

EXTENDING THE ROLE OF CAPNOGRAPHY DURING MECHANICAL VENTILATION

PhD Thesis

Anita Korsós, MD

Doctoral School of Multidisciplinary Medical Sciences
University of Szeged

Supervisors:

Barna Babik, MD, PhD

Department of Anaesthesiology and Intensive Therapy, University of Szeged

Ferenc Peták, PhD, DSc

Department of Medical Physics and Informatics, University of Szeged

2022.

INTRODUCTION

Noninvasive monitoring of gas exchange and ventilation is an essential component of general anaesthesia and intensive therapy. Technologies that support the noninvasive monitoring of expired CO₂ and inspired O₂ have existed for decades. Monitoring of the numeric value of end-tidal CO₂ (PetCO₂) expressed as either a partial pressure (mmHg, kPa) or as a percentage fraction of the expired gas is referred to as capnometry. Conversely, capnography refers to the continuous, breath-by-breath display of expired CO₂ concentration plotted against time or expired gas volume.

The monitoring airway patency and the adequacy of ventilation in ventilated patients are the most common and acknowledged indications for capnography and capnometry, and these contribute greatly to patient safety. However, technological refinement of capnography enables its application to a broader indication, which subsequently fosters methodological developments in ventilation therapy and a better understanding of complex respiratory disorders.

Definition of capnography

Capnography is a non-invasive, continuous, online, dynamic, bedside, effort- and cooperation independent, simple to use, inexpensive, numeric and graphical analysis of the exhaled CO₂ concentration. Registration of expired CO₂ breath-by-breath over time or in the volume domain can be considered as an indicator curve of lung ventilation. Accordingly, this monitoring modality detects technical complications in the ventilator circuit, and is able to reveal defects in alveolar ventilation and/or in matching ventilation to perfusion.

The capnogram curve: phases and shape factors

The expiratory phase of the time and volumetric capnogram can be divided into three phases. Phase I. is identified at the beginning of expiration, where the gas mixture originates from the anatomic and/or from the instrumental dead space in the case of mechanical ventilation. Phase II. is the transition zone, in which the increasing concentration of CO₂ can be attributed to the diffusion and convection gas mixing between the gases originating from the dead spaces and the alveolar compartment. Phase III. refers to the CO₂ content of the gas originating from the alveolar compartment. Its shape is similar to a gradually ascending plateau with a slope in the

time domain of 2-3 Hgmm/s or 0.3-0.4 kPa/s (S3T), or in the volumetric domain of 0.5-2.5 kPa/ml. The physiologic slope of this phase originates from the gas mixing via diffusion, and the fact that breathing is cyclic but the capillary circulation is continuous, and CO₂ diffuses constantly to a gradually decreasing alveolar volume during expiration. The highest point of this phase defines the end-tidal CO₂ concentration, with a normal value of 30-43 Hgmm, or 4.0-5.7 kPa (4-5.6 vol%). By the end of the phase III, the pCO₂ on the capnogram curve exhibits a steep drop to reach baseline, where it continues until the beginning of the next expiration. In general, dead space refers to the fraction of tidal volume that does not participate in gas exchange, as this gas compartment does not come into contact with pulmonary capillary circulation. Ventilation dead space can be expressed as an absolute gas volume, its proportion to the tidal volume (V_D/V_T) or its proportion to the minute ventilation. Dead space indices can be categorized as anatomic and physiologic parameters.

Dead space parameters

Anatomic dead space according to Fowler (V_{DF}) incorporates the volume of conductive airways where gas exchange does not take place and the gas volume in the ventilator circuit behind the Y-piece. Its normal value is approximately 2 ml/BWkg with exact normal values depending also on the height of the patient.

Physiologic dead space according to Bohr (V_{DB}) incorporates the anatomic dead space (V_{DF}) and the gas volume of the alveoli with decreased or no perfusion, where gas exchange is subsequently compromised or does not occur. Its normal value is approximately 2.2-2.5 ml/BWkg.

Physiologic dead space according to Enghoff (V_{DE}) can be determined in order to estimate the ventilation/perfusion mismatch. Compared to Bohr's dead space, the V_{DE} also contains alveoli with maintained perfusion but decreased or no ventilation (i.e. alveolar shunt).

Other parameters assessed by capnography

Alveolo-arterial pCO₂ difference (PaCO₂-PetCO₂): The physiological value of PaCO₂-PetCO₂ is 2-3 mmHg. Ventilation-perfusion (V/Q) mismatch, such as shunt circulation and dead-space ventilation may increase its value. However, this difference may be reduced in the presence of a severe sequential ventilation heterogeneity. Concomitant ventilation-perfusion mismatch and sequential ventilation heterogeneity influences the PaCO₂-PetCO₂ in opposite directions and, thus, changes may neutralize each other.

