Diplomarbeit

Volumetric capnography and slope-CO_2 in mechanically ventilated infants and children under the age of 36 months

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Joachim Zobel

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unter der Anleitung von:

Univ.-Prof. Dr. Ernst Eber

Dr. Stefan Ring

Graz, am 18. Februar 2015

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Zusammenfassung

Ziele: Die volumetrische Kapnographie enthält wichtige Informationen über die respiratorische Funktion von maschinell beatmeten Kindern. Von der volumetrischen Kapnographie ermittelte Parameter können zur Berechnung verschiedener Totraumfraktionen benützt werden und zudem können sie Aussagen über die Dauer der maschinellen Beatmung und deren Mortalität treffen. Das Hauptaugenmerk unserer Studie lag auf den CO_2-Parametern ($paCO_2$, $petCO_2$, $pACO_2$, $pECO_2$, VCO_2, pa-$etCO_2$ und pa-ACO_2), den Totraumfraktionen (VDalv/VT, VDphys/VT, VDaw/VT, VDBohr/VT), und dem slope-CO_2. Ziel unserer Studie war es, den Unterschied zwischen den einzelnen Parametern anhand zweier Gruppen (maschinelle Beatmung < 48 Stunden und ≥ 48 Stunden) zu zeigen. Des Weiteren untersuchten wir die Werte der Gruppe B (≥ 48 Stunden) im zeitlichen Verlauf und die Korrelationen zwischen einzelnen Parametern.

Material und Methoden: Im Rahmen unserer retrospektiven Studie wurden die Daten von 51 Patienten/Innen ausgewertet, welche auf 2 Gruppen aufgeteilt wurden. Das Hauptunterscheidungsmerkmal zwischen den Gruppen war die Dauer der maschinellen Beatmung (Gruppe A < 48 Stunden; Gruppe B ≥ 48 Stunden). Die statistische Analyse beinhaltete eine deskriptive Analyse der einzelnen Parameter, sowie einen Vergleich beider Gruppen am ersten Tag der maschinellen Beatmung. Zudem wurden bei den Langzeitbeatmeten die Daten an 3 zusätzlichen Zeitpunkten ermittelt (Tag 2, Tag 3 und Extubationstag). Außerdem untersuchten wir die Korrelation von VDalv/VT, VDphys/VT, VDBohr/VT, slope-CO_2 und VCO_2 mit anderen, auf der volumetrischen Kapnographie basierenden Parametern.

Ergebnisse: An Tag 1 der maschinellen Beatmung fanden wir bei folgenden Parametern einen signifikanten Unterschied zwischen beiden Gruppen: $pACO_2$, $pECO_2$, VCO_2, pa-$etCO_2$, pa-ACO_2, slope-CO_2, VDalv/VT und VDphys/VT. Zudem fanden wir in der Gruppe der Langzeitbeatmeten bei $petCO_2$, $pACO_2$, VCO_2, pa-$etCO_2$, pa-ACO_2, VDalv/VT und VDphys/VT einen signifikanten Unterschied über den zeitlichen Verlauf. Des Weiteren fanden wir eine Korrelation zwischen VDphys/VT und der Dauer der maschinellen Beatmung, sowie zwischen VDphys/VT und VDalv/VT. Zusätzlich korrelierten beide Totraumfraktionen (VDphys/VT und VDalv/VT) gut mit pa-$etCO_2$ und pa-ACO_2. Zu Letzt analysierten wir auch noch den slope-CO_2 und fanden keinen signifikanten Unterschied im zeitlichen Verlauf in der

Gruppe der Langzeitbeatmeten. In der Gruppe der Patienten/Innen mit RSV-Infektion fanden sich jedoch signifikante Unterschiede zwischen Tag 2 und dem Extubationstag, sowie zwischen Tag 3 und dem Extubationstag.

Schlussfolgerung: Die volumetrische Kapnographie erlaubt die Darstellung von CO_2-bezogenen Parametern, sowie die Darstellung von CO_2-/Zeitkurven und CO_2-/Volumenkurven für jeden einzelnen Atemzug. Sie führt zu einer Verbesserung des Verständnisses von pathophysiologischen Prozessen respiratorischer Erkrankungen, erlaubt eine optimale Einstellung des PEEP bei Patienten/Innen mit ARDS und gibt zudem nützliche Informationen über das Ausmaß der Lungenschädigung und die Dauer der maschinellen Beatmung.

Abstract

Objectives: Volumetric capnography (VCAP) provides useful information about respiratory function in mechanically ventilated patients. Therefore VCAP-derived parameters could be used to calculate dead space fractions, and further on as prognostic factors in terms of the duration of mechanical ventilation and the mortality. In our study the main focus was on CO_2-derived parameters ($paCO_2$, $petCO_2$, $pACO_2$, $pECO_2$, VCO_2, pa-$etCO_2$, and pa-ACO_2), dead space fractions (VDalv/VT, VDphys/VT, VDaw/VT, VDBohr/VT), and slope-CO_2. The aim of our study was to show the difference of those parameters in patients with short-term (< 48 hours) and long-term mechanical ventilation (≥ 48 hours), and further on over the course of time in Group B (≥ 48 hours). Furthermore, we wanted to show the correlation between certain parameters.

Materials and methods: In our retrospective study we separately analysed the values of 51 patients, which were divided into two subgroups, according to the duration of mechanical ventilation (Group A < 48 hours; Group B ≥ 48 hours). In Group A (< 48 hours) we analysed the data of the day of intubation only, whereas in Group B (≥ 48 hours) we analysed three more points in time (day 2, day 3 and the day of extubation). The statistical analyses were divided into a descriptive analysis of all values, a comparison of both groups on day 1 of mechanical ventilation, and a comparison of day 1, day 2, day 3 and the day of extubation in Group B. Further, we analysed the correlation of VDalv/VT, VDphys/VT, VD-Bohr/VT, slope-CO_2, VCO_2 and other VCAP-derived parameters.

Results: There was a significant difference in CO_2-derived parameters ($pACO_2$, $pECO_2$, VCO_2, pa-$etCO_2$ and pa-ACO_2, slope-CO_2), and in physiologic and alveolar dead space fractions between patients with short-term, and with long-term mechanical ventilation. Physiologic and alveolar dead space fractions and CO_2-derived parameters ($petCO_2$, $pACO_2$, VCO_2, pa-$etCO_2$ and pa-ACO_2) changed significantly over time in the group of patients with prolonged mechanical ventilation. Physiologic dead space fraction showed a correlation with the duration of mechanical ventilation. Further, there was a correlation between alveolar and physiologic dead space fractions. In addition, both dead space fractions correlated with the arterial to end-tidal CO_2, and with arterial to alveolar pCO_2 differences.

Whereas slope-CO_2 showed no significant difference in the whole group of patients with prolonged mechanical ventilation over time, in patients with RSV-infection slope CO_2 was significantly lower on the day of extubation compared with the data on days 2 and 3 of mechanical ventilation.

Conclusion: VCAP is a very useful monitoring tool for paediatric patients, displaying different CO_2-parameters, and furthermore time based and volume based capnograms breath-by-breath. It improves our understanding about pathophysiologic changes in respiratory disorders, helps to optimize PEEP-titration in patients with ARDS and gives us useful information about severity of lung disease and the duration of mechanical ventilation.

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Abbreviations

ALI	Acute lung injury
APVcmv	Adapted pressure ventilation
ARDS	Acute respiratory distress syndrome
ASD	Atrial septal defect
AVC	Atrio-ventricular canal defect
BPD	Bronchopulmonary dysplasia
BTPS	Body temperature ambient pressure, saturated
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
Cstat	Static compliance
EIP	End-inspiratory pause
EIT	Electrical impedance tomography
$FACO_2$	Alveolar fraction of carbon dioxide
$FECO_2$	Mixed-expiratory fraction of carbon dioxide
FiO_2	Fraction of inspired oxygen
Hb	Haemoglobin
ICU	Intensive care unit
I:E-ratio	Inspiration to expiration ratio
max	Maximum
MIGET	Multiple inert gas elimination technique
min	Minimum
MV	Mechanical ventilation
MV-days	Days of mechanical ventilation
n	Number
N_2	Nitrogen
O_2	Oxygen
$paCO_2$	Arterial partial pressure of carbon dioxide
$pACO_2$	Alveolar partial pressure of carbon dioxide
pa-$etCO_2$	Arterial to end-tidal difference of partial pressure of carbon dioxide
pa-ACO_2	Arterial to alveolar difference of partial pressure of carbon dioxide

paO_2/FiO_2-ratio	Arterial partial pressure of oxygen to inspired oxygen fraction ratio
Paw	Mean airway pressure
pCO_2	Partial pressure of carbon dioxide
PCVcmv	Pressure controlled ventilation
PDA	Persistent ductus arteriosus
$pECO_2$	Mean expiratory partial pressure of carbon dioxide
PEEP	Positive end-expiratory pressure
PIP	Peak inspiratory pressure
Pplat	Plateau pressure
PSV	Pressure supported ventilation
PST	Pulmonary valve stenosis
$pvCO_2$	Venous partial pressure of carbon dioxide
$petCO_2$	End-tidal partial pressure of carbon dioxide
PICU	Paediatric intensive care unit
paO_2	Arterial partial pressure of oxygen
pO_2	Partial pressure of oxygen
pvO_2	Venous partial pressure of oxygen
QS	Shunt volume
QS/QT-ratio	Shunt volume to total cardiac output ratio
QT	Total cardiac output
rCMP	Restrictive cardiomyopathy
Rexp	Expiratory airway resistance
Rinsp	Inspiratory airway resistance
RR	Respiratory rate
RSV	Respiratory syncytial virus
SII	Slope of phase II of the volumetric capnogram
SIII	Slope of phase III of the volumetric capnogram
SBT-CO_2	Single breath test for carbon dioxide
SaO_2	Arterial oxygen saturation
SpO_2	Pulse oximetry saturation
SpO_2/FiO_2-ratio	Pulse oximetry saturation to fraction of inspired oxygen ratio
STPD	Standard temperature and pressure, dry
SvO_2	Venous oxygen saturation

TCexp	Expiratory time constant
TCinsp	Inspiratory time constant
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
VA	Alveolar volume
VCAP	Volumetric capnography
VCO_2	Minute volume of expired carbon dioxide
$VeCO_2$	Tidal volume of expired carbon dioxide
VCO_2,br	Volume of expired carbon dioxide per breath
VDalv	Alveolar dead space
VDalv/VT-ratio	Alveolar dead space fraction
VDaw	Airway dead space
VDaw/VT-ratio	Airway dead space fraction
VDBohr	Dead space calculated by Bohr's equation
VDBohr/VT-ratio	Dead space fraction calculated by the Bohr equation
VDphys	Physiological dead space (calculated by Enghoff's modification of Bohr's equation = VDBE)
VDphys/VT-ratio	Physiological dead space fraction
V/Q-ratio	Ventilation to perfusion ratio
VSD	Ventricular septal defect
VT	Tidal volume
VTe	Expiratory tidal volume
VTi	Inspiratory tidal volume

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1 Introduction

Over the past decades capnography became an important factor in critical care medicine and was introduced in the every day practice of many intensive care units (ICUs). But what is capnography? Suarez-Sipmann et al. defined capnography as "the measurement and graphical display of CO_2-concentration within the expired gas". (1)

Time-based capnography is foremost being used in anaesthesia for monitoring patients and furthermore to ensure the right placement of the endotracheal tube. (1) Therefore the expired partial pressure of carbon dioxide is plotted against time and the graphical display allows an easy evaluation of the capnogram. Though, time-based capnography gives no information about the expired gas volume.

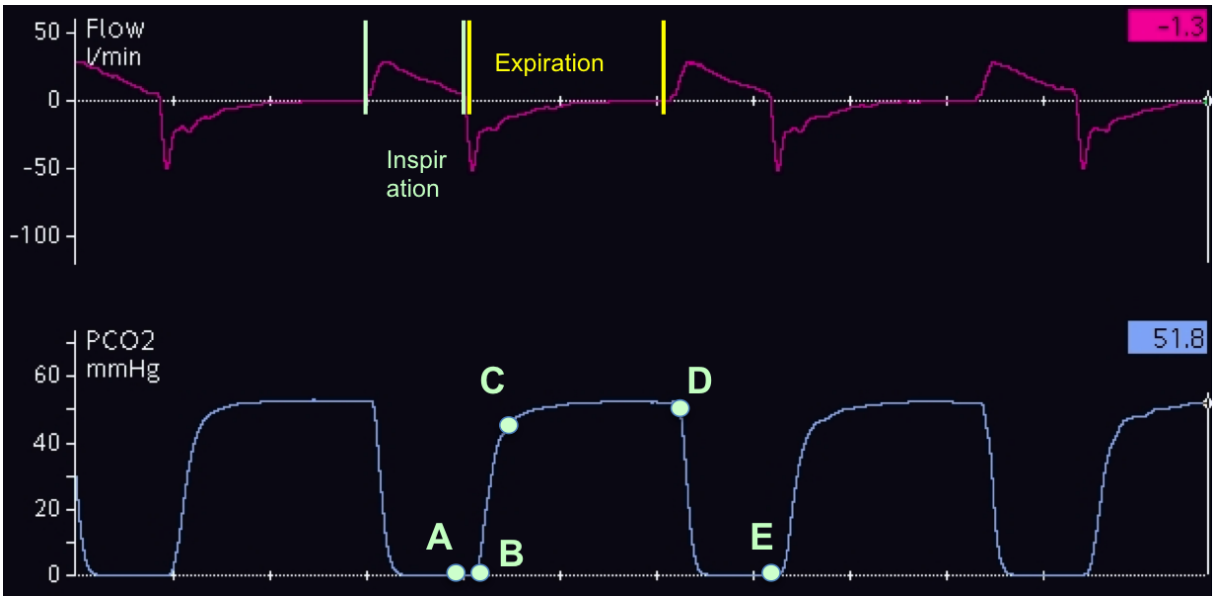


Figure 1: Time-based capnography

A-B = early stage of expiration (= CO2-free air of the upper respiratory tract); B-C = mixed air of the lower respiratory tract and the early-emptying alveolar units; C-D = CO2-rich air of the alveolar units; D = partial pressure of end-tidal CO2; D-E = Inspiration.

Nowadays there's a second method of capnography, which is trying to break through in modern critical care medicine. This kind of capnography plots the expired CO_2-concentration against the expired gas volume of a single breath (SBT-CO_2) and is therefore also called volumetric capnography (VCAP). (1–3) Volume-based

monitoring of CO_2 has been known for many years, but wasn't paid too much attention. (2) Over the last years there was a rethinking in terms of intensive care practice, which allowed VCAP to break through.
Furthermore, the volume-based capnography allows the measurement of physiological dead space volume and is therefore discussed as a prognostic factor in terms of duration of mechanical ventilation and mortality. (4–6)

Regarding VCAP there are some important variables and terms, which have to be known. Table 1 shows the most common variables, which are related to VCAP:

Variable	Explanation	Unit
$VTCO_{2,br}$	Is the breath-by-breath elimination of CO_2. The $VTCO_{2,br}$ is creating the possibility to analyse alveolar ventilation and dead space for each breath.	ml
VCO_2	Represents the volume of CO_2, which is eliminated per minute. In steady state conditions VCO_2 represents the equal to metabolic CO_2-production.	ml/min
$petCO_2$	Is the end-tidal partial pressure of CO_2 in the expired air. Is often been used as an equal to the alveolar partial pressure of CO_2.	mmHg
$pECO_2$	Is representing the mixed-expired partial pressure of CO_2, which is used in Bohr's equation to calculate the physiological dead space.	mmHg
$pACO_2$	Is the mean alveolar partial pressure of carbon dioxide, which Bohr is using in his equation.	mmHg
$paCO_2$	Is the arterial partial pressure of CO_2. In Enghoff's modification of the Bohr-equation $paCO_2$ is taking the place of $pACO_2$.	mmHg
$pa\text{-}etCO_2$	Represents the arterial to end-tidal gradient for pCO_2. Is an index for the gas exchange. Normal values are from 3-5 mmHg.	mmHg
$pa\text{-}ACO_2$	Represents the gradient between arterial and alveolar pCO_2. Is a more accurate index for the gas exchange than the $pa\text{-}etCO_2$. Normal values are from 4-8 mmHg.	mmHg

Table 1: Variables related to VCAP

This table shows VCAP-related variables adapted from Suarez-Sipmann et al. (1)

1.1 Phases of the volumetric capnogram

The volumetric capnogram can be divided into three phases: (2,3)

Phase I: phase I represents the first portion of the expired air and is therefore more or less free of carbon dioxide. (2,3) The CO_2-concentration is the same than in the inspired air (about 0,038%). (7)
In mechanically ventilated patients the apparatus-dead space is also part of this phase. (3) Pearsall and Feldman define the apparatus dead space “as portions of the breathing circuit that have bidirectional flow”. (8) Especially in paediatric patients changes in the apparatus dead space may have a major impact on the VD/VT-ratio. (8)

Phase II: this phase represents the mixed air of the convective airways and of the alveolar units. Furthermore, this phase represents the transition between the terminal airways and the early emptying alveoli. (2,3)
The ascent of the tracing of this phase of the capnogram is normally very steep, because more and more CO_2 streams out of the alveolar units. (2)

Phase III: in phase III the tracing reaches a plateau, where the CO2-concentration in the expired air is reaching a more or less constant level. (2,3) This phase of the capnogram represents the CO_2-rich air of the alveolar units. (2,3) Normally the CO_2-concentration reaches its highest values at the end of the expiration (= end-tidal pCO_2). The CO_2-fraction at this time could be about 30-40 mmHg. (7)

Fig. 2 is showing the three phases of a volumetric capnogram and the variables related to it.

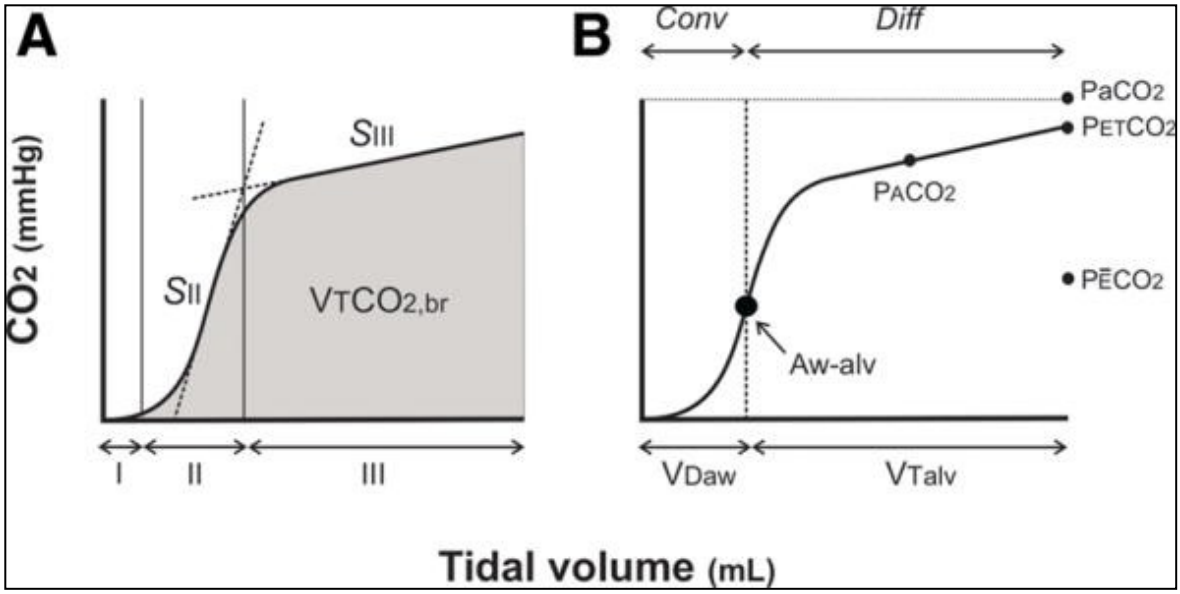


Figure 2: Phases of a volumetric capnogram

The figure shows the phases of the volumetric capnogram.(1) I,II,III = phase I,II and III of the volumetric capnogram; SII = slope of phase II; SIII = slope of phases III. $VTCO_{2,br}$ = expired volume of CO_2 per breath; VDaw = airway dead space; VTalv = alveolar tidal volume; AW-alv = turning point from airway to alveolar gas; $pECO_2$ = mean expiratory partial pressure of CO_2; $pACO_2$ = alveolar partial pressure of CO_2; $petCO_2$ = end-tidal partial pressure of CO_2; $paCO_2$ = arterial partial pressure of CO_2; Conv = convection; Diff = diffusion. Suarez-Sipmann F, Bohm SH, Tusman G. Volumetric capnography: the time has come. Curr Opin Crit Care. 2014;20(3):333–339.

1.2 slope-CO_2

The slope of phase III (SIII) represents the mean value of the ascent of phase III, and is an essential part in terms of analysing a volumetric capnogram. (3,9) Over the last years, a relation between SIII and the V/Q-ratio was postulated. (10,11) Therefore analysing the values of SIII could be a simple and non-invasive method to detect inhomogeneities in ventilation and in perfusion, as caused by bronchospasm, atelectasis and emphysema. (11)

1.2.1 Calculation of SIII

To calculate the mean value of SIII, the transition between phase II and phase III has to be determined. (11) Therefore the intersection point of the lines, which represent SII and SIII, has to be found. (11) Phase III is defined as the distance of the

intersection point to the end of the expiration. (11) In the next step phase three will be divided into three thirds. (11) Then ten equidistant points in the second third are determined and the mean value of those ten points is used to calculate the mean value of SIII. (11)

Figure 3 is showing how to calculate the slope of phase III.

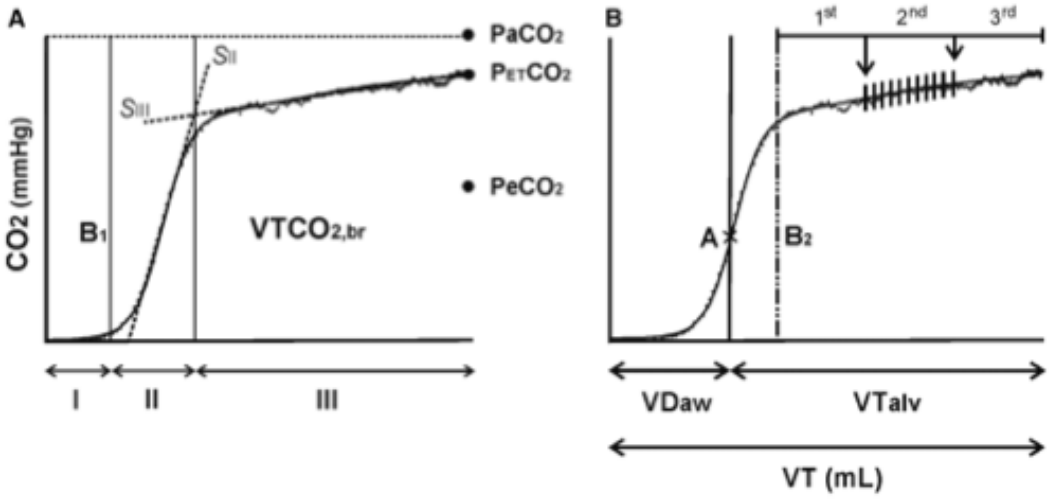


Figure 3: Calculation of SIII

The figure shows the calculation of SIII as described by Tusman et al. (11) I,II,III = phase I,II and III of the volumetric capnogram; SII = slope of phase II; SIII = slope of phase III. $VTCO_{2,br}$ = expired volume of CO_2 per breath; $pECO_2$ = mean expiratory partial pressure of CO_2; $petCO_2$ = end-tidal partial pressure of CO_2; $paCO_2$ = arterial partial pressure of CO_2; VDaw = airway dead space; VTalv = alveolar tidal volume; VT = tidal volume; A = inflection point of the entire curve - limit between VDaw and VTalv; B1 = left maximum of the third derivate; B2 = right maximum of the third derivate. Tusman G, Suarez-Sipmann F, Bohm SH, Borges JB, Hedenstierna G. Capnography reflects ventilation/perfusion distribution in a model of acute lung injury. Acta Anaesthesiol Scand. 2011;55(5):597–606.

1.2.2 Analyses of changes in SIII

Normally, the third phase of the capnogram represents the CO_2-rich air of the alveoli. (2,3) Therefore the tracing reaches a plateau phase, which shows that the alveolar units have been deflated simultaneously. However, under pathological circumstances the plateau phase could alternate its aspects. (11)

Recent publications suggest that under physiological conditions, the value of SIII is determined by age, height, and tidal volume of the subject. (7,12) In children the ascent of phase III is normally steeper than in adults, which is caused by the smaller total surface of the alveolar system. (7,12)
Previous studies showed that the mean value of SIII is rising in different lung diseases, associated with a maldistribution of ventilation. (11) This implicates that a higher value of SIII correlates with a deterioration of the global V/Q-ratio. (11) On the other side, a decrement of SIII is an expression of an amelioration of the global V/Q-ratio. (11)

Furthermore, an increase of the slope of phase III is correlating with higher values of alveolar dead space to tidal volume ratio (VDalv/VT). (11) Therefore SIII could be a useful, non-invasive prognostic factor in patients with ALI or ARDS.

However, in obstructive lung diseases the slope of phase III changes as a consequence of the consecutive deflation of the alveoli. Better-ventilated areas of the lung with a lower pCO_2 are deflated earlier than the worse ventilated parts of the lung with a higher pCO_2. (7) This results in a typical ascent of the third phase. (7) With the knowledge of these changes, obstructive lung diseases could easily be detected by evaluating the capnogram.

1.3 Volumetric capnography and dead space

One of the main advantages of volumetric capnography (SBT-CO_2) over other methods to measure expiratory CO_2-partial pressure (like the Douglas-bag-method), is that VCAP provides information about the changes in dead space volume for every breath. (3)

The SBT-CO_2 is based on Fowler's method to identify airway dead space. (2,13) Therefore phase 2 of the capnogram is divided into two triangles of equal size (areas p and q in Fig. 4) by drawing a perpendicular. Afterwards the capnogram is divided into three more areas: (2,3,13)

Area X: represents the volume of CO_2, which gets eliminated

Area Y: represents the alveolar dead space

Area Z: represents the airway dead space

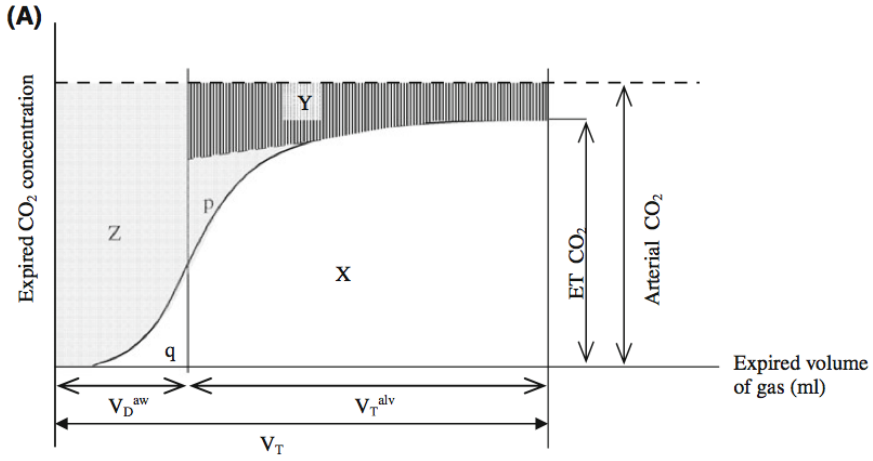


Figure 4: Components of SBT- CO_2

The figure shows the different components of SBT-CO_2, as described by Fletcher et al. (2,3) Area X = CO_2-elimination volume; area Y = alveolar dead space volume; area Z = airway dead space volume, where areas p and q are equal; VT = tidal volume; VDaw = airway dead space; VTalv = alveolar tidal volume; etCO_2 = end-tidal concentration of carbon dioxide. Sinha P, Flower O, Soni N. Deadspace ventilation: a waste of breath! Intensive Care Med. 2011;37(5):735–746.

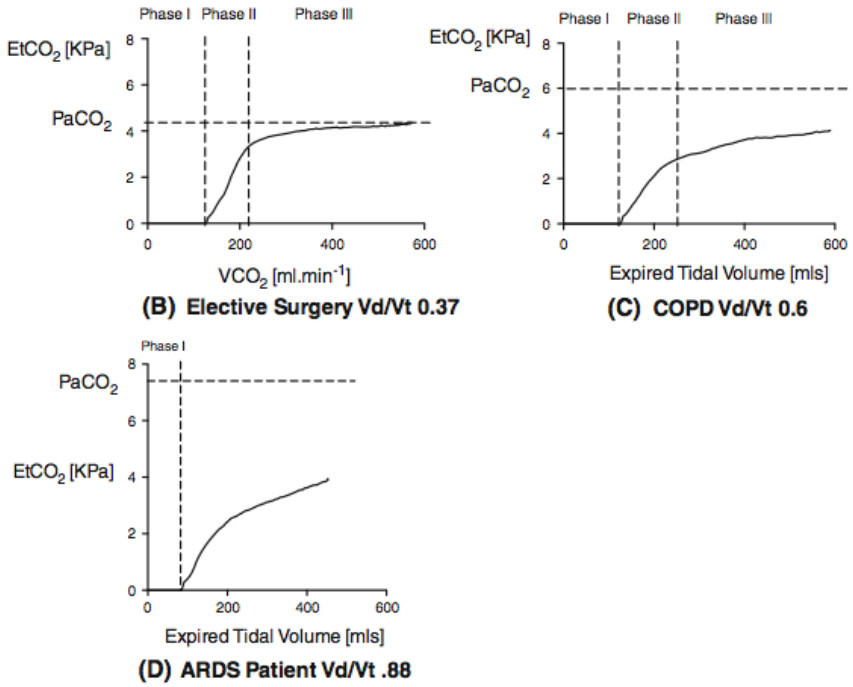


Figure 5: Aspects of VCAP in different diseases

The figure shows the differences in the capnogram in different respiratory and non-respiratory diseases. Furthermore, it shows the difficulties in establishing a border between phase two and three, when there's a constant and steep ascent of the tracing. (3) $etCO_2$ = end-tidal concentration of CO_2; $paCO_2$ = arterial partial pressure of CO_2; Vd/Vt = dead space to tidal volume ratio. Sinha P, Flower O, Soni N. Deadspace ventilation: a waste of breath! Intensive Care Med. 2011;37(5):735–746.

