A Comparison of Micropore Membrane Inlet Mass Spectrometry–Derived Pulmonary Shunt Measurement with Riley Shunt in a Porcine Model

Bastian Duenges, PhD*

Andreas Vogt, MD†

Marc Bodenstein, MD*

Hemei Wang, MD, PhD*‡

Stefan Böhme, MS*

Bernd Röhrig, PhD§

James E. Baumgardner, MD, PhD‖

Klaus Markstaller, MD*

BACKGROUND: The multiple inert gas elimination technique was developed to measure shunt and the ratio of alveolar ventilation to simultaneous alveolar capillary blood flow in any part of the lung (V_A'/Q') distributions. Micropore membrane inlet mass spectrometry (MMIMS), instead of gas chromatography, has been introduced for inert gas measurement and shunt determination in a rabbit lung model. However, agreement with a frequently used and accepted method for quantifying deficits in arterial oxygenation has not been established. We compared MMIMS-derived shunt (M-S) as a fraction of total cardiac output (CO) with Riley shunt (R-S) derived from the R-S formula in a porcine lung injury model.

METHODS: To allow a broad variance of atelectasis and therefore shunt fraction, 8 sham animals did not receive lavage, and 8 animals were treated by lung lavages with 30 mL/kg warmed lactated Ringer's solution as follows: 2 animals were lavaged once, 5 animals twice, and 1 animal 3 times. Variables were recorded at baseline and twice after induction of lung injury (T1 and T2). Retention data of sulfur hexafluoride, krypton, desflurane, enflurane, diethyl ether, and acetone were analyzed by MMIMS, and M-S was derived using a known algorithm for the multiple inert gas elimination technique. Standard formulas were used for the calculation of R-S.

RESULTS: Forty-four pairs of M-S and R-S were recorded. M-S ranged from 0.1% to 35.4% and R-S from 3.7% to 62.1%. M-S showed a correlation with R-S described by linear regression: M-S = $-4.26 + 0.59 \times$ R-S ($r^2 = 0.83$). M-S was on average lower than R-S (mean = −15.0% CO, SD = 6.5% CO, and median = −15.1), with lower and upper limits of agreement of −28.0% and −2.0%, respectively. The lower and upper limits of the 95% confidence intervals were −17.0 and −13.1 ($P < 0.001$, Student's *t*-test).

CONCLUSIONS: Shunt derived from MMIMS inert gas retention data correlated well with R-S during breathing of oxygen. Shunt as derived by MMIMS was generally less than R-S.

(Anesth Analg 2009;109:1831–5)

The multiple inert gas elimination technique (MIGET) is an established and well-accepted method for determining pulmonary shunt and the ratio of alveolar ventilation to simultaneous alveolar capillary blood flow in any part of the lung (V_A'/Q') distributions.[1–13] MIGET has provided useful insights into the mechanisms of gas exchange pathophysiology in many experimental studies.[1–7,9–15] A drawback of the method, however, is a time-consuming analysis of the inert gases by gas chromatography. The recently introduced micropore membrane inlet mass spectrometry (MMIMS) measures inert gas partial pressures rapidly in small blood samples with little chance for technical errors.[14] MMIMS-derived shunt (M-S) fraction, however, has not been validated against a reference method for shunt measurement.

Calculation of Riley shunt (R-S) from arterial, mixed venous, and assumed pulmonary end-capillary blood gas data is a frequently used method for quantifying deficits in arterial oxygenation.[4,9,12,16] R-S combines the contributions of shunt (0 V_A'/Q') with the contributions of low V_A'/Q' lung units to explain hypoxemia in terms of a single hypothetical admixture compartment and gives little information about the

From the *Department of Anesthesiology, Johannes Gutenberg-University, Mainz, Germany; †University Department of Anesthesiology and Pain Therapy, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; ‡Beijing Institute of Pharmacology and Toxicology, Beijing, China; §Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), Johannes Gutenberg-University, Mainz, Germany; and ‖Oscillogy®, LLC, Folsom, Pennsylvania.

Accepted for publication July 28, 2009.

Supported by German Research Foundation DFG Ma 2398/3, Swiss National Foundation SNF POIB—117065/1 and an institutional grant of the Department of Anesthesiology, Inselspital, Bern University Hospital, and University of Bern.