Clinical indications of capnography and capnometry

Securing the airway and patient safety: Capnography can provide technical assistance in the rapid and correct positioning of the endotracheal tube or supraglottic airway devices. It may also be helpful during blind intubation and as well as the early detection of technical complication, such as the disconnection of the ventilation circuit, malpositioning of the endotracheal tube, insufficient sealing around the ET-tube cuff, or exhausted CO₂ absorbent soda.

Monitoring of clinical parameters: Capnography draws attention to various clinical scenarios resulting from ventilation (V) or perfusion (Q) defect or V/Q mismatch, which should be evaluated along with other clinical signs and symptoms. Capnography may provide important information during ventilator weaning by observing high or low PetCO₂ values or a pathologic shape of Phase III. Capnography is an essential tool in assessing the efficacy of cardiopulmonary resuscitation. Monitoring of expired CO₂ concentration is also an integral part of critical care via its ability to help in guiding ventilatory therapy even in patients without primary ventilation problems. Assessment of the arterio-venous CO₂-gap can also reveal alterations in the cardiac output by factoring in the amount of exhaled CO₂. Sudden and profound deterioration of circulation (e.g. ventricular fibrillation, asystole) can be detected more promptly with capnography than with pulse oximetry.

Capnography beyond tube position and patient safety: based on the methodological background detailed above, capnography provides a wide array of pathologically and clinically relevant information on both ventilation and circulation. While this monitoring technique is a standard part of multimodal monitoring modality in general anaesthesia and intensive care, the monitoring value of capnography is far from being completely utilized. Therefore, any attempt to broaden the area of clinical application of capnography contributes to improving patient safety. This simple, non-invasive and real-time monitoring modality can help steer clinical decision-making by optimizing facilities when a risk of ventilator shortage arises, such as was observed during the outbreak of COVID-19 pandemic or in catastrophe medicine in combat hospitals. Furthermore, capnography allows obtaining more complete information about the cardiopulmonary status of a ventilated patient, which has particular importance in metabolic disorders with pulmonary consequences.

The SARS-CoV2 pandemic

At the beginning of 2020, the newly emerged SARS-CoV-2 virus caused a worldwide outbreak referred to as the COVID-19 pandemic. This new coronavirus may cause viral pneumonia with severe respiratory insufficiency requiring mechanical ventilation in up to 2.3-33% of the hospitalized cases. Recent epidemiologic studies about hospitalized COVID-19 patients report that the need for invasive mechanical ventilation in intensive care units ranges from 29.1% to 89.9%.

The need for ventilatory support at any critical moment is influenced by various factors. First, the virus spreads quickly in the community causing a rapid rise in the number of infected patients in a relatively short timeframe. Secondly, as critical care physicians became more familiar with the detrimental course of the COVID-19, expert opinions and consensus statements suggest initiating invasive ventilation as early as possible following respiratory symptom escalation. Finally, the majority of patients requiring mechanical ventilation generally depend on the ventilator for a prolonged period of time, which may last up to 14 days. Under extreme circumstances, these factors may lead to a need for a high number of mechanical ventilators in order to meet the demand for the simultaneous life support.

However, the increased need for ventilators is transient, ventilatory equipment is expensive and their immediate manufacturing is proven to be difficult. Therefore, the supply is limited by economic and technical factors that may lead to a scenario when intensivists are bound to rely on the number of available ventilators in their units. Hence, the actual need for ventilators may exceed the number of available devices in case of a severe regional outbreak of COVID-19 epidemic. This may lead to an inevitable triage and a quick and difficult decision making regarding the rational utilisation of critical care means based on the promptly available information. This ultimately raises ethical concerns, since the chance of survival of patients with severe respiratory insufficiency without mechanical ventilation is unquestionably lower in the presence of viral pneumonia. Therefore it is reasonable not to dismiss the concept of ventilator splitting as a life saving maneuver, which means ventilating multiple lungs of similar patients with one apparatus. Such an emergency approach has been previously described and more recently its feasibility was confirmed in a bench-test study. However, many potential issues need clarification before considering this approach in clinical situations.

Respiratory consequences of obesity and diabetes

Capnography carries bedside information about the pathophysiological alterations in ventilation, perfusion and ventilation-perfusion matching along with respiratory mechanics. Characterization of these fundamental aspects of metabolic disorders, such as obesity and diabetes, present major public health concerns, and pose a global challenge for health care providers. Type 2 diabetes (T2DM) is the largest subtype (90% to 95%) and is a consequence of relative or absolute insulin deficiency. The number of patients with diagnosed or undiagnosed diabetes requiring critical care management is continuously increasing, with incidence reaching 25% to 40%, and has continued to expand rapidly in the past decade. Therefore, there is a particular need for an increased awareness of diabetes in critically ill patients.

The pathophysiological changes are also expected to affect the lungs. The endocrine and paracrine consequences of endothelial dysfunction may trigger airway and lung parenchymal remodelling related to AGEs, oxidative stress, imbalance between NO and ET-1 pathways, and decreased prostaglandin I₂ level. All these processes may contribute to deterioration of lung function at the organ level. Since the pulmonary vessels and extracellular matrix cells express glucose transporter 1, glucose influx from the blood to the interstitium is not limited.