1.4 Dead space

Dead space is defined as the fraction of the tidal volume (VT), which is not participating in gas exchange. Therefore, dead space ventilation is also called “wasted ventilation”. (1,3) The total dead space volume consists of different compartments, which could be distinguished by different criteria: (2,3,14)

Airway dead space (anatomical or series dead space): (2,14)

Airway dead space (VDaw) is created by the convective part of the respiratory system. (2) Those parts are not involved in gas exchange. (2) The functions of the convective airways, next to its transporting function, are to warm, clean and moisturize the inhaled air. (15)
In mechanically ventilated patients the airway dead space furthermore consists of the dead space the apparatus is creating, like the tracheal tube, the connector and the y-piece. (2,7)
The airway dead space is influenced by various factors, such as the height of the patient, the position of the neck and jaw, the presence of a tracheostomy or a tracheal tube and changes in airway calibre. (2)

Alveolar dead space (intrapulmonary or parallel dead space): (2,14)

The alveolar dead space is defined as those parts of the alveolar system, which are not participating in the gas exchange. (2,3) Under ideal physiological conditions alveolar dead space does not exist, because all the alveolar units are ventilated and perfused. (3)

The reasons for alveolar dead space could be found in a mismatch between ventilation and perfusion of the alveolar system (= V/Q-mismatch). (1–3) Alveolar dead space in strict sense is the volume of the alveolar system, which is ventilated, but yet lacks perfusion. (1)
Although, in a more global approach venous admixture, or right-to-left-shunting could also be seen as dead space, or at least is affecting the dead space volume. (1)

To calculate dead space, the following equations are commonly used: (2)

(1) VT = VDphys + VA

In equation (1) VT represents the tidal volume, VA the alveolar volume and VDphys the physiological dead space. VDphys is defined as the sum of alveolar (VDalv) and airway dead space (VDaw). This implicates that: (2)

(2) VDalv = VDphys – VDaw

The border between airway and alveolar dead space is not stationary and is determined by airway geometry, inspiratory flow and the diffusion coefficient of the inhaled gas. (2) Most likely the interface is anywhere in the region of the respiratory bronchioles. (2) Because of the fact that this interface is not stationary, the airway dead space has to be seen more as a functional volume. (2)
A high inspiratory flow moves the border towards the alveolar system and therefore creates a higher airway dead space volume. (2) Vice versa a low inspiratory flow, together with an end-inspiratory pause (EIP), decreases the volume of VDaw. (2)

1.4.1 Historical aspects of dead space and volumetric capnography

1.4.1.1 VD-Bohr

In 1891 the Danish physiologist Christian Bohr was the first, who described respiratory dead space. (16) He used the term “schädlicher Raum” for those parts of the respiratory system, which did not participate in gas exchange. (16)

In his studies Bohr found that the end-expiratory concentration of CO_2 is not the same as the CO_2-concentration in the tracheal air. (16) He assumed that the concentration of CO_2 in the alveolar units is even higher, and that the alveolar air was mixing with the conducted air during the process of expiration. (16) Furthermore, Bohr was assuming that there was no carbon dioxide in the inspired air and that all the carbon dioxide in the mixed expired air was coming from the alveolar units. (3)

Bohr was using the following equation to calculate dead space: (3)

(3) $VT \times FECO2 = VA \times FACO_2$

In this equation VT represents the tidal volume, $FECO_2$ is the mixed expiratory fraction of CO2, VA is the alveolar volume and $FACO_2$ is the alveolar CO_2-fraction.
By filling in the equation from above (VA = VT – VD) we get: (3)

(4) $VT \times FECO_2 = (VT - VD) \times FACO_2$

That means that we get for VD/VT: (3)

(5) $VD/VT = (FACO_2 - FECO_2) / FACO_2$

By substituting the CO_2 fractions with the partial pressures of CO_2, we get: (3)

(6) $VD/VT = (pACO_2 - pECO_2) / pACO_2$

This equation is widely known as the Bohr-equation and is using the alveolar partial pressure of CO_2 ($pACO_2$) to calculate dead space. (1–3,16) Since back in 1891 there was no possibility to take arterial CO_2-samples, this was the best method to determine dead space.

Nevertheless, this equation is limited by the methods, which are used to measure the alveolar pCO_2. Using the end-tidal pCO_2 to estimate $pACO_2$ is inaccurate, when the tracing isn't reaching a plateau phase. (17) In cases like that $petCO_2$ tends to overestimate $pACO_2$. (17)
Furthermore, there are publications suggesting that using the Bohr equation is leading to an underestimation of alveolar dead space. (1,18,19)

1.4.1.2 VD-Bohr-Enghoff

In 1938 Henrik Enghoff from Uppsala, Sweden, was modifying Bohr's equation by using the arterial partial pressure of CO_2 ($paCO_2$) instead of the alveolar partial pressure of CO_2 ($pACO_2$) to calculate what he called "Volumen inefficax". (20) Enghoff was referring to a publication from A. and M. Krogh in 1910, where they stated that under physiological conditions the arterial and alveolar CO_2 partial pressures are the same or that the difference between them is at least not considerable. (20,21) With the use of $paCO_2$ instead of $pACO_2$, Enghoff found a simple way to calculate physiological dead space. (20)

Enghoffs modification of the Bohr-equation: (3)

$$(7) \qquad VD/VT = (paCO_2 - pECO_2) / paCO_2$$

Because of its simplicity the Bohr-Enghoff-equation is still the most common method to calculate physiological dead space. (1) However, modern studies suggested that the use of this equation may lead to an overestimation of physiological dead space volume. (1) Furthermore, Enghoff's equation is still an invasive method, because it requires the taking of arterial blood samples. (1)

1.4.1.3 Differences between Bohr's and Enghoff's approaches

The main difference is the use of arterial pCO_2 instead of the alveolar pCO_2 in Enghoff's modification of Bohr's equation. (1,2,16,20) This could easily lead to an overestimation of the dead space, because the equation includes the full range of V/Q-mismatches, whereas Bohr's equation is only calculating the alveolar dead space in strict sense. (1)

This contamination of alveolar dead space in Enghoff's equation is called "shunt-related dead space". (1) Tusman et al. define Enghoff's equation as a "global index of the efficiency of gas exchange but not a dead space in the classical sense of the word". (1)

However, previous studies showed that there has to be a large fraction of shunt volume (20-30%) to affect dead space fractions. (1)

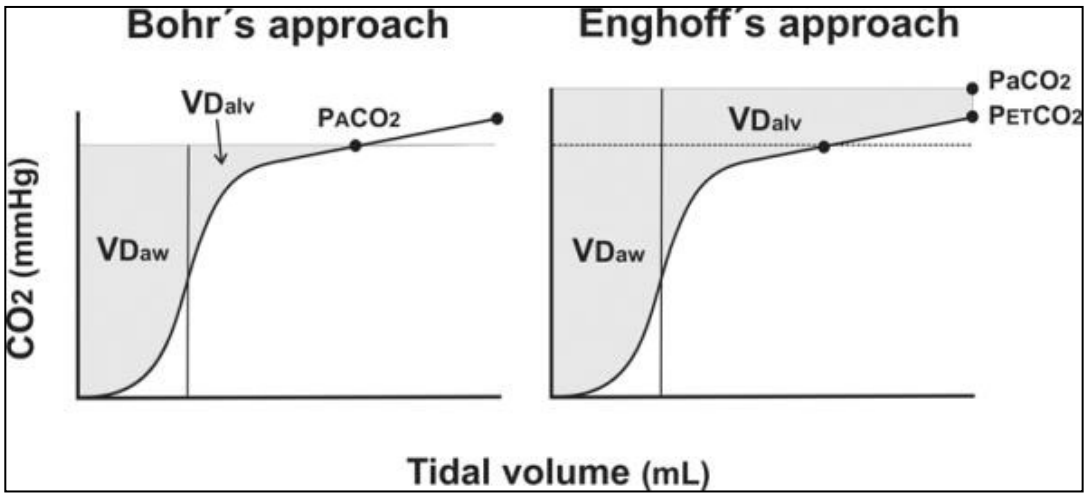


Figure 6: Differences in the approaches of Bohr and Enghoff

The figure shows a graphical display of the differences in the approaches of Bohr and Enghoff as described by Tusman et al. (22) VDaw = airway dead space; VDalv = alveolar dead space; $pACO_2$ = alveolar partial pressure of CO_2; $paCO_2$ = arterial partial pressure of CO_2; $petCO_2$ = end-tidal partial pressure of CO_2. Tusman G, Sipmann FS, Bohm SH. Rationale of dead space measurement by volumetric capnography. Anesth Analg. 2012;114(4):866–874.

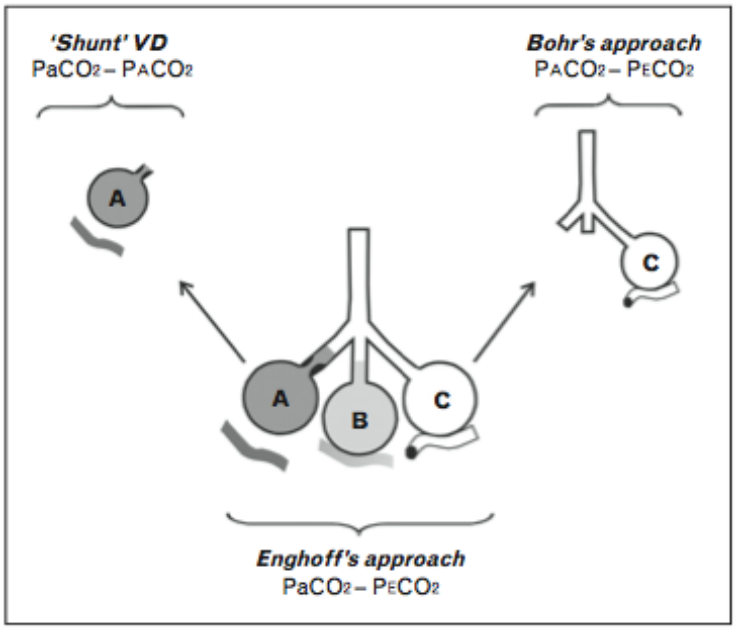


Figure 7: Scheme of Riley and Cournand's three-lung model

The figure shows a schematic representation of Riley's "three lung model", adapted by Suarez Sipmann et al., considering the differences between Bohr's and Enghoff's approaches. (1) Suarez-Sipmann F, Bohm SH, Tusman G. Volumetric capnography: the time has come. Curr Opin Crit Care. 2014;20(3):333–339.

1.4.1.4 VD-Fowler

In 1948 Ward S. Fowler from Philadelphia, Pennsylvania developed a geometrical approach to determine airway dead space. (13) His method was based on the continuous and simultaneous measurement of expired gas flow and expired N_2 in subjects breathing 99,6% oxygen. (3,13)

Fowler divided the expired volume into three “nitrogen-fraction phases”. (3,13) The first phase represented the inspired gas of the upper respiratory tract. (3,13) In the second phase the N_2-concentration was constantly and rapidly rising, which was representing a mixture of inspired gas and alveolar gas. (3,13) Finally, in the third phase the N_2-concentration was more or less constant. (3,13) Fowler interpreted this fact as a possible representation of the alveolar gas volume. (3)

Fowler was using a line to extrapolate the plateau phase (phase 3) to the left. He then drew a perpendicular through phase 2, which was dividing phase 2 in two triangles of equal size. (3,13) Following this he defined the airway dead space as the volume to the left of the perpendicular (see Fig. 8). (3,13) Fowler’s considerations could be used in a similar way for CO_2-concentrations.

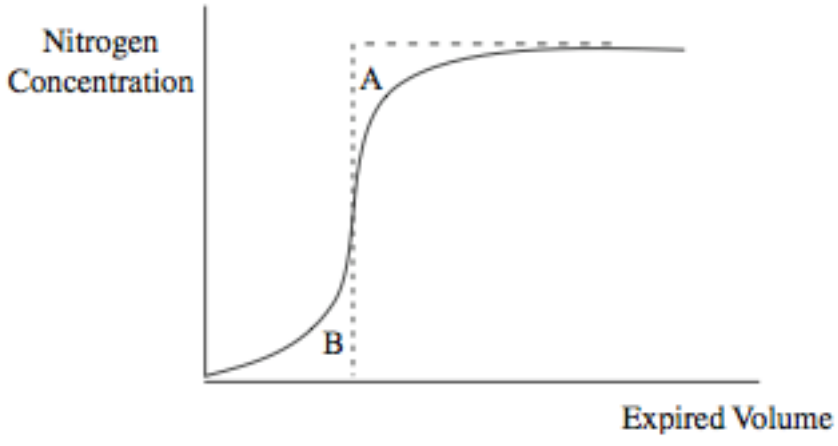


Figure 8: VD-Fowler

Fowler’s approach to determine airway dead space. (3) Sinha P, Flower O, Soni N. Deadspace ventilation: a waste of breath! Intensive Care Med. 2011;37(5):735–746.

Although Fowler's method still is in use for the non-invasive measurement of airway dead space, there are some limitations, which can affect its accuracy, like the shape of the capnogram. (3) In cases of a steep and steady ascent of the tracing the border between phase II and phase III could be hard to determine and therefore the accuracy of Fowler's method is restricted. Over the last years new mathematical approaches to calculate VDaw were developed. (3)

1.4.1.5 VD-Langley

In 1975 Langley et al. presented an alternative to Fowler's model by plotting the expired carbon dioxide in ml against the total expired gas volume. (2,3,23) This leads to an almost linear ascent of the tracing, which could be elongated towards the x-axis till it intersects it. At the point of intersection the airway dead space volume could be read off the x-axis. (2,3,23)

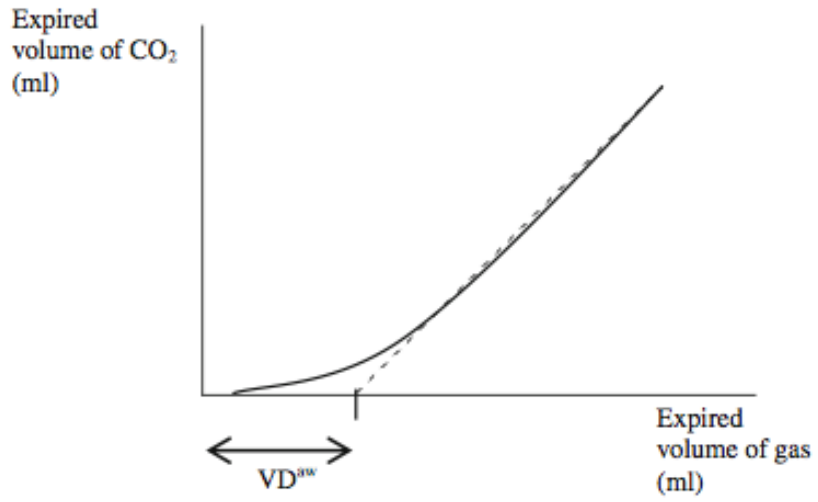


Figure 9: VD-Langley

The figure shows Langley's approach to estimate VDaw. (3) VDaw = airway dead space. Sinha P, Flower O, Soni N. Deadspace ventilation: a waste of breath! Intensive Care Med. 2011;37(5):735–746.

1.4.1.6 V/Q-ratio and Riley's "three lung model"

The V/Q-ratio is used to constitute the proportion of ventilation and perfusion of the alveolar units. Under physiological conditions the V/Q-ratio is anywhere between 0.8

and 1.0. (15) If the alveolar unit is better ventilated than perfused the V/Q-ratio rises to values higher than 1.0. (15) On the other hand the V/Q-ratio falls under 0.8, if the perfusion of the alveolar unit is better than its ventilation. (15)

In 1949 Riley and Cournand presented their “three-lung model”, which is considering the influence of ventilation and perfusion on gas exchange and dead space. (24,25)
In their model, the lung consists of 3 compartments, which can be distinguished in terms of ventilation and perfusion. (1,24)

The first compartment (A) is not ventilated, but perfused, which means that there’s no oxygenation of the blood and therefore shunt volume is generated (V/Q-ratio: 0). (3) The second compartment (B) is perfused and ventilated, which is the ideal scenario. (3) The blood gets oxygenated and there’s a normal V/Q-ratio (0,8-1,0). (3) The last compartment is ventilated but not perfused (= true alveolar dead space). In this case the V/Q-ratio is getting infinitely high. (1,3,24,25)

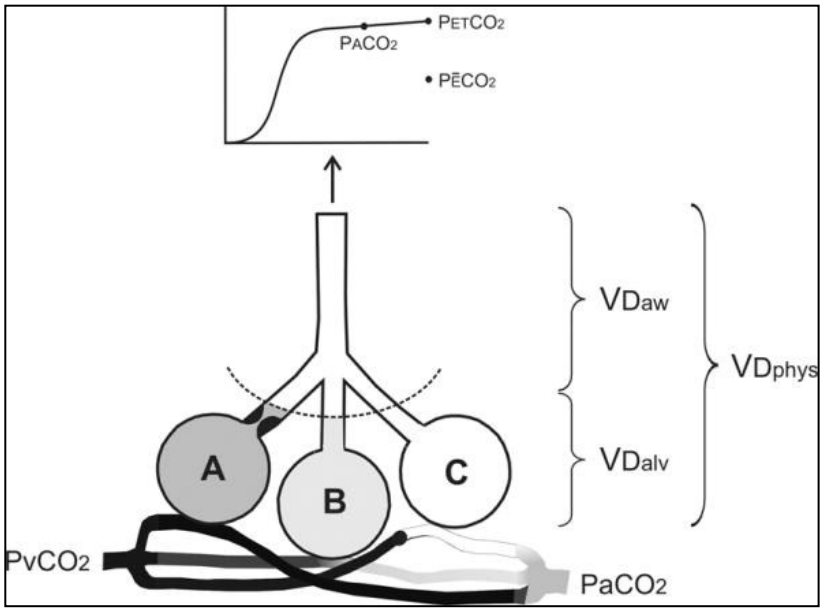


Figure 10: Three-lung model

The figure is showing Riley and Cournand's model of the lungs adapted by Tusman et al. (22) In this adaptation of Riley's 3-compartment model of the lungs (A) is representing shunt, (B) an ideal unit, and (C) dead space. VDaw = airway dead space; VDalv = alveolar dead space; VDphys = physiological dead space; $pACO_2$ = alveolar partial pressure of CO_2; $petCO_2$ = end-tidal partial pressure of CO_2; $pECO_2$ = mean expiratory partial pressure of CO_2; $pvCO_2$ = venous partial pressure of CO_2; $paCO_2$ = arterial partial pressure of CO_2. Tusman G, Sipmann FS, Bohm SH. Rationale of dead space measurement by volumetric capnography. Anesth Analg. 2012;114(4):866–874.

1.4.2 Modern aspects of dead space

Riley and Cournand's "three-lung model" is still influencing the modern theories of physiological dead space. (3) The three compartments, which Riley and Cournand described are representing areas of the lung with major differences in perfusion and ventilation.

1.4.2.1 Dead space and shunt volume

As mentioned above, "shunt dead space" is caused by those areas of the lung, which are perfused, but not ventilated. (3) Therefore there's no oxygenation of the blood and $paCO_2$ and $pvCO_2$ are the same. That means that the higher the value of shunt volume is, the higher is the value of $paCO_2$. (26) Tang et al. showed the correlation of $paCO_2$ and shunt volume in a computerized model. (27)

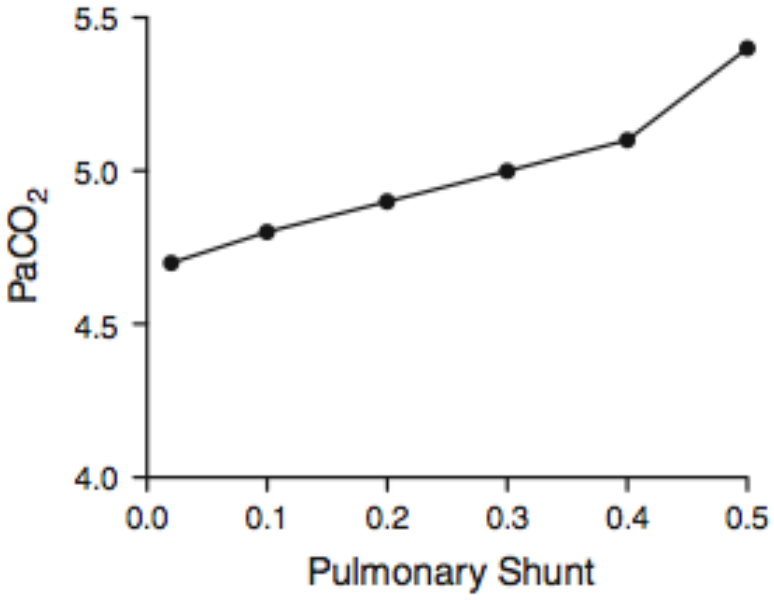


Figure 11: Correlation between pulmonary shunt volume and $paCO_2$

The figure shows the correlation between values of $paCO_2$ and pulmonary shunt volume as shown by Tang et al. (3,27) $paCO_2$ = arterial partial pressure of CO_2. Sinha P, Flower O, Soni N. Deadspace ventilation: a waste of breath! Intensive Care Med. 2011;37(5):735–746.

"Shunt dead space", as a consequence of atelectasis, is an important factor in respiratory diseases and affects the total physiological dead space volume. (1)

Although “shunt dead space” in strict sense is not part of physiological dead space, it still represents an abnormality in V/Q-ratio and furthermore is part of Enghoff’s modification of the Bohr equation. (1)

The influence of shunt volume on dead space can be expressed with the relation of shunt volume (QS) and total cardiac output (QT). The influence of QS/QT on dead space is non-linear, which is illustrated in Fig. 12. (28) At a low QS/QT-ratio the influence of shunt volume on dead space is negligible. Nevertheless, at higher fractions of QS/QT there’s a rapid increase in dead space volume. (1,28,29)

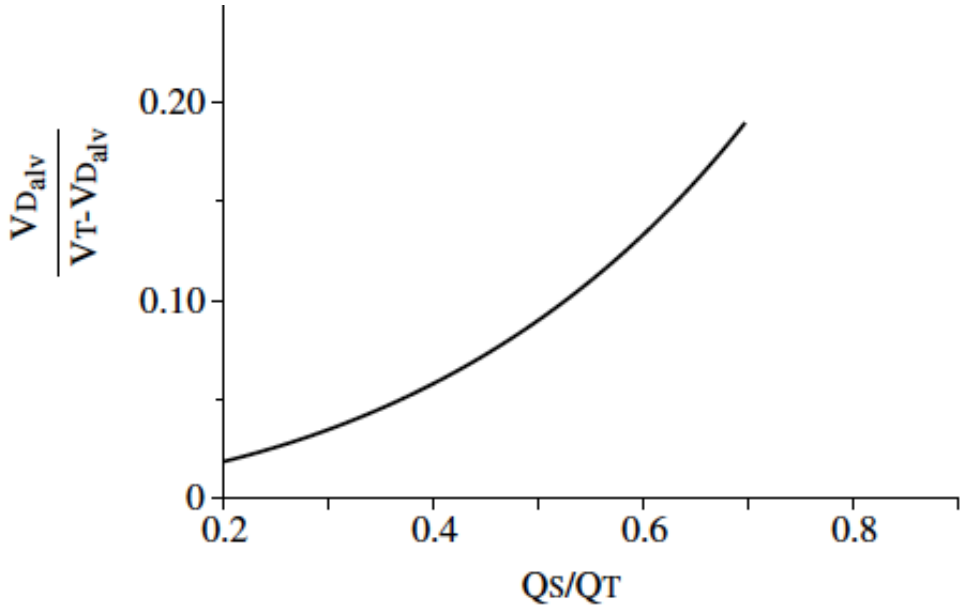


Figure 12: Effect of QS/QT-ratio on alveolar dead space

The figure shows the effect of QS/QT-ratio on alveolar dead space as described by Mecikalski et al. (28) VDalv/(VT-VDalv) = alveolar dead space fraction; QS/QT = shunt volume to cardiac output ratio. Mecikalski MB, Cutillo AG, Renzetti AD. Effect of right-to-left shunting on alveolar dead space. Bull Eur Physiopathol Respir. 1984;20(6):513–519.

Although the effect of shunt volume on alveolar dead space is not deniable, high V/Q-ratios have a much more significant impact on alveolar dead space and are therefore more important in pathophysiological concerns of alveolar dead space. (1)

1.4.2.2 ALI/ARDS and dead space

Acute respiratory distress syndrome (ARDS) is describing an acute and severe respiratory failure, which is not caused by heart failure or volume overload. (30) In 2012, the European Society of Intensive Care Medicine together with the American Thoracic Society and the Society of Critical Care Medicine established the following criteria for ARDS, which are also known as “Berlin criteria”: (30)

- Acute onset of the lung injury with a progression of the respiratory symptoms
- Bilateral infiltrates in chest radiography, which are not explained by other pulmonary entities
- Respiratory failure, which is not caused by heart failure or volume overload
- Decrease in paO_2/FiO_2-ratio (with a minimum PEEP of 5 mbar):
    - Mild ARDS: paO_2/FiO_2-ratio between 201 and 300 mmHg
    - Moderate ARDS: paO_2/FiO_2-ratio between 101 and 200 mmHg
    - Severe ARDS: paO_2/FiO_2-ratio equal to or under 100 mmHg

Those criteria, in matters of paO_2/FiO_2, replaced the former definition (AECC 1994), where ARDS and ALI (= acute lung injury) have been separated: (31)

- ALI: paO_2/FiO_2-ratio under 300 mmHg
- ARDS: paO_2/FiO_2-ratio under 200 mmHg

However, over the past decades the main criteria to detect ARDS or ALI was the paO_2/FiO_2-ratio. (30,31) Nowadays there are different studies, which claim that physiological dead space or the physiological dead space to tidal volume ratio and pa-$etCO_2$ are better predictive factors in terms of acute lung injury. (32,33) An increase of the VD/VT-ratio is reflecting the dimension of lung injury and related with a higher mortality in early and intermediate stages of ARDS. (34)

What are the pathophysiological reasons for the increase of VD/VT in patients with acute lung injury? Foremost, the increase of physiological dead space is caused by a distribution of the tidal volume to badly or non-perfused areas of the lung. (3) Therefore alveolar dead space is increasing. Furthermore, mechanical ventilation and especially the positive end-expiratory pressure (= PEEP) are leading to an additional increase of dead space. (3) The high ventilatory pressures lead to a high

V/Q-ratio and therefore generate dead space. (3) Additionally, the high ventilatory pressures are causing an overdistension of the well-ventilated alveolar units, which again leads to a worsening of gas exchange and therefore generates further dead space volume. (3,18)

Latest trials showed that activated protein C plays an important role in the appearance of micro-embolism, which leads to a further increase of V/Q-mismatch. (3) Furthermore, Ong et al. demonstrated that there's also a correlation between the angiopoietin 2 and 1-ratio and the occurrence of dead space. (35) This may be caused by endothelial damage. (3,35)

However, there's also an increase of shunt volume in patients with ARDS, which again contributes to the height of VD/VT-ratio. (3)

Nevertheless, the importance of monitoring CO_2 in patients with ARDS is nowadays not deniable. Using the VD/VT-ratio could provide more important information about the outcome of the disease and is a valid prognostic factor in terms of ARDS/ALI. (3,11,36)

1.4.2.3 Dead space and PEEP

Another important factor concerning dead space in mechanically ventilated patients with ALI/ARDS is the positive end expiratory pressure (PEEP). (3,37–39) PEEP is used to avoid an alveolar collapse of "unstable pulmonary units" at the end of expiration. (37) Furthermore, a positive end-expiratory pressure can be used to re-inflate previously collapsed areas of the lung. (37) Therefore, PEEP is an important part of so-called "recruitment manoeuvres". (37)

Nevertheless, the main goal is to keep the PEEP as low as possible, in order to avoid an overdistension of the ventilated alveoli. (37) So the ideal PEEP values, where the highest amount of alveolar units can be recruited without an overdistension of certain other units, are difficult to reach and are the reason for several studies. (37)

However, dead space may reflect changes in terms of alveolar-recruitment and collapse of lung areas. (37) An overdistension of the lung leads to an increase of alveolar dead space and a decrement of expired CO_2-volume, which leads to a higher difference in pa-etCO_2-values. (37) On the contrary, recruitment manoeuvres can decrease the pa-etCO_2-gradient and therefore reduce dead space volume by decreasing pulmonary shunt volume. (37)

Pfurtscheller et al. stated that alveolar dead space fraction could help to find ideal PEEP-settings. (40)

Tusman et al. showed in an animal trial that VDalv, VDalv/VTalv and pa-etCO_2 “were closely correlating with atelectatic lung areas” and therefore can be used to detect hyper- and hypo-inflated lung areas. (37)

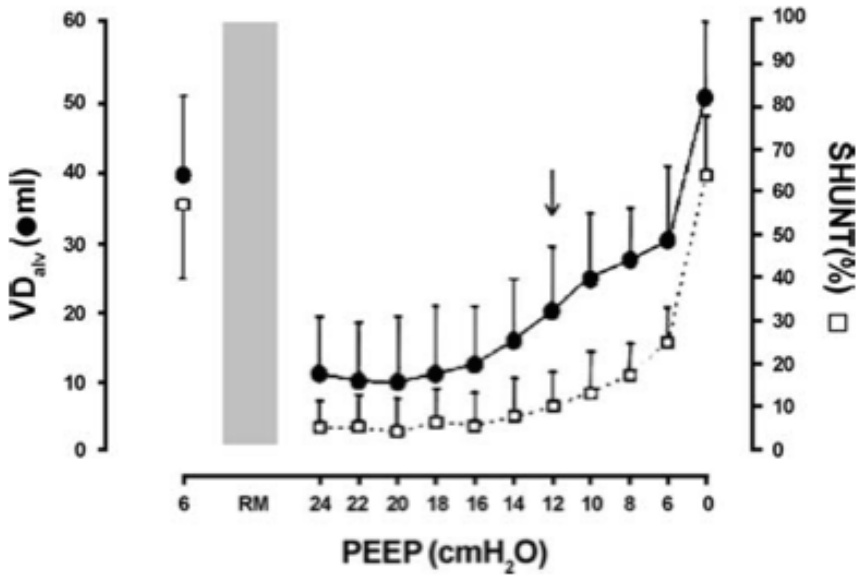


Figure 13: PEEP and VDalv

The figure shows the effect of PEEP-titration on alveolar dead space (VDalv). (37) The arrow indicates the moment of lung collapse. VDalv = alveolar dead space; PEEP = positive end-expiratory pressure. Tusman G, Suarez-Sipmann F, Böhm SH, Pech T, Reissmann H, Meschino G, et al. Monitoring dead space during recruitment and PEEP titration in an experimental model. Intensive Care Med. 2006;32(11):1863–1871.