J. E. Baumgardner is President of Oscillogy® LLC, the manufacturer of the MIGET by MMIMS system.

Address correspondence and reprint requests to Andreas Vogt, MD, University Department of Anesthesiology and Pain Therapy, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. Address e-mail to andreas.vogt@insel.ch.

DOI: 10.1213/ANE.0b013e3181bbc401

true underlying V_A'/Q' distribution. For the particular case of an inspired oxygen fraction (F_{IO_2}) of 1.0 and complete denitrogenation, however, even low V_A'/Q' units will have a high alveolar PO_2, and only true 0 V_A'/Q' will contribute to oxygenation deficits. During oxygen breathing, R-S can therefore be used as a measure of true shunt fraction. In several studies in which subjects were breathing oxygen, R-S was shown to be highly correlated with true shunt fraction from conventional MIGET.[2,4,9,11]

The aim of this study was to compare shunt fraction derived from MMIMS-measured inert gas retention data with R-S in subjects breathing 100% oxygen. We hypothesized that M-S should be significantly correlated with R-S, and that the relationship should be similar to previously reported relationships between shunt determined by conventional MIGET (using gas chromatography) and R-S.

METHODS

Instrumentation

With state animal care committee approval, 16 anesthetized pigs (24 ± 1 kg, mean ± SD) were investigated in this study, which was performed at the Department of Anesthesiology, Johannes Gutenberg-University Mainz, Germany. After premedication (azaperone 8 mg/kg IM and atropine 0.02 mg/kg IM), anesthesia was induced by propofol 4 mg/kg IV and by fentanyl 4 μg/kg. Animals were positioned supine. Maintenance of anesthesia before surgical placement of arterial and venous catheters and during the experiment was performed by continuous infusion of propofol 10–20 $mg \cdot kg^{-1} \cdot h^{-1}$ and 5 μg/kg boluses of fentanyl. The airway was secured by endotracheal intubation (tracheal tube of internal diameter 9 mm; Ruesch, Kernen, Germany) facilitated by pancuronium 4 mg IV. Pressure-controlled ventilation was adjusted appropriately to allow initial normocapnia (AVEA™, Viasys, Viasys Healthcare, Palm Springs, CA).

Arterial and venous catheters were inserted for arterial blood pressure monitoring (Sirecust, Siemens, Erlangen, Germany) by femoral and cervical cut down. A balloon-tipped flow-directed pulmonary artery (PA) catheter was introduced into the PA for measurement of intermittent cardiac output (CO) by thermo dilution (Baxter Healthcare, Deerfield, IL), PA pressures, PA occlusion pressure, and mixed venous blood gas sampling. For CO determination, the mean of 3 thermodilution measurements was taken. Typical pressure waveforms obtained by pressure tracings were used to verify the position of all catheters. The mid-chest level was chosen as reference for all intravascular pressures. Flows and airway pressures were assessed by conventional spirometry (S/5 Monitoring, Datex-Ohmeda, Duisburg, Germany).

No additional crystalloids were given beyond the infusion of inert gases for M-S. Decreases of mean arterial blood pressure of >20% from baseline (BL) were treated with boluses of 100 mL of hydroxyethyl starch 140/0.3 (Voluven, Fresenius Kabi, Bad Homburg, Germany) with a maximum of 500 mL for the entire experiment.

To allow a broad variance of atelectasis and therefore shunt fraction, 8 sham animals did not receive lavage, and 8 animals were treated by lung lavages with 30 mL/kg warmed lactated Ringer's solution[17] as follows: 2 animals were lavaged once, 5 animals twice, and 1 animal 3 times. To avoid bias from systematic errors, animals were randomly assigned to the sham and lavage groups by flipping a coin.