In an attempt to clarify the pulmonary effects of diabetes, spirometric studies have revealed deteriorations in lung function indices. Nevertheless, lack of detrimental changes in spirometric outcomes was also reported. The well-established methodological limitation of spirometry (99, 100) and the substantial differences among study populations (e.g. type and severity of diabetes, age and comorbidities) may have contributed to this discrepancy. Furthermore, the effect of obesity as a potential confounding factor was not assessed separately, and this may have further confused the findings.

AIMS AND HYPOTHESES

Studies included in the present thesis were designed to verify the use of capnography and extend its indications field in special patient groups and/or unique clinical situations. We characterized the ability of capnography to support clinical decision-making about the optimization of ventilator facilities during the outbreak of COVID-19 pandemic or in other catastrophic situations, such as combat casualty care. Furthermore, we also sought to investigate whether capnography contributes to revealing novel information about the cardiopulmonary status of a

ventilated patient with metabolic disorders. Accordingly, the specific aims of the present thesis can be defined as follows.

Study I.:

To establish the use of capnography to verify emergency ventilator sharing in the COVID-19 era by

- i) testing the use of capnography as a simple, noninvasive, online and goal-oriented bedside method for controlling the adequacy of splitted ventilation in each patients,
- ii) investigating the presence of potential collateral gas flow between the two lungs with different time constants, and
- iii) offering a simulation-based algorithm for ensuring equal tidal volumes by counterbalancing the difference in compliances by adjusting the resistance on the contralateral side.

Study II.:

To assess similarities and differences in the alterations of respiratory mechanics and gas exchange abnormalities in metabolic disorders by

- i) characterizing the effects of diabetes and obesity separately on the airway function and viscoelastic properties of the respiratory tissues,
- ii) establishing how diabetes alone would affect ventilation heterogeneity, ventilation–perfusion matching, and gas exchange in cardiac surgery patients, with particular focus on the applicability of the findings in intensive care clinical practice.

MATERIALS AND METHODS

Study I.: Use of capnography to verify emergency ventilator sharing in the COVID-19 era

Ethical approval was not necessary in this bench-test study, as no data of animal or human origin were considered.

The experimental setup

Testing apparatus included two symmetrical model lungs. The model on each side was built from a 7-mm inner diameter commercial endotracheal tube to mimic the airways, and a commercially available artificial lung (type VA8001, Great Group Medical Co., Ltd., Taiwan) to represent compliant respiratory tissues. This double-lung system was ventilated with a commercially used ventilator (Dräger Evita XL, Dräger Medical, Lübeck, Germany). The ventilator circuit was divided symmetrically into two inspiratory and expiratory limbs by introducing Y-piece connectors close to the inlet and outlet ports of the ventilator. The length of each limb was 110 cm.

Two mainstream capnographs (Capnogard 1265, Novamatrix, Andover, MA, USA) were connected to each circuit. The airflow (V') on each side was measured by a 11-mm internal diameter pneumotachograph (PNT Series, Hans Rudolph, Shawnee, KS, USA) connected to a miniature differential pressure transducer (24PCE-FA6D Honeywell, Charlotte, NC, USA). The pressure inside each model lung respectively was measured via connecting identical pressure sensors (24PCE-FA6D Honeywell, Charlotte, NC, USA) to the lateral ports. A rubber band was used on one side referred as Low C to decrease the compliance, whereas a Hoffmann clamp was placed around the endotracheal tube on the contralateral side referred as High R.

Plastic tubing was attached to the apex of each test lung allowing a seal-proof CO₂ gas inflow from a CO₂ reservoir bag supplied by a medical CO₂ cylinder. To ensure identical amount of CO₂ delivery into each side, a roller pump (Terumo Sarns 9000 Heart-Lung Machine, Terumo Europe NV, Leuven Belgium) was used as a flow generator to feed the CO₂ tubing system divided with a T-piece with an on-off clamp on each side. This system guaranteed the delivery of the same CO₂ concentration alternately even if the impedance of the artificial lung is varied depending on the applied elastic and/or resistive load. This setup mimics physiological CO₂ production with a constant rate of 200 ml/min. The CO₂ delivery system also enabled monitoring the adequacy of ventilation via measuring the end-tidal partial pressure of CO₂ on each side, respectively. In addition, unilateral CO₂ delivery combined with bilateral

capnography allows the assessment of the potential collateral gas flow between the two lungs with different time constants.