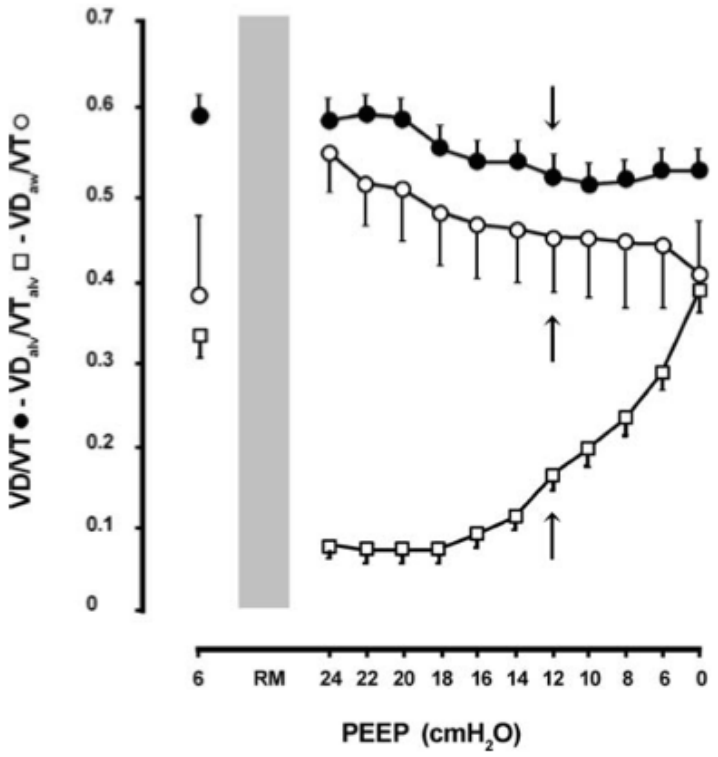


Figure 14: PEEP and dead space fractions

The figure shows the effect of airway-distension on the VD/VT-, VDalv/VT- and VDaw/VT-ratios. (37) The arrows indicate the moment of lung collapse. VD/VT = physiological dead space-to-tidal volume ratio; VDalv/VTalv = alveolar dead space-to-alveolar tidal volume ratio; VDaw/VT = airway dead space-to-tidal volume ratio; PEEP = positive end-expiratory pressure. Tusman G, Suarez-Sipmann F, Böhm SH, Pech T, Reissmann H, Meschino G, et al. Monitoring dead space during recruitment and PEEP titration in an experimental model. Intensive Care Med. 2006;32(11):1863–1871.

In addition to the ideal PEEP-settings prone position is discussed as a factor, which could ameliorate the ventilation of dorsal lung areas in critically ill patients. (40) Previous studies showed an improvement of oxygenation in prone position, without an effect on the outcome of ARDS. (41–47) However, recent studies showed a better middle-term outcome in patients with ARDS. (48)

Pfurtscheller et al. showed a significant improvement of oxygenation and CO_2-elimination in prone position in a porcine ALI model. (40) Further, they stated that EIT (= electrical impedance tomography) is a useful technique to visualize a homogeneous distribution of ventilation. (40)

1.4.3 Standard values of dead space and VCAP in infants

There are few publications concerning dead space values in children. However, those standard values are important to refer on, when analysing dead space values and VCAP. Foremost, all the published data are based on Enghoff's modification of Bohr's equation, which is including all the V/Q-inhomogeneities.

Riou et al. published dead space-data measured by SBT-CO_2 and calculated by the Bohr-Enghoff-equation. (49)

Furthermore, the VD/VT-ratio is an important factor in clinical practice. There were some publications concerning values of VD/VT-ratio. Coss-Bu et al. published a table with a comparison of different studies relying on the calculation of VD/VT-ratio in critical ill children with ALI. (19)

Study	VD/VT	Method/Equation	*t* Test vs Coss-Bu Study
Present study (n = 45)	0.48 ± 0.2†	Metabolic Monitor/Bohr-Enghoff	
Wenzel et al[26] (n = 33)	0.50 ± 0.12†	Capnogard/Bohr-Enghoff	$t = 0.51$; $p = 0.61$
Arnold et al[24] (n = 52)	0.32–0.71	Metabolic monitor/Bohr-Enghoff	NA
Arnold et al[25] (n = 102)	0.35–0.98	Metabolic monitor/Bohr-Enghoff	NA
Lum et al[33] (n = 12)	0.38 ± 0.15†	Metabolic monitor/Bohr-Enghoff	$t = -1.61$; $p = 0.11$
Shimada et al[16] (n = 14)	0.53 ± 0.04†	Douglas bag/Bohr	$t = 0.92$; $p = 0.35$
Kiiski et al[13] (n = 9)	0.47 ± 0.03‡	Metabolic monitor/Bohr	$t = -0.14$; $p = 0.86$
Kiiski et al[6] (n = 15)	0.46 ± 0.03‡	Metabolic monitor/Bohr	$t = -0.34$; $p = 0.67$

*NA = not available.
†Values given as mean ± SD.
‡Values given as mean ± SEM.

Table 2: Comparison of VD/VT-ratio-calculations

The table shows different studies and their standard values of VD/VT as described by Coss-Bu et al. (19) VD/VT = physiological dead space to tidal volume ratio. Coss-Bu JA, Walding DL, David YB, Jefferson LS. Dead Space Ventilation in Critically Ill Children With Lung Injury*. Chest. 2003;123:2050–2056.

1.4.4 Dead space as a predictive factor

Dead space as a non-invasive parameter represents an easy-to-obtain and valid possibility to predict the duration of mechanical ventilation and the outcome of mechanical ventilation. (5,6,50,51) Therefore VCAP provides useful information, which could be obtained for each and every breath.

Ong et al. found that in infants with cardiac surgery, an elevated VD/VT-ratio correlated with a longer period of mechanical ventilation and furthermore with an elongation of the hospitalization. (5) They stated that a VD/VT-ratio of over 0,50 has a "positive predictive value of 80% for the requirement of mechanical ventilation beyond 48 hours". (5)

Nuckton et al. showed a correlation between high values of VD/VT at the onset of the disease and mortality in adult patients with ARDS. (50) In the group of patients who died, the VD/VT-ratio was significantly higher than in the group of the survivors. Furthermore, there was no significant correlation between $petCO_2$ and the mortality. (50)

There have been similar findings concerning the correlation of VD/VT-ratio and mortality in patients with ARDS in studies by Raurich et al. and Matthay and Kallet. (6,51)

1.5 VCAP – Examples and explanations

Now I want to show some examples of volumetric capnography in respiratory and non-respiratory diseases. These examples should illustrate the usefulness of VCAP in the everyday routine of critical care medicine.

Furthermore, some pathophysiological considerations will be made, which are important for the understanding of the advantages VCAP is providing concerning those diseases.

1.5.1 RSV-infection

RSV (respiratory syncytial virus) is the main reason for acute infections of the lower respiratory tract (pneumonia, bronchiolitis) in infants under the age of 2 years. (52,53) In the first two years of life almost every child suffers from RSV-infection, but only about 2 to 3% get hospitalized. (52) Though, RSV still is the main reason, why healthy infants get hospitalized. (52)

In Central Europe there's normally an annual accumulation of RSV-infections in the winter months. (52)

In severe cases, RSV can cause major respiratory problems, which in the worst case can lead to acute lung injury. (52,53) In infants, RSV is the main reason for bronchiolitis, an inflammatory disease of the bronchioles, which leads to an obstruction of the small airways and interferes with the ability to eliminate CO_2. (53) The major issue of bronchiolitis is that it affects airways with a narrow calibre. (52)

RSV-bronchiolitis can cause a V/Q-mismatch and generate an increase of physiological dead space. (36) This yet again shows, why VCAP could be a valid method to detect RSV-bronchiolitis and could be a predictive factor in terms of the duration of mechanical ventilation.

Figure 15 shows a volumetric capnogram of a patient with RSV-bronchiolitis, whereas in comparison figure 16 represents the volumetric capnogram of a patient without impairment of lung function.

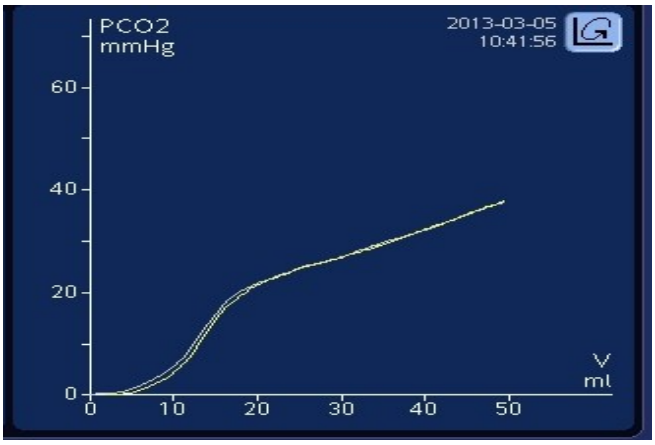


Figure 15: Volumetric capnogram of a patient with RSV-bronchiolitis

The figure shows a screenshot-image of a S1-respirator® by Hamilton. pCO_2 = partial pressure of CO_2; V = expired gas volume.

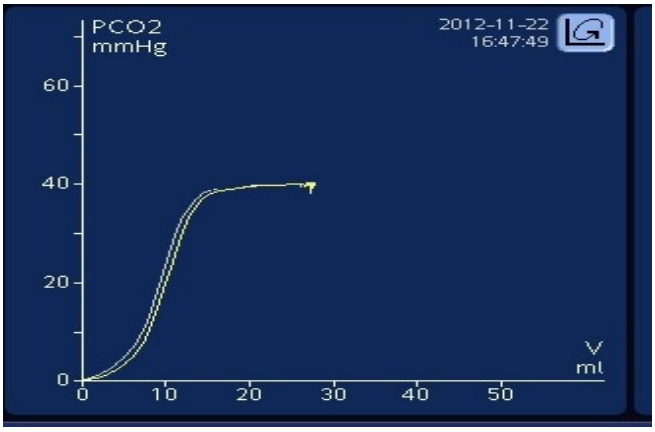


Figure 16: Volumetric capnogram of a normally ventilated lung

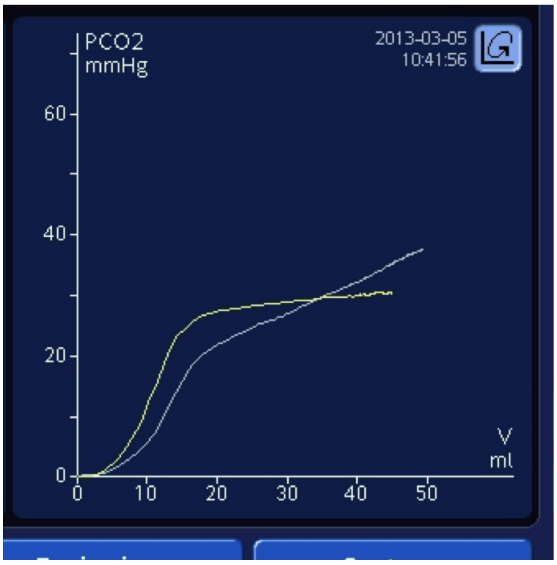
The figure shows a screenshot-image of a S1-respirator® by Hamilton. pCO_2 = partial pressure of CO_2; V = expired gas volume.

The typical volumetric capnogram of a patient with RSV-infection (Fig.15) shows a more or less constant ascent of the tracing. Phase II is elongated and the ascent is not as steep as in regularly ventilated lungs. The transition between phases II and III is difficult to determine and in phase III the tracing is not reaching its typical plateau, but keeps ascending. This on the one hand is caused by the earlier deflation of better-ventilated alveolar units with a lower pCO_2 and the later deflation of units with

a higher partial pressure of CO_2 and on the other hand it's caused by the lower expiratory flow, which leads to a delay of the CO_2-clearance.

However, the increase of SIII in cases of severe bronchiolitis correlates with higher values of alveolar dead space and VDalv/VT-ratio.

Moreover, slope-CO_2 is a useful tool to display the changes in pulmonary impairment over the course of time. The following figure shows the capnogram and CO_2-derived parameters of an infant with severe bronchiolitis on day 5 and day 9 of mechanical ventilation.



day	5	9
slope-CO2,Vol%/L	77.82	24.32
Vdphys/VT,%	0.695	0.543
Vdaw/VT, %	0.22	0.24
Vdalv/VT, %	0.475	0.298

Figure 17: slope-CO_2 on day 5 and day 9 of MV

The figure shows a comparison of slope-CO_2 on day 5 and day 9 of mechanical ventilation in an infant with severe bronchiolitis. VDphys/VT = physiological dead space fraction; VDaw/VT = airway dead space fraction; VDalv/VT = alveolar dead space fraction. The figure shows a screenshot-image of a S1-respirator® by Hamilton.

The following figure shows the changes of slope-CO_2 in an infant with severe bronchiolitis. The figure demonstrates that the peak value of slope-CO_2 isn't normally reached on day 1 of mechanical ventilation, but increases over the course of time and decreases again, after reaching a peak level.

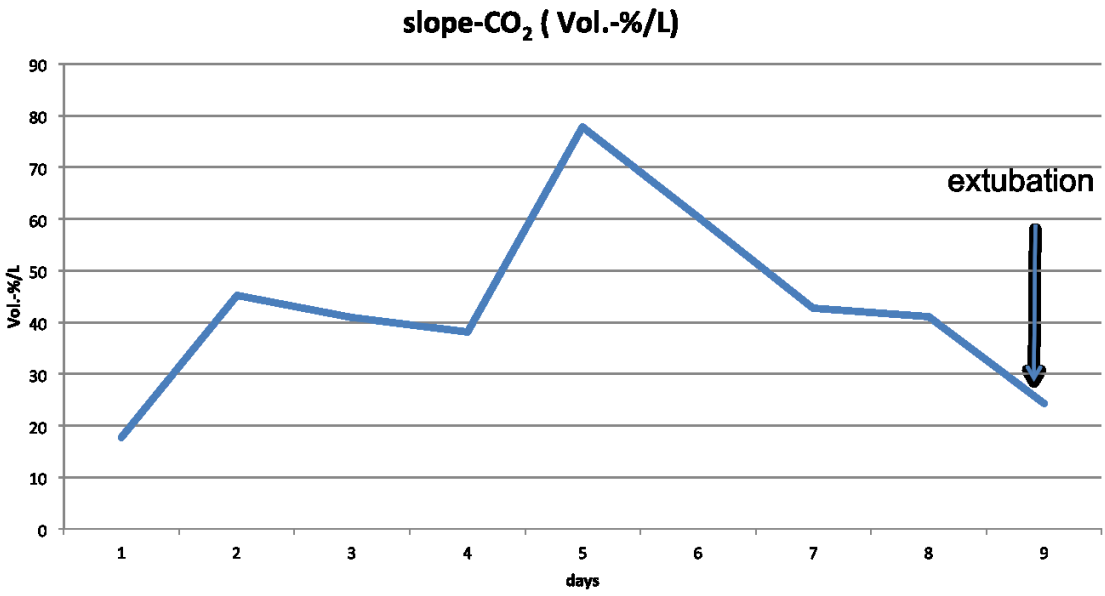


Figure 18: Trend-analysis of slope-CO_2

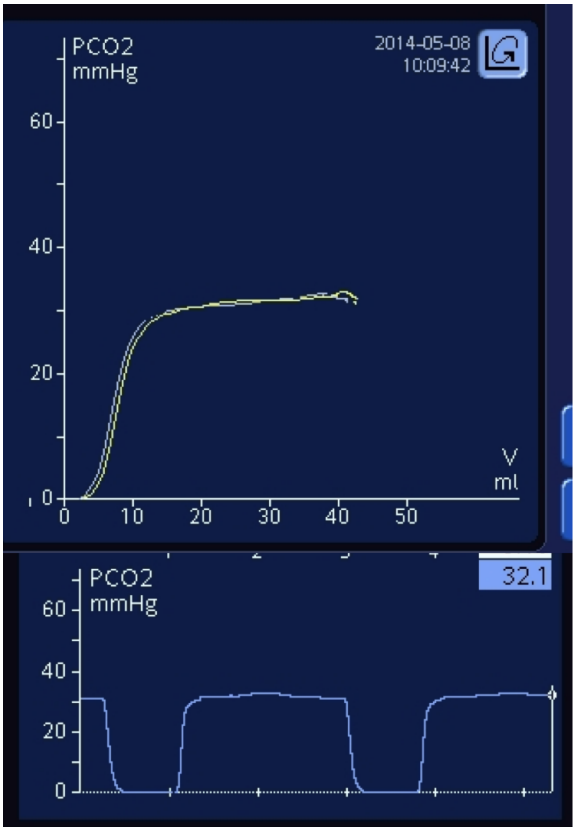
The figure shows the trend of slope-CO_2 over the course of mechanical ventilation in an infant with severe bronchiolitis.

Further, there are differences in the capnogram of patients with RSV-bronchiolitis and patients with RSV-pneumonia. The calculated slope-values of patients with RSV-bronchiolitis are clearly higher than the values of patients with RSV-pneumonia. This is correlating with the different appearance of the capnogram, where the tracing reaches a plateau in phase III. The different slopes (SIII) are caused by the differences in alveolar emptying. The obstructive component of the bronchiolitis results in a serial deflation of the alveolar units, whereas in pneumonia there's a simultaneous emptying of the alveoli. (11,54,55)

Furthermore, there are also differences in the dead space-fractions. Although the airway dead spaces in both cases are nearly the same, there's a big difference in VDphys, which is caused by the discrepancy in alveolar dead spaces (VDalv).

1.5.2 VCAP after cardiac surgery

Another important group of patients, where VCAP could provide useful information in terms of monitoring the trend of respiratory function, are patients, who underwent cardiac surgery. In those patients VCAP is used to overview the postoperative respiratory function, and to detect alveolar dead space. VCAP is providing the possibility to detect early signs of respiratory dysfunction and yet again to measure dead space values.



pH	7.37
paCO2,torr	40.1
petCO2,torr	33
pECO2,torr	20.1
pACO2,torr	24.4
pa-etCO2,torr	7.1
pa-ACO2,torr	15.6
slope-CO2,Vol.-%/L	10.8
Vdaw/VT,%	0.162
Vdalv/VT,%	0.336
Vdphys/VT,%	0.499
VDBohr/VT,%	0.178

Figure 18: VCAP and TCAP after cardiac surgery

The figure shows volume- and timed-based capnograms, CO_2-derived parameters and dead space fractions of a 5-months-old infant after cardiac surgery. This is a screenshot-picture of a S1-respirator® by Hamilton. pCO_2 = partial pressure of CO_2; V = expired gas volume; $paCO_2$ = arterial partial pressure of carbon dioxide; $petCO_2$ = end-tidal partial pressure of carbon dioxide; $pECO_2$ = mean expiratory partial pressure of carbon dioxide; $pACO_2$ = alveolar partial pressure of carbon dioxide; pa-$etCO_2$ = arterial to end-tidal difference of pCO_2; pa-ACO_2 = arterial to alveolar difference of pCO_2; VDaw/VT = airway dead space fraction; VDalv/VT = alveolar dead space fraction; VDphys/VT = physiological dead space fraction; VDBohr/VT = dead space fraction calculated by the Bohr equation.

However, changes in terms of slope-CO_2 and dead space could be an indication of respiratory involvement. There were studies concerning dead space values after cardiac surgery in infants, which showed that initially higher values of dead space were correlating with a longer period of mechanical ventilation.(56)

The physiological dead space (VDphys) could be affected by the appearance of shunt volume. (1) Therefore Enghoff's modification of the Bohr equation could be used in patients after cardiac surgery to calculate VD/VT-ratio and to evaluate the influence of shunt volume on dead space values.

2 Materials and Methods

2.1 General information

The study was hosted by the paediatric intensive care unit (= PICU) of the Medical University of Graz. The main goal of this retrospective study was to examine the advantages of volumetric capnography and slope-CO_2 in the daily clinical routine of a paediatric intensive care unit. Furthermore, the utility of dead space-derived parameters was analysed. Capnography-based parameters of mechanically ventilated children, under the age of 36 months, were evaluated.

The parameters were surveyed by using the Hamilton-S1-Respirator®. All the data has been recorded in the everyday clinical practice over a period of two years (2012-2014). Therefore no additive examinations were needed.

The mechanically ventilated children were divided into two different groups. The main differentiating factor of the two groups was the time of mechanical ventilation. By definition the time of mechanical ventilation in Group A had to be shorter than 48 hours, whereas the patients of Group B had to be mechanically ventilated for at least 48 hours or longer. Furthermore, in Group B, data were collected over four different points in time: on day 1, day 2 and day 3 of mechanical ventilation and on the day of extubation.

The analysis of the data included a comparison of the parameters of the two groups (Group A and B) and a comparison of the four different points in time of Group B. Additionally, we evaluated the correlation between different parameters.

The Ethics Committee of the Medical University of Graz approved the study.

2.2 Clinical procedure and VCAP-derived parameters and variables

2.2.1 Respirator settings

All patients were nasotracheally intubated and mechanically ventilated in a pressure controlled- (PCVcmv), or adapted pressure ventilation mode (APVcmv). Routine settings included:

- a respiratory rate between 24 and 30 breaths/minute
- a PEEP between 4-6 mbar
- a pressure amplitude of 15-20 mbar or a tidal volume of 8ml/kg
- an I:E-ratio of 1:2, and
- an inspired oxygen fraction (FiO2), which allowed SpO_2-values of at least 95%.

2.2.2 Airway monitoring

Respiratory monitoring included respiratory rate (RR), inspiratory and expiratory tidal volumes (VTi, VTe), airway pressures - peak inspiratory pressure (PIP), plateau pressure (Pplat), mean airway pressure (Paw), positive end-expiratory pressure (PEEP), static compliance (Cstat), in- and expiratory airway resistances (Rinsp, Rexsp) and in- and expiratory time constants (TCinsp, TCexp) using the Hamilton infant flow sensor®.

Pulse oximetry was measured continuously using the Masimo Radical-7® technology.

2.2.3 Capnography and dead space fractions

Time based capnography and volumetric capnography were measured by the Capnostat V infrared mainstream sensor (Neonatal/Paediatric Airway Adapter, Respironics®), which was placed at the airway opening, between the endotracheal tube and the Hamilton infant flow sensor®. The Capnostat V system is an integrated

part of the Hamilton S1 ventilator and displays a time-based capnogram, a volumetric capnogram, etCO_2, VCO_2, $VeCO_2$, slope-CO_2 and airway dead space (VDaw/VT). Physiologic dead space fraction was calculated according to the Bohr-Enghoff formula VDphys/VT = ($paCO_2$ – $pECO_2$) / $paCO_2$. Alveolar dead space fraction (VDalv/VT) was calculated to show the difference between physiologic dead space fraction and airway dead space fraction.

Arterial and central venous blood samples were taken for measurements of haemoglobin (Hb), oxygen saturation (SaO_2, SvO_2), arterial and venous pO_2 (paO_2, pvO_2) and pCO_2 ($paCO_2$, $pvCO_2$), pH (a-pH, v-pH) using an automatic blood gas system (ABL 725® Radiometer, Copenhagen).

2.2.4 Conversion factors

The normal respirator settings were valid for STPD-conditions (standard temperature pressure dry). But those conditions do not correlate with the physiologic conditions in the human body. Therefore the values were converted into BTPS-conditions (body temperature pressure saturated), using the following equation:

(8) BTPS = STPD x 1.21

CO_2 conversion factors:

(9) 1 Vol.-% = 7.6 mmHg

(10) 1 kPa = 7.5 Torr (mmHg)

(11) 1Torr = 0.133 kPa

2.2.5 VCAP-derived equations

To calculate VDphys, VDBohr, $pACO_2$ and $pECO_2$ we used the following standardized equations: (1)

(12) $pECO_2 = (VCO_{2br}/VTe) \times (pB - pH_2O)$

(13) $pACO_2 = (VCO_{2br}/VTalv) X (pB-pH_2O)$

(14) $VDBohr = (pACO_2 - pECO_2) / pACO_2$

(15) $VDphys = (paCO_2 - pECO_2) / paCO_2$

2.2.6 Medication

Sedo-analgesia was obtained by continuously infusing Midazolam (0.2 - 0.4 mg/kg/h), and Fentanyl (0.02 - 0.03 µg/kg/min). Cisatracurium was infused for muscle relaxation (0.2 - 0.3 mg/kg/h) in cases of severe postoperative low cardiac output, severe pulmonary hypertension and in cases of severe bronchiolitis.

2.2.7 Weaning and extubation

Controlled mechanical ventilation was followed by a short period of synchronized pressure or volume based intermittent mechanical ventilation. Before starting the weaning process from mechanical ventilation, drug weaning was initiated and adapted according to the duration of mechanical ventilation. Spontaneous pressure supported ventilation (PSV) was applied before extubation.
Criteria of extubation were:

- Stable hemodynamic situation without fluid overload
- Spontaneous breathing with sufficient muscle strength and neurologic alertness
- $FiO_2 < 0.4$
- Respiratory rate below 50 breaths/min (infants < 12 months) or below 40 breaths/min (children < 24 months)
- PEEP below 6 mbar
- Pressure amplitude < 15 mbar and tidal volume > 5 ml/kg

After extubation patients either required minimal oxygen supply, a nasal CPAP or a high flow oxygen support system.

Furthermore, in cases of severe bronchiolitis the following criteria were used as an indication for mechanical ventilation:

- Recurrent severe apnea
- Persistent hypoxemia (SpO_2/FiO_2-ratio < 130)
- Persistent hypercapnia (pCO_2 > 70 torr, pH < 7.25)
- Hemodynamic instability despite intravenous volume support
- Persistent Bronchiolitis score > 15

2.3 Groups, inclusion and exclusion criteria

All patients under the age of 36 months, who were mechanically ventilated with the Hamilton-S1-Respirator®, were included in the study. Altogether 51 patients matched those criteria. Furthermore, those 51 patients were divided into two subgroups. The differentiating factor between the subgroups was the duration of mechanical ventilation (< 48 hours and ≥ 48 hours).

The patients of Group A were extubated within the first 48 hours after intubation, which implicated that they had no major restrictions of the respiratory system. 16 patients matched the criteria. Of those 16 patients, 15 underwent cardiac surgery, and one suffered from sepsis.

The second group (Group B) included 35 patients. All of them required mechanical ventilation for at least 48 hours. Assumingly those patients primarily suffered from respiratory failure or cardiorespiratory failure.

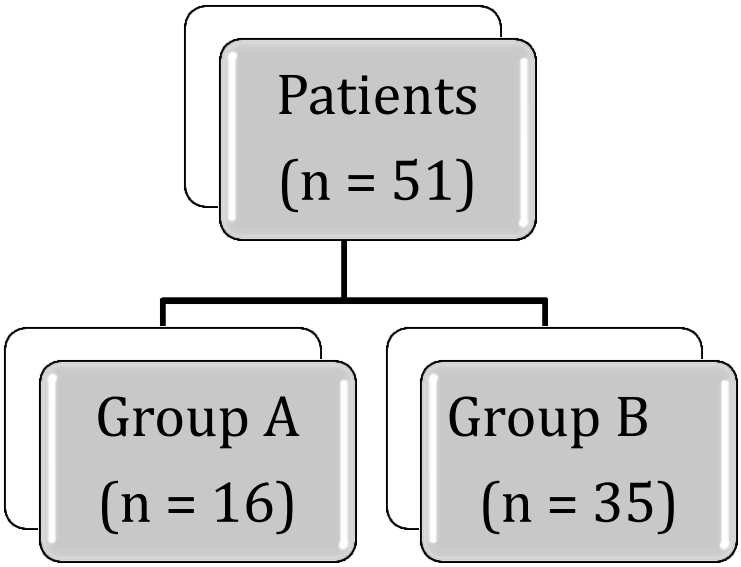


Figure 19: Distribution of patients

The figure shows the distribution of patients according to the duration of mechanical ventilation. Group A = patients, who required mechanical ventilation for not longer than 48 hours. Group B = patients, who were mechanically ventilated for at least 48 consecutive hours.

2.4 Data acquisition

All parameters were taken at 6:30 a.m., in the absence of nursing care activities and under stable cardiorespiratory conditions including ventilator synchrony. In Group A the measurements were only taken on the day of intubation, whereas in Group B there were measurements over four points in time:

- I: day of intubation (day 1)
- II: day 2 of mechanical ventilation
- III: day 3 of mechanical ventilation
- IV: day of extubation

2.5 Cases of death and cases of long-term ventilation

Two of the 51 patients died with complex congenital heart defects, because of irreversible cardiorespiratory failure, after 22 and 77 days of mechanical ventilation after cardiac surgery.

Furthermore, two patients underwent a tracheostomy according to the need of long-term ventilation. In those 2 cases, the fourth measurement could not be taken on the day of extubation. Therefore the fourth measurement was taken on the 21st day of mechanical ventilation.

	Age (months)	Sex	Year	Main Diagnosis
1	36	female	2013	Diaphragmatic hernia
2	0.22	female	2013	Tetralogy of Fallot; Absent pulmonary valve syndrome

Table 3: Cases of long-term-ventilation

2.6 Statistical analyses

In a first step we tested if our data were normally distributed. Therefore we used the Kolmogorov-Smirnov test together with the Lilliefors significance correction. (57) We assumed that the data were normally distributed with p-values of at least 0,200 or higher. Additionally, we used the Shapiro-Wilk test. (57)

Tests of Normality						
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
$petCO_2$-1	.123	35	.200*	.939	35	.052
*. This is a lower bound of the true significance.						
a. Lilliefors Significance Correction						

Table 4: Example of the tests of normality

df = number of values; Sig.= significance level; $petCO_2$-1 = end-tidal partial pressure of carbon dioxide on day 1.

For descriptive analysis of our data we used median, minimum and maximum. (57) We separately tested both groups (Group A and B) and further we separately analysed all four points in time of Group B.

Following the descriptive analysis we compared the values of both groups on day 1. Therefore we either used the two-tailed student's t-test for unpaired samples (for normally distributed data), or the Mann-Whitney-U-Test (for non-normally distributed data). (57)

Afterwards we separately compared day 1, day 2 and day 3 of Group B with the day of extubation (in the 2 cases of long-term ventilation we used the 21st day of mechanical ventilation as the fourth point in time). We used the two-tailed student's t-test for paired samples, when the data were normally distributed and the Wilcoxon rank-sum test, when the data were not normally distributed. (57)

If we compared more than two groups, we used the Kruskal-Wallis-Test for non-parametric data. (57)

P-values ≤ 0,05 were considered significant. (57) The following table is showing the different levels of significance:

P-values	Significance
p > 0.05	No significance
p ≤ 0.05	Significance
p ≤ 0.01	High significance
p ≤ 0.001	Very high significance

Table 5: Levels of significance

Furthermore, we tested the correlation of different parameters at certain points in time. Therefore we either used Pearson's correlation coefficient for normally distributed values, or Spearman's correlation coefficient for non-normally distributed values. (57) To determine the level of correlation we used Bühl's interpretation of correlation. (57)

R	Interpretation
< 0.2	Very low correlation
< 0.5	Low correlation
< 0.7	Moderate correlation
< 0.9	High correlation
≥ 0.9	Very high correlation

Table 6: Correlation coefficient (= R)

Interpretation of the correlation coefficient according to Bühl. (57)

To perform the statistical analysis we used IBM SPSS Statistics, Version 22.

