EXTENDING THE DIAGNOSTIC VALUE OF CAPNOGRAPHY IN VENTILATED PATIENTS

Ádám László Balogh MD

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Department of Anaesthesiology and Intensive Therapy
University of Szeged, Hungary

Doctoral School of Multidisciplinary Medical Sciences

Supervisor: Barna Babik

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List of scientific papers included in this thesis

I. Balogh AL, Petak F, Fodor GH, Tolnai J, Csorba Z, Babik B. Capnogram slope and ventilation dead space parameters: comparison of mainstream and sidestream techniques. *Br J Anaesth* 2016; **117**: 109–17.

II. Balogh AL, Petak F, Fodor GH, Sudy R, Babik B. Sevoflurane relieves lung function deterioration following cardiopulmonary bypass. *J Cardiothorac Vasc Anesth.* 2017; *(Epub ahead of print)*

List of related but not included scientific papers

III. Csorba Z, Petak F, Nevery K, Tolnai J, Balogh AL, Rarosi F, Fodor GH, Babik B.: Capnographic Parameters in Ventilated Patients: Correspondence with Airway and Lung Tissue Mechanics. *Anaesth Analg.* 2016; **122**: 1412–20.

1. Introduction

1.1 The current applications of capnography

Capnography is a non-invasive, continuous, analysis of the exhaled carbon dioxide (CO_2) partial pressure, an essential monitoring modality for the improvement of patient safety in anaesthesia and intensive therapy. While the assessment of capnogram shape factors is not standard part of the patient monitoring yet, they have the promise to possess routine information on airway patency, lung recoil tendency, ventilation-perfusion matching and the metabolic status of the body.

In clinical practice, two techniques are available based on the measurement site of CO_2. Mainstream capnography applies an infrared sensor located proximally to the patient between the tracheal tube and the Y-piece and thus, allows a rapid and accurate analysis of the CO_2 partial pressure of the exhaled gas. This method has the disadvantages posed by the potential local heating of the head, and the weight of the sample cell increasing the risk of tracheal tube dislocation. As an alternative, sidestream capnography is often used in the operating theatre because it is easily manageable and allows the monitoring of other gases. These devices analyse the gas sample distally from the patient, and therefore have the drawbacks of a prolonged total response time, the occurrence of axial mixing and a variable suction flow rate. All these processes result in a dynamic distortion of the CO_2 partial pressure curve and thus, have a potential to bias the derived capnographic parameters.

There have been a few previous attempts to compare capnographic parameters obtained by sidestream and mainstream techniques, but they were either manufacturer’s educational material, focused only on the end-tidal CO_2 value in experimental and clinical studies, or were limited to a small cohort of infants. However, there is a lack of information about the relationship between capnographic indices obtained by sidestream and mainstream techniques in mechanically ventilated adults.

1.2 Respiratory effects of sevoflurane

The bronchodilator activity of volatile anaesthetics against an elevated bronchial tone caused by exogenous constrictor agonists has been consistently proved in experimental studies and clinical investigations. Another relevant trigger of perioperative bronchoconstriction is cardiopulmonary bypass (CPB) applied during open-heart surgery. The use of this technique induces well-described multimodal detrimental changes in the lungs involving interstitial oedema and bronchoconstriction.

The effects of sevoflurane on lung function have been investigated extensively in humans as well as in animal models. However, in these studies simple bronchial challenges were applied, mainly inducing specific bronchoconstriction of cholinergic or histaminergic origin. While the beneficial pulmonary profile of sevoflurane following CPB can be anticipated, its effect on lung functional changes, particularly increased interstitial oedema and ventilation heterogeneity after this complex stimulus have not been investigated.