Data acquisition

Data epochs containing 30-s registrations of airflow and pressure signals of each test lung were digitized at a sampling rate of 256 Hz and recorded via a custom-made data acquisition software. The time-series datasets were analysed by using the LabChart software (version 7, ADInstruments, Sydney, Australia). The peak inspiratory (PIF) and expiratory flow rates (PEF), and the peak inspiratory pressure (Ppi) were determined via peak analyses. Tidal volumes (V_T) for each lung were calculated by integrating the corresponding V' signals. Respiratory parameters characterising both lungs together were registered from the display of the respirator. Values of V_T , PIF, PEF, Ppi and $P_{et}CO_2$ were averaged over the 30-s measurement period; since the bench test results were highly reproducible, the scatters in the parameters were negligible (coefficient of variation $<0.7\%$).

Simulation study

A mathematical simulation study was performed to assess the magnitude of the resistance necessary to counterbalance the decreased compliance on the contralateral side to meet the clinical need of delivering equal tidal volumes to both patients connected to the splitted ventilation circuit. The simulation was based on the postulation that equal tidal volumes are delivered to both lungs if the absolute values of the loading impedances are identical, even if the resistive and elastic components are different on the two sides.

Measurement protocol

The first set of data were collected in a system with intact test lungs possessing identical compliance and resistance parameters. Under this baseline condition (BL), volume-control mode with decelerating flow (Drager Autoflow®) was applied with a total V_T of 840 ml divided into 420 ml on each side. The end-expiratory pressure (PEEP) was set to 5 cmH₂O and the resulting Ppi was 22 cmH₂O. Mechanical parameters of ventilation (V_T , PIF, PEF and Ppi) were measured in parallel for each lung side. $P_{et}CO_2$ values were registered alternately in each lung by clamping the contralateral limb of CO₂ tubing to avoid shunting of CO₂ delivery to the lung side with lower loading impedance. After completing these baseline measurements, the compliance was compromised with placing the elastic rubber band around one of the test lungs. In this unilateral low-compliance condition (LC), the same measurements were carried out as in condition BL. To counterbalance the decreased compliance on the low compliance side, the

resistance was then adjusted with the Hoffmann in this high-resistance condition (HR) as in the BL stage.

The ventilation was then changed to pressure-controlled mode. The pressure control level was set to maintain the same V_T as in the volume-control mode, i.e. 22 cmH₂O. Another set of BL data with symmetrical lungs and under Low C condition were then collected identical to the volume-control mode. In the third phase of the measurement when high compliance on one side was associated with high resistance on the other side, the pressure control level was elevated to 29 cmH₂O to provide physiological V_T and PetCO₂ in both model lungs.

Study II.: Obesity and diabetes: similar respiratory mechanical, but different gas exchange abnormalities

Ethical considerations

The study protocol was approved by the Human Research Ethics Committee of University of Szeged, Hungary (no. WHO 2788), and the patients gave their informed consent to participate in the study. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study followed the applicable CONSORT guidelines.

Patients and study groups

This was a prospective study that enrolled 177 patients who underwent elective cardiac surgery (trial registration No. NCT03768973). Patients were assigned into four groups based on the metabolic status. Study subjects with body mass index (BMI) <30 kg/m² were divided into the control non-diabetic (C-N, n=73) and diabetic (D-N, n=31) groups. Obese patients (BMI ≥30 kg/m²) were divided according to the presence (D-O, n=30) or absence (C-O, n=43) of diabetes. T2DM was defined if the medical history of the patient included a diagnosis of T2DM and/ or the haemoglobin A1c (HbA1c) level was >6.4%. The following exclusion criteria were applied for this study: older than 80 years of age, poor ejection fraction (<40%), and medical history of smoking or chronic obstructive pulmonary disease (COPD).

Anaesthesia and patient monitoring

One hour before the surgery, patients were premedicated with lorazepam (*per os*, 2.5 mg). Anaesthesia was induced by intravenous (iv) administration of midazolam (30 µg/kg), sufentanil (0.4–0.5 µg/kg), and propofol (0.3–0.5 mg/kg) and was maintained with iv propofol (50 µg/kg/min). Neuromuscular blockade was ensured by intravenous boluses of rocuronium

(0.8 mg/kg for induction and 0.2 mg/kg every 30 minutes for maintenance). Endotracheal intubation was performed using a cuffed endotracheal (ET) tube with an internal diameter of 7, 8, or 9 mm. Patients were mechanically ventilated (Dräger Zeus, Lübeck, Germany) in volume-controlled mode with a tidal volume of 7 ml/kg and a positive end-expiratory pressure of 4 cmH₂O with decelerating flow. The ventilation frequency was adjusted to 12–14 breaths/min to achieve an end-tidal carbon dioxide partial pressure of 36–40 mmHg and the fraction of inspired oxygen was maintained at 0.5 during the study period. As a standard part of the cardiac anaesthesia procedure, oesophageal and rectal temperature probes were introduced, and a central venous line was secured in the right jugular vein. The left radial artery was also cannulated for monitoring systolic, diastolic and mean arterial blood pressures and taking arterial blood gas samples.