Study Protocol

During the study protocol, animals' lungs were ventilated with pressure-controlled ventilation. The respiratory settings were set as follows: respiratory rate (RR) fixed to 8 bpm; positive end-expiratory pressure of 5 cm H_2O; peak airway pressure and the resulting tidal volume were varied to maintain permissive hypercapnia up to 50 mm Hg; and F_{IO_2} was set to 1.0. The following respiratory variables were applied before BL measurements: peak airway pressure 40 mbar and RR 30 bpm for 30 s. To get a broad variation in shunt measurements with an increased number of data points, variables were recorded at BL and twice (T1 = 2 h and T2 = 5 h) after induction of lung injury as follows: heart rate, arterial and pulmonary arterial blood pressures, central venous pressure, expiratory tidal volume, RR, arterial and mixed venous blood gas analysis, hemoglobin concentration, and temperature.

Micropore Membrane Inlet Mass Spectrometry

The inert gases and the mass spectrometer peaks used to measure the inert gas partial pressures were identical to a previously described report.[14] The 6 gases used and their corresponding atomic mass unit peaks were sulfur hexafluoride at 127, krypton at 84, desflurane at 101, enflurane at 117, diethyl ether at 59, and acetone at 58.

The inert gas solution was prepared by equilibration of 15 mL sulfur $hexafluoride_6$ and 4 mL krypton gases with 500 mL normal saline, followed by addition of 300 μL desflurane, 340 μL enflurane, 1 mL diethyl ether, and 5.4 mL acetone as liquids. Inert gases dissolved in normal saline were infused IV for 50 min at a rate of 12.5 mL/min and for 10 min at a rate of 20 mL/min by a roller pump. After 1 h, arterial and mixed venous blood samples (5 mL each) were sampled into citrated, gas-tight glass syringes (Perfektum®, Popper & Sons, New Hyde Park, NY) over at least 5 full respiratory circles. The temperature of blood samples was maintained equal to the body temperature of the animal. The injected volume of blood into the MMIMS system (Beta Version 1.0, Oscillogy®, Folsom, PA) for each blood sample was 4 mL. The MMIMS system measured inert gas partial pressures in the blood samples directly (i.e., with no extraction into a headspace gas) with an analysis time

Table 1. Data of Spirometry, Hemodynamics, Hemoglobin, and Temperature Data

	Baseline	T1	T2
Spirometry			
Paw mean (cm H_2O)	10 (10, 11)	11 (10, 14)	11 (10, 15)
E'_{CO2} (mm Hg)	37 (33, 41)	36 (31, 41)	35 (32, 41)
AMV (L)	3.4 (3.0, 3.7)	3.5 (3.2, 4.0)	3.6 (3.4, 4.0)
Hemodynamics			
MAP (mm Hg)	91 (82, 99)	72 (66, 79)	68 (61, 75)
MPAP (mm Hg)	27 (24, 32)	26 (23, 30)	29 (25, 33)
PAOP (mm Hg)	11 (7, 13)	8 (6, 13)	9 (5, 13)
CO (L/min)	5.1 (4.0, 7.6)	6.8 (4.2, 8.8)	8.0 (5.3, 10.7)
Hb (g/L)	82 (78, 88)	77 (74, 85)	71 (67, 79)
Temp (°C)	35.6 (34.9, 36.9)	36.9 (36.1, 37.4)	37.4 (36.7, 37.5)

Spirometry, hemodynamic, hemoglobin concentration and temperature data of the animals [as median (Q1, Q3)].

Paw mean = mean airway pressure; E'_{CO2} = end-tidal carbon dioxide; AMV = alveolar minute ventilation; MAP = mean arterial blood pressure; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary arterial occlusion pressure; CO = cardiac output; Hb = hemoglobin; Temp = temperature.

