SUPPLEMENTAL DIGITAL CONTENT

**CAPNOGRAPHIC PARAMETERS IN VENTILATED PATIENTS: CORRESPONDENCE WITH AIRWAY AND LUNG TISSUE MECHANICS**

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METHODS

***Patients’ characteristics***

One hundred and one patients (age range 30−88 yrs) undergoing elective open heart surgery were examined in a prospective, consecutive manner. The heart surgery was necessitated by aortic (n=70) and/or mitral (n=27) valve disease combined with ischemic heart disease (n=28), and/or other types of cardiac malformation (n=6), myxoma or aneurysm of the ascending aorta. Based on earlier medical reports, the patients exhibited wide-ranging variations in pulmonary status: some had no pulmonary symptoms (i.e. no history of lung disease, a normal BMI, no pleural effusion, no pulmonary congestion, no smoking history, no wheezing periods within the past 6 months, and no history of the use of bronchodilator drugs; n=16), whereas others had lung abnormalities causing restrictive (pulmonary congestion (n=56) and/or obesity (BMI≥31) (n=31)) and/or obstructive changes (emphysema (n=28), asthma (n=8) or chronic bronchitis (n=20)).

***Cardiopulmonary bypass***

Prior to cardiopulmonary bypass (CPB), 1500 ml of lactated Ringer’s solution was used to prime the membrane oxygenator and the tube set. Heparin (300 IU/kg) was administered with the activated anticoagulation time maintained above 400 s. At the beginning of the CPB, mild hypothermia was generally applied to maintain esophageal temperature of 32 °C. During cardioplegic cardiac arrest, the lung ventilation was stopped, the ventilator was disconnected and no positive airway pressure was maintained in the lungs. The lungs were then inflated 3-5 times to a peak airway pressure of 30 cmH2O before declamping of the aorta in order to facilitate the removal of gas emboli from the heart and to perform lung recruitment.

***Forced oscillatory measurements***

Airway and tissue mechanical properties were assessed by measuring the low-frequency forced oscillatory input impedance of the pulmonary system (ZL), as detailed previously ([1](#_ENREF_1)). The common side of a T-piece was attached to a distal ET tube. The other sides of the T-piece containing two collapsible segments were connected to the respirator and the forced oscillatory measurement apparatus. Before the oscillatory measurements, the lungs were inflated to a pressure of approximately 30 cm H2O to standardize the volume history. During short (15-s) apneic periods, this equipment allowed switching the patient from the respirator to the forced oscillatory system while pseudorandom pressure excitations were generated into the trachea. The pressure forcing signal contained 15 integer-multiple components in the frequency range 0.4-6 Hz. ZL was computed from the power spectra of the airway opening pressure (Pao) and tracheal airflow (V’). Pao was measured with a pressure transducer (ICS model 33NA002D; ICSensors, Milpitas, CA, USA), and V’ was measured with a 28-mm ID screen pneumotachograph connected to the identical pressure transducer. A well-validated 4-parameter model ([2](#_ENREF_2)) 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) was fitted to the mean ZL data by minimizing the weighted differences between the measured and modeled impedance values:

ZL = Raw + jωIaw + (G - jH)/ωα

where ω is the angular frequency (2πf) and α=2/π·arctan(H/G). The tissue resistive component (Rti) at the ventilation frequency (0.2 Hz) was calculated from the parenchymal damping coefficient (Rti = G/ωα). The total lung resistance (RL) was determined as the sum of the airway resistance (Raw) and the Rti (RL = Raw + G/ωα).

***Dead space measurements***

*Fowler dead space*

Fowler dead space (VDF), represents the anatomic dead-space volume of the conducting airways (Fig. 1). This was assessed by determining the inflection point on phase II of volumetric capnogram that separates the conductive and the alveolar space volumes ([3](#_ENREF_3),[4](#_ENREF_4)).

