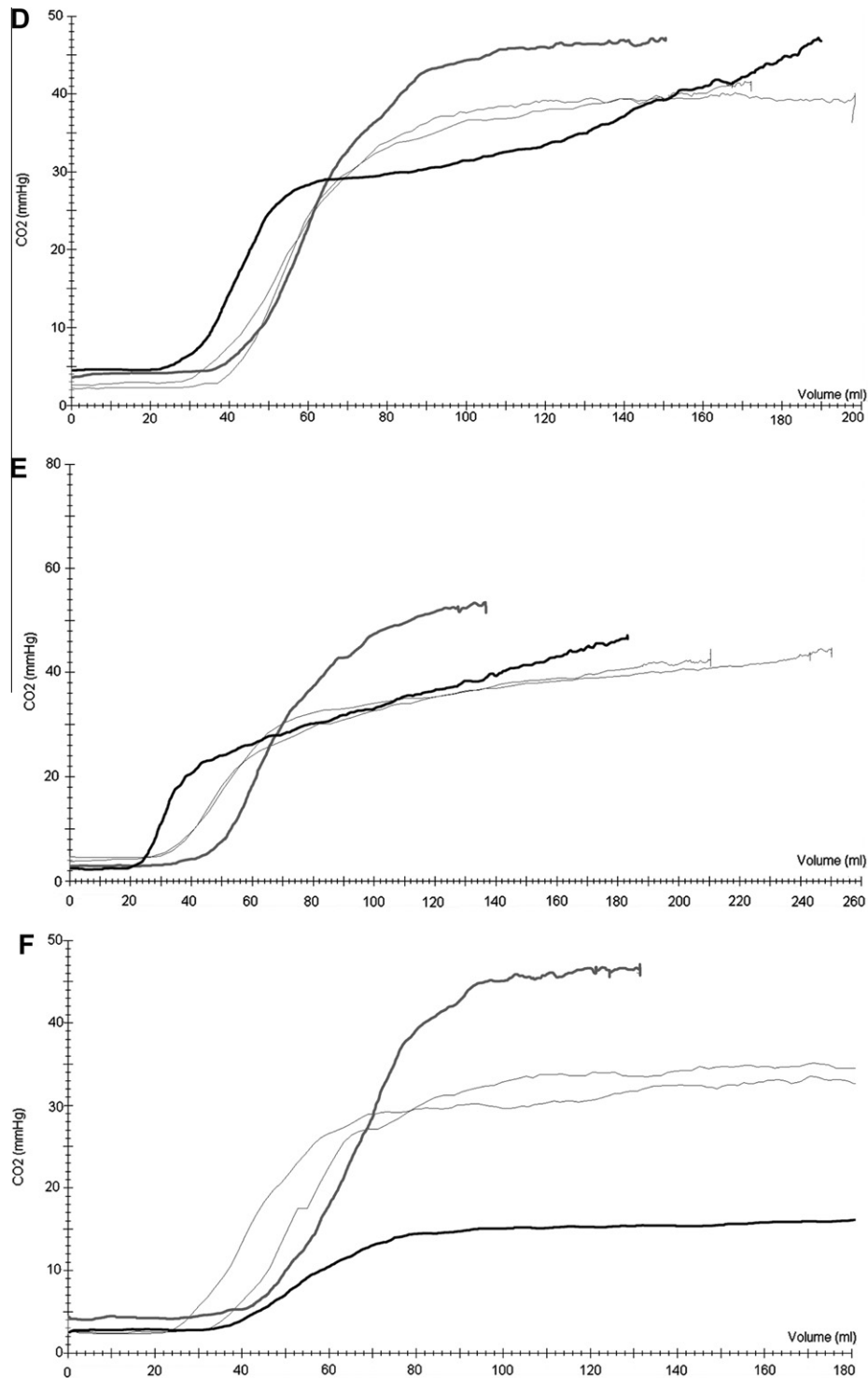


Fig. 2 (continued)

and therefore no connection to an anaesthetic machine or even infusion pumps (not enough space in the chamber) was possible.

The major limitation of this study is the small number of study objects. However, even with the small number of dogs significant changes for the main non-invasive parameters were found over time and the aim to find a correlation with R_L was met. Furthermore the power calculated for all our significant results of more or equal than 0.95 shows that our significance levels were not random, but conclusive findings.

Future studies with greater numbers of study objects are necessary to not only qualify but also quantify the degree of bronchoconstriction with using different non-invasive parameters measured from the V_C curve. The focus should be on a combination of non-invasive indices and the indices requiring arterial blood gases rather than one single parameter. Multiple factors influence all non-invasive parameters; therefore the authors strongly believe that several indices have to be used to diagnose a complex pathology like pulmonary bronchoconstriction.

This study shows that the graphical and mathematical analysis of a V_C curve can be used to diagnose changes in airway diameter in anaesthetised spontaneously breathing dogs. Beside the non-invasive values of slope III and airway dead space alveolar dead space parameters revealed a good to high correlation to the consecutively measured R_L .

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