Table 2. Blood Gas Analysis Data of Arterial and Mixed Venous Blood Both Groups

	Baseline		T1		T2	
	Sham	Lavage	Sham	Lavage	Sham	Lavage
Arterial blood gases						
PaO_2 (mm Hg)	467 (381, 514)	527 (487, 541)	412 (342, 488)	108 (81, 309)	206 (189, 340)	165 (98, 400)
$Paco_2$ (mm Hg)	54 (49, 62)	57 (50, 71)	53 (46, 58)	71 (56, 76)	61 (52, 71)	74 (48, 83)
Base excess	−0.7 (−2.4, 2.1)	1.0 (−0.4, 2.6)	−0.8 (−3.7, 1.6)	−2.0 (−2.8,−1.2)	−2.9 (−4.1, 1.6)	−4.8 (−9.5, −2.8)
pH	7.27 (7.22, 7.30)	7.31 (7.25, 7.38)	7.27 (7.24, 7.32)	7.20 (7.18, 7.29)	7.23 (7.16, 7.25)	7.12 (7.07, 7.27)
PA blood gases						
$PPao_2$ (mm Hg)	72 (61, 75)	65 (61, 85)	58 (53, 68)	61 (51, 66)	60 (57, 71)	61 (59, 65)
$PPaco_2$ (mm Hg)	63 (57, 72)	67 (60, 75)	61 (54, 66)	77 (67, 87)	75 (60, 81)	83 (55, 87)
Base excess	−0.2 (−2.1, 1.6)	0.35 (−0.25, 2.4)	−0.6 (−3.8, 2.1)	−3.2 (−4.4, −1.48)	−2.7 (−4.6, 0.7)	−4.8 (−9.4, −2.1)
pH	7.27 (7.21, 7.30)	7.27 (7.22, 7.33)	7.27 (7.23, 7.32)	7.16 (7.14, 7.26)	7.23 (7.16, 7.25)	7.14 (7.06, 7.23)

Data are presented as median (Q1, Q3). Arterial and mixed venous blood gas data of the sham (n = 8) and lavage (n = 8) group animals.

Pao_2 = arterial oxygen tension; $Paco_2$ = arterial carbon dioxide tension; PA = pulmonary arterial; $PPao_2$ = pulmonary arterial oxygen tension; $PPaco_2$ = pulmonary arterial carbon dioxide tension.

of 6 min for each blood sample. Retention was calculated as the ratio of inert gas partial pressure in the arterial sample to the inert gas partial pressure in the mixed venous sample.[12] Retention data and solubility coefficients were subsequently transformed into perfusions (percentage CO) of 50 compartments of predefined ventilation-to-perfusion ratios by algorithms as described by Evans and Wagner[18] for MIGET. The compartment of interest was defined as follows: shunt $\equiv V_A'/Q' < 0.005$.[6]

Simultaneously to blood samples for MMIMS inert gas analysis, arterial and mixed venous blood samples were taken for conventional blood gas analysis (Rapidlab 248, Bayer Healthcare, Leverkusen, Germany) and analyzed with correction for the animal's temperature. Calibration of the Rapidlab 248 was performed according to the manufacturer's instructions.

Standard formulas were used for the calculation of R-S: R-S = $(CcO_2 - CaO_2)/(CcO_2 - CvO_2)$ where CcO_2 is the end capillary, CaO_2 is the arterial, and CvO_2 is the mixed venous oxygen content.

CcO_2 was calculated using an alveolar gas equation (ambient pressure was set to 760 mm Hg, gas, and PH20 was set to 47 mm Hg). CaO_2 and CvO_2 were calculated by the standard formula for oxygen content of the blood. In this calculation, PO_2, pH, Pco_2, base excess, temperature, and hemoglobin concentration were measured variables. To determine species-dependent hemoglobin saturation from oxygen partial pressure, we used a model of the oxygen dissociation curve published by Serianni et al.[19] To correct for CO_2, pH, and temperature effects on the oxygen dissociation curve, we included a factor according to Severinghaus.[20] The formulas used are presented in the Appendix.

Statistics

Data collection, data management, and data analysis were performed with the statistical package SPSS® Version 15 (Chicago, IL). For metrical variables, statistical measures such as mean and SD (mean ± SD) and/or quartiles (25th percentile, median, and 75th percentile) were calculated. For the difference between M-S and R-S, descriptive analyses were used. Correlation of both methods was described by linear regression analysis and a detailed Bland-Altman[21,22] analysis.

The analyses of data were done in a descriptive manner, and the outcome of a statistical test with a P value <0.05 was considered as the level of significance.

RESULTS

Spirometry, hemodynamics, hemoglobin, and temperature data are shown in Table 1. In both groups, Pao_2 decreased and $Paco_2$ increased from BL to T2 (Table 2).