Recording and analyses of the volumetric capnogram

Changes in the CO₂ partial pressure in the exhaled gas during mechanical ventilation were measured with a calibrated mainstream capnograph (Capnogard Model 1265, Novamatrix, Andover, MA). The measured 15-second long signals were digitized at a sampling rate of 102.4 Hz, stored on a computer and analysed with a custom-made software, as detailed previously.

The slopes of phase III of the time (S3T) and volumetric (S3V) capnograms were determined by fitting a linear regression line to the last 60% of phase 3 both on the time and volumetric capnograms, respectively (8). S3T expresses the change in the partial CO₂ pressure of the exhaled gas per unit time [mmHg/s] and S3V per unit in the exhaled gas volume (mmHg/l).

Ventilation dead space parameters were calculated from the volumetric capnograms and their values were related to the V_T. The anatomical dead space according to Fowler (V_{DF}), the physiological dead space according to Bohr (V_{DB}), and Enghoff dead space (V_{DE}) were calculated. Difference between V_{DE}-V_{DB} were calculated as a surrogate of the intrapulmonary shunt.

Measurement protocol

Before starting the surgical procedure, the measurements were carried out on the mechanically ventilated patients under general anaesthesia and muscle relaxants. After securing the invasive and non-invasive monitoring equipment, lung recruitment was performed to standardize the volume history by inflating the lungs to an intratracheal pressure of 30 cmH₂O. A five-minute period was then allowed to reach steady-state hemodynamic and respiratory mechanical

conditions while the PEEP was maintained at a level of 4 cmH₂O. Arterial and central venous blood gas samples were taken, and the R and C were registered from the display of the respirator. Registration of at least two technically acceptable capnogram curves in 1 min intervals was also performed.

Statistical analyses

For numerically reported data, the scatters in the measured variables are expressed as the half width of the 95% confidence interval for the mean. The normality of the data was tested with the Shapiro–Wilk test. Two-way analysis of variance (ANOVA) with factors of diabetes and obesity was used to assess the effects of these disorders on the measured variables. The Holm–Sidak multiple comparison method was used to test pairwise differences between the protocol groups. Sample sizes were estimated to enable detection of a clinically relevant 25% difference in the primary outcome parameter, the airway resistance. Accordingly, sample size estimation based on an ANOVA test with four groups of patients indicated that at least 28 patients were required in each group to detect a statistically significant difference between the protocol groups, with assumed variability of 10%, power of 80%, and a significance level of 5%. The statistical tests were performed with a SigmaPlot statistical software package (Version 13, Systat Software, Inc. Chicago, IL, USA), with a significance level of $p < 0.05$. All reported p values were two-sided.

RESULTS

Study I.: Use of capnography to verify emergency ventilator sharing in the COVID-19 era

Compliance parameters displayed by the ventilator during the measurements in volume- (VC) and pressure-controlled (PC) ventilation modes, and the calculated time constant ($\tau = R \cdot C$) were registered. Readings were made under baseline conditions (BL), after unilateral decrease in compliance (LC) and contralateral compensation with high resistance (LC + HR). To assess the level of asymmetry in the mechanical parameters, individual compliance values were calculated by using the measured individual tidal volumes and distending pressures on each side. Estimation of individual resistances characterizing each side were based on equation.

Under baseline conditions, the curves obtained on two lung sides overlap, indicating no difference in the mechanical properties between the two test lungs. After compromising the compliance unilaterally (condition LC), the reduced VT on the stiffer lung side was associated with an increased VT on the other side without intervention. Consequently, the PetCO₂ became higher in the lung with low compliance and reduced on the reference side. Following the

contralateral elevation of resistance, the V_T and $PetCO_2$ values were re-equilibrated, whereas the flow pattern exhibited marked differences with restrictive and obstructive flow patterns on the Low C and High R sides, respectively. The plateau pressure levels elevated stepwise after each intervention, with no difference between the two communicating sides.

Under baseline conditions (BL), the V_T was equally distributed between the two model lungs, with no difference between the capnographic and mechanical parameters both in volume- and pressure-control modes. The unilateral decrease in compliance in volume control mode resulted in an uneven distribution of V_{TS} with lower volume on the interventional side and elevated V_T on the intact model lung. These volume differences were also manifested in the $PetCO_2$ asymmetry. The decrease in global compliance caused elevations in P_{pi} equally on both sides. Unilateral stiffening during pressure-control ventilation decreased V_T and increased $PetCO_2$ on the restricted side, whereas the intact side remained at the baseline level determined by the constant driving pressure level. Counterbalancing the lung restriction contralaterally with an increased flow resistance redirected the ventilation to the stiffer lung. This intervention led to different airflow profiles between the two sides (PIF, PEF) redistributing the mechanical ventilation as evidenced by the normalized V_T and $PetCO_2$ levels on both sides. These effects are uniform in volume- and pressure-controlled ventilation modes, however the P_{pi} need to be increased intentionally in pressure-controlled mode.