3 Results

3.1 Demographic information

3.1.1 Number of patients, gender, age and weight

In total 51 patients were included into the study. 28 (54.9%) of those were male, 23 (45.1%) were female. The 51 patients were further divided into two subgroups, which were determined by the time of mechanical ventilation in days. In the first group (Group A) 16 patients were included. Of those 16 patients, 8 (50%) were male and 8 (50%) female. Group B included 35 patients. 20 (57.1 %) were male, 15 (42.9%) were female.

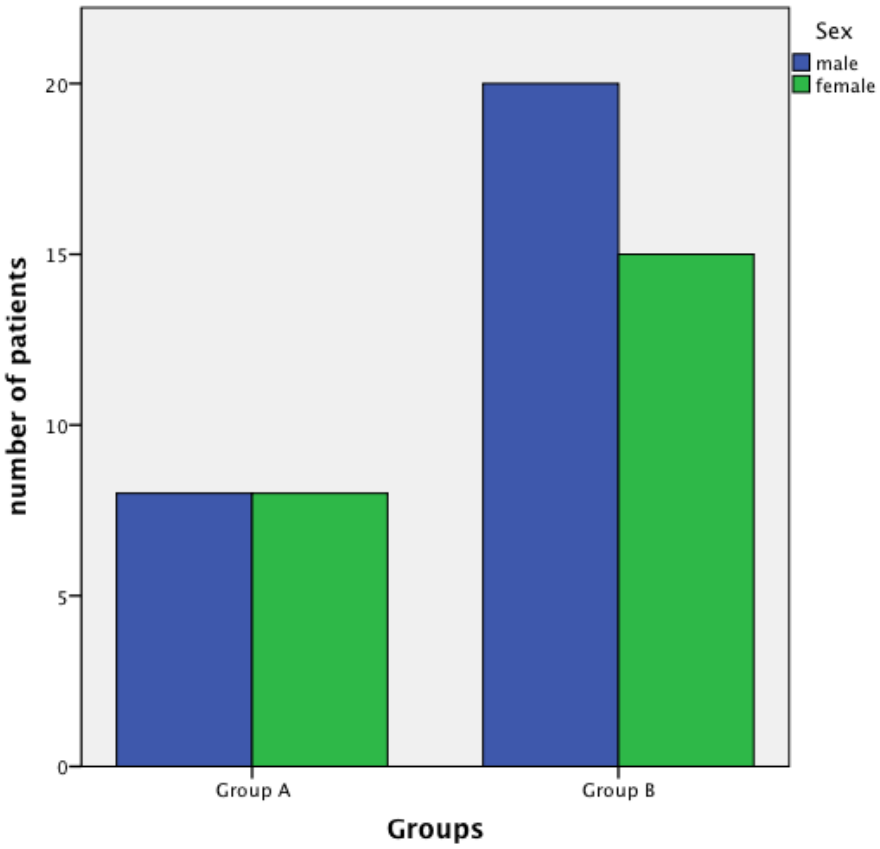


Figure 20: Distribution of sex

Group A = mechanical ventilation < 48 hours; Group B = mechanical ventilation ≥ 48 hours.

Due to the inclusion criteria, all patients were younger than 36 months. The median age of all patients was 7.4 months. The median age in Group A was 9.5 months, whereas the median age in Group B was 2 months.

The median weight of all patients was 6.3 kg, whereas it was 8.4 kg in Group A and 4.4 kg in Group B.

	Patients (n)	**Gender m/f (%)**	**Weight (kg)**	**Age (months)**
Total	51	54.9 / 45.1 %	6.3	7.4
Group A	16	50 / 50 %	8.4	9.5
Group B	35	57.1 / 42.9 %	4.4	2

Table 7: Demographic information

The table shows the number of patients, the sex in per cent, the median weight and the median age for all patients (= Total), Group A and Group B.

3.1.2 Duration of mechanical ventilation

We separately analysed the duration of mechanical ventilation for both groups.
In Group A the median value was 0.95 days with a range from 0.25 to 2 days.
In Group B the median value was 7 days. The minimum was 3 days, whereas the maximum value was 22 days.

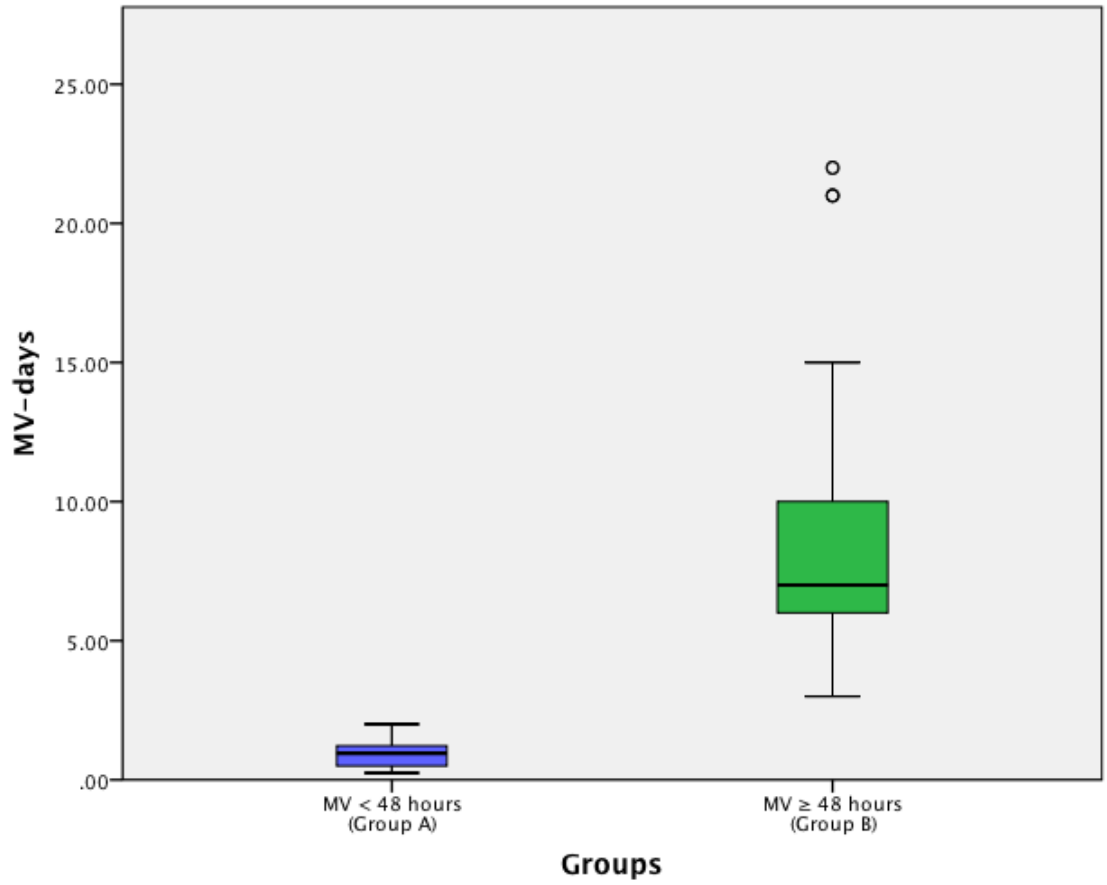


Figure 21: Box Plot of MV-days

The horizontal line represents the median value; the box contains 25th to 75th percentiles; the caps represent 10 and 90%. MV-days = days of mechanical ventilation. Group A = mechanical ventilation < 48 hours; Group B = mechanical ventilation ≥ 48 hours.

3.1.3 Diagnoses

The following table shows the main diagnoses separated for the two groups. Group A represents the patients, who required mechanical ventilation for less than 48 hours, whereas Group B represents those, who were ventilated for at least 48 hours.

Other co-morbidities were not considered in this table.

Main diagnoses	Group A	Group B	Total
Cardiac lesions			
Ventricular septal defect (VSD)	7	7	**14**
Coarctation of the aorta	3	6	**9**
Pulmonary valve stenosis (PST)	4		**4**
Tetralogy of Fallot (TOF)		3	**3**
Transposition of the great arteries (TGA)		3	**3**
Persistent ductus arteriosus (PDA)	1		**1**
Restrictive cardiomyopathy (rCMP)		1	**1**
Atrio-ventricular canal defect (AVC)		1	**1**
Aortopulmonary window		1	**1**
Contegra graft stenosis		1	**1**
Pulmonary illness			
RSV-infection		7	**7**
Diaphragmatic hernia		1	**1**
Pleuropneumonia	1		**1**
Bronchopulmonary dysplasia (BPD)		1	**1**
Others		3	
Total	**16**	**35**	**51**

Table 8: Main diagnoses

The main diagnoses were separated for each group. The subgroup “Others” included patients with the following diseases: one with Streptococcus-B-sepsis, one with Toxicosis and one with renal dysplasia. Group A = mechanical ventilation < 48 hours; Group B = mechanical ventilation ≥ 48 hours”, Total= total number of patients.

3.2 CO_2-derived parameters

3.2.1 $paCO_2$

A descriptive analysis was done of both groups on day 1 of mechanical ventilation. In Group A, all 16 values were valid. The median value was 35.15 mmHg. The minimum value was 29.9 mmHg, whereas the maximum value was 41.2 mmHg. In Group B, 35 valid values were documented. The median was 37.0 mmHg, the minimum was 29.3 mmHg and the maximum was 50 mmHg.

We compared the values of day 1 of both groups. We used the Mann-Whitney-U-Test, because the values were not normally distributed. We found no significant differences (p = 0.264) between the two groups.

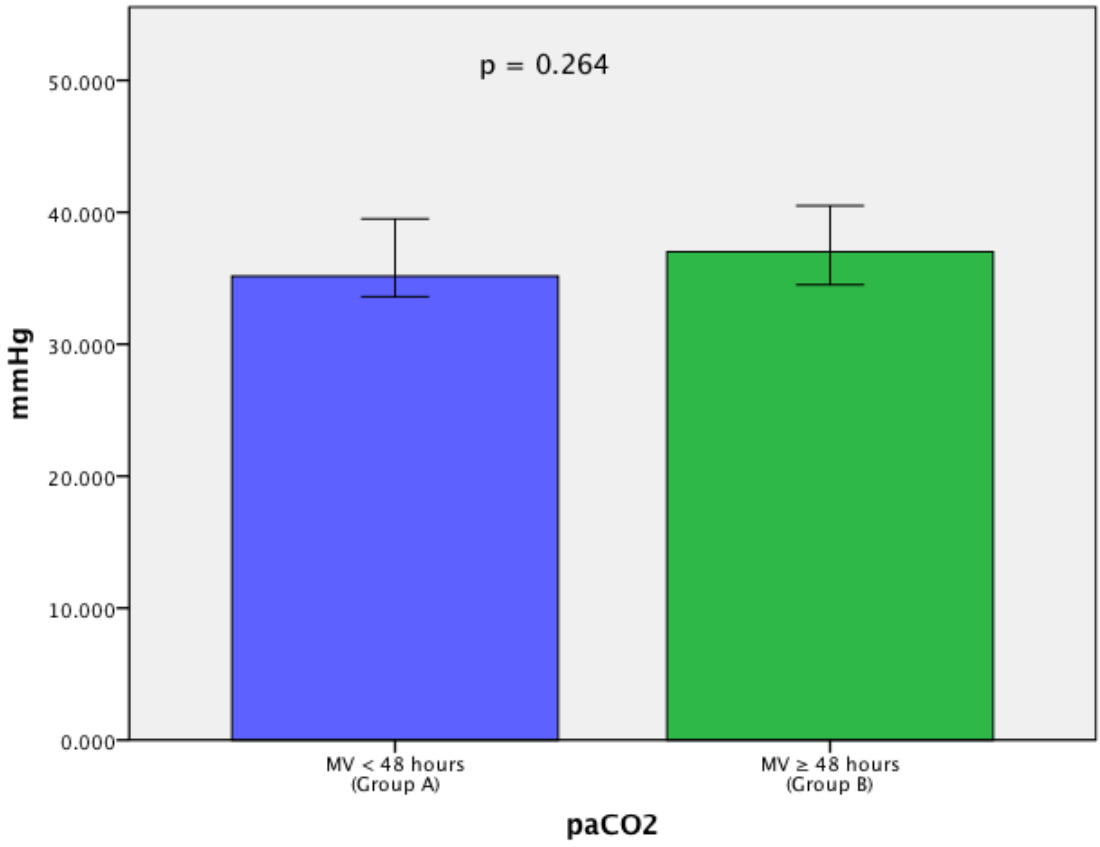


Figure 22: $paCO_2$ on day 1

The figure shows a comparison of the median $paCO_2$ of the two groups on day 1. Confidence interval = 95 %. $paCO_2$ = arterial partial pressure of carbon dioxide.

We separately compared the values of day 1, day 2 and day 3 with the values of the day of extubation in those patients who required mechanical ventilation for at least 48 hours. We used the Wilcoxon rank-sum test and found no significant differences.

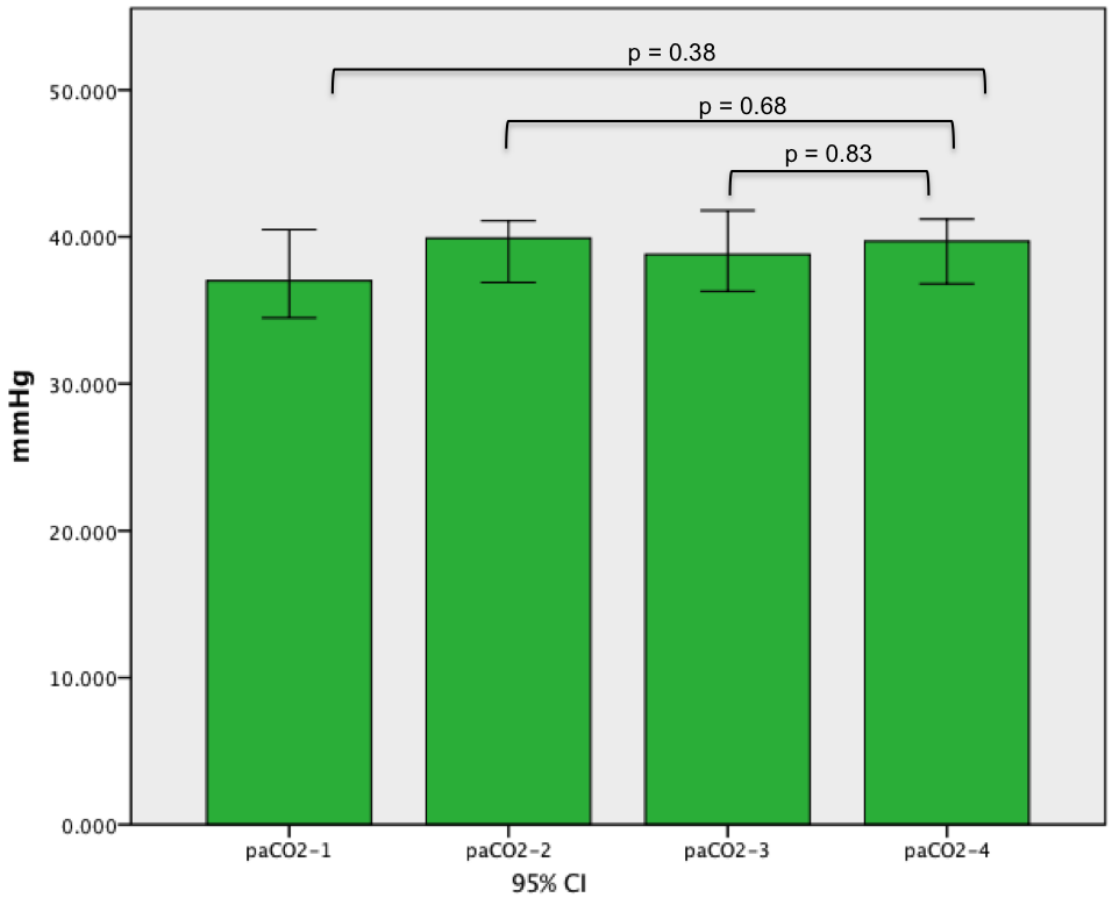


Figure 23: $paCO_2$ over the points in time

The figure shows comparisons of the median $paCO_2$ over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid. P-values: $paCO_2$-1 and $paCO_2$-4 = 0.38, $paCO_2$-2 and $paCO_2$-4 = 0.68, $paCO_2$-3 and $paCO_2$-4 = 0.83. $paCO_2$ = arterial partial pressure of carbon dioxide; CI = confidence interval.

3.2.2 $petCO_2$

A descriptive analysis of day 1 was done of both groups. In both groups all values were valid. In Group A the median value of $petCO_2$ was 34.0 mmHg. The range of values was from 32 mmHg to 41 mmHg. In Group B the range of values was from 25 to 44 mmHg, with a median of 32 mmHg.

We compared the values of day 1 of both groups. The values were not normally distributed. We used the Mann-Whitney-U-Test. The result wasn't significant with a p-value of 0.200.

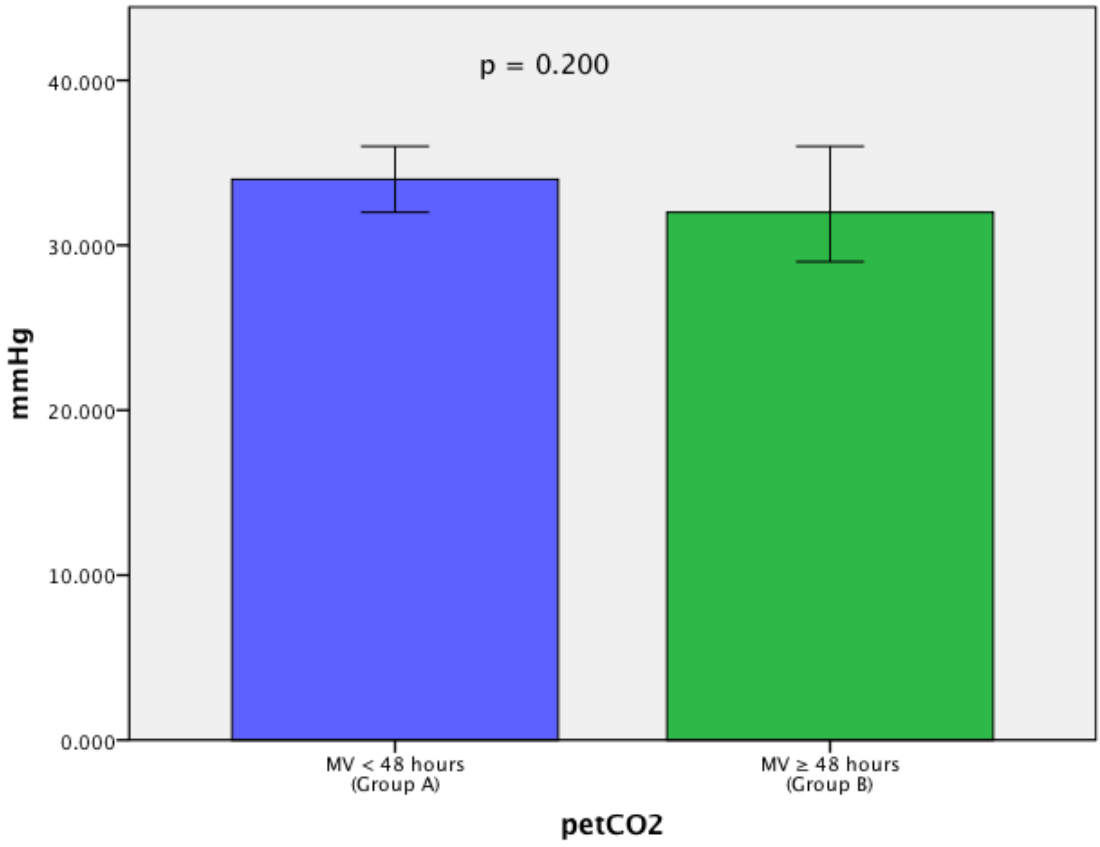


Figure 24: $petCO_2$ on day 1

The figure shows a comparison of the median $petCO_2$ of the two groups on day 1. Confidence interval = 95%; $petCO_2$ = end-tidal partial pressure of carbon dioxide.

We compared the values of $petCO_2$ of those patients who were mechanically ventilated for 48 hours or longer over the four different points in time. For that reason we compared each of the first three days with the fourth point in time. We used the two-tailed student's t-test for two paired samples, because the Kolmogorov-Smirnov-Test showed that the values were normally distributed. The results are shown in the following figure:

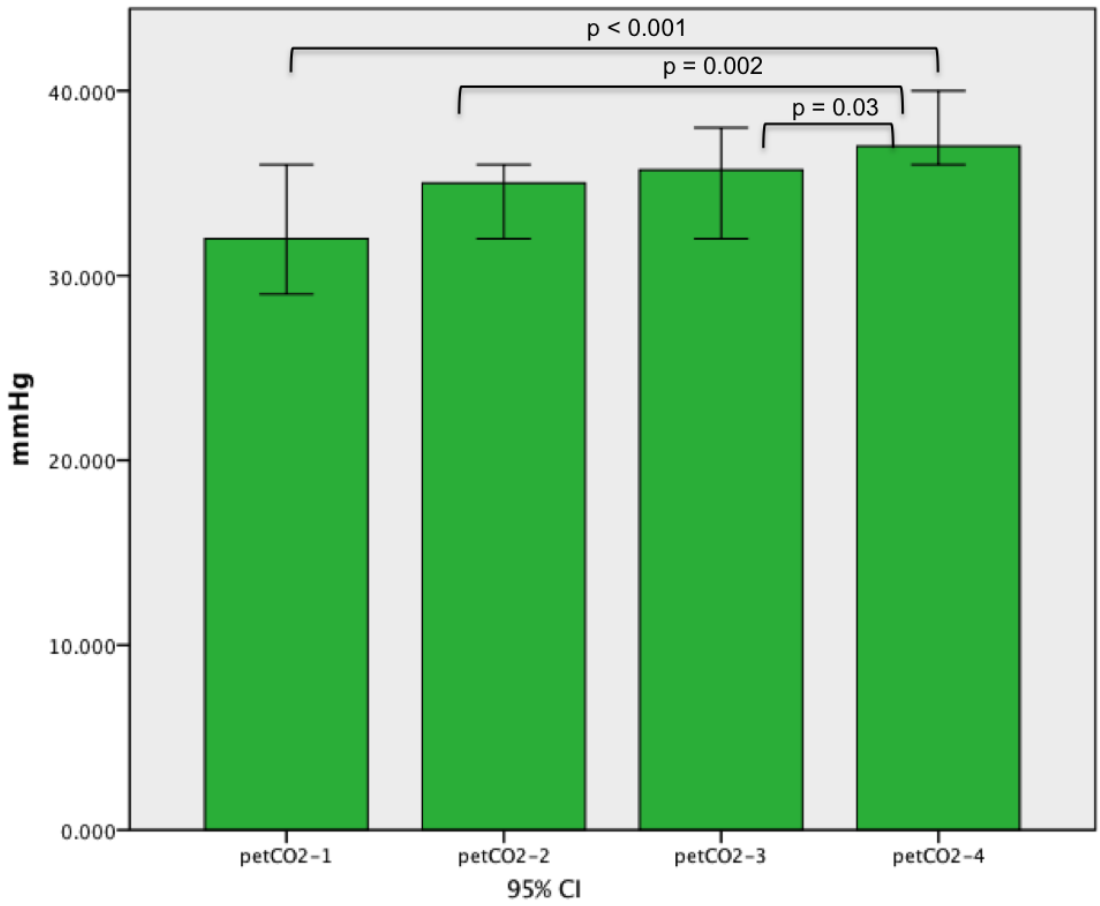


Figure 25: $petCO_2$ over the points in time

The figure shows comparisons of the median $petCO_2$ over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid. P-values: $petCO_2$-1 and $petCO_2$-4 < 0.001, $petCO_2$-2 and $petCO_2$-4 = 0.002, $petCO_2$-3 and $petCO_2$-4 = 0.03. $petCO_2$ = end-tidal partial pressure of carbon dioxide; CI = confidence interval.

3.2.3 $pACO_2$

We analysed the alveolar partial pressure of carbon dioxide. As done before we started with a descriptive analysis of both groups on day 1. In both groups all values were valid. The median value of Group A was 24.4 mmHg, the minimum value was 17.17 mmHg and the maximum value was 32.1 mmHg. In Group B the median was 19.81 mmHg, with a range from 10.92 to 26.3 mmHg.

The comparison of the two groups on day 1 was done using the two-tailed student's t-test for unpaired samples, because the values were normally distributed. The result was significant with a p-value of < 0.001.

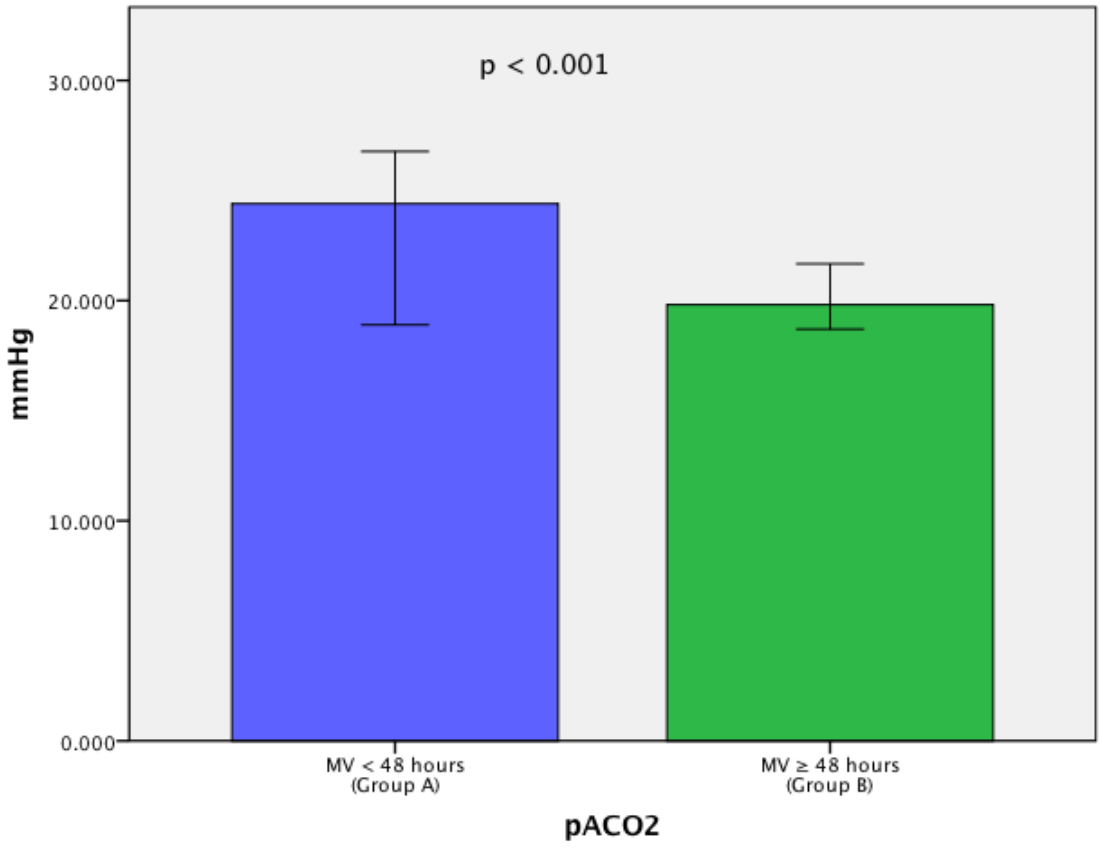


Figure 26: $pACO_2$ on day 1

The figure shows a comparison of the median $pACO_2$ of the two groups on day 1. Confidence interval = 95%; $pACO_2$ = alveolar partial pressure of carbon dioxide.

We compared the values of $pACO_2$ of those patients, who required mechanical ventilation for 48 hours or longer, over the four different points in time. Each of the first three days was compared with the fourth point in time.

We used the two-tailed student's t-test for paired samples and the Wilcoxon rank-sum test, because the Kolmogorov-Smirnov-Test showed that the values were normally distributed on day 1, day 3 and day 4, but that they were not normally distributed on the 2nd day.

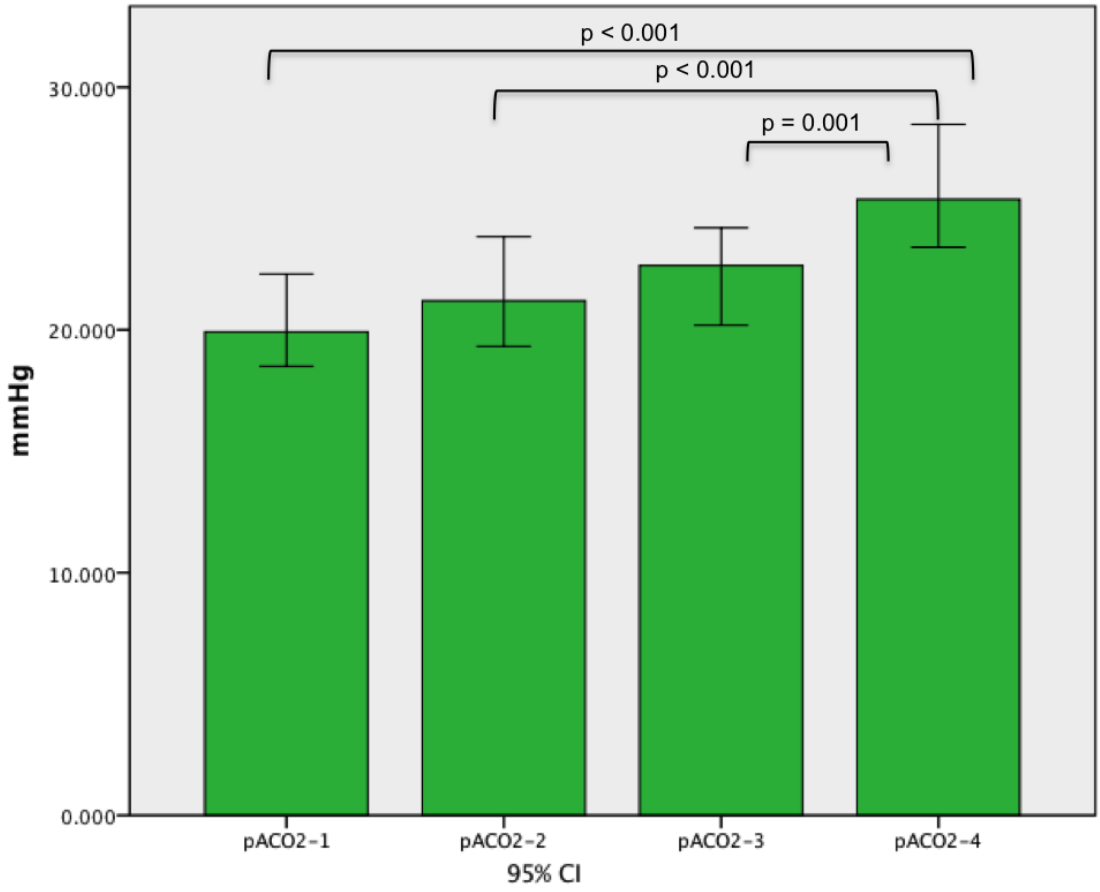


Figure 27: $pACO_2$ over the points in time

The figure shows comparisons of the median $pACO_2$ over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on day 1,2 and 3. On the day of extubation 34 values were valid. P-values: $pACO_2$-1 and $pACO_2$-4 < 0.001, $pACO_2$-2 and $pACO_2$-4 < 0.001, $pACO_2$-3 and $pACO_2$-4 = 0.0013. $pACO_2$ = alveolar partial pressure of carbon dioxide; CI = confidence interval.