Table 3. Descriptive Statistics of M-S, R-S

	Baseline	T1	T2
M-S (Percentage CO)	7.0 ± 6.9 (2.0, 7.2, 9.4)	12.9 ± 9.0 (5.1, 10.0, 22.0)	15.2 ± 8.4 (10.4, 14.6, 16.7)
R-S (Percentage CO)	16.0 ± 9.5 (11.7, 14.4, 17.6)	32.3 ± 16.3 (20.8, 27.1, 48.7)	34.1 ± 11.1 (24.8, 35.8, 40.9)

Data of all animals are presented as mean ± SD (Q1, median, Q3).

M-S = MMIMS shunt; R-S = Riley shunt; CO = cardiac output.

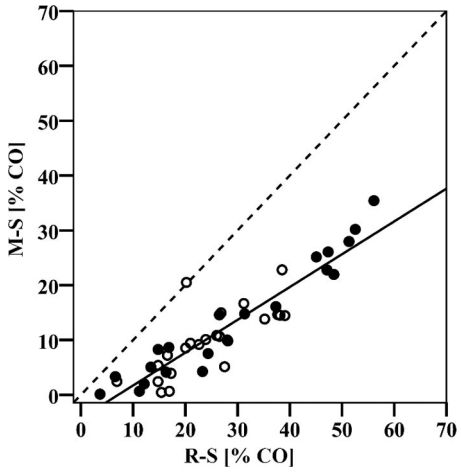

Figure 1. Linear regression of micropore membrane inlet mass spectrometry–based shunt (M-S) on Riley shunt (R-S): M-S = −4.26 + 0.59 × R-S (r^2 = 0.83). Solid = regression line; dotted = line of identity; open circles = sham; and closed circles = lavage. Data from all 16 pigs included.

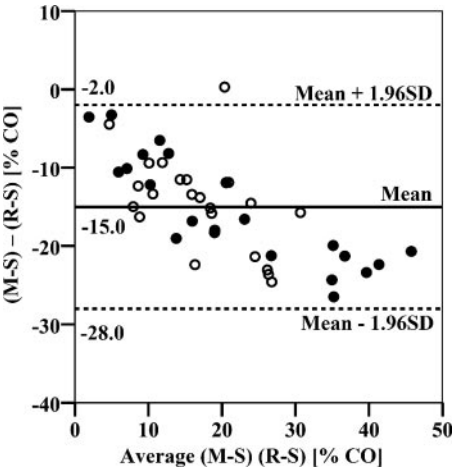

Figure 2. Bland-Altman analysis of micropore membrane inlet mass spectrometry–based shunt (M-S) and Riley shunt (R-S). Solid line = mean bias; dotted lines = lower and upper limits of agreement; open circles = sham; and closed circles = lavage. Data from all 16 pigs included.

Correlation and Agreement of M-S and R-S

M-S values were not obtained for 2 measurements. In 1 recording, the arterial inert gas concentrations were higher than the mixed venous, probably because of mismatch of the sample probes. In the second, the mixed venous tracing was missed because of clotting of the probe, thus no retention could be calculated. R-S values were missed at 1 measurement for technical reasons. One lavaged animal died 5 h after lung injury. For the analysis of agreement of M-S and R-S, all values from BL, T1, and T2 were pooled.

Forty-four pairs of M-S and R-S were recorded. M-S and R-S ranged from 0.1% to 35.4% and 3.7% to 62.1%, respectively. M-S and R-S increased from BL to T2 (Table 3). A linear regression analysis is shown in Figure 1. Both regression coefficients were statistically significant ($P < 0.001$). The intraclass correlation coefficient was 0.278 (95% confidence interval [CI]: −0.020, 0.528).

M-S was on average lower than R-S (mean = −15.0% CO, SD = 6.5% CO, and median = −15.1), with lower and upper limits of agreement of −28.0% and −2.0%, respectively (Fig. 2). The lower and upper limits of 95% CI were −17.0 and −13.1 ($P < 0.001$, Student's *t*-test).

The MMIMS inert gas retention dataset had a residual sum of squares (RSS): RSS <5.3 in 29%, RSS <10.6 in 49%, and RSS <16.8 in 69%, which served as an indicator of experimental error.[8] For the 31% of measurements with RSS >16.8, RSS mean ± SD (range) in the sham group was 34.3 ± 13.8 (21.9–55.6) and in the lavage group 80.2 ± 55.4 (26.0–202.0).