The results of the mathematical simulation show the resistance values necessary to counterbalance the asymmetry in compliance values to deliver the same tidal volumes to both patients connected to the splitted ventilation circuit. The compliance values of the two ventilated sides are indicated on the labelled curves and the x-axes, and the targeted contralateral resistance values can be read from the y-axes.

Study II.: obesity and diabetes: similar respiratory mechanical, but different gas exchange abnormalities

The study groups had no differences in height, age, and ejection fraction. As expected, body weight and body mass index (BMI) were significantly higher in the obese patients than in non-obese patients ($p<0.001$). Elevated levels of serum glucose ($p<0.001$) and HbA1c ($p<0.001$) were observed in patients with diabetes.

Diabetes had no statistically significant effect on R regardless of the presence of obesity. However, obesity elevated R significantly in the patients without diabetes ($p<0.005$), with no

such effect detectable in the presence of diabetes. Obesity caused significant diminishment of C in diabetic and non-diabetic patients ($p < 0.005$ for both). Diabetes had a significant effect on C only in the patients without obesity ($p < 0.005$).

Shape factor and dead space parameters obtained by capnography: significantly elevated levels of S3T and S3V were obtained for patients with T2DM alone ($p < 0.05$ for both). On the other hand, diabetes had no significant effects on the ventilation dead space parameters or intrapulmonary shunt ($V_{DE} - V_{DB}$). Both time domain and volumetric phase 3 slope parameters were significantly greater in obese patients than in non-obese patients ($p < 0.001$ for S3T and S3V), whereas V_{DF} ($p < 0.001$) and V_{DB} ($p < 0.001$) decreased with obesity. Obesity had no effect on the V_{DE} , but it significantly increased the $V_{DE} - V_{DB}$ ($p < 0.005$).

The presence of diabetes had no significant effects on PaO_2/FiO_2 and Qs/Q_t . Conversely, obesity significantly diminished PaO_2/FiO_2 and Qs/Q_t ($p < 0.001$ for both).

DISCUSSION

Beyond the well-established indications of capnography in airway and ventilation management, we extended the field of indication of this monitoring modality to unique emergency clinical situations as well as to reveal cardiorespiratory pathologies in diabetic and/or obese patient population. Our capnographic assessments demonstrated the potential for adequate gas exchange during emergent shared ventilation with no collateral airflow between the split sides, even in the case of great differences in mechanical load. In another study on a large cohort of mechanically ventilated patients, the separate effects of diabetes and obesity on lung ventilation and ventilation–perfusion matching were characterised. Diabetes had no effect on the total respiratory resistance and decreased respiratory system compliance. These mechanical abnormalities were associated with an elevated capnographic phase III slope. A remarkable finding of this study is that these adverse mechanical and ventilatory changes in diabetes did not result in pathologic gas exchange, in terms of ventilation dead space, intrapulmonary shunting or lung oxygenation index. Obesity caused similar detrimental changes in respiratory mechanics and alveolar heterogeneity; however, these alterations were reflected in the compromised gas exchange.

Study I.: Use of capnography to verify emergency ventilator sharing in the COVID-19 era

A problem-oriented attitude motivated the concept of ventilator sharing as a life-saving manoeuvre, meaning that one apparatus may be used to ventilate multiple lungs. However, ventilator splitting between two patients raises several concerns needing clarification before this approach can be considered in clinical settings. A notable challenge arises from the fact, that the simultaneously ventilated individuals may differ in their respiratory mechanics due to the asymmetry in anthropologic features and/or severity of their respiratory symptoms. The feasibility of solving this problem was recently demonstrated, where low compliance in one side was counterbalanced by an elevation of flow resistance contralaterally. In the current bench-test study, we also confirmed the validity of this concept. Given the fact that individual tidal volumes are distributed equally if the magnitude of the input impedances are equal, we offered a quick simulation-based algorithm for ensuring equal tidal volumes by overcoming differences in respiratory mechanics. It is important to note, however, that the patients may differ in their metabolic rates and diffusion capacities. Thus, equal distribution of tidal volumes does not guarantee adequate ventilation on both sides. Consequently, an additional monitoring modality is mandatory to verify the adequacy of ventilation in both individuals. Therefore, we implemented capnography as a simple, non-invasive, online and bedside method for controlling the adequacy of ventilation. Since the expiratory capnogram reflects alveolar ventilation, capillary gas diffusion, and lung perfusion, this monitoring tool allows the assessment of the adequacy of ventilation individually in a goal-oriented manner. Indeed, the results of the present study confirmed that diminished V_T resulting from mechanical asymmetry was associated with hypercapnia in the low compliance side. This can be attributed to the maintained CO_2 production in a smaller gas compartment. Our findings demonstrate that capnography serves as a safe control modality to individualize the redirection of V_T into the stiffer side. Ventilation with circuit splitting may generate a further concern related to the potential collateral bias flow between the patients. However, the pressure regimen during the ventilation cycle did not differ between the two sides independent of the ventilation mode. The lack of difference in the driving pressure at any point in time of expiration rules out the presence of collateral gas flow. The cross-breathing can also be excluded by the capnographic findings, i.e. there was no detectable CO_2 in one lung side when the CO_2 inflow was driven only into the other lung. The compliance values of the model lungs with baseline compliance values of 27 ml/cmH₂O used in the current bench-test mimic diseased lungs restricted by virus pneumonitis. When asymmetry was generated, differences in the compliance values nearly doubled. This condition resembles to a splitted ventilation of a moderately and a severely injured lung. Redirection of airflow by