3.2.4 $pECO_2$

We analysed the mean expiratory partial pressure of carbon dioxide (= $pECO_2$) on day 1. In Group A, all 16 values were valid with a median value of 19.8 mmHg and a range from 13.5 to 27.4 mmHg. In Group B 35 values were valid. The median was 15.2 mmHg. The lowest value was 9.0 mmHg, whereas the highest value was 19.7 mmHg.

The descriptive analysis was followed by a comparison of the two groups on day 1. We used the two-tailed student's t-test for unpaired samples. The result was significant with a p-value of < 0.001.

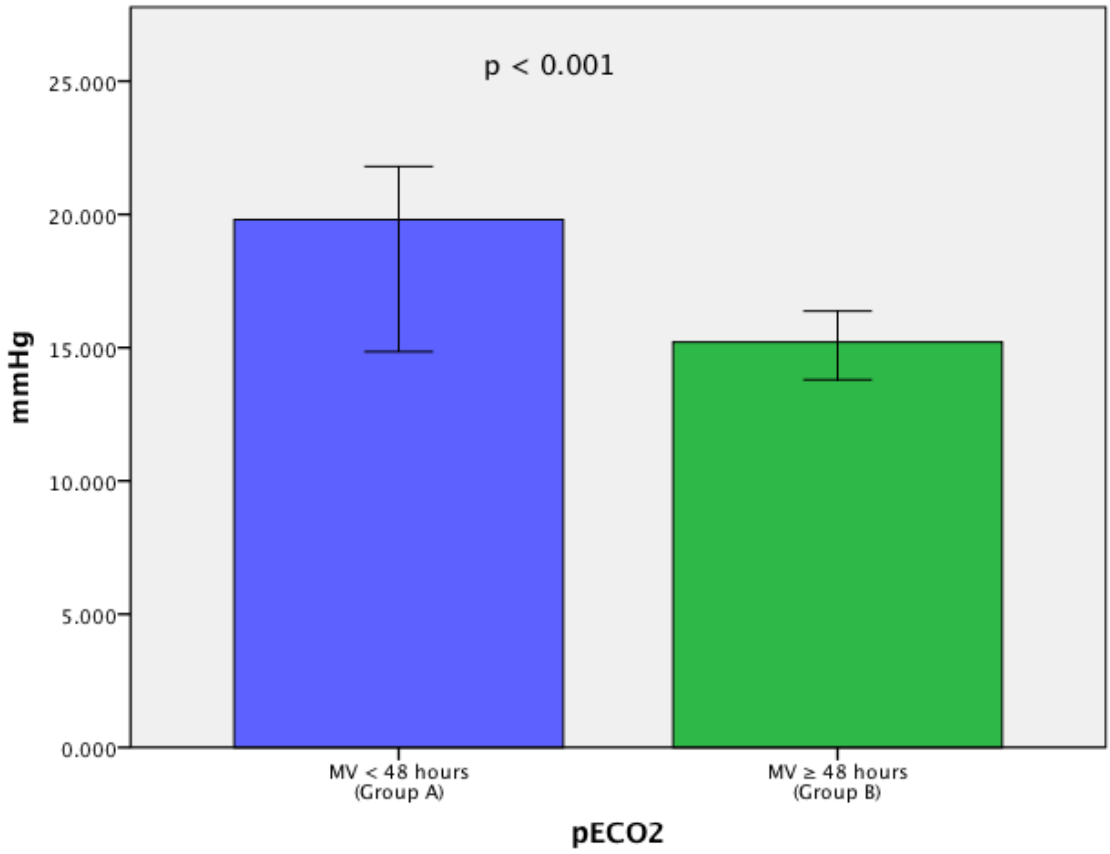


Figure 28: $pECO_2$ on day 1

The figure shows a comparison of the median $pECO_2$ of the two groups on day 1. Confidence interval = 95%. $pECO_2$ = mean expiratory partial pressure of carbon dioxide.

We compared day 1, day 2 and day 3 with the fourth point in time. We used the two-tailed student's t-test for paired samples for day 1 and day 4 and also for day 2 and 4. We compared day 3 and day 4 by using the Wilcoxon rank-sum test.

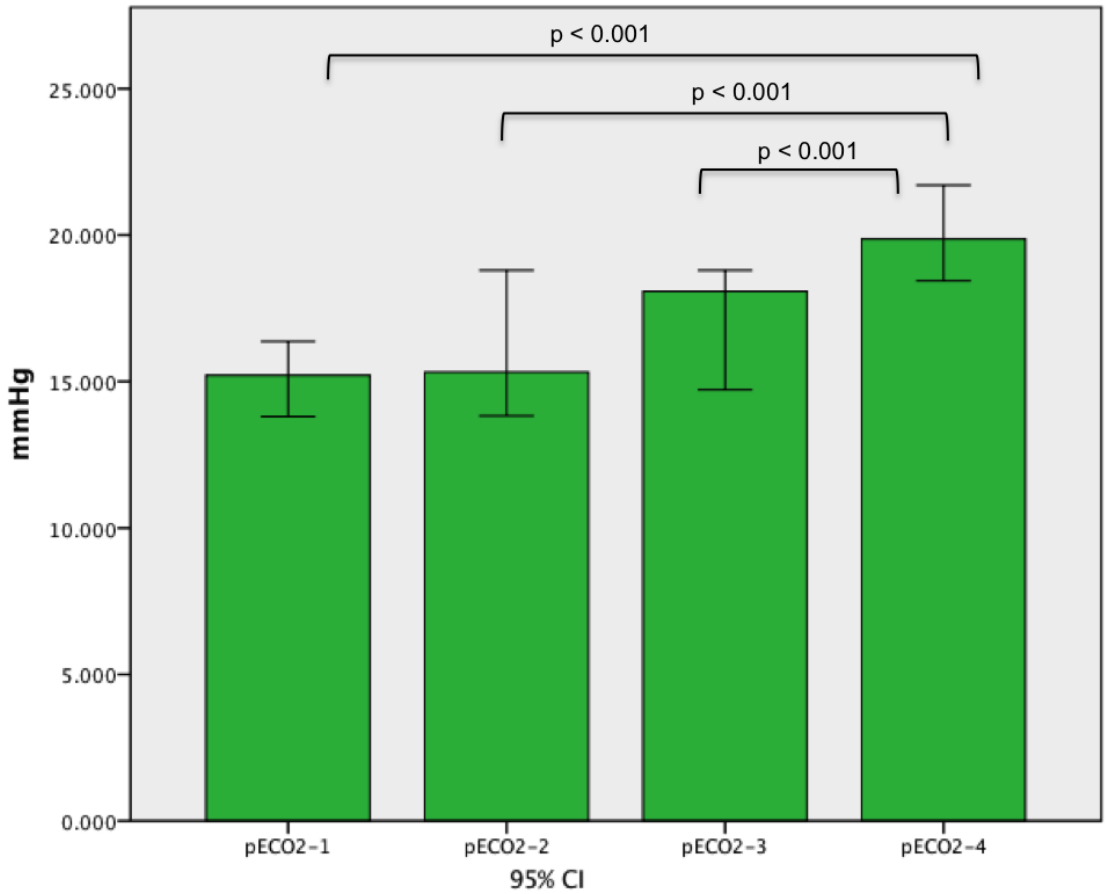


Figure 29: $pECO_2$ over the points in time

The figure shows comparisons of the median $pECO_2$ over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on day 1,2 and 3. On the day of extubation 34 values were valid. P-values: $pECO_2$-1 and $pECO_2$-4 < 0.001, $pECO_2$-2 and $pECO_2$-4 < 0.001, $pECO_2$-3 and $pECO_2$-4 < 0.001. $pECO_2$ = mean-expiratory partial pressure of carbon dioxide; CI = confidence interval;

3.2.5 VCO_2

We analysed the expired CO_2-volume (VCO_2). We started with a descriptive analysis of both groups on day 1 of mechanical ventilation.
In Group A, all 16 values were valid. The median was 50.1 ml/min, whereas the range of values was from 25.99 to 88.1 ml/min. In Group B, all 35 values were valid. The median was 22.6 ml/min. The lowest value was 6.8 ml/min and the highest value was 131 ml/min.

We compared both groups on day 1 by using the Mann-Whitney-U-Test. The result was significant with a p-value of < 0.001.

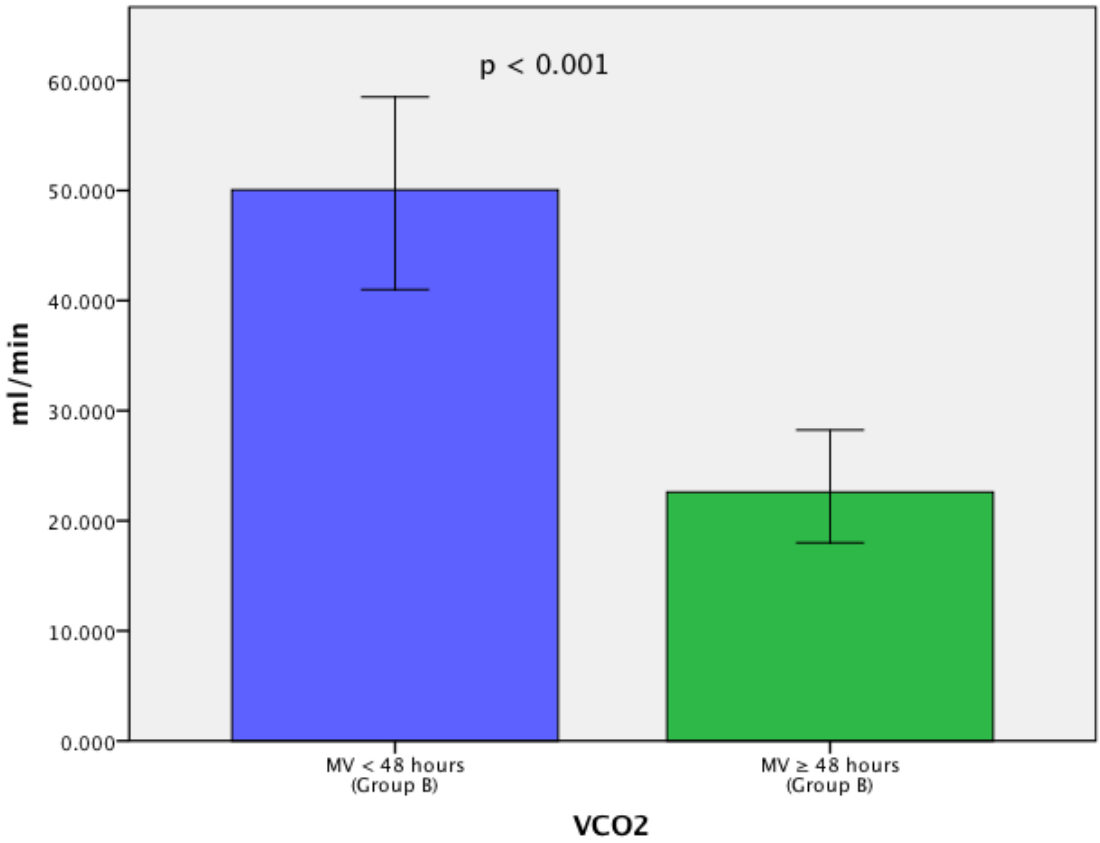


Figure 30: VCO_2 on day 1

The figure shows a comparison of the median VCO_2 of the two groups on day 1. Confidence interval = 95%. VCO_2 = volume of expired CO_2.

We compared the values of day 1, day 2 and day 3 with the day of extubation in Group B. We used the Wilcoxon rank-sum test, because the values were not normally distributed.

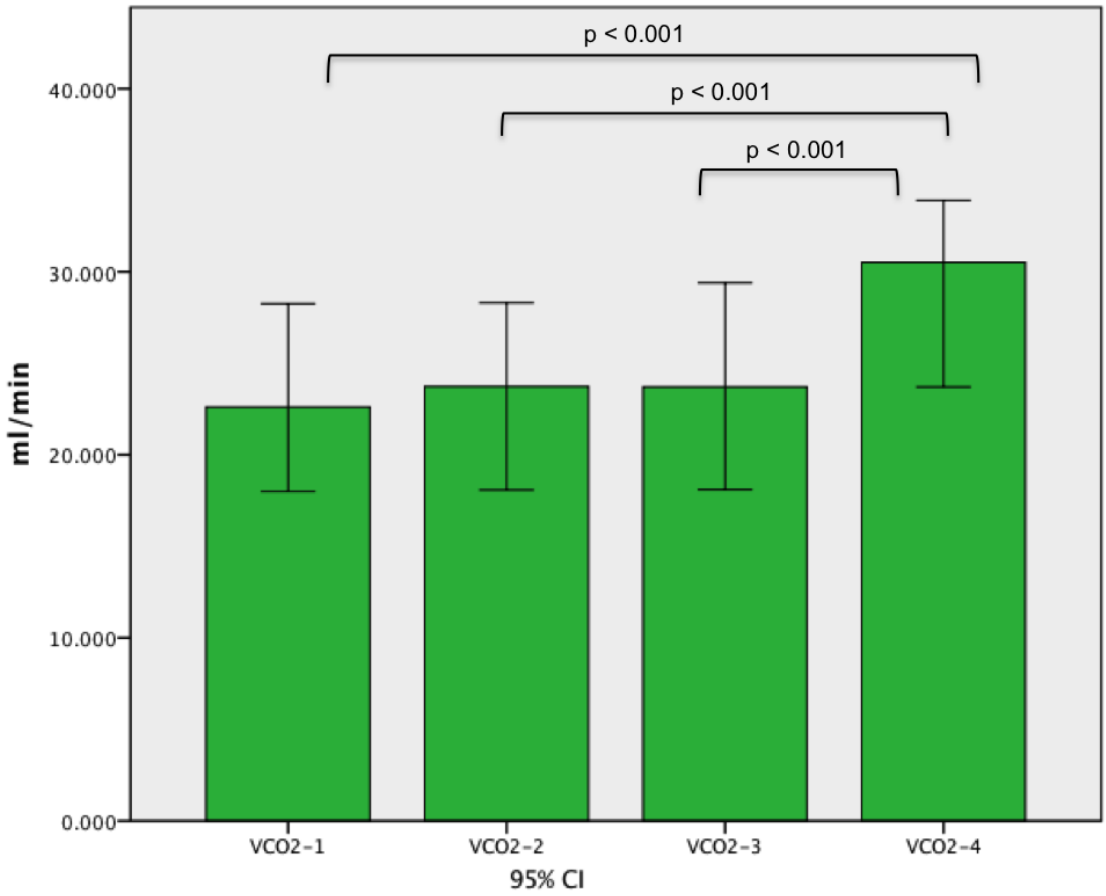


Figure 31: VCO_2 over the points in time

The figure shows comparisons of the median VCO_2 over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on all 4 days. P-values: VCO_2-1 and VCO_2-4 < 0.001, VCO_2-2 and VCO_2-4 < 0.001, VCO_2-3 and VCO_2-4 < 0.001. VCO_2 and 4 = volume of expired carbon dioxide; CI = confidence interval.

3.3 Dead space fractions

3.3.1 Airway dead space fraction (VDaw/VT)

A descriptive analysis was done of both groups on the first day of mechanical ventilation. In Group A, 16 values were valid. The median was 0.195, the minimum was 0.122 and the maximum was 0.357. In Group B, 35 values were valid with a median of 0.240 and a range of values from 0.123 to 0.346.

We compared the two groups on day 1 by using the Mann-Whitney-U-Test (p = 0.28).

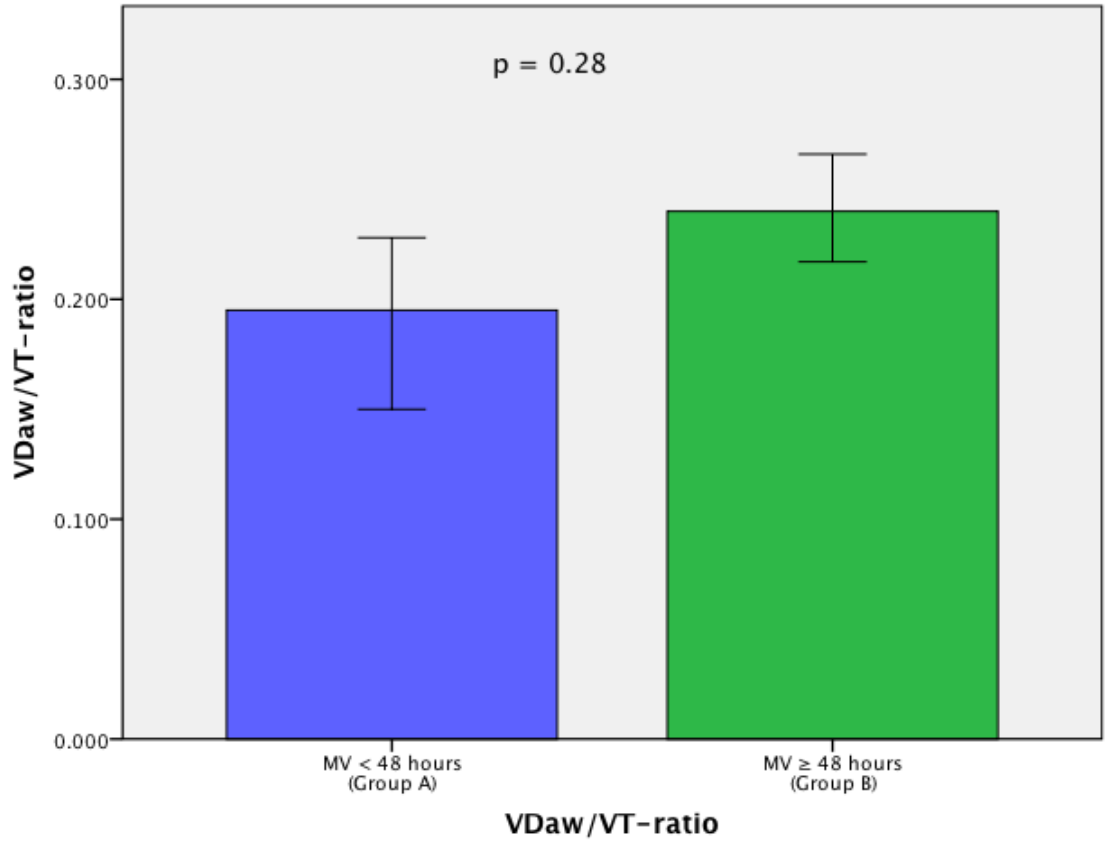


Figure 32: VDaw/VT-ratio on day 1

The figure shows a comparison of the median VDaw/VT-ratio of the two groups on day 1. Confidence interval = 95%. VDaw/VT-ratio = airway dead space fraction.

We compared day 1, day 2 and day 3 of group B with the day of extubation using the two-tailed student's t-test for paired samples.

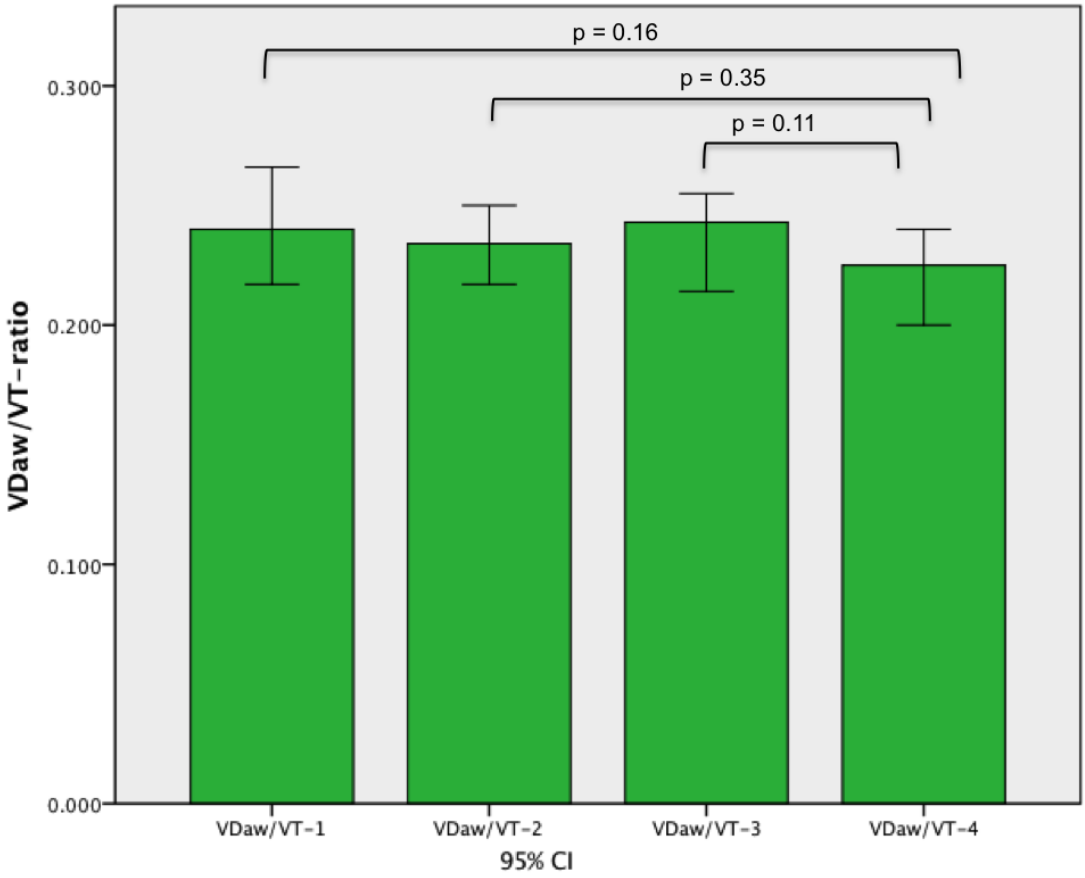


Figure 33: VDaw/VT-ratio over the points in time

The figure shows comparisons of the median VDaw/VT-ratio over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on all 4 days. P-values: VDaw/VT-1 and VDaw/VT-4 = 0.16, VDaw/VT-2 and VDaw/VT-4 = 0.35, VDaw/VT-3 and VDaw/VT-4 = 0.11. VDaw/VT-ratio = airway dead space fraction; CI = confidence interval.

3.3.2 Alveolar dead space fraction (VDalv/VT)

As done before we started with a descriptive analysis of the values of day 1. In both groups all values were valid (16 in Group A and 35 in Group B). In Group A the median was 0.239, whereas the lowest value was 0.142 and the highest was 0.377. In Group B the range of values was from 0.140 to 0.477 with a median of 0.390.

The descriptive analysis was followed by a comparison of both groups on day 1. Therefore we again used the Mann-Whitney-U-Test. The result was significant with a p-value of < 0.001.

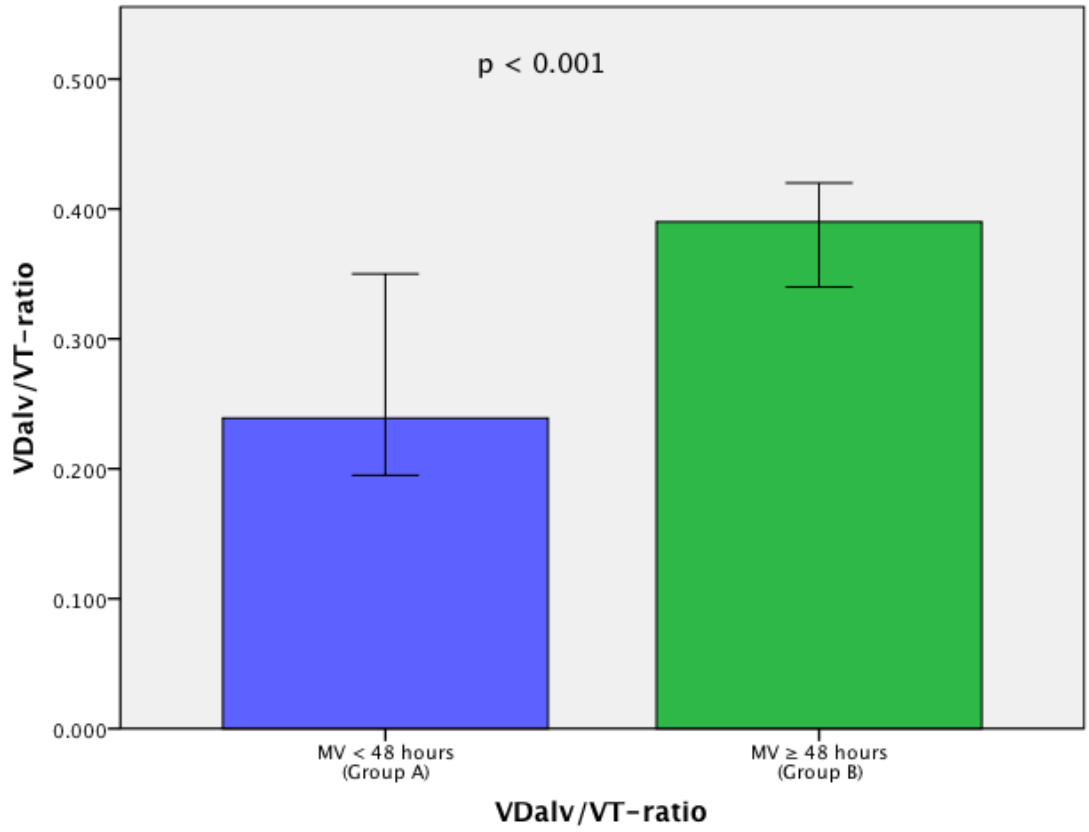


Figure 34: VDalv/VT-ratio on day 1

The figure shows a comparison of the median VDalv/VT-ratio of the two groups on day 1. Confidence interval = 95%. VDalv/VT-ratio = alveolar dead space fraction.

We compared the first three points in time of Group B with the day of extubation. To compare day 1 and day 4 we used the Wilcoxon rank-sum test. For day 2 and day 4, as well as for day 3 and day 4 we used the two-tailed student's t-test for paired samples.

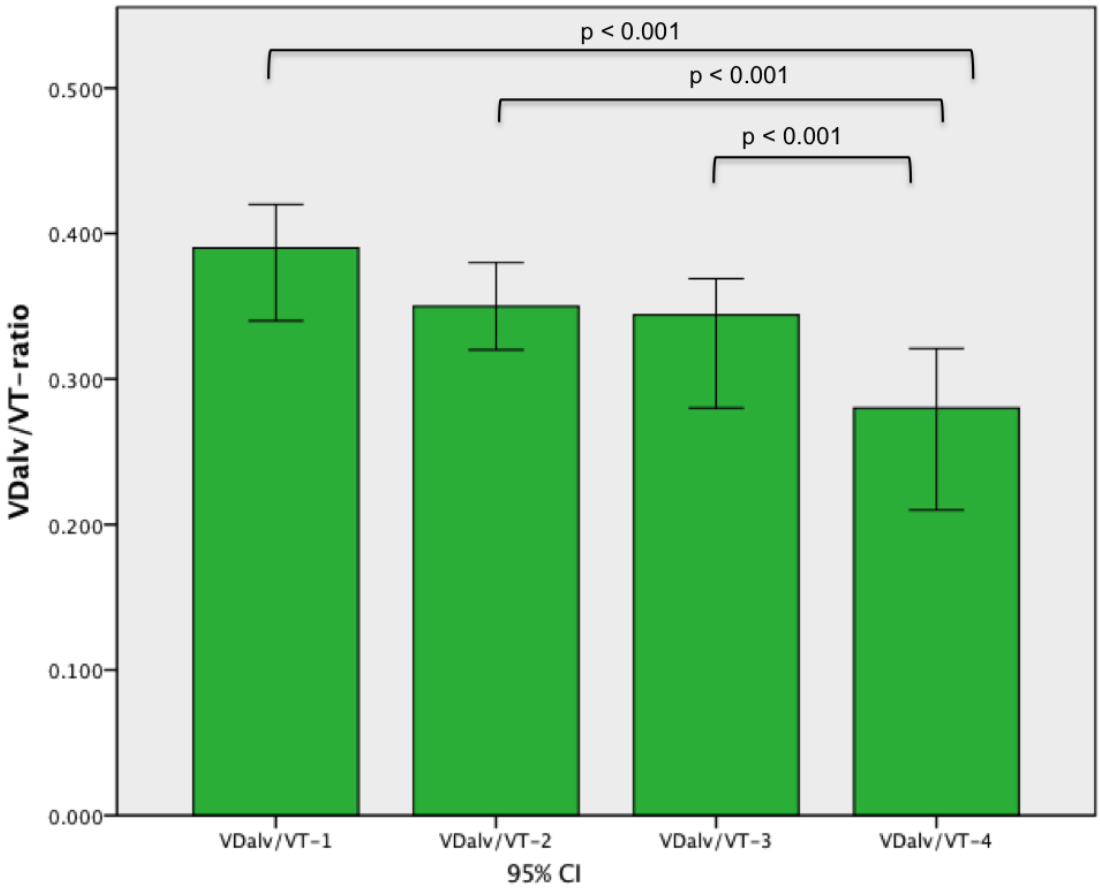


Figure 35: VDalv/VT-ratio over the points in time

The figure shows comparisons of the median VDalv/VT-ratio over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on all 4 days. P-values: VDalv/VT-1 and VDalv/VT-4 < 0.001, VDalv/VT-2 and VDalv/VT-4 < 0.001, VDalv/VT-3 and VDalv/VT-4 < 0.001. VDalv/VT-ratio = alveolar dead space fraction.

3.3.3 Physiological dead space fraction (VDphys/VT)

We analysed the physiological dead space, which we calculated with Enghoff's modification of the Bohr equation (VDphys = VD-BE). On day 1, all 16 values of Group A were valid. The median was 0.475, the minimum was 0.301 and the maximum was 0.600. In the second group (Group B), all 35 values were valid. The range of values was from 0.410 to 0.748 with a median value of 0.607.