2. Aims and hypotheses

The studies included in the present thesis aimed at extending the monitoring and diagnostic value of capnography. For this purpose, we investigated the accuracy of the easier accessible, more widespread sidestream technique in the estimation of capnogram parameters. To assess the applicability of capnography for the qualitative monitoring in a clinical model of rapidly developing pulmonary mechanical and functional deteriorations, we simultaneously measured respiratory mechanics, oxygenation and ventilation heterogeneity in a large cohort of patients intraoperatively. The specific aims of the studies included in the present thesis were:

- to validate the ability of the sidestream technique to provide adequate quantitative bedside information about uneven alveolar emptying and ventilation-perfusion mismatch;
- to determine which capnogram parameters (shape factors, respiratory dead spaces) can be reliably assessed by applying the sidestream technique by comparing the sidestream outcomes to those obtained by a mainstream technique as a reference;
- to assess the effect of respiratory compliance on the accuracy of the sidestream capnography measurement;
- to examine the effects of sampling flow and sampling tube length on the accuracy of sidestream measurement;
- to assess adverse alterations in airway and lung tissue mechanics, ventilation heterogeneity, ventilation-perfusion matching and gas exchange induced by CPB, and to estimate the potential of sevoflurane to reverse these detrimental changes.

We hypothesized that sidestream capnography is suitable to measure indices obtained from the quasi-static phases of the capnogram, whereas phases with transient CO_2 partial pressure changes are exposed to the measurement bias. We also postulated that after deleterious lung function changes to CPB, the expected bronchodilation by sevoflurane is associated with improvements in lung tissue viscoelasticity and diminished ventilation heterogeneities, which may enhance oxygenation.

3. Methods

3.1 Patients

The study protocols were approved by the Human Research Ethics Committee of the University of Szeged, Hungary (no. WHO 2788). Patients undergoing elective open-heart surgery were enrolled in the studies. Written informed consent was obtained from each patient. Patients with severe cardiopulmonary disorders (pleural effusion>300 ml, ejection fraction<30%, endocarditis, BMI>35 kg/m^2 or intraoperative acute asthma exacerbation) were excluded.

In Study I, twenty-nine patients (female/male: 13/16, 71 (57–85) yrs) were enrolled in a prospective consecutive manner.

In Study II, patients were randomly assigned to the sevoflurane group (SEV) or the control group (CTRL). Measurement data of one hundred and ninety patients (SEV: n=99, CTRL: n=91; 107 males, 83 females, 63 yrs of age (range 32–85 yrs)) were included in the analysis.

3.2 Anaesthesia and surgery

Anaesthesia was induced with intravenous midazolam (30 μg/kg), sufentanil (0.4-0.5 μg/kg) and propofol (0.3–0.5 μg/kg), and was maintained by an intravenous propofol infusion (50 μg/kg/min). Neuromuscular blockade was achieved by intravenous boluses of rocuronium (0.2 mg/kg every 30 min).

After tracheal intubation with a cuffed tracheal tube with an internal diameter of 7, 8 or 9 mm was achieved, the patients' lungs were mechanically ventilated in volume-controlled mode with descending flow by setting the tidal volume to 7 ml/kg, the ventilator frequency to 9–14 breaths per minute, and the positive end-expiratory pressure (PEEP) to 4 cmH_2O. The fraction of inspired oxygen (F_{iO_2}) was set to 0.5 before CPB and 0.8 after CPB.

3.3 Recording and analyses of the expiratory capnogram

Simultaneous 15-s recordings of the CO_2 signals of the mainstream and sidestream capnographs and the ventilation flow were digitized (sampling frequency 102.4 Hz) and analysed with custom-made software. Volumetric capnograms were constructed from the time capnograms and the integrated flow data.

The slopes of phase II ($S_{II,T,SS}$ and $S_{II,V,SS}$) and III ($S_{III,T,MS}$ and $S_{III,V,MS}$)of the time and volumetric capnograms determined by mainstream and sidestream capnography were assessed by linear regression.

Fowler dead space was determined by taking the volume expired up to the inflexion point of phase II from the mainstream and sidestream capnograms ($V_{DF,MS}$ and $V_{DF,SS}$). The physiological dead space according to Bohr ($V_{DB,MS}$ and $V_{DB,SS}$) reflecting the alveolar volume with decreased or no perfusion was calculated from the mainstream and sidestream capnograms as: $V_{DB,MS}/V_T = (P_{ACO_2,MS} – P_{\bar{E}CO_2,MS})/P_{ACO_2,MS}$ and $V_{DB,SS}/V_T = (P_{ACO_2,SS} – P_{\bar{E}CO_2,SS})/P_{ACO_2,SS}$

where $P_{ACO_2,MS}$ and $P_{ACO_2,SS}$ are the mean alveolar partial pressures of CO_2, determined from the midpoint of phase III in the mainstream and sidestream capnograms respectively. $P_{\bar{E}CO_2,MS}$ and $P_{\bar{E}CO_2,SS}$ are the mixed expired CO_2 partial pressure, obtained by calculating the area under the mainstream and sidestream volumetric capnogram curves via integration and dividing the resulting values by V_T.