increasing resistance on the higher compliance side compromised lung emptying, which was indicated by the distortion of the expiratory flow curve. Following the application of this mechanical load, the flow pattern approached zero by the end expirations. Further need for such compensation in resistance may evoke incomplete lung emptying and thereby induce dynamic hyperinflation on the high-compliance high-resistance side. This finding points to the limitation of the volume-shifting methodology by unilateral resistance manipulation. The results of this study also revealed the differences between the volume- and pressure-controlled ventilation modes to optimize ventilation parameters in a split system. In the case on volume-controlled ventilation, the opposite changes in V_T and $P_{et}CO_2$ were observed between the two sides. However, using the pressure-controlled mode affected only the manipulated side. It is of note that the pressure-control level determining the P_{pi} has to be elevated to counteract the resistive load used to shift V_T into the stiff side.

Study II. Obesity and diabetes: similar respiratory mechanical but different gas exchange defects

Effects of diabetes on respiratory function

While markedly increased airway resistance was obtained in patients with diabetes, regardless of the presence of obesity, this airway abnormality was not apparent from the global resistive parameter displayed by the ventilator. This seemingly controversial result can be explained by the involvement of significant components in R not specific to changes in airway geometry, such as flow-resistance of the ET-tube and the instrumental tubing, and resistance of the respiratory tissues. Interestingly, the deteriorations in respiratory mechanics in diabetic patients were not followed by adverse alterations in gas exchange parameters, such as ventilation dead space obtained by volumetric capnography, or in blood gas outcomes that reflect lung oxygenation and intrapulmonary shunting. The underlying mechanisms responsible for the maintained gas exchange despite the compromised respiratory mechanics were not entirely clear. Patients with diabetes are prone to enhanced general vasoconstrictive responses due to endothelial dysfunction. This pathology is supposed to be present in an enhanced pulmonary vascular contractility in a hypoxic tissue environment (i.e. hypoxic pulmonary vasoconstriction). In this population, more rigorous and effective redirection of intrapulmonary blood into the ventilated lung regions may occur subsequently, thereby, reducing ventilation–perfusion mismatch. This relatively effective compensatory mechanism was supported by the lack of difference between the indices of intrapulmonary shunt expressed by capnography ($V_{DE}-V_{DB}$) and blood gas (Q_s/Q_t).

Effects of obesity on respiratory function

In the present study, obesity as a potential confounding factor was assessed separately from diabetes to gain distinct insights into the respiratory consequences of these common pathologies. This approach revealed identical direction and comparable magnitudes of changes in the respiratory mechanical parameters (R and C), and alveolar heterogeneity in obesity and diabetes. The respiratory mechanical changes in obesity were in accordance with previous results that demonstrated impaired respiratory resistance and tissue compliance and inhomogeneous lung emptying in obese patients. The underlying mechanisms responsible for such mechanical changes in obesity are markedly different from those in diabetes, and primarily involve the development of regional atelectasis and lung volume loss, which are caused by the external mechanical load exerted by the cranial displacement of the diaphragm.

Unlike in diabetes, the decline in respiratory mechanics in obesity was reflected in compromised gas exchange. The somewhat smaller anatomical dead space (V_{DF}) may be attributed to compression of the lung parenchyma, which leads to loss of gas volume in the conducting airways. The slightly reduced physiological (V_{DB}) dead space in obese patients can be explained by the cranial shift of the lung and the heart, resulting in possible reduction of lung regions with West I zones. Furthermore, the reduced PaO_2/FiO_2 in obese patients demonstrates the compromised oxygenation ability of the lung, which is consistent with abnormal pulmonary vascular contractility.

SUMMARY AND CONCLUSIONS

The extended application area of capnography was verified in a bench test study and clinical investigation.

The in vitro study involving artificial lungs with different mechanical properties gave insight into the uneven ventilation distribution driven by the markedly altered resistive and/or elastic properties of the individual sides. These findings contributed to a better understanding of ventilation heterogeneities in a lung, including compartments with different time constants.