Table 4. Results of Prior Studies Comparing Gas Chromatography MIGET Shunt and R-S

Study	Intercept	Slope	*r*
Wagner et al.[11]	−1.29	1.02	0.96
Hlastala et al.[4]	NR	NR	0.97
Sato et al.[9]	−4.32	1.35	0.94
Own data (M-S)	−4.3	0.60	0.91

The reported relationships of GC MIGET shunts and R-S have been inverted to the equivalent relationship in the format shunt as *Y* versus R-S as *X*, to facilitate comparison of current M-S/R-S relationships.

MIGET = multiple inert gas elimination technique; *r* = correlation coefficient; NR = not reported; own data shunt = M-S of this study.

DISCUSSION

This study shows that M-S correlates with R-S (r^2 = 0.83) but also underestimates R-S (Fig. 1). Bland-Altman analysis[22] showed a highly dependent difference and magnitude of both methods, reflected in the significant negative correlation of the difference against the average of the 2 methods (Fig. 2).

In previous studies, MIGET was used as the "gold standard" for determining the shunt fraction.[4,9,11] In this study, we compared M-S with R-S as the gold standard (Table 4). When F_{IO_2} = 1.0 and denitrogenation is complete, R-S has been previously validated as a measure of true shunt fraction.[11] The motivation for assessing the accuracy of M-S is that inert gas methods are expected to retain their accuracy independent of

APPENDIX

$$SO_2 = \frac{(k \times PO_2)^n}{(k \times PO_2)^n + \beta}$$

Formula (1): Calculation of SO_2 by PO_2 as it was described by Serianni et al. k, n, β: species specific empiric constants. For porcine blood, we used: $k = 0.13534$, $n = 3.02$, and $\beta = 91.2$.

$$\Delta(PO_2) = 10^{-B \times (pH - 7.400) + 0.0013 \times BE + 0.024 \times (T - 37)}$$

Formula (2): Severinghaus factor to standardize PO_2 by pH, base excess, and temperature. B is also species dependent: $B = 0.42$ for porcine blood.

$$P_{means}O_2 = P_{stand}O_2 \times \Delta(PO_2)$$

Formula (3): Relation between measured and standardized PO_2 by the Severinghaus factor.

F_{IO_2}. In our study, the correlation of M-S with R-S yielded comparable precision with previously published studies[4,9,11] but with less accuracy than some previous studies. Hlastala et al.[4] compared shunt determined by the oxygen method (R-S) and the inert gas infusion method (MIGET) and reported a correlation coefficient (r) of 0.986. Shunt was induced by atelectasis and oleic acid. Below 20% of CO, the results of the oxygen technique were consistently higher than the inert gas technique ($r = 0.863$).[4] It was concluded that the differences between the 2 methods were attributable to 1) presence of extra pulmonary shunt, and 2) errors in measurement of high PO_2 in the blood. In this study, a surfactant depletion lung injury model was used. The differences in results between the study by Hlastala et al. and our study could in part be a result of the different injury models and their effects on CO.

We observed that R-S increased at higher CO (R-S = 1.1 + 3.9 × CO [$r = 0.69$]) at a steeper slope than M-S (M-S = −3.5 + 2.3 × CO [$r = 0.75$]). These findings are consistent with previous work. In a study from Breen et al.,[2] inert gas shunt and R-S were similar at normal CO and oxygen breathing but increased with increasing CO. In that study, inert gas shunt in the range from 0% to 40% CO underestimated R-S in the range from 0% to 60% CO similar to our study. Intralobar redistribution and increased pulmonary blood flow were the suggested mechanisms for this phenomenon. An increase in extrapulmonary shunt fraction, however, may not explain the whole underestimation of R-S by M-S in the higher range.

One explanation for our findings may be that the current β 1.0 version of MMIMS is not capable of discriminating true shunt from V_A'/Q'_{LOW}. The version of MMIMS technology used in this study has a single-pore MMIMS probe with limited sensitivity compared with the laboratory version used in a former study.[14] Automation, however, of inert gas measurement technique and temperature control were very much improved compared with that version of MMIMS. Consistent with this explanation, the amount of variability around the M-S to R-S regression (Fig. 1) is larger than the variability reported in similar regressions for intact animal preparations[4,11] using conventional MIGET.