Enghoff's approach contains all ventilation-perfusion mismatch. Hence, besides the V_{DB}, it also incorporates the intrapulmonary shunt, i.e. the alveolar volume with decreased or even loss of ventilation with perfusion maintained:

$V_{DE,MS}/V_T = (P_{aCO_2} – P_{\bar{E}CO_2,MS})/P_{aCO_2}$ and $V_{DE,SS}/V_T = (P_{aCO_2} – P_{\bar{E}CO_2,SS})/P_{aCO_2}$, where P_{aCO_2} is the partial pressure of CO_2 in the arterial blood.

Additionally we calculated the normalized differences between the Enghoff and Bohr dead spaces obtained by mainstream ($V_{s,MS}/V_T = [V_{DE,MS} – V_{DB,MS}]/V_T$) and sidestream capnography ($V_{s,SS}/V_T = [V_{DE,SS} – V_{DB,SS}]/V_T$), which reflects the all the mixed venous blood entering the arterial system. These include Thebesian veins, part of the bronchial veins and intrapulmonary shunt circulation, i.e. the virtual gas volume of the alveolar units with perfusion with decreased or no ventilation. The amount of the CO_2 exhaled during each expiration was calculated as the area under the volumetric CO_2 partial pressure curve obtained by mainstream ($V_{CO_2,MS}$) and sidestream ($V_{CO_2,SS}$) capnography.

3.4 Forced oscillatory measurements

Changes in the airway and tissue mechanical properties from CPB and sevoflurane were assessed by measuring the low-frequency forced oscillatory input impedance of the lungs. The mean lung impedance data were fitted by a well-validated 4-parameter model containing a frequency-independent airway resistance (Raw) and inertance (Iaw) and a constant-phase tissue compartment characterized by the coefficients of damping (G) and elastance (H) such that the difference between measured and modelled impedance values were minimal. Lung tissue hysteresivity was calculated as $\eta = G/H$. Raw represents the flow resistance of the bronchial tree, and Iaw is related to the mass of the gas in the airways. The tissue parameters characterize the resistive (G) and elastic properties of the lung parenchyma (H), while η reflects the coupling between the resistive and elastic properties.

3.5 Blood gas analysis

The partial pressure of oxygen in the arterial blood (P_{aO_2}) was determined from arterial blood gas samples for the P_{aO_2}/F_{iO_2} ratio and the arterial to end-tidal CO_2 gradient ($P_{a\text{-}ETCO_2}$). The intrapulmonary shunt fraction (Q_s/Q_t) was determined by means of the Berggren equation: $Q_s/Q_t = (C_{cO_2} – C_{aO_2})/(C_{cO_2} – C_{vO_2})$, where C_{cO_2}, C_{aO_2} and C_{vO_2} are the oxygen contents of the pulmonary capillary and arterial and central venous blood, respectively. C_{cO_2} was calculated per the alveolar gas equation, assuming the O_2 saturation of haemoglobin in the pulmonary capillaries to be 100%: $C_{cO_2} = 1.34\ \text{ml/g} \cdot \text{Hb} + \text{Sol} \cdot (F_{iO_2} \cdot 713\ \text{mmHg} – P_{aCO_2}/0.8)$, where 1.34 ml/g is Hüfner’s constant, Hb is the haemoglobin concentration in g, Sol is 0.0031 ml/100 ml/mmHg, 713 mmHg is the total dry gas pressure, P_{aCO_2} is the partial pressure of CO_2 in the arterial blood, and 0.8 is the respiratory exchange ratio.

3.6 Measurement protocol

3.6.1 Measurement protocol of Study I

Eight 15-s traces were recorded per patient (approximately 20 pairs of expirations). For the assessment of P_{aCO_2}, arterial blood gas samples were taken under each measurement condition, and the resistance (R) and compliance (C) values displayed by the ventilator were also registered.