The comparison of day 1 showed a significant result with a p-value of < 0.001. The analysis was done using the two-tailed student's t-test for unpaired samples.

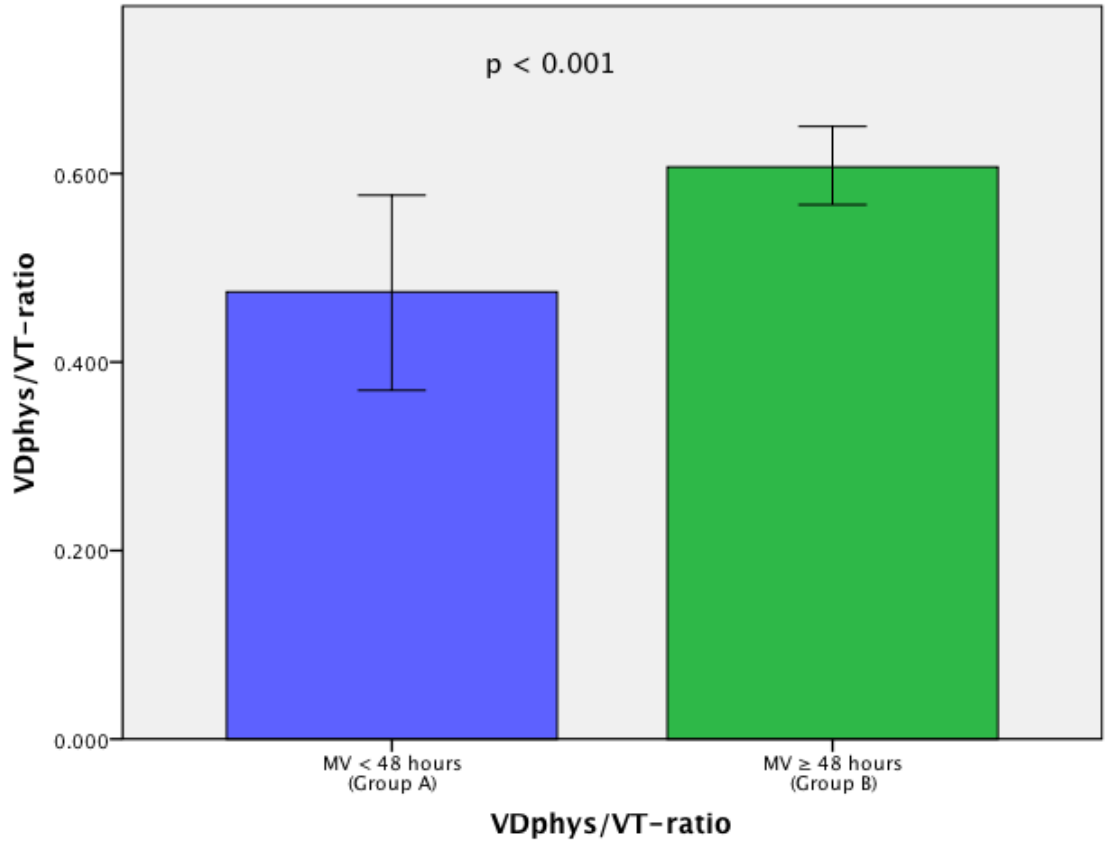


Figure 36: VDphys/VT-ratio on day 1

The figure shows a comparison of the median VDphys/VT-ratio of the two groups on day 1. Confidence interval = 95%. VDphys/VT-ratio = physiological dead space fraction.

We compared day 1, day 2 and day 3 of Group B with the day of extubation. We used the two-tailed student's t-test for paired samples for the comparison of day 1 and day 4 and day 3 and day 4. The comparison of day 2 and day 4 was made using the Wilcoxon rank-sum test.

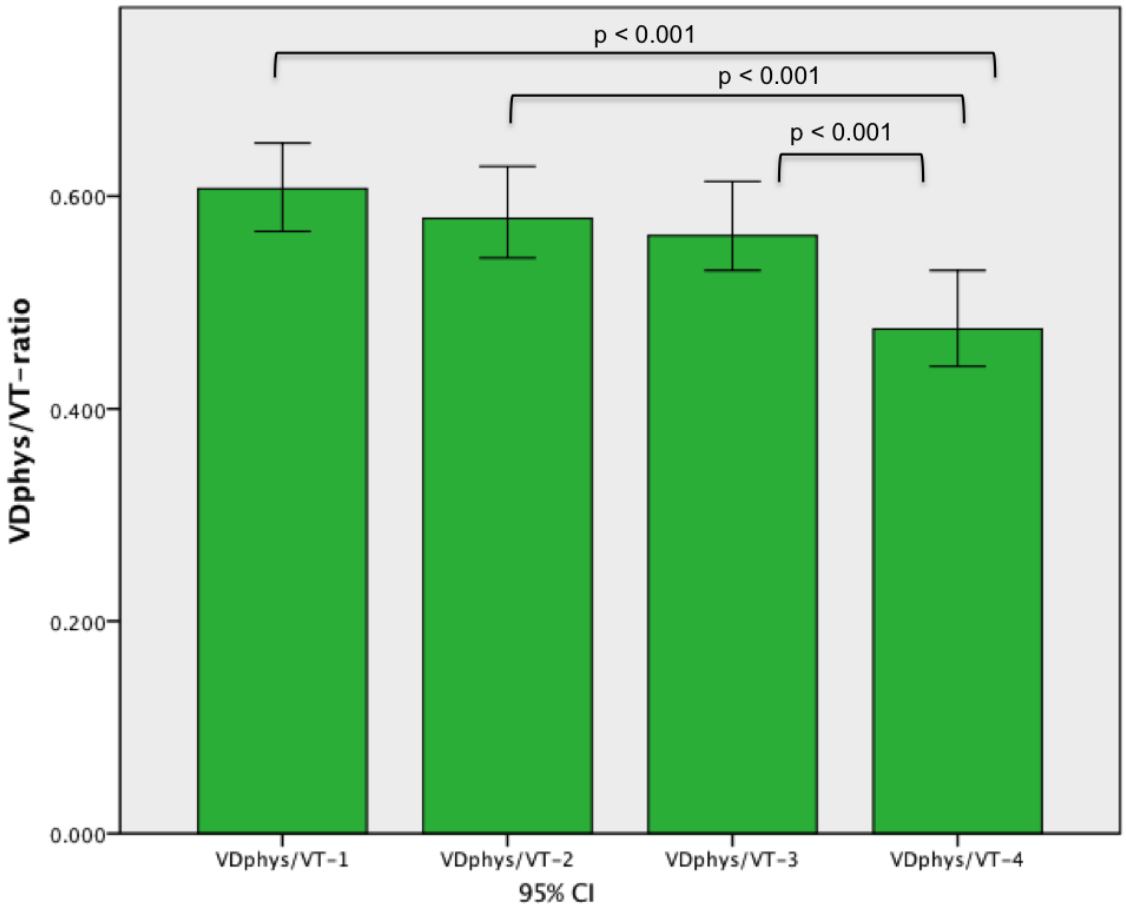


Figure 37: VDphys/VT-ratio over the points in time

The figure shows comparisons of the median VDphys/VT-ratio over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on all 4 days. P-values: VDphys/VT-1 and VDphys-4/VT < 0.001, VDphys/VT-2 and VDphys/VT-4 < 0.001, VDphys/VT-3 and VDphys-4/VT < 0.001. VDphys/VT-ratio = physiological dead space fraction; CI = confidence interval.

Further, we divided the patients into quartiles according to the height of physiological dead space fraction. Then we assessed the median duration of mechanical ventilation for each of the four groups and compared them by using the Kruskal-Wallis-Test (p = 0.013). Along the quartiles there was a significant trend concerning an increase of the duration of mechanical ventilation with the highest values of MV-duration in the group with the highest VDphys/VT-ratio (≥ 0.65).

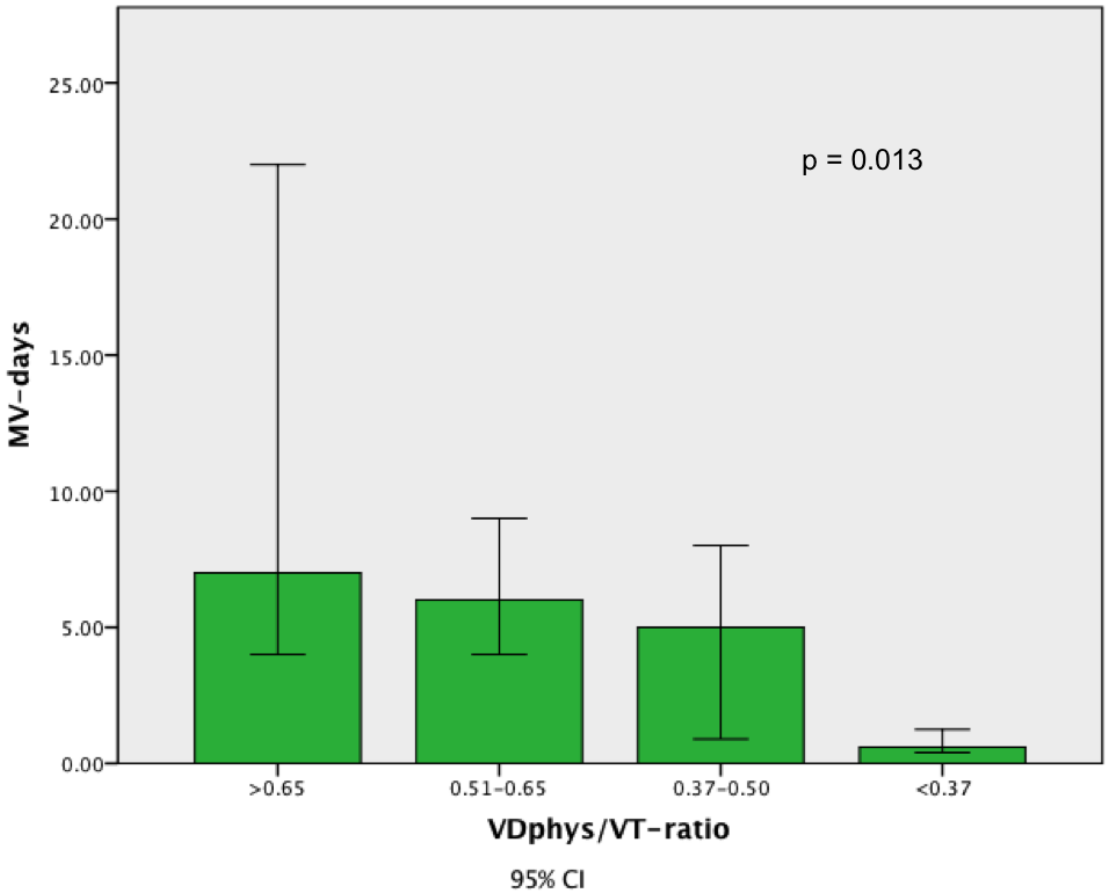


Figure 38: VDphys/VT-ratio and duration of MV

The figure shows the median durations of mechanical ventilation by quartile of physiological dead space fraction. (> 0.65, n = 9; 0.65 – 0.51, n = 27; 0.50 – 0.37, n = 11; < 0.37, n = 4). The analysis of variance was done using the Kruskal-Wallis-Test (p = 0.013). VDphys/VT-ratio = physiological dead space fraction calculated by Enghoff's modification of the Bohr equation; MV-days = duration of mechanical ventilation.

3.3.4 VD-Bohr/VT

Additionally, we used Bohr's equation to calculate dead space. As done before we started with a descriptive analysis of both groups on day 1. In Group A, all 16 values were valid. The median value was 0.212, the minimum value was 0.144 and the maximum value was 0.373.

In Group B 35 values were valid. The range was from 0.139 to 0.357 with a median of 0.268.

We compared the first day of the two groups by using the Mann-Whitney-U-Test (p-value = 0.02).

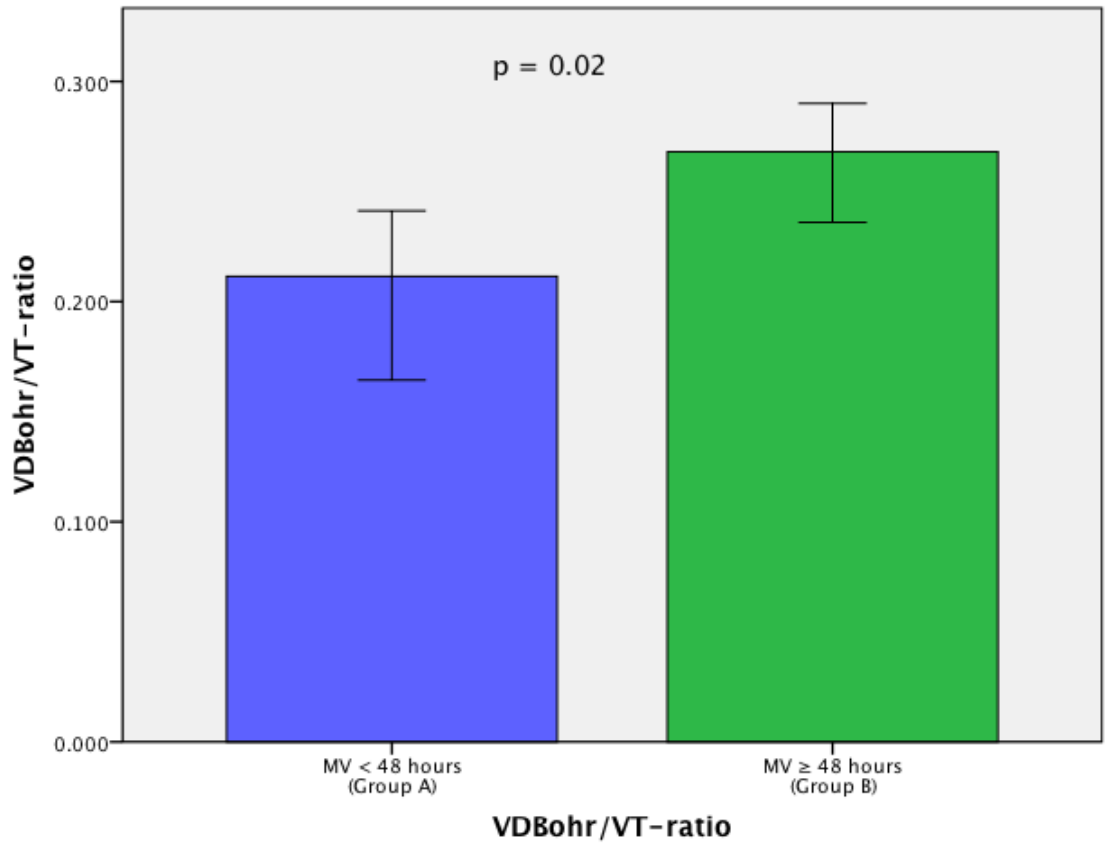


Figure 39: VDBohr/VT-ratio on day 1

The figure shows a comparison of the median VDBohr/VT-ratio of the two groups on day 1. Confidence interval = 95%. VDBohr/VT-ratio = dead space fraction calculated by the Bohr-equation.

We compared day 1, day 2 and day 3 of Group B with the fourth point in time, either using the Wilcoxon rank-sum (day 2 and day 4) test or the two-tailed student's t-test for paired samples (day 1 and day 4, day 3 and day 4).

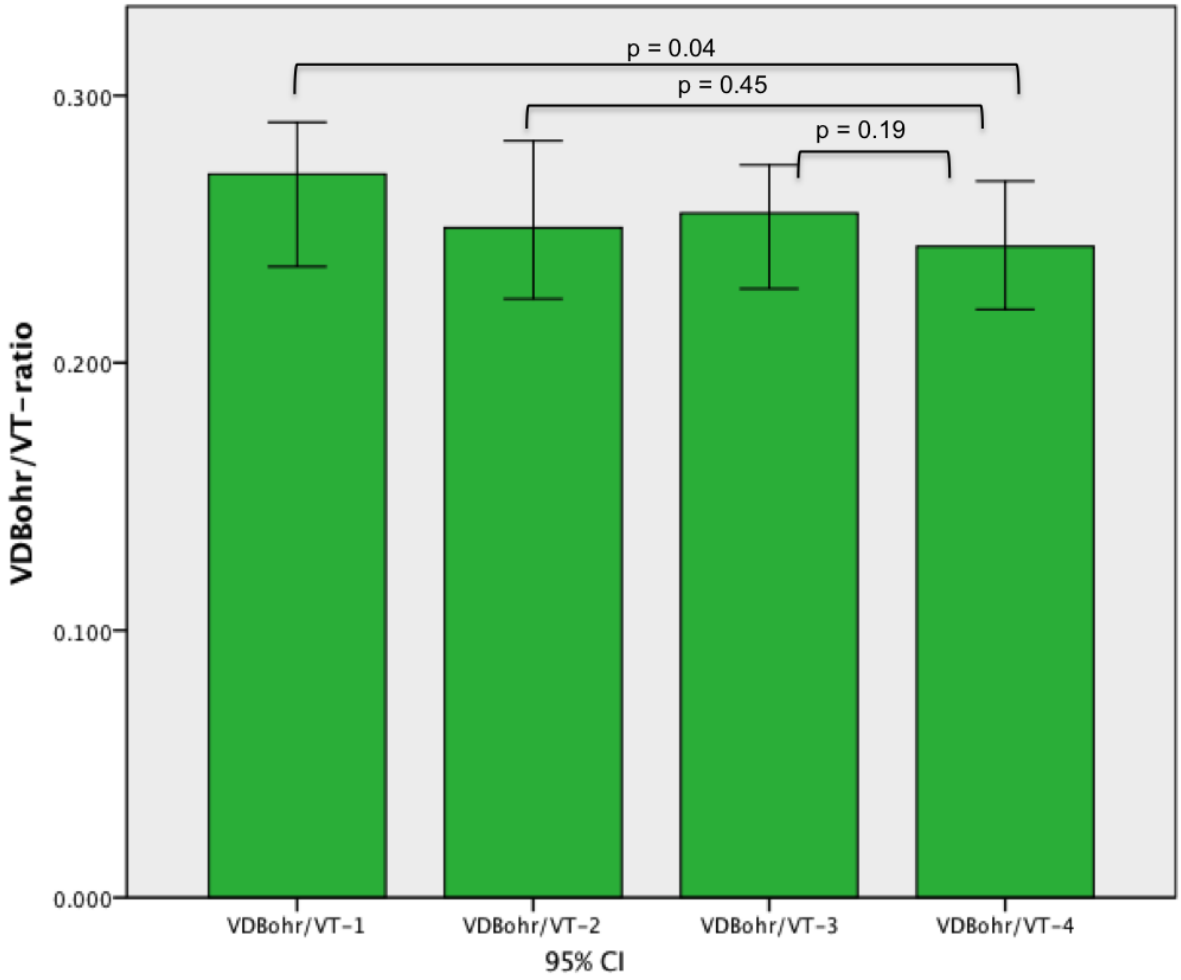


Figure 40: VDBohr/VT-ratio over the points in time

The figure shows comparisons of the median VDBohr/VT-ratio over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on day 1, 2 and 3, whereas on day 4, 34 of 35 values were valid. P-values: VDBohr/VT-1 and VDBohr/VT-4 = 0.04, VDBohr/VT-2 and VDBohr/VT-4 = 0.45, VDBohr/VT-3 and VDBohr/VT-4 = 0.19. VDBohr/VT-ratio = dead space fraction calculated by the Bohr-equation; CI = confidence interval.

3.4 pa-etCO$_2$ and pa-ACO$_2$

Two other important parameters related to the CO_2-metabolism and CO_2-clearance were the arterial to end-tidal difference of pCO_2 and the arterial to alveolar difference of pCO_2.

3.4.1 pa-etCO$_2$

In Group A, all 16 values of the 1st day were valid. The range was from – 2 mmHg to 7.1 mmHg with a median of 0.6 mmHg. In Group B, 35 values were valid. The values were between – 3.9 and 17.5 mmHg. The median value was 5.7 mmHg.

To compare both groups on day 1, we used the two-tailed student's t-test for unpaired samples. The result showed significance with a p-value of < 0.001.

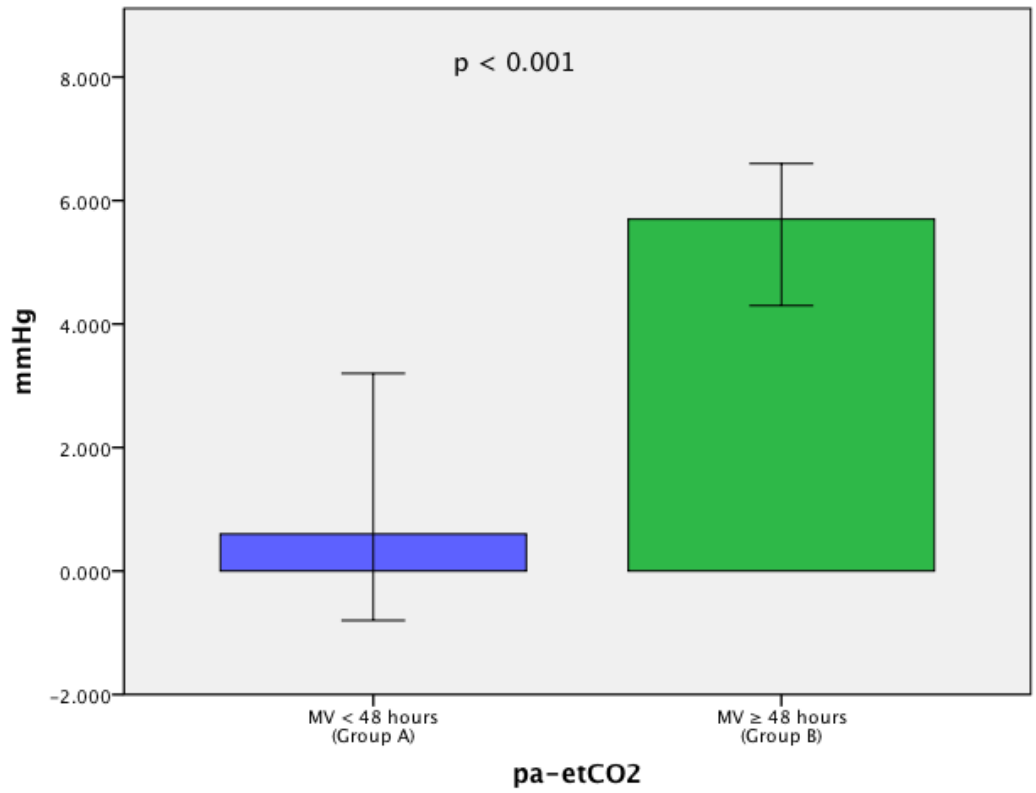


Figure 41: pa-etCO$_2$ on day 1

The figure shows a comparison of the median pa-etCO$_2$ of the two groups on day 1. Confidence interval = 95%. pa-etCO$_2$ = arterial to end-tidal difference of pCO_2.

We compared the first three points in time of Group B with the day of extubation. We used the Wilcoxon rank-sum test, because the values weren't normally distributed.

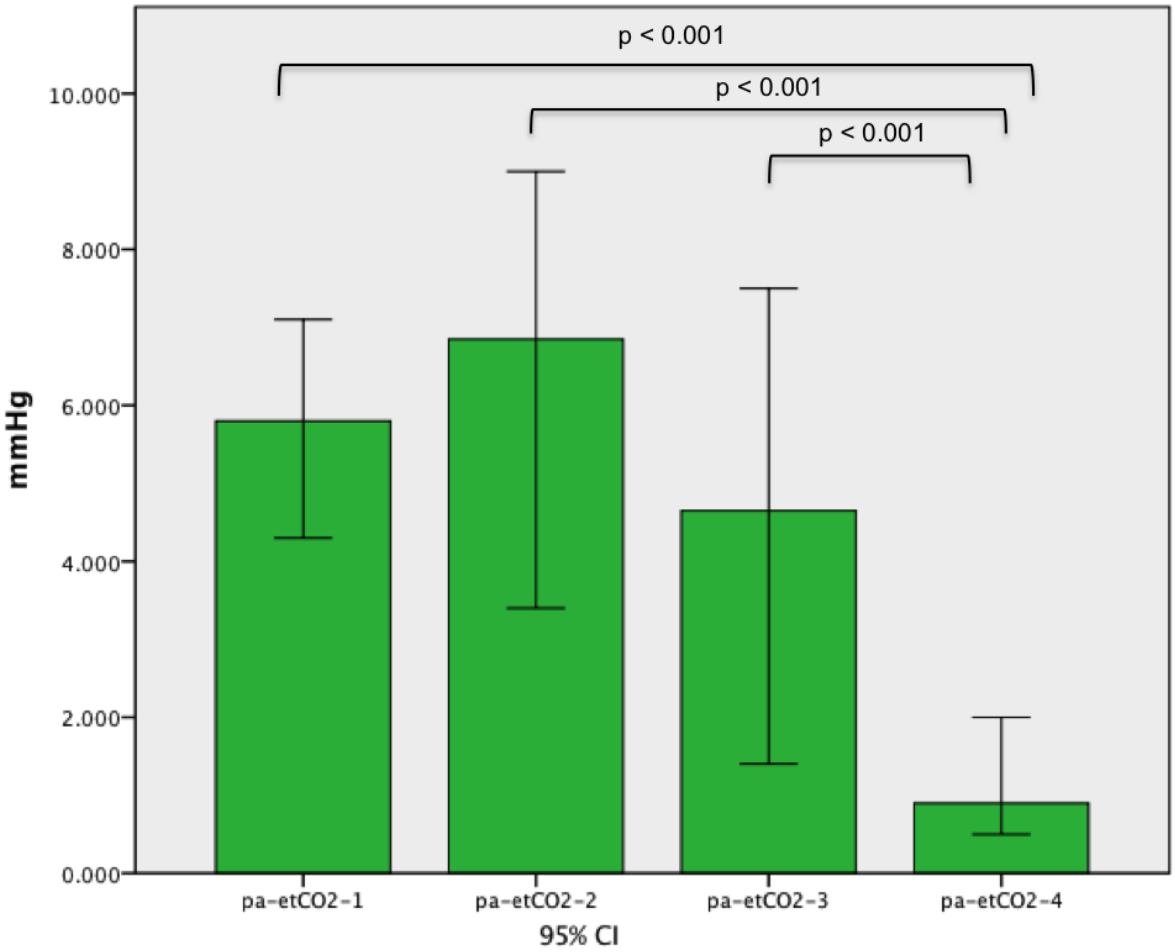


Figure 42: pa-etCO$_2$ over the points in time

The figure shows comparisons of the median pa-etCO$_2$ over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on day 1, day 2 and the day of extubation, whereas on day 3, 34 of 35 values were valid. P-values: pa-etCO$_2$-1 and pa-etCO$_2$-4 < 0.001, pa-etCO$_2$-2 and pa-etCO$_2$-4 < 0.001, pa-etCO$_2$-3 and pa-etCO$_2$-4 < 0.001. pa-etCO$_2$ = arterial to end-tidal difference of pCO$_2$; CI = confidence interval.

3.4.2 pa-ACO_2

On day 1, all values were valid (16 of Group A and 35 of Group B). In Group A the range was from 5.3 to 18.1 mmHg with a median of 11.5 mmHg, whereas the values in Group B were between 3.6 and 35.2 mmHg with a median of 17.0 mmHg.

For a comparison of both groups on day 1 we used the Mann-Whitney-U-Test. The result was significant with a p-value of 0.002.

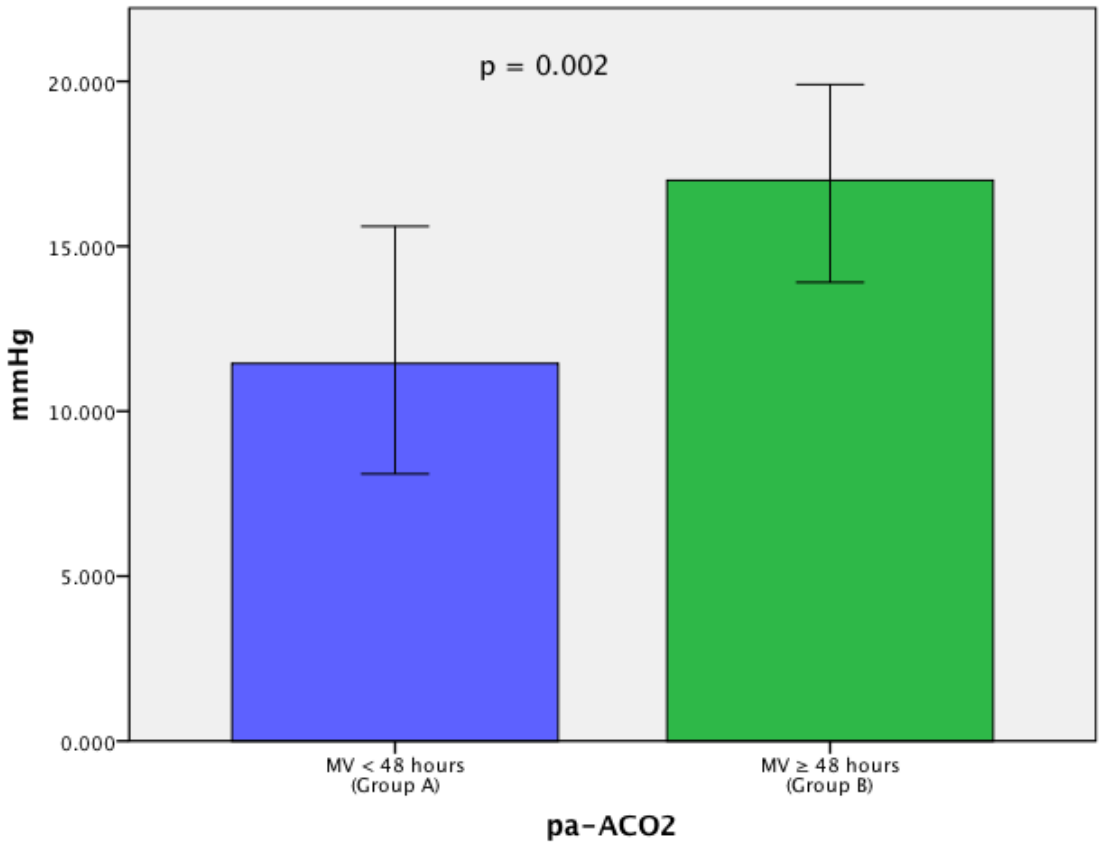


Figure 43: pa-ACO_2 on day 1

The figure shows a comparison of the median pa-ACO_2 of the two groups on day 1. Confidence interval = 95%. pa-etCO_2 = arterial to end-tidal difference of pCO_2.