*Bohr dead space*

The physiological dead space, including also the alveolar volume not involved in gas exchange, was assessed by using the Bohr method (VDB) ([5](#_ENREF_5)):

VDB = (PACO2- PĒCO2) / PACO2

where PACO2 is the mean alveolar CO2 concentration located at the midpoint of the phase III in the expired CO2 curve, and PĒCO2 is the mixed partial pressure of CO2 during the entire expiration ([6](#_ENREF_6),[7](#_ENREF_7)). The latter is calculated as the ratio of the tidal elimination of CO2 (VCO2) obtained by integrating the flow and CO2 signals over the entire breath and the tidal volume ([6](#_ENREF_6),[7](#_ENREF_7)).

*Enghoff dead space*

The dead space according to Enghoff’s modification (VDE) takes also into account the ventilated but not perfused alveoli ([8](#_ENREF_8)), and can therefore be calculated as

VDE = (PaCO2- PĒCO2) / PaCO2

where PaCO2 is the partial pressure of CO2 in the arterial blood.

***Statistical analyses***

Standard error of means (SEM) was used to express scatters in measured variables. The normality of the data was tested with the Kolgomorov-Smirnov test with the Lilliefors correction. In the event of normality, paired t-tests were used to examine the statistical significance induced by CPB in the parameters. Wilcoxon signed-rank tests were utilized to verify the significance of the changes in the mechanical, capnographic or gas-exchange parameters. The Pearson test was applied to analyze the correlations between the different variables under each measurement condition, and to test the strength of the associations between the CPB-induced changes in the various parameters. The statistical tests were performed with a SigmaPlot statistical software package (Version 12.5, Systat Software, Inc. Chicago, IL, USA). All reported p values were two-sided.

SUPPLEMENTAL RESULTS

The patients exhibited substantial interindividual variability in the lung mechanical and capnographic parameters (Table 1S), as reflected in the high coefficient of variation values before, after and the differences between after and before values.

|  |  |  |  |
| --- | --- | --- | --- |
|   | Before | After | After-Before CPB |
| Raw | 116 | 98 | 109 |
| G | 69 | 127 | 227 |
| H | 41 | 44 | 262 |
| SnII,T | 36 | 33 | 1163 |
| SnIII,T | 169 | 96 | 113 |
| VDF | 26 | 24 | -134 |
| VDB | 25 | 24 | -138 |
| VDE | 28 | 32 | 156 |
| VDE-VDB | 50 | 45 | 114 |

**Table 1S.** Coefficients of variations for the lung mechanical (Raw, G and H) and capnographic parameters (SnII,T, SnIII,T, VDF, VDB, VDE, VDE-VDB).

The key parameters obtained by forced oscillations and capnography for the individual patients are demonstrated on Fig. 1S (continuous thin lines), and for the group means (symbols with thick lines). Based on their starting pulmonary function, the cohort was divided into 3 groups: patients with the highest 25% (red), the medium 50% (grey) and the lowest 25% HQ (green). There was no evidence for a statistical significance between the groups in the lung mechanical parameters (Raw, G and H) and capnographic shape factors (SnII,T and SnIII,T). This can be attributed to the complex pathophysiological processes involved in the gas exchange, including ventilation, perfusion and ventilation/perfusion. Accordingly, there is no direct link between individual lung mechanical or capnogram parameters with gas exchange indices. Conversely, capnographic parameters primarily affected by lung perfusion (VDF, VDB, VDE and VDE-VDB) exhibit statistically significant differences in the different HQ groups.



The interdependence of the main shape factors obtained from the time capnogram with lung mechanical parameters representing the airway resistance (Raw) and lung elastance (H) under the baseline conditions are demonstrated in Fig. 2S. The magnitude of SnIII,T depends more on Raw than on H (Panel A), whereas the level of SnII,T appears to be determined primarily by H, with lower correlations with Raw (Panel B). The capnographic parameters expressing the transition from phase II to phase III (D2min) displayed stronger, but opposite dependence on H than on Raw (Panel C).



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