3.6.2 Measurement protocol of Study II

When stable hemodynamic and respiratory mechanical conditions had been reached after sternotomy, baseline measurements were performed 5 min before starting CPB. Measurements included recordings of four 15-s capnogram traces, analyses of arterial and central venous blood gas samples, registration of the dynamic respiratory compliance displayed by the ventilator (C) and collection of four impedance data epochs. The same set of data was gathered 5 min after weaning from CPB, when stable circulatory and ventilator conditions were re-established. Subsequently, in group SEV, 1 age-related minimal alveolar concentration (MAC), of sevoflurane was administered for 5 minutes. Ventilation was maintained without intervention in the patients in group CTRL for a matching period. The third data collection step was taken in the same manner as detailed earlier in both groups of patients.

4. Results

4.1 Comparison of mainstream and sidestream capnography

The difference in mainstream and sidestream P_{ETCO_2} was small, although statistically significantly higher with the former technique ($p<0.001$). The V_{CO_2} was systematically underestimated by the sidestream method ($p<0.0001$), despite the presence of good correlation between these variables ($R^2=0.91$, $p<0.0001$). An excellent correlation ($R^2=0.92$, $p<0.0001$) and good agreement were observed between $S_{III,T,MS}$ and $S_{III,T,SS}$, although the sidestream method slightly but significantly overestimated $S_{III,T}$ ($p<0.0001$). Strong correlation and good agreement were found between the volumetric S_{III} values ($R^2=0.93$, $p<0.0001$), with a systematic overestimation of $S_{III,V,MS}$ by $S_{III,V,SS}$ ($p<0.0001$

Although $S_{II,T,SS}$ correlates significantly with $S_{II,T,MS}$ ($R^2=0.58$, $p<0.0001$), there is no agreement between these slopes because of the substantial underestimation by the sidestream method ($p<0.0001$). A rather poor correlation and a lack of agreement were observed between the phase II slopes in the volume domain ($R^2=0.02$, $p<0.002$), with a similar underestimation by sidestream capnography ($p<0.0001$). Significant correlation but poor agreement was found between the two types of α angle ($R^2=0.89$, $p<0.0001$), with α_{SS} slightly but consistently overestimating α_{MS} ($p<0.0001$). Although $V_{DF,MS}$ and $V_{DF,SS}$ correlated moderately ($R^2=0.56$, $p<0.0001$), their agreement was rather poor, and the sidestream method overestimated the mainstream values ($p<0.0001$).

Moderate, but statistically significant correlation was found between the normalized dead space parameters $V_{DB,MS}/V_T$ and $V_{DB,SS}/V_T$ ($R^2=0.37$, $p<0.0001$), with overestimation of the mainstream Bohr dead space by the sidestream method ($p<0.0001$). In the measurement of the Enghoff dead space, the two methods exhibited good correlation ($R^2=0.61$, $p<0.0001$) and a slight overestimation by the sidestream capnograph ($p<0.0001$). Since P_{aCO_2} shows excellent agreement between the two techniques ($R^2=0.95$, $p<0.0001$), the dissociations between physiological dead space parameters can be ascribed to the discrepancies in $P_{\bar{E}CO_2}$ (R^2, $p<0.0001$). The overestimations of V_{DE} and V_{DB} by the sidestream technique resulted in a strong correlation in their difference (i.e. the lung volume with the intrapulmonary shunt; $R^2=0.92$, $p<0.0001$ between $V_{s,SS}/V_T$ and $V_{s,MS}/V_T$). This relationship was associated with good agreement between the shunt volumes, with the sidestream method only slightly underestimating the mainstream values ($p<0.0001$).

4.2 The effect of sevoflurane on respiratory mechanics and gas exchange after CPB

No significant difference was found between the protocol groups in age, height or weight. The distribution of gender, surgery types and respiratory comorbidities were independent of group allocation. The CPB-induced changes in any of the measured parameters in group CTRL were not significantly different from those in group SEV. CPB induced a significant change in all the mechanical parameters, with the most pronounced elevations in Raw, marked decreases in Iaw and increases in, while rises in H and η were smaller. Sevoflurane induced marked drops in Raw, rises in Iaw, reductions in G ($p<0.001$ for all) and moderate decreases in H and η ($p<0.02$). There was no evidence of a statistically significantly detectable change in any of the parameters in the corresponding time-matched changes in group CTRL.