We used the two-tailed student's t-test for paired samples to compare day 1, day 2 and day 3 of Group B with the day of extubation.

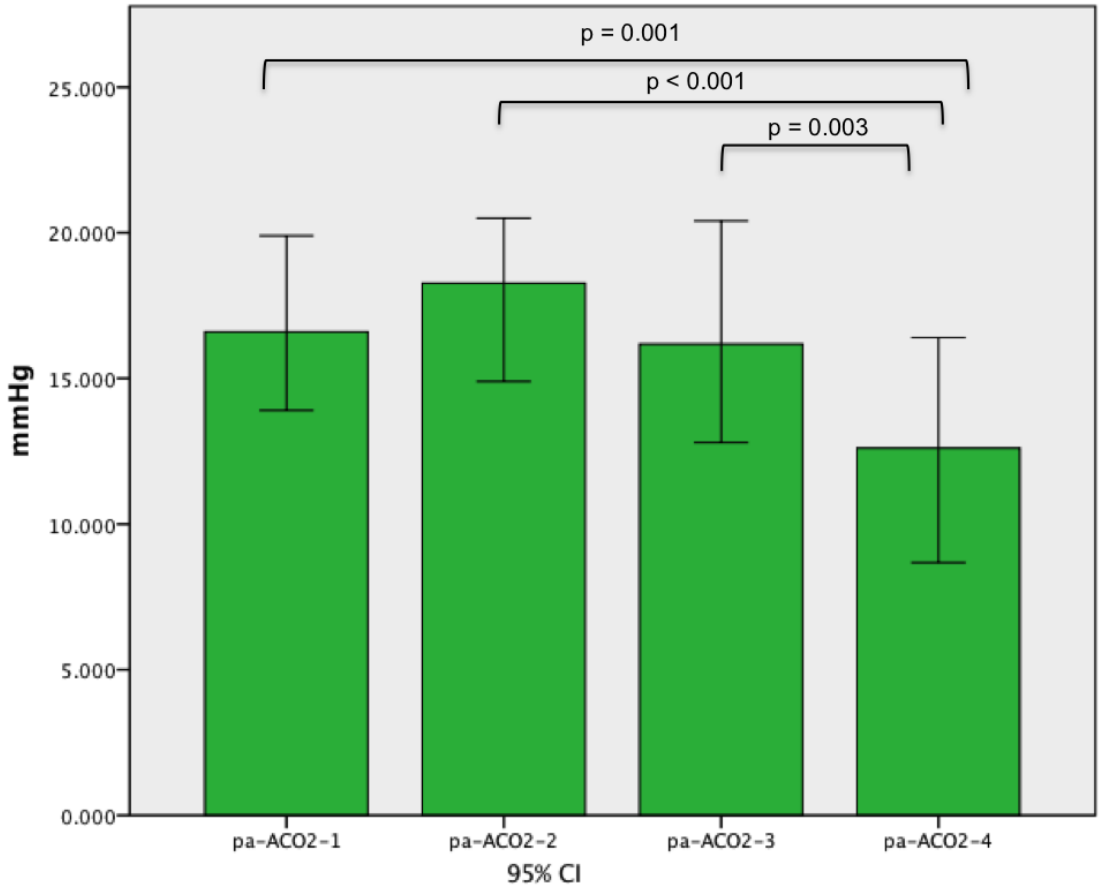


Figure 44: pa-ACO_2 over the points in time

The figure shows comparisons of the median pa-ACO_2 over the four different points in time in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on day 1,2 and 4, whereas on day 3, 34 of 35 values were valid. P-values: pa-ACO_2-1 and pa-ACO_2-4 = 0.001, pa-ACO_2-2 and pa-ACO_2-4 < 0.001, pa-ACO_2-3 and pa-ACO_2-4 = 0.003. pa-ACO_2 = arterial to alveolar difference of pCO_2; CI = confidence interval.

3.5 slope-CO_2

16 values in Group A and 35 values in Group B were valid on day 1. The range of values in Group A was between 0.5 and 27.7 Vol.-%/L with a median value of 6.175 Vol.-%/L. In Group B the values were between – 0.2 and 100.1 Vol.-%/L with a median of 24.9 Vol.-%/L

To compare the values of both groups on day 1 we used the Mann-Whitney-U-Test, which showed a significant result (p = 0.001).

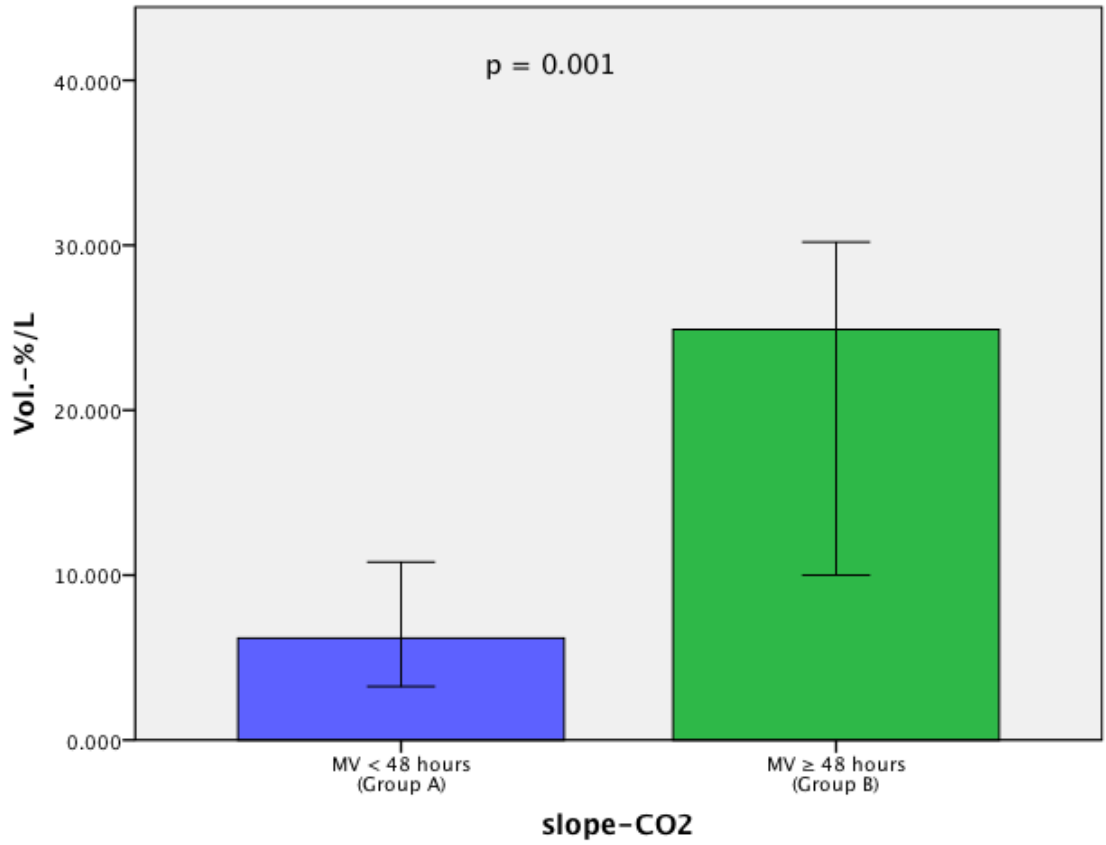


Figure 45: slope- CO_2 on day 1

The figure shows a comparison of the median slope-CO_2 of the two groups on day 1. Confidence interval = 95%.

We compared the values of day 1, day 2 and day 3 with day 4 of Group B using the Wilcoxon rank-sum test.

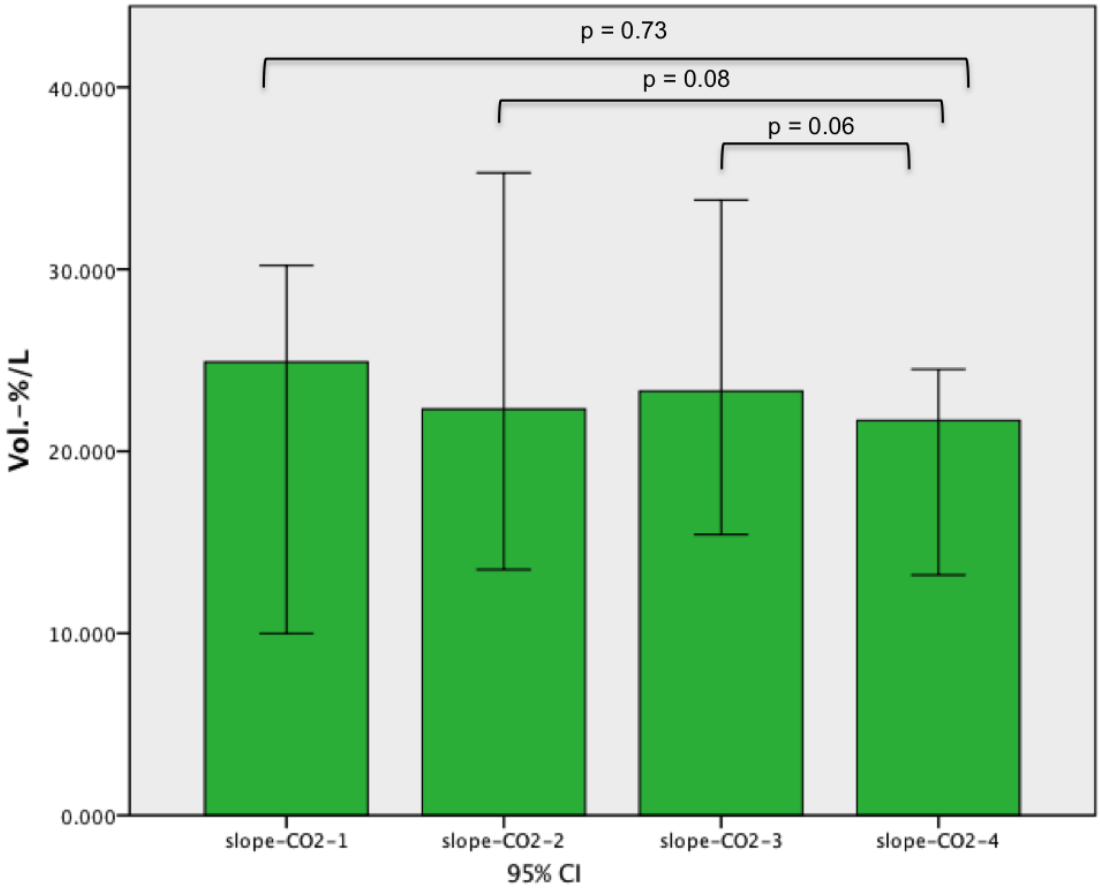


Figure 46: slope-CO_2 over the points in time

The figure shows comparisons of median slope-CO_2 over the four different points in patients, who were mechanically ventilated for 48 hours or longer. 35 values were valid on all four days. P-values: slope-CO_2-1 and slope-CO_2-4 = 0.73, slope-CO_2-2 and slope-CO_2-4 = 0.08, slope-CO_2-3 and slope-CO_2-4 = 0.06. CI = confidence interval.

3.6 Correlation of parameters

Further, our interest was to show correlations between different parameters of Group B. To test the correlation we either used Pearson's correlation coefficient for normally distributed values or Spearman's correlation coefficient for those values, which were not normally distributed.

3.6.1 Dead space fractions

In a first step we analysed the dead space fractions (VDalv/VT and VDphys/VT) for a correlation with other VCAP-derived parameters:

3.6.1.1 Alveolar dead space fraction (VDalv/VT)

We tested VDalv/VT for a correlation with: VDphys/VT, pa-etCO_2, pa-ACO_2 and slope-CO_2. We either used Pearson's correlation coefficient or Spearman's correlation coefficient.

For the analysis of day 1 we used Spearman's correlation coefficient. VDalv/VT-1 showed a positive correlation with VDphys/VT (R = 0.837), pa-ACO_2 (R = 0.838), pa-etCO_2 (R = 0.435) and slope-CO_2 (R = 0.613).

	Parameter	Correlation Coefficient	R
VDalv/VT-1	pa-ACO_2-1	Spearman rho	0.838
	VDphys/VT-1	Spearman rho	0.837
	slope-CO_2-1	Spearman rho	0.613
	pa-etCO_2-1	Spearman rho	0.435

Table 9: Correlations with VDalv/VT on day 1

R = correlation coefficient; VDalv/VT = alveolar dead space fraction; pa-ACO_2 = arterial to alveolar difference of pCO_2; VDphys/VT = physiological dead space fraction; pa-etCO_2 = arterial to end-tidal difference of pCO_2.

On day 2 of mechanical ventilation we used the Spearman correlation coefficient for a correlation with slope-CO_2-2 and VDphys/VT-2. For the correlation with pa-ACO_2-2 and pa-etCO_2-2 we used the Pearson correlation coefficient.

VDalv/VT-2 showed a positive correlation with VDphys/VT-2 (R = 0.868), pa-ACO_2-2 (R = 0.783), pa-etCO_2-2 (R = 0.582) and slope-CO_2-2 (R = 0.264).

	Parameter	Correlation Coefficient	R
VDalv/VT-2	VDphys/VT-2	Spearman rho	0.868
	pa-ACO_2-2	Pearson	0.783
	pa-etCO_2-2	Pearson	0.582
	slope-CO_2-2	Spearman rho	0.264

Table 10: Correlations with VDalv/VT on day 2

R = correlation coefficient; VDalv/VT = alveolar dead space fraction; pa-ACO_2 = arterial to alveolar difference of pCO_2; VDphys/VT = physiological dead space fraction; pa-etCO_2 = arterial to end-tidal difference of pCO_2.

We tested the correlation of VDalv/VT-3 and VDphys/VT-3 (R = 0.893), pa-ACO_2-3 (R = 0.785), pa-etCO_2-3 (R = 0.543) and slope-CO_2-3 (R = 0.427).

	Parameter	Correlation Coefficient	R
VDalv/VT-3	VDphys/VT-3	Pearson	0.893
	pa-ACO_2-3	Pearson	0.785
	pa-etCO_2-3	Spearman rho	0.543
	slope-CO_2-3	Spearman rho	0.427

Table 11: Correlations with VDalv/VT on day 3

R = correlation coefficient; VDalv/VT = alveolar dead space fraction; pa-ACO_2 = arterial to alveolar difference of pCO_2; VDphys/VT = physiological dead space fraction; pa-etCO_2 = arterial to end-tidal difference of pCO_2.

We tested the correlation of VDalv/VT-4 and VDphys/VT-4 (R = 0.923), pa-ACO_2-4 (R = 0.825), pa-$etCO_2$-4 (R = 0.387) and slope-CO_2-4 (R = 0.312).

VDalv/VT-4	Parameter	Correlation Coefficient	R
	VDphys/VT-4	Pearson	0.923
	pa-ACO_2-4	Pearson	0.825
	pa-$etCO_2$-4	Spearman rho	0.387
	slope-CO_2-4	Spearman rho	0.312

Table 12: Correlations with VDalv/VT on the day of extubation

R = correlation coefficient; VDalv/VT = alveolar dead space fraction; pa-ACO_2 = arterial to alveolar difference of pCO_2; VDphys/VT = physiological dead space fraction; pa-$etCO_2$ = arterial to end-tidal difference of pCO_2.

3.6.1.2 Physiological dead space fraction (VDphys/VT)

We tested the correlation of VDphys/VT and different parameters (pa-$etCO_2$, pa-ACO_2 and slope-CO_2) over the four points in time.

On day 1 of mechanical ventilation we used Spearman's correlation coefficient for the correlation of VDphys/VT-1 and pa-$etCO_2$-1 (R = 0.512) and slope-CO_2-1 (R = 0.764). Further, we used Pearson's correlation coefficient for the correlation of VDphys/VT-1 and pa-ACO_2-1 (R = 0.762).

VDphys/VT-1	Parameter	Correlation Coefficient	R
	pa-ACO_2-1	Pearson	0.762
	pa-$etCO_2$-1	Spearman rho	0.512
	slope-CO_2-1	Spearman rho	0.764

Table 13: Correlations with VDphys/VT on day 1

R = correlation coefficient; VDphys/VT = physiological dead space fraction; pa-ACO_2 = arterial to alveolar difference of pCO_2; pa-$etCO_2$ = arterial to end-tidal difference of pCO_2.

On the second day of mechanical ventilation we used Spearman's correlation coefficient for the correlation of VDphys/VT-2 and all three other parameters: pa-$etCO_2$-2 (R = 0.597), slope-CO_2-2 (R = 0.360) and pa-ACO_2-2 (R = 0.727).

VDphys/VT-2	Parameter	Correlation Coefficient	R
	pa-ACO_2-2	Spearman rho	0.727
	pa-$etCO_2$-2	Spearman rho	0.597
	slope-CO_2-2	Spearman rho	0.360

Table 14: Correlations with VDphys on day 2

R = correlation coefficient; VDphys/VT = physiological dead space fraction; pa-ACO_2 = arterial to alveolar difference of pCO_2; pa-$etCO_2$ = arterial to end-tidal difference of pCO_2.

For the third day of mechanical ventilation we used Spearman's correlation coefficient to test the correlation of VDphys/VT-3 and pa-$etCO_2$-3 (R = 0.518) and slope-CO_2-3 (R = 0.604). We used Pearson's correlation coefficient for the correlation of VDphys/VT-3 and pa-ACO_2-3 (R = 0.727).

VDphys/VT-3	Parameter	Correlation Coefficient	R
	pa-ACO_2-3	Pearson	0.727
	pa-$etCO_2$-3	Spearman rho	0.518
	slope-CO_2-3	Spearman rho	0.604

Table 15: Correlations with VDphys/VT on day 3.

R = correlation coefficient; VDphys/VT = physiological dead space fraction; pa-ACO_2 = arterial to alveolar difference of pCO_2; pa-$etCO_2$ = arterial to end-tidal difference of pCO_2.

On the last day of mechanical ventilation we used Spearman's correlation coefficient for testing the correlation of VDphys/VT-4 and pa-etCO_2-4 (R = 0.412) and slope-CO_2-4 (R = 0.451). We used Pearson's correlation coefficient for the correlation of VDphys/VT-4 with pa-ACO_2-4 (R = 0.812).

VDphys/VT-4	Parameter	Correlation Coefficient	R
	pa-ACO_2-4	Pearson	0.812
	pa-etCO_2-4	Spearman rho	0.412
	slope-CO_2-4	Spearman rho	0.451

Table 16: Correlations with VDphys on day 4

R = correlation coefficient; VDphys = physiological dead space; pa-ACO_2 = arterial to alveolar difference of pCO_2; pa-etCO_2 = arterial to end-tidal difference of pCO_2.

3.6.1.3 VD-Bohr/VT-ratio

We tested the correlation of VDBohr/VT and VDaw/VT. The results are shown in table 17.

VDBohr/VT	Parameter	Correlation Coefficient	R
	VDaw/VT-1	Pearson	0.931
	VDaw/VT-2	Spearman rho	0.875
	VDaw/VT-3	Pearson	0.836
	VDaw/VT-4	Pearson	0.745

Table 17: Correlations of VDBohr/VT and VDaw/VT

VDBohr/VT = dead space fraction calculated by Bohr's equation; VDaw/VT = airway dead space fraction.

3.6.2 slope-CO_2

We tested the correlation of slope-CO_2 and the expiratory airway resistance (Rexp) over the four points in time. We used Spearman's correlation coefficient. The results are shown in table 19:

	Parameter	Correlation Coefficient	R
slope-CO_2	Rexp-1	Spearman rho	0.700
	Rexp-2	Spearman rho	0.619
	Rexp-3	Spearman rho	0.783
	Rexp-4	Spearman rho	0.762

Table 18: Correlations of slope-CO_2 and Rexp

Rexp = expiratory airway resistance.

3.7 RSV-Infection

The usefulness of volumetric capnography in patients with RSV-infections as shown in the introduction led us to a separate analysis of those values. In total 7 of the 51 patients suffered from an RSV-infection. The median duration of mechanical ventilation was 10 days with a range from 6.9 to 11 days. The median age of the patients was 3 months.

3.7.1 Dead space fractions

As done before, we separately analysed VDaw/VT, VDalv/VT, VDphys/VT and VDBohr/VT.

3.7.1.1 Airway dead space fraction (VDaw/VT)

The median on day 1 was 0.22 (min: 0.12, max: 0.29). On day 2 the median was 0.22 (min: 0.12, max: 0.27). The median on day 3 was 0.22 (min: 0.17, max 0.27) and on the day of extubation the median was 0.22 (min 0.17, max 0.27). There were no significant differences between the four points in time.

3.7.1.2 Alveolar dead space fraction (VDalv/VT)

On day 1 the median was 0.39 (min: 0.22, max: 0.44). On the 2nd day the median was 0.35 (min: 0.31, max: 0.51). On day 3 the median was 0.37 (min: 0.26, max: 0.48), whereas the median on the day of extubation was 0.31 (min: 0.08, max: 0.37). We found a significant difference between day 1 and 4 ($p = 0.017$), as well as between day 2 and 4 ($p = 0.018$). There was no significant difference between day 3 and 4 ($p = 0.091$).

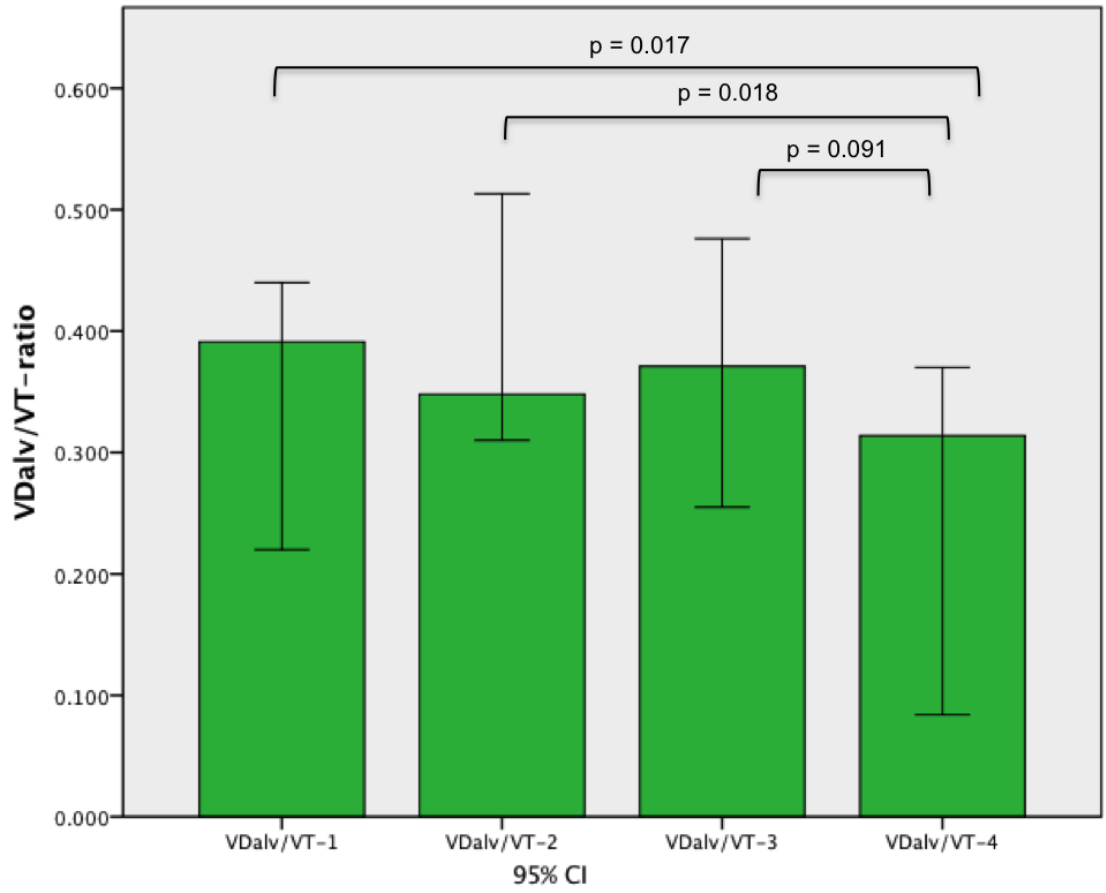


Figure 47: VDalv/VT-ratios in patients with RSV-infection

The figure shows the median VDalv/VT-ratios over the four points in time in patients with RSV-infection. 7 values were valid. P-values: VDalv/VT-1 and VDalv/VT-4 = 0.017, VDalv/VT-2 and VDalv/VT-4 = 0.018, VDalv/VT-3 and VDalv/VT-4 = 0.091 VDalv/VT-ratio = alveolar dead space fraction; CI = confidence interval.

3.7.1.3 Physiological dead space fraction (VDphys/VT)

The median on day 1 was 0.60 (min: 0.44, max: 0.72). On day 2 the median was 0.55 (min: 0.45, max 0.73). On the 3rd day the median was 0.62 (min: 0.42, max: 0.71) and on the 4th point in time the median was 0.49 (min: 0.33; max: 0.64). There was a significant difference between day 1 and 4 (p = 0.005) and day 2 and 4 (p = 0.042). We found no significant difference between day 3 and 4 (p = 0.113).

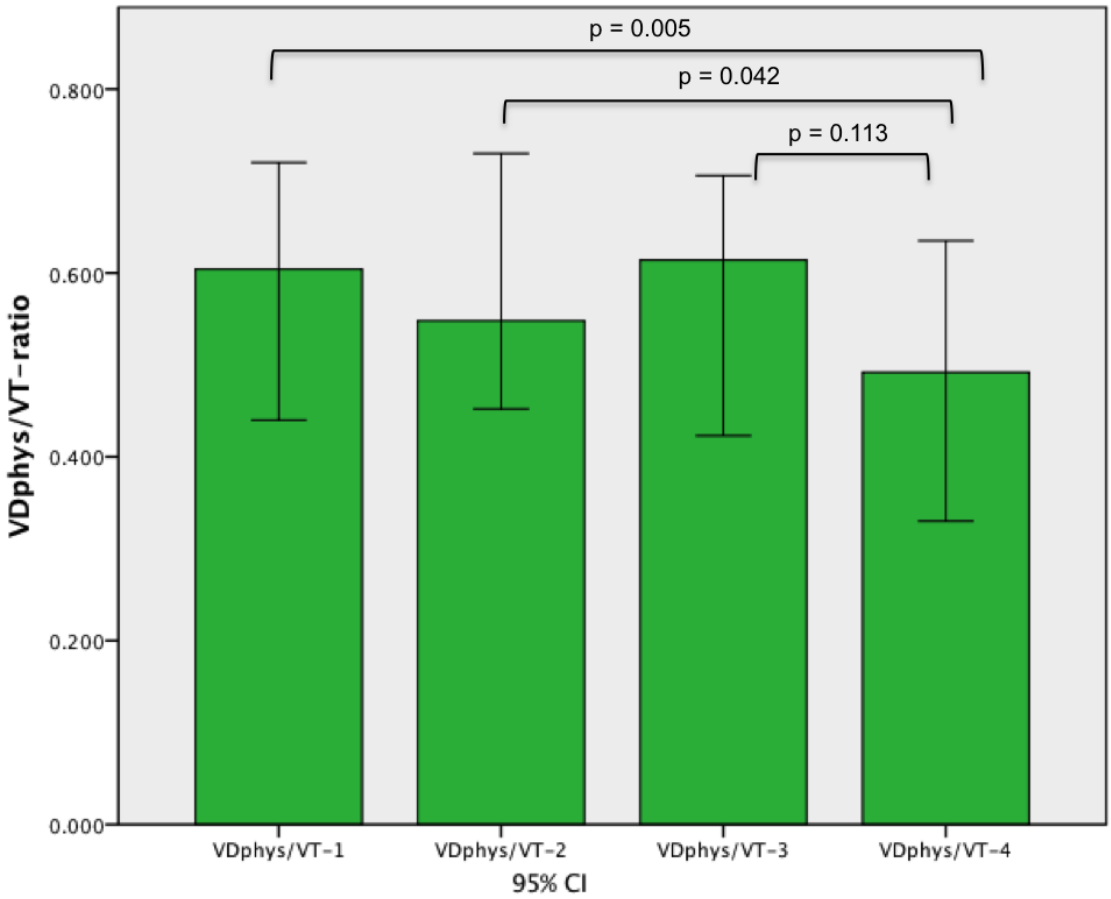


Figure 48: VDphys/VT-ratios in patients with RSV-infection

The figure shows the median VDphys/VT-ratios over the four points in time in patients with RSV-infection. 7 values were valid. P-values: VDphys/VT-1 and VDphys/VT-4 = 0.005, VDphys/VT-2 and VDphys/VT-4 = 0.042, VDphys/VT-3 and VDphys/VT-4 = 0.113; VDphys/VT = physiological dead space fraction; CI = confidence interval.

3.7.1.4 VDBohr/VT

The median on day 1 was 0.29 (min: 0.14, max: 0.33). On day 2 the median was 0.25 (min: 0.14, max: 0.33). On the 3rd day the median was 0.25 (min: 0.17, max: 0.34). On the 4th point in time the median was 0,25 (min: 0.19, max: 0.39). We found no significant differences over the 4 points in time.

3.7.2 pa-etCO$_2$ and pa-ACO$_2$

3.7.2.1 pa-etCO$_2$

We tested the arterial to end-tidal difference of pCO$_2$. On day 1 the median of pa-etCO$_2$ was 4.9 mmHg (min: - 3.9 mmHg, max: 16.6 mmHg), whereas on day 2 the median of pa-ACO$_2$ was 10.0 mmHg (min: - 2.6 mmHg, max: 17.6 mmHg). The median on day 3 was 6.0 mmHg (min: - 3.9 mmHg, max: 9.9 mmHg). On the 4th point in time the median was 1.2 mmHg (min: - 0.4 mmHg, max: 10.3 mmHg).

We compared the four different points in time and found no significant differences.