Due to the high reproduction number of SARS-CoV-2 virus, there may be a sudden increase in the number of patients requiring mechanical ventilation. This can lead to an acute shortage of ventilators in critical care. Using capnography in Study I., we demonstrated that the adequacy of ventilator splitting can be verified. However, ventilator splitting can only be considered as a

rescue intervention to provide adequate tidal volumes without collateral airflow for two subjects with different respiratory systems. Our experimental results support that this split ventilation modality can be applied without the risk of diminishing patient safety if emergencies arise due to temporal shortages of mechanical ventilators. Therefore, the risk of non-ventilation is higher than that of controlled shared ventilation in terms of morbidity. Moreover, goal-oriented capnography can serve as a bedside approach to ensure the adequacy of tidal volumes on both lungs during this life saving intervention. Capnography as a routinely available monitoring modality may help in emergencies (i.e. in pandemics or combat hospitals) when there is a lack of equipment and/or health care professionals. From this aspect, ventilator sharing can be regarded as a lifesaving manoeuvre in catastrophe medicine. This alternative may have importance during the exacerbation of an upcoming epidemic wave, or devastating war-related tragic events when intensive care specialists may be faced with a shortage of ventilators.

Study II. demonstrated that, diabetes affects airway function and the elastic properties of the respiratory tissues, leading to ventilation heterogeneities. This inhomogenous alveolar emptying was confirmed by capnography showing an elevated phase III slope. These intrinsic mechanical and ventilation abnormalities in diabetes were counterbalanced by the increased contractile response of the pulmonary vasculature to hypoxic stimuli, which was able to maintain the normal intrapulmonary shunt fraction and oxygenation ability of the lungs. On the other hand, obesity similarly deteriorated the global respiratory mechanics, and the external trigger worsened gas exchange. The simultaneous presence of diabetes and obesity had additive effects on the worsened respiratory resistance. This synergistic effect may be related to the combination of the external mechanical overload exerted by the upward shift of the diaphragm in obesity, and the enhanced susceptibility of the alveoli to collapse subsequent to type II pneumocyte dysfunction in the presence of diabetes secretion. These pathophysiological changes highlight the importance of lung protective ventilation with high PEEP and low V_{TS} not only in obesity, but also in patients with diabetes.

Taking together the findings of the two studies may have clinical relevance. Since a high proportion of the critically ill COVID-19 patients are diabetic and/or obese, detailed information obtained by capnography may help to optimize mechanical ventilation in the case of a necessity for shared ventilation in a population overwhelmed by diabetic and/or obese patients.

AKNOWLEDGEMENT

I would like to express my gratitude to my supervisors, Barna Babik and Ferenc Peták for introducing me to clinical research. I greatly appreciate the opportunities they provided to me. I thank the colleagues at my workplace, the Department of Anaesthesiology and Intensive Therapy for facilitating my work.

I would like to thank Laura Lászik for her contributions in reviewing the english version.

I am grateful to my family for their continuous encouragement.

List of scientific papers included in this thesis

Study I.

Korsós A, Peták F, Südy R, Schranc Á, Fodor GH, Babik B. Use of capnography to verify emergency ventilator sharing in the COVID-19 era. *Respir Physiol Neurobiol.* 2021; 285: 103611. doi: 10.1016/j.resp.2020.103611. [IF: 2.821]

Study II.

Südy R, Peták F, Kiss L, Balogh ÁL, Fodor GH, **Korsós A**, Schranc Á, Babik B. Obesity and diabetes: similar respiratory mechanical but different gas exchange defects. *Am J Physiol Lung Cell Mol Physiol.* 2021; 320: L368-L376. doi: 10.1152/ajplung.00439.2020. [IF: 6.011]

List of scientific papers related to the thesis

Korsós A, Kupcsulik Sz, Lovas A, Hankovszky P, Molnár T, Szabó Zs, Babik B. Diagnostic consideration and bedside estimation of the prognosis in COVID-19 patients. *Orv. Hetil.* 2020; 161: 667- 671. doi: 10.1556/650.2020.31815. [IF: 0.540]

Wendel Garcia PD, Aguirre-Bermeo H, Buehler PK, Alfaro-Farias M, Yuen B, David S, Tschoellitsch T, Wengenmayer T, **Korsós A**, Fogagnolo A, *et al.* (RISC-19-ICU Investigators): Implications of early respiratory support strategies on disease progression in critical COVID-19: a matched subanalysis of the prospective RISC-19-ICU cohort. *Crit Care* 2021; 25, 1752. doi: 10.1186/s13054-021-03580-y [IF: 19.346]

Kovács BN, Südy R, Peták F, Balogh ÁL, Fodor HG, Tolnai J, **Korsós A**, Schranc Á, Lengyel C, Babik B. Respiratory consequences of obesity and diabetes. *Orv. Hetil.* 2022; 163: 63-73. doi: 10.1556/650.2022.32335. [IF: 0.707]

Lovas A, Hankovszky P, **Korsós A**, Kupcsulik S, Molnár T, Szabó Z, Babik B. Importance of the imaging techniques in the management of COVID-19-infected patients. *Orv. Hetil.* 2020; 161: 672-677. doi: 10.1556/650.2020.31814. [IF: 0.540]