The phase III slope of the capnogram exhibited markedly significant increases following CPB in both protocol groups ($p<0.0001$). After application of sevoflurane, S_{III} decreased ($p<0.02$), whereas it did not change significantly in group CTRL. No significant difference was found in S_{II} between the protocol groups at any stage ($p>0.13$). The phase II slope decreased markedly after CPB ($p<0.0001$) and increased slightly at the last stage in both groups ($p<0.02$). The changes in the P_{aO_2}/F_{iO_2} ratio, C, Q_s/Q_t and $P_{a\text{-}ETCO_2}$ subsequent to CPB did not differ significantly between the protocol groups. The P_{aO_2}/F_{iO_2} ratio and C exhibited significant decreases post CPB, while Q_s/Q_t and $P_{a\text{-}ETCO_2}$ increased ($p<0.0001$ for all). Sevoflurane reversed the decreases in the P_{aO_2}/F_{iO_2} ratio and C ($p<0.0001$ for both) and reduced Q_s/Q_t and $P_{a\text{-}ETCO_2}$ ($p<0.03$). The corresponding changes in the P_{aO_2}/F_{iO_2} ratio, C and Q_s/Q_t in group CTRL were not significant.

Sevoflurane decreased Raw in all but one patient, whereas the changes in S_{III} were far less uniform; the administration of sevoflurane resulted in further elevations in S_{III} in 36 out of 99 cases. In contrast, 28 out of the 91 patients in group CTRL exhibited further elevations in Raw during the corresponding period, and S_{III} increased in 35 cases. No statistically significant correlation was observed between the P_{aO_2}/F_{iO_2} ratio and its change after sevoflurane ($R^2=0.05$), whereas strong negative correlation was found between $P_{a\text{-}ETCO_2}$ and its change after sevoflurane ($R^2=0.51$, $p<0.001$).

Group SEV was divided into two subgroups based on the sign of the change in S_{III} (i.e. increase or decrease). After CPB, S_{III} was still lower in subgroup SEV_i than in SEV_d ($p<0.01$). The baseline C values normalized to body weight were lower in group SEV_i ($p<0.05$), whereas increments elicited by sevoflurane were greater in this group ($p<0.02$). These changes were associated with smaller changes in S_{II} ($p<0.05$) and η ($p<0.002$) in group SEV_i.

5. Discussion

5.1 Comparison of mainstream and sidestream capnography

The results of the Study I revealed that the sidestream capnography led to a dynamic distortion of the CO_2 partial pressure curve compared with the mainstream approach regarded as a reference technique. Thus, the sidestream method biased the solid indices obtained from capnogram regions in which rapid changes in CO_2 partial pressure occur (i.e. phase II slopes, the transition from phase II to III, the end-tidal portion, V_{CO_2} and derived parameters such as the Fowler and Bohr dead spaces). However, the sidestream technique does provide a good approximation of capnogram parameters characterizing periods of low rates of change in CO_2 (phase III slopes) and intrapulmonary shunt.

The differences between the sidestream and mainstream techniques can be explained by physical principles. The transport delay of the gas in the sampling tube introduces a predictable time lag in the detection of the CO_2 partial pressure, and gives rise to axial mixing of the gas residing in the sampling tube. The blurring process of axial in-line diffusion equilibrates the partial pressure differences between the gas compartments. Shortening the sampling tube (from 3 to 1.5 m) in 5 additional patients led to fairly proportional improvements in the sidestream estimates to the ratio of the tube lengths ($S_{II,T,SS}/S_{II,T,MS}$ of 37.4% and 60.2%; $V_{DF,SS}/V_{DF,MS}$ of 154.2% and 128.5% with long and short tubes, respectively). Similarly, increasing the sampling flow rate decreased the difference between sidestream and mainstream estimates ($S_{II,T,SS}/S_{II,T,MS}$ of 47% and 76%; $S_{III,T,SS}/S_{III,T,MS}$ of 146% and 99% for suction rates of 100 and 350 ml/min, respectively). These results suggest the possibility of improving the accuracy of shape factor estimates by using sidestream capnography.