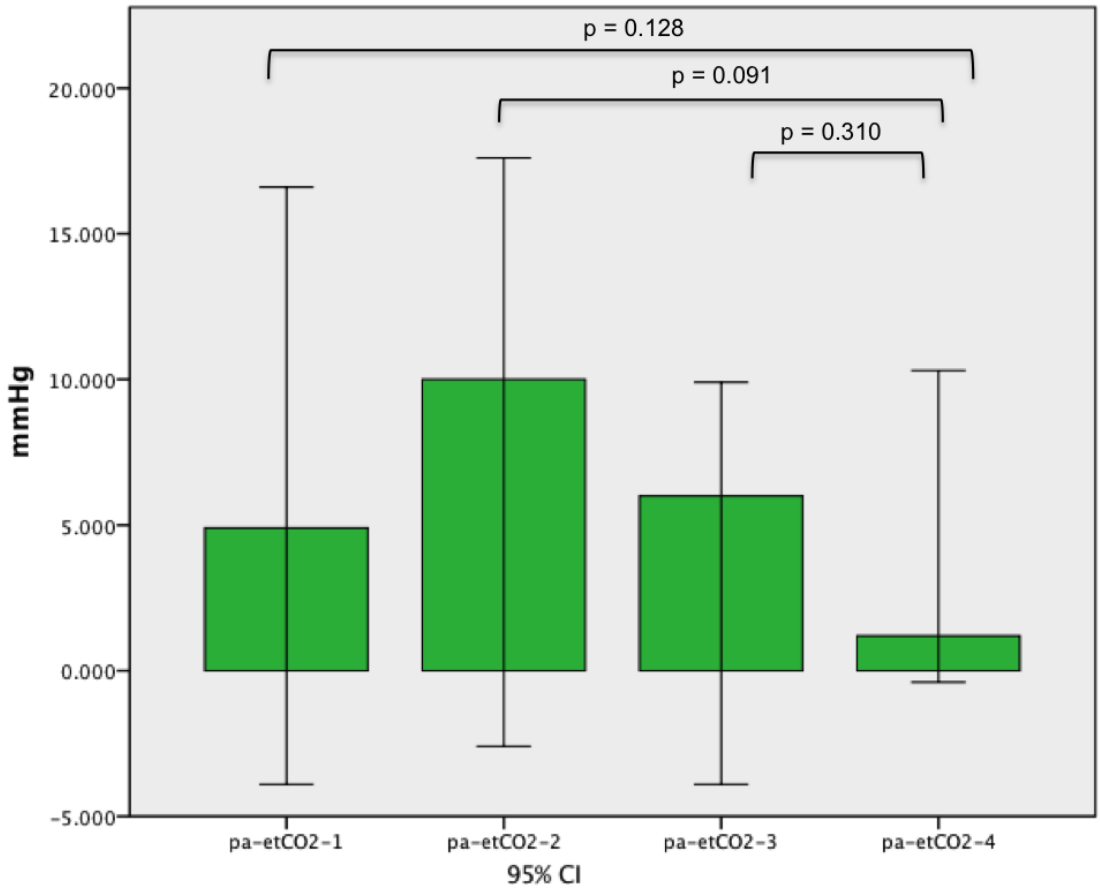


Figure 49: pa-etCO$_2$ in patients with RSV-infection

The figure shows the median pa-etCO$_2$ over the four points in time in patients with RSV-infection. All 7 values were valid. P-values: pa-etCO$_2$-1 and pa-etCO$_2$-4 = 0.128, pa-etCO$_2$-2 and pa-etCO$_2$-4 = 0.091, pa-etCO$_2$-3 and pa-etCO$_2$-4 = 0.310; pa-etCO$_2$ = arterial to end-tidal difference of pCO$_2$; CI = confidence interval.

3.7.2.2 pa-ACO_2

The median on day 1 of mechanical ventilation was 16.19 mmHg (min: 9.46 mmHg, max: 35.2 mmHg). The median on day 2 was 19.39 mmHg (min: 11.85 mmHg, max: 34.4 mmHg). On the third day the median was 23.85 mmHg (min: 10.02 mmHg, max: 28.92 mmHg). On the last point in time the median was 13.77 mmHg (min: 0.42 mmHg, max: 21.19 mmHg).

We found a significant difference between day 1 and 4 (p = 0.029) and between day 2 and 4 (p = 0.035). There was no significant difference between day 3 and 4 (p = 0.074).

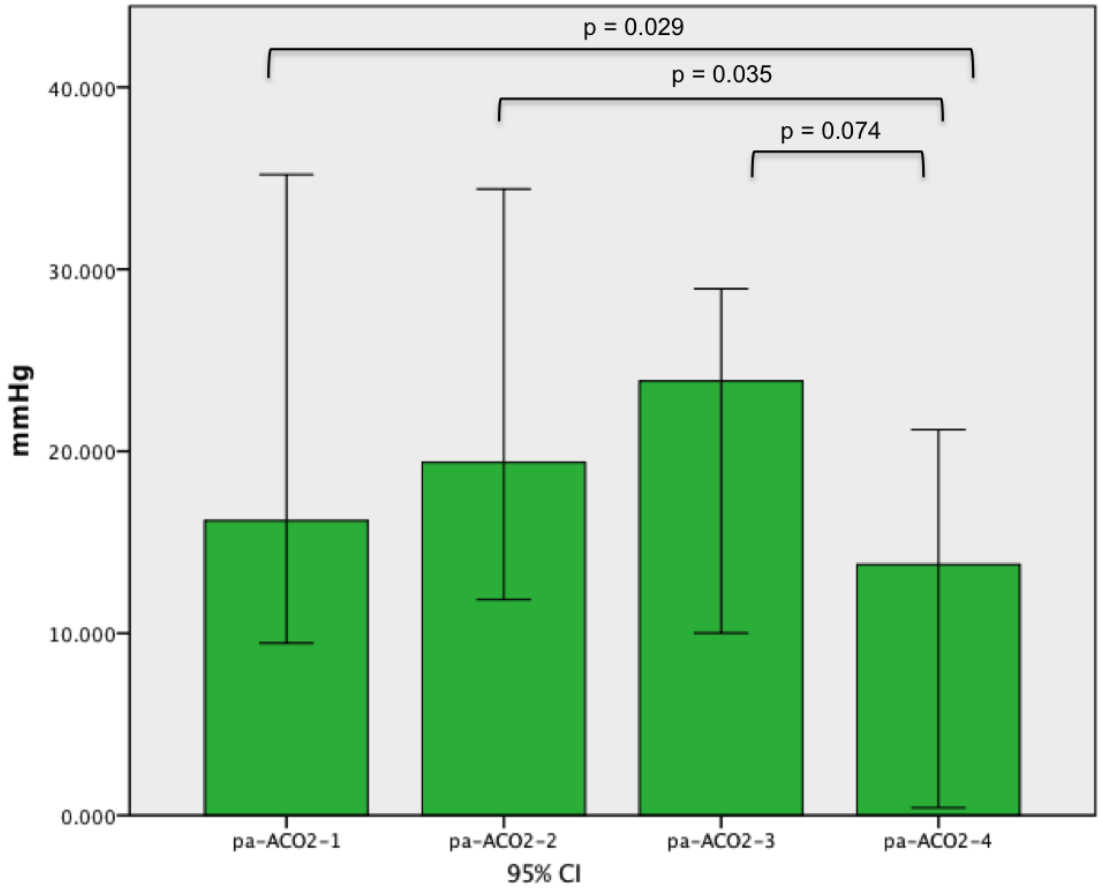


Figure 50: pa-ACO_2 in patients with RSV-infection

The figure shows the median pa-ACO_2 over the four points in time in patients with RSV-infection. 7 values were valid. P-values: pa-ACO_2-1 and pa-ACO_2-4 = 0.029, pa-ACO_2-2 and pa-ACO_2-4 = 0.035, pa-ACO_2-3 and pa-ACO_2-4 = 0.074. pa-ACO_2 = arterial to alveolar difference of pCO_2. CI = confidence interval.

3.7.3 slope-CO_2

The median value of slope-CO_2 on day 1 was 25.9 Vo.-%/L (min: 2.7 Vol.-%/L, max: 87.2 Vol.-%/L), whereas the median on day 2 was 35.3 Vol.-%/L (min: 2.02 Vol.-%/L, max: 68.99 Vol.-%/L). The median on day 3 was 35.51 Vol.-%/L (min: 4.12 Vol.-%/L, max: 88.45 Vol.-%/L) and the median on day 4 was 17.11 Vol.-%/L (min: 2.94 Vol.-%/L, max: 61.62 Vol.-%/L).

We separately compared day 1, day 2 and day 3 with the day of extubation. The p-values were 0.051 for day 1 and day 4, 0.037 for day 2 and day 4 and 0.026 for day 3 and day 4.

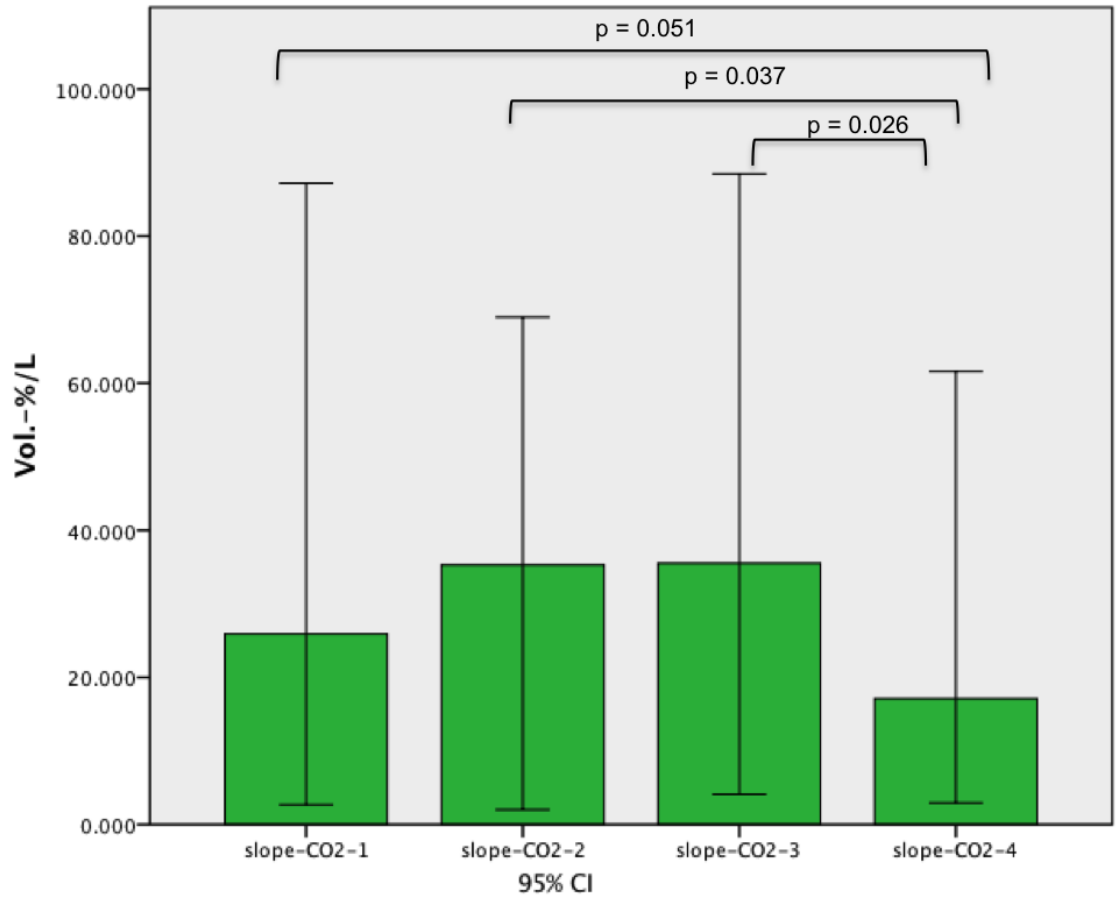


Figure 51: slope-CO_2 in patients with RSV-infection

The figure shows the median slope-CO2 over the four points in time in patients with RSV-infection. 7 values were valid. slope-CO_2-1 and slope-CO_2-4 = 0.051, slope-CO_2-2 and slope-CO_2-4 = 0.037, slope-CO_2-3 and slope-CO_2-4 = 0.026. CI = confidence interval.

4 Discussion

The aim of this study was to analyse our existing data and to verify the benefits of VCAP in mechanically ventilated patients. Furthermore, the study should be the basis for future projects regarding this topic. Our main focus was on the dead space fractions and their correlation with the duration of mechanical ventilation. CO_2-derived parameters were analysed and their utility concerning duration and outcome of mechanical ventilation was evaluated.

The main findings of our retrospective study in infants and children, who required mechanical ventilation, were:

1. On day one of mechanical ventilation CO_2-derived parameters ($pACO_2$, $pECO_2$ and VCO_2) were significantly higher in the group of patients with short-term mechanical ventilation (< 48 hours) than in the group with long-term mechanical ventilation (≥ 48 hours).
2. The mentioned CO_2-derived parameters increased significantly over time in the group of patients with prolonged mechanical ventilation (≥ 48 hours).
3. VDphys/VT and VDalv/VT were significantly lower in the group of patients with short-term mechanical ventilation (< 48 hours) compared with the group of patients with prolonged mechanical ventilation (≥ 48 hours).
4. Both dead space fractions (VDphys/VT and VDalv/VT) decreased over time in the group of prolonged mechanical ventilation (≥ 48 hours).
5. Physiologic dead space fraction (VDphys/VT) showed a good correlation with the duration of mechanical ventilation (MV-days).
6. VDBohr/VT showed a good correlation with VDaw/VT but not with VDphys/VT (using Engoff's modification of Bohr's equation).
7. The differences between arterial and end-tidal pCO_2 (pa-etCO2) and arterial and alveolar pCO_2 (pa-ACO2) were significantly lower in the group of short-term mechanical ventilation (< 48 hours).
8. Both parameters (pa-etCO2 and pa-ACO2) decreased over time in the group of prolonged mechanical ventilation (≥ 48 hours).
9. slope-CO_2 was significantly lower in the group with short-term mechanical ventilation (< 48 hours) compared to the group with long-term mechanical ventilation (≥ 48 hours).

10. There was a good correlation between alveolar and physiologic dead space fractions. In addition, both dead space fractions correlated with the arterial to end-tidal CO_2 and arterial to alveolar pCO_2 differences.
11. slope-CO_2 showed no significant difference in the whole group of infants and children with prolonged mechanical ventilation (≥ 48 hours) over the course of time, whereas slope-CO2 showed a significant change in the group with RSV-infection on the day of extubation compared with the data on days 2 and 3 of mechanical ventilation.

4.1 Limitations

When interpreting our data some limitations have to be considered. First the total number of only 51 patients and the unequal distribution between Group A (n= 16) and Group B (n= 35) could have affected the outcome of our study. Especially when analysing the patients with RSV-infection, the number of cases was a major limitation to our study. Only 7 patients suffered from RSV-infection and only 4 of them were diagnosed with RSV-bronchiolitis.
Another restriction was the use of duration of mechanical ventilation as main criterion for allocating the patients to the two groups. This was caused by the heterogeneity of patients' diagnosis, which didn't allow a classification of patients according to their main diagnoses.
Further, not all of our patients were extubated, therefore we had to define a fourth point in time for those patients, who required long-term mechanical ventilation.
Moreover, the values of $pACO_2$ were calculated and not determined by VCAP, as suggested in a previous publication of Tusman et al. (17)

Finally, there are only few publications concerning standard values of VDphys/VT-ratio in infants. Most of the previous studies were done in adults and are therefore difficult to compare with our study.

4.2 Pulmonary dead space fractions

In critically ill patients physiological (VDphys) and alveolar dead space (VDalv) are important factors concerning mortality and outcome of mechanical ventilation. Previous studies showed that patients with higher initial pulmonary dead space fractions required a longer duration of mechanical ventilation and that higher pulmonary dead space fractions were further associated with a prolonged hospital stay. (5,34,50) Further, Nuckton et al. found a correlation between an early increase of pulmonary dead space fraction and mortality in patients with ARDS. (50) Cepkova et al. confirmed the findings in patients with ARDS and they could further show similar findings in patients with ALI (using the European-American consensus criteria for ALI/ARDS). (34) A main difference to previous studies was the use of a low-tidal-volume ventilation strategy, which showed a significant benefit concerning patients' mortality and might as well be the reason for lower VD/VT-ratios. (34) In addition, Cepkova et al. recommended the use of VD/VT-ratio as a prognostic factor in the clinical routine, as it is a simple, non-invasive parameter, which provides useful information in patients with ALI/ARDS. (34)

The main focus of our study was on the VDphys/VT-ratio. We first looked at those patients, who were a mechanically ventilated for at least 48 hours. On day 1 those patients showed a median value of VDphys/VT of 0.607. This value was similar to recent publications concerning VDphys/VT-ratios in patients with ARDS/ALI. (5,6,34,50) Nuckton et al. found a significantly higher VDphys/VT-ratio in patients who died after suffering from ARDS, than in those who survived. (50) Raurich et al. and Cepkova et al. found similar results in patients with ARDS/ALI. (6,34) Further, Raurich et al. stated that there's an independent association between the height of VDphys/VT and mortality not only in the early phases, but also in the intermediate phases of ARDS. (6) The first week after the onset of ARDS was considered the early phase, whereas the second week represented the intermediate phase. (6) The classification was based on a publication by Gattinoni et al. (6,58)

Several mechanisms were discussed as the reason for an elevated VDphys/VT-ratio in the early and intermediate stages of ARDS. (4,6,34,50) A combination of

hemodynamic and vascular injury mechanism could be a valid explanation for the increase of physiological dead space fraction. (4,6,34,50)
However, changes in pulmonary blood flow like pulmonary hypo- or hyperfusion lead to V/Q-inhomogeneities and further to an increase of VDphys/VT-ratio. (4) Pulmonary hyperperfusion is associated with hyperdynamic cardiovascular states (like sepsis) and is therefore an important issue in patients with ARDS/ALI. (4)
Further, as a consequence of vascular injury vasoconstriction, macro- and micro-thromboembolism, endothelial cell swelling and mechanical compression of pulmonary capillaries (caused by extravascular oedema) generate higher alveolar dead space fractions and therefore as well higher physiological dead space fractions. (4,59–61)

Since the initial VDphys/VT-ratio was elevated in our patients, who required prolonged mechanical ventilation (MV ≥ 48 hours) we compared the values of day 1 with those of the day of extubation to see if there was a significant difference. As expected the median value of VDphys/VT on the fourth point in time was only 0.475 and therefore varied significantly ($p < 0.001$) from the values of day 1.

Additionally, we compared the patients, who required prolonged mechanical ventilation with those, who were mechanically ventilated for no longer than 48 hours on day 1 and found a highly significant result with a p-value of < 0.001. Similar results were found by Ong et al. in infants after cardiac surgery. (5)

To get more detailed information about the correlation of the height of VDphys/VT and the length of mechanical ventilation we divided the patients into quartiles (> 0.65; 0.65 - 0.51; 0.50 - 0.37; < 0.37). Previous studies showed that this is a valid method to evaluate the correlation between VDphys/VT and length of mechanical ventilation. (5,50) Our results could confirm those findings, with a significantly longer time of mechanical ventilation in the group with the highest VDphys/VT-ratio ($p = 0.013$).

As a matter of fact, physiological dead space (VDphys) consists of two separate compartments: alveolar dead space (VDalv) and airway dead space (VDalv).
We suggested that higher values of physiological dead space fraction in patients with respiratory failure were based on higher values of alveolar dead space fraction. Due

to vascular injury and hemodynamic changes in patients with ARDS an increase of VDalv would result in higher values of VDphys with more or less stable values of VDaw. To proof this theory we evaluated the correlation of VDphys/VT with VDalv/VT and VDaw/VT. As expected we found a high correlation between VDalv/VT and VDphys/VT on day 1 of mechanical ventilation with a correlation coefficient of 0.837 and we further found an even higher correlation on the day of extubation with a correlation coefficient of 0.923.

In contrast, we tested VDaw/VT over the four points in time to see if there were any changes in airway dead space. Again as expected the values of VDaw/VT remained constant over the four points in time with a median value of 0.24 on day 1 and a median value of 0.22 on the day of extubation ($p = 0.107$). When we additionally tested the correlation of VDaw/VT and VDphys/VT we found no correlation over all four points in time.

Therefore the results confirmed our expectations concerning the influence of VDalv/VT and VDaw/VT on physiological dead space fraction.

Riou et al. found similar values of VDaw using single-breath-test of carbon dioxide (= VCAP) for calculation. (49) In their study they tested different approaches to determine dead space fractions in mechanically ventilated children. (49) Next to the single-breath-test of carbon dioxide they calculated VDaw by using the Bohr equation and found significantly higher values of VDaw when using Bohr's equation. (49) They suggested that the higher values of VDaw could be explained by the rebreathing of carbon dioxide, which leads to an increase of $pECO_2$ and $petCO_2$. (49)

The results of Riou et al. went along with findings of Fletcher, who found a significant difference between VCAP and calculations done by using the Bohr equation. (62) Fletcher stated that the use of Bohr's equation leads to a massive overestimation of airway dead space. (62)

Furthermore, Wenzel et al. investigated the differences in VDaw either using VCAP or the Bohr equation in mechanically ventilated neonates. (63) However, they couldn't find a significant difference between the two methods having a high range of values, which could possibly be explained by high heterogeneity of diseases. (63)

Tusman et al. demonstrated that Bohr's equation could be more adequate to calculate physiological dead space than Enghoff's modification of Bohr's equation. (17)

Over the past decades Enghoff's modification of the Bohr equation has been widely used to determine physiological dead space. Tusman et al.'s approach is based on the idea that $paCO_2$ is not representing the alveolar partial pressure of carbon dioxide and therefore is overestimating alveolar dead space (VDalv). (17) Because of the difficulties measuring the alveolar partial pressure of carbon dioxide, Tusman et al. suggested to use VCAP instead of arterial blood samples to estimate $pACO_2$. (17) Therefore they used the mean $pACO_2$, which was first mentioned by Aitken and Clark-Kennedy. (17,64) The mean $pACO_2$ is defined as the midpoint of phase III of the volumetric capnogram according to Fletcher et al. (2) Tusman et al. compared VCAP-derived $pACO_2$ values with MIGET-derived $pACO_2$ and found nearly identical values of $pACO_2$ with both methods. (17) Further, they determined $paCO_2$, $petCO_2$ and $pECO_2$ to show that the first two values were higher than the mean $pACO_2$ and that $pECO_2$ was significantly lower. (17) Following their results they suggested that the use of mean $pACO_2$ could be more accurate for calculating alveolar dead space than previous methods. (17)

In response to these results Jeronimo Graf stated in a letter to the editor that VDBohr would correspond with VDaw and not with VDalv and referred to an experimental work by Breen and Mazumdar showing that especially in pulmonary embolism VDalv can only be determined when $paCO_2$ is used in the formula of VDphys. (65,66)
Our data completely confirmed Graf's ideas about VDBohr and respiratory dead space.

In another publication Breen et al. calculated alveolar dead space by using arterial and mean alveolar pCO_2. (67) They suggested that the use of paCO2 together with $petCO_2$ may overestimate $pACO_2$ and therefore underestimate alveolar dead space in cases with accelerating slopes of phase III (like in cases of PEEP-titration), and that therefore the use of mean $pACO_2$ is more appropriate. (67)

In our study we calculated VD-Bohr/VT for both groups and further for all four points in time of Group B (MV ≥ 48 hours). Afterwards we compared day 1 of mechanical ventilation of Group A and B and additionally compared day 1,2 and 3 with the day of extubation in those patients, who required mechanical ventilation for at least 48 hours (= Group B).

Although we found a significant difference between both groups on day 1 ($p = 0.02$), we failed to show a significant difference over the four points in time.
Additionally, as suggested by Tusman et al. we tested the correlation of VDBohr/VT and $pACO_2$, but found no correlation over all four points in time in Group B. (17)

Further, we tested the correlation of VDBohr/VT and VDaw/VT and found very high correlations on day 1 ($R = 0.931$) and a high correlation on day 2 ($R = 0.875$), day 3 ($R = 0.836$) and on the day of extubation ($R = 0.745$).

According to our results VDBohr/VT is more appropriate to determine airway dead space, than alveolar dead space. We believe that the reason for our lower values of VDBohr/VT was the fact that we calculated the mean $pACO_2$, instead of measuring it with VCAP as suggested by Tusman et al. (17)

The VCAP-technique in modern ventilators should display alveolar and mixed-expiratory CO_2-tensions and VDBohr breath by breath. As VDBohr only reflects changes in airway dead space, a VCAP software option to enter arterial pCO_2 would allow to intermittently display VDphys (= VDBE). This would further improve the understanding of respiratory pathophysiology in critically ill patients with different respiratory disorders and lead to optimized ventilator settings. However, our ideas have to be confirmed in future studies.

4.3 pa-etCO_2 and pa-ACO_2

As mentioned before the end-tidal partial pressure of CO_2 (petCO_2) is commonly used as a surrogate for pACO_2 and to calculate alveolar dead space fractions. Hardman and Aitkenhead described pa-etCO_2 as a predictor to estimate alveolar dead space. (68) Nunn and Hill also postulated a correlation between pa-etCO_2 and alveolar dead space. (69)
According to Breen et al. the use of petCO_2 is a valid method in cases of a horizontal alveolar plateau phase in the volumetric capnogram, when the end-tidal and arterial pCO_2 are not differing too much. (67) However, when there are changes in phase III, which lead to an ascent of the slope, petCO_2 tends to overestimate pACO_2. (67) In an animal trial Breen et al. found out that the titration of PEEP leads to a significant increase of the slope and therefore to significantly higher values of petCO_2 in comparison to the mean pACO_2. (67) The same problem occurs in obstructive lung diseases, which as well lead to an increase of the slope of phase III. (67) In very severe cases petCO_2 could be even higher than paCO_2. (67) This emphasises why Fletcher et al. stated the importance of considering the entire phase III and therefore the mean alveolar partial pressure of CO_2, when analysing alveolar dead space. (2,67)

Tusman et al. suggested that pa-ACO_2 should replace pa-etCO_2, because it represents a better reflection of the alveolar gas concentration. (17) According to Tusman et al. pa-etCO_2 only represents few alveolar units “with low V/Q-ratios and/or a long expiratory time constant”. (17)

Other studies gave attention to the influence of FiO_2 on petCO_2 and therefore as well on pa-etCO_2. (26,70,71) Larson and Severinghaus reported an increase of pa-etCO_2 in adult awake patients, when inhaling higher inspiratory fractions of O_2. (70) Whitesell et al. failed to prove that correlation in adult anaesthetized patients. (71)
Further, Yamauchi et al. found a significant correlation between a higher FiO_2 and pa-etCO_2 as well as between a higher FiO_2 and alveolar dead space (VDalv) in adult anaesthetized patients. (26) They assumed that the increase of VDalv was caused by a reduction of vascular resistance in highly perfused areas of the lung, which led

to an even higher perfusion of those areas and vice versa to an even worse perfusion of the initially low perfused areas of the lung. (26)
Further, pa-etCO_2 could be affected by intrapulmonary shunt. (26) Intrapulmonary shunt leads to higher values of paCO_2, which results in higher values of pa-etCO_2. (26) Therefore the presence of shunt volume contributes to the height of VDphys, when using Enghoff's modification of Bohr's equation. (26)

On day 1 of mechanical ventilation we found significantly higher values ($p < 0.001$) of pa-etCO_2 in those patients, who were mechanically ventilated for at least 48 hours. This was a result of a combination of higher values of paCO_2 and lower values of petCO_2. A possible explanation could be the co-existence of intrapulmonary shunt and an increase of VDalv. (26) This was confirmed, when comparing the four different points in time of Group B. Day 1, day 2 and day 3 differed significantly ($p < 0.001$) from the day of extubation.
Furthermore, we found a significant difference between pa-ACO_2 of Group A and Group B on the first day of mechanical ventilation ($p = 0.002$). Additionally, we found a significant difference between day 1, day 2 and day 3, when comparing them to the day of extubation.
When we compared pa-etCO_2 and pa-ACO_2 of Group B, we found clearly higher values of pa-ACO_2. This could be explained by the differences between pACO_2 and petCO_2. That once again showed that petCO_2 isn't really representative for the alveolar partial pressure of CO_2. Nevertheless, we have to admit that we calculated pACO_2, what perhaps led to an underestimation of pACO_2 and therefore to an overestimation of pa-ACO_2.
We agree with Tusman et al. that pa-ACO_2 is a better index of gas exchange than pa-etCO_2, as it uses mean alveolar pCO_2 instead of end-tidal pCO_2.

4.4 slope-CO_2

To analyse slope-CO_2 we used the values, which were calculated by the Hamilton S1-respirator®. In the group of patients, who were mechanically ventilated for at least 48 consecutive hours (= Group B), the slope-CO_2 was significantly higher on the first day of mechanical ventilation than in Group A ($p = 0,001$). We suggest that this on the one hand could be caused by ventilation-perfusion mismatch or on the other hand by serial deflation of the alveolar units in severely injured lungs. (11,54,55) Suarez-Sipmann et al. described a close relation of the slope of phase III to "the matching of ventilation and perfusion", which indicated that there is a close relation between high values of slope-CO_2 and the severity of lung injury. (1) Further, Tusman et al. found a close correlation of SIII and the V/Q-inhomogeneity measured by MIGET. (11) They suggested that any increase of SIII, under constant ventilator conditions and constant body metabolism, reflects a worsening of respiratory function. (11)

We could not find any significant differences over the four points in time of Group B, and assume that the small number of patients with obstructive lung diseases is the reason for this finding.

Regarding to Tusman et al.'s findings concerning the correlation of slope-CO_2 and VDalv/VTalv-ratio we expected that higher values of slope-CO_2 go along with an increase of VDphys/VT and VDalv/VT. (11) We found a moderate correlation between slope-CO_2 and VDphys/VT on day 1 and day 3 and a low correlation between slope-CO_2 and VDphys/VT on day 2 and the day of extubation. Further, we found a low correlation between slope-CO_2 and VDalv/VT on day 1, day 3 and the day of extubation and we found no correlation between slope-CO_2 and VDalv/VT on day 3.

We found that the slope of phase III and the respiratory resistance were increased in obstructive lung diseases, which indicated that there could be a correlation between slope-CO_2 and the expiratory airway resistance. We found a high correlation between slope-CO_2 and the expiratory airway resistance (= Rexp) on day 1, day 3 and the day of extubation. On day 2 we found a moderate correlation. High expiratory airway

resistance affects the convective CO_2-transport within the airways, resulting in increased values of slope-CO_2. Based on slope-CO_2 values VCAP allows to distinguish between infants with RSV-pneumonia and RSV-bronchiolitis. As the number of infants with severe RSV-bronchiolitis was too low, the statistical analysis could not show the expected significance in terms of VCAP values.

Furthermore, we failed to show a correlation between slope-CO_2 and the duration of mechanical ventilation. Nevertheless, we are confident that future studies with higher numbers of infants with severe bronchiolitis could show significances in VCAP values including slope-CO_2 data.

4.5 Conclusion

VCAP is a very useful monitoring tool for adult, as well as for paediatric patients, displaying on the one hand different CO_2-parameters and on the other hand time based and volume based capnograms breath-by-breath. It improves our understanding about pathophysiologic changes in respiratory disorders, helps to optimize PEEP-titration in patients with ARDS and gives useful information about lung disease severity and the duration of mechanical ventilation. The option to measure VDBohr continuously and VDphys (= VDBE) intermittently would be a further step for improved respiratory monitoring at bedside.
In addition, slope-CO_2 gives real-time information about ventilation-perfusion mismatch in diseased lungs and could be useful to document small airway disease in small infants with bronchiolitis.

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