In summary, shunt as measured by this single-pore version of MMIMS correlated well with R-S during oxygen breathing, but it also underestimated R-S. Further refinements in this developing technology will be required to achieve an accuracy equivalent to conventional MIGET.

REFERENCES

1. Batchinsky AI, Weiss WB, Jordan BS, Dick EJ Jr, Cancelada DA, Cancio LC. Ventilation-perfusion relationships following experimental pulmonary contusion. J Appl Physiol 2007;103:895–902
2. Breen PH, Schumacker PT, Hedenstierna G, Ali J, Wagner PD, Wood LD. How does increased cardiac output increase shunt in pulmonary edema? J Appl Physiol 1982;53:1273–80
3. Dembinski R, Henzler D, Bensberg R, Prusse B, Rossaint R, Kuhlen R. Ventilation-perfusion distribution related to different inspiratory flow patterns in experimental lung injury. Anesth Analg 2004;98:211–9
4. Hlastala MP, Colley PS, Cheney FW. Pulmonary shunt: a comparison between oxygen and inert gas infusion methods. J Appl Physiol 1975;39:1048–51
5. Lynch JP, Mhyre JG, Dantzker DR. Influence of cardiac output on intrapulmonary shunt. J Appl Physiol 1979;46:315–21
6. Neumann P, Hedenstierna G. Ventilation-perfusion distributions in different porcine lung injury models. Acta Anaesthesiol Scand 2001;45:78–86
7. Rees SE, Kjaergaard S, Andreassen S, Hedenstierna G. Reproduction of MIGET retention and excretion data using a simple mathematical model of gas exchange in lung damage caused by oleic acid infusion. J Appl Physiol 2006;101:826–32
8. Roca J, Wagner P. Contribution of multiple inert gas elimination technique to pulmonary medicine. 1. Principles and information content of the multiple inert gas elimination technique. Thorax 1994;49:815–24
9. Sato S, Hlastala MP, Hildebrandt J. Intrapulmonary shunt in excised dog lobes: comparison of oxygen and inert gas methods. J Appl Physiol 1993;74:951–8
10. Wagner PD, Dantzker DR, Dueck R, Clausen JL, West JB. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest 1977;59:203–16
11. Wagner PD, Laravuso RB, Goldzimmer E, Naumann PF, West JB. Distribution of ventilation-perfusion ratios in dogs with normal and abnormal lungs. J Appl Physiol 1975;38:1099–109
12. Wagner PD, Laravuso RB, Uhl RR, West JB. Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100 percent O_2. J Clin Invest 1974;54:54–68
13. Yu G, Yang K, Baker AB, Young I. The effect of bi-level positive airway pressure mechanical ventilation on gas exchange during general anaesthesia. Br J Anaesth 2006;96:522–32
14. Baumgardner JE, Choi IC, Vonk-Noordegraaf A, Frasch HF, Neufeld GR, Marshall BE. Sequential V(A)/Q distributions in the normal rabbit by micropore membrane inlet mass spectrometry. J Appl Physiol 2000;89:1699–708
15. Dunges B, Karmrodt J, Baumgardner JE, Markstaller K. [Ventilation-perfusion distributions in the lungs: a novel technique for rapid measurement.] Anaesthesist 2007;56:612–6
16. Berggren SM. The oxygen deficit of arterial blood caused by nonventilating parts of the lung. Acta Physiol Scand 1942;4(suppl II):1–92
17. Lachmann B, Robertson B, Vogel J. *In vivo* lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesiol Scand 1980;24:231–6
18. Evans JW, Wagner PD. Limits on VA/Q distributions from analysis of experimental inert gas elimination. J Appl Physiol 1977;42:889–98
19. Serianni R, Barash J, Bentley T, Sharma P, Fontana JL, Via D, Duhm J, Bunger R, Mongan PD. Porcine-specific hemoglobin saturation measurements. J Appl Physiol 2003;94:561–6
20. Severinghaus JW. Blood gas calculator. J Appl Physiol 1966;21:1108–16
21. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10
22. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999;8:135–60