A further factor contributing to the distortion of the sidestream capnogram is the variable sampling flow rate resulting from the alternating positive airway pressure during mechanical ventilation. Since this phenomenon acts during inspiratory/expiratory phase transitions, it ultimately modifies the ascending and descending limbs of the capnograms. The physical principles described above are of less importance in the assessment of the capnogram phase III slope. The reason for the good correlation and agreement is the relatively steady-state CO_2 partial pressure and constant gas sampling flow during this period. In the only previous study, where the sidestream and mainstream phase III slopes were compared, substantially greater differences were observed in infants, which can be attributed to the higher ventilation rate (~32/min).

The initial part of the capnogram comprising the phase II slopes, angle α and V_{DF}, coincides with a high rate of change in the CO_2 partial pressure and with sudden pressure alterations in the breathing circuit causing variable sampling flow rate in the tube of the sidestream capnograph. Consequently, in agreement with previous results on ventilated infants, the phase II slope of the sidestream capnogram is lower than that obtained by the mainstream technique. This drop in $S_{II,T,SS}$ of necessity infers weak relationships between the anatomic dead spaces $V_{DF,MS}$ and $V_{DF,SS}$, and the sidestream-derived α_{SS}.

The ventilation-perfusion mismatch can be divided into alveolar dead space ventilation and shunt perfusion. We obtained weak correlations and agreements of both the normalized Bohr and Enghoff dead space fractions. The correlation analyses revealed that these dissociations can be ascribed to the discrepancies in the $P_{\bar{E}CO_2}$, resulting from the dynamic distortion of the sidestream capnogram. Taking the difference between the Enghoff and Bohr dead spaces eliminates these discrepancies, which explains the excellent correlations and good agreement between $V_{s,MS}$ and $V_{s,SS}$. The differences between the two estimates in the dead space and shunt parameters depend on the level of C, with greatest deviations in patients with low compliance. Around the ventilation frequency, the respiratory system impedance is dominated by the elastic forces. Since low compliance involves higher airway pressures, variations in sampling flow rate are expected to be augmented within the respiratory cycle in the presence of increased stiffness. This implies that the use of dead space parameters determined by sidestream technique may result in false interpretations. Conversely, the assessment of the shunt fraction is feasible by using sidestream capnography, though a slight underestimation is expected in patients with a less compliant respiratory system. Our measurements demonstrate that the most frequently utilized capnogram parameter, the P_{ETCO_2}, is underestimated by a value with clinically minimal relevance (0.2 mmHg). This concordance between the two techniques supports the conclusions of previous studies.

5.2 The effect of sevoflurane on respiratory mechanics and gas exchange after CPB

The results of Study II demonstrated the ability of sevoflurane to reverse detrimental changes in lung function induced by extracorporeal circulation in a large cohort of cardiac surgery patients. Administration of sevoflurane led to marked airway dilations uniformly in almost all the patients, resulting in improved function of the lung as an oxygenator. Conversely, this beneficial profile of sevoflurane was reflected in distinctly different changes in the capnogram parameter related to ventilation heterogeneities (S_{III}). While the parameters presented improved unanimously after the administration of sevoflurane, none of them showed significant changes in group CTRL during the matching period.

5.2.1 Airway and lung tissue mechanics

Sevoflurane induced significant improvements in the airway and tissue mechanics compromised by CPB. This finding is in accordance with previous results, where the beneficial profile of sevoflurane was demonstrated against bronchoconstriction induced by exogenous cholinergic agonists or following a release of endogenous mediators. Since Raw mainly reflects the flow resistance of the central conducting airways, the marked drops in this parameter are likely to reflect the prominent dilation of proximal airway regions. A probable mechanism responsible for the improvement in tissue parameters may be due to alveolar recruitment secondary to bronchodilation and homogenization of alveolar ventilation. Accordingly, the drops in G can be explained by decreasing time constant inequalities arising from the heterogeneous constriction of small airways. Since sevoflurane induced greater drops in G than in H, their ratio η decreased after sevoflurane, supporting the notion of lung homogenization. The improved lung aeration from sevoflurane is also supported by the increases in a routinely assessed mechanical parameter reflecting overall lung tissue stiffness (C).

5.2.2 Ventilation and oxygenation

The phase III slope of the capnogram is mostly determined by the ventilation of the lungs. Accordingly, the decrement in the mean S_{III} in the present study implies the reduction of ventilation heterogeneity from sevoflurane. This result is in accordance with the beneficial lung mechanical changes, as described above.

The improvement of ventilation from sevoflurane was manifested in better ventilation-perfusion matching as reflected by the decreased Q_s/Q_t and a related, easier accessible parameter, $P_{a\text{-}ETCO_2}$. In the present study, the striking bronchodilation from sevoflurane opened shunted alveolar regions with sustained perfusion in both lungs. The resultant improvement in ventilation-perfusion matching most likely outweighed the potential loss of protective hypoxic pulmonary vasoconstriction, as reflected in the decreased Q_s/Q_t and $P_{a\text{-}ETCO_2}$. These beneficial changes ultimately resulted in better oxygenation, as reflected by the increased P_{aO_2}/F_{iO_2} ratio. A further noteworthy observation is that the higher the $P_{a\text{-}ETCO_2}$ after CPB the greater its improvement to sevoflurane. While this relationship is less apparent for the absolute changes in P_{aO_2}/F_{iO_2} to sevoflurane, this is of greater importance in patients with low P_{aO_2}/F_{iO_2} post-CPB. These findings indicate the particular benefit of sevoflurane in patients with severely compromised gas exchange.

5.2.3 Effect of sevoflurane on ventilation heterogeneity

Despite the association between airway calibre and S_{III}, the magnitude of the decrement in S_{III} following the administration of sevoflurane did not match that in Raw. While Raw decreased spontaneously in about two-thirds of the patients in group CTRL after CPB, bronchodilation was observed in all the patients in group SEV but one. Despite this uniform change in Raw in the latter group, S_{III} exhibited diverse changes, with further elevations in more than one-third of the patients. This suggests that in these cases airway dilation resulted in a more heterogeneous alveolar emptying. It is noteworthy that oxygenation was equally improved in both subgroups.

Patients in subgroup SEV_i may originally have had closed dependent lung regions and homogeneously open, less compliant areas after CPB. In these patients, administration of sevoflurane induced bronchodilation and opened some alveolar units, thus giving rise to C and P_{aO_2}/F_{iO_2}. Nevertheless, alveolar re-openings increased the heterogeneity of ventilation indicated by the rise in S_{III}, i.e., creating a cycle of unstable alveoli opening and closing. Consequently, monitoring the changes in S_{III} offers a possibility to recognize alveolar recruitment within the respiratory cycle.

6. Conclusions

In conclusion, we evidenced that the sidestream capnography allows reliable measurement of P_{ETCO_2}, time and volumetric phase III slopes, and the intrapulmonary shunt. Thus, sidestream capnography is suitable for quantification of the unevenness of the alveolar ventilation, and the ventilation-perfusion mismatch. However, the anatomical and physiological dead space parameters were considerably overestimated by the sidestream technique, especially in patients with low pulmonary compliance. Although the accuracy of sidestream capnography can be improved by increasing the sampling flow or shortening the sampling tube, these measures have limited feasibility due to patient safety and practical reasons. Therefore, reliable assessments of the phase II slope, the anatomical and physiological dead spaces, and the rate of elimination of CO_2 necessitate the combined application of mainstream volumetric capnography and sophisticated bedside information technology tools.

Furthermore, we demonstrated that bronchoconstriction with subsequent development of atelectasis and intrapulmonary shunt triggered by CPB can be effectively alleviated with the application of sevoflurane. This benefit may be of particular importance in patients with airway hyperresponsiveness, where severe bronchoconstriction is likely to develop following CPB. In such cases, switching anaesthesia management from a total intravenous approach to an inhalational technique may be recommended. The potential increase in ventilation heterogeneity after sevoflurane may necessitate the elevation of PEEP and/or applying recruitment manoeuvres.

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