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Comparison of pneumotachography and anemometry for flow measurement during mechanical ventilation with volatile anesthetics

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Abstract

Volatile anesthetics alter the physical properties of inhaled gases, such as density and viscosity. We hypothesized that the use of these agents during mechanical ventilation would yield systematic biases in estimates of flow ($\dot{V}$) and tidal volume (V_T) for two commonly used flowmeters: the pneumotachograph (PNT), which measures a differential pressure across a calibrated resistive element, and the hot-wire anemometer (HWA), which operates based on convective heat transfer from a current-carrying wire to a flowing gas. We measured $\dot{V}$ during ventilation of a spring-loaded mechanical test lung, using both the PNT and HWA placed in series at the airway opening. Delivered V_T was estimated from the numerically-integrated $\dot{V}$. Measurements were acquired under baseline conditions with room air, and during ventilation with increasing concentrations of isoflurane, sevoflurane, and desflurane. We also evaluated a simple compensation technique for HWA flow, which accounted for changes in gas mixture density. We found that discrepancies in estimated V_T between the PNT and HWA occurred during ventilation with isoflurane ($6.3 \pm 3.0\%$), sevoflurane ($10.0 \pm 7.3\%$), and desflurane ($25.8 \pm 17.2\%$) compared to baseline conditions. The magnitude of these discrepancies increased with anesthetic concentration. A simple compensation factor based on density reduced observed differences between the flowmeters, regardless of the anesthetic or concentration. These data indicate that the choice and concentration of anesthetic agents are primary factors for differences in estimated V_T between the

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PNT and HWA. Such discrepancies may be compensated by accounting for alterations in gas density.

Keywords

Anesthetics; Flowmeters; Artificial respiration

1 Introduction

The accuracy of respiratory flow measurements is affected by changes in the physical properties of inhaled gases, such as density (ρ) and viscosity (μ). Previous work has demonstrated how gas composition, temperature, and flow-rate, among other factors, can influence these properties [1–3]. Consequently such changes can bias estimates of airway flow ($\dot{V}$), as well as flow-derived parameters such as tidal volume (V_T), respiratory resistance, and respiratory compliance. A recent study [4] demonstrated that variations in ρ , due to changes in carrier gas composition or volatile anesthetic concentration, will alter delivered V_T during feedback-controlled ventilation due to inaccuracies in measured $\dot{V}$. These findings were observed using a variable-orifice flowmeter, implying that other flow measuring devices may similarly be influenced by changes in gas mixture.

Two devices commonly used for flow measurement during mechanical ventilation are the pneumotachograph (PNT) and the hot-wire anemometer (HWA). The PNT measures differential pressure (P) across a calibrated resistive element, and assumes that P varies linearly with $\dot{V}$ during viscous laminar flows [5, 6]. The P to $\dot{V}$ relationship for the PNT depends on μ but, and in theory should be unaffected by changes in other gas properties [7]. By contrast, the HWA relies on convective heat transfer from a current-carrying wire to a flowing gas. The $\dot{V}$ estimated by the HWA is related either to changes in wire temperature and resistivity (constant current mode), or to fluctuations in the wire-heating current (constant temperature mode) [8], both of which depend on ρ [9–11].

Given the differences in the physical principles of measurement between the PNT and the HWA, we hypothesized that mechanical ventilation with volatile anesthetics, which are known to differentially affect μ and ρ of a gas mixture at clinically relevant concentrations [12], would systematically bias estimates of measured $\dot{V}$ along with flow-derived estimates of V_T . Accordingly, the goal of this study was to characterize the differences between these two flow-measuring devices for three commonly used volatile anesthetic agents, over a range of clinically relevant concentrations, ventilator rates, and V_T .

2 Flow measurement theory

The use of the PNT assumes that P across its resistive element is directly proportional to $\dot{V}$ when flow is laminar. The screen PNT comprises one or more fine wire meshes that laminarize flow, and in combination act as a linear resistive element [6]. The relationship between the estimated flow from the PNT, $\dot{V}_{\text{PNT}}$, and P across the wire mesh is given by [13]:

$$\dot{V}_{PNT} = \left(\frac{C_m}{\alpha} \right) \left(\frac{1}{\mu} \right) \Delta P \quad (1)$$

where α is a viscous resistance coefficient and C_m is a coefficient determined by the geometrical properties of the mesh (i.e., screen thickness, total screen area, screen volume void fraction, and wire surface area). For a given screen PNT, α and C_m are assumed to be constant [13]. Thus $\dot{V}_{PNT}$ varies in direct proportion to ΔP , but in inverse proportion to μ , provided that the measured flow is within the linear range of the PNT.

For the HWA, the sensing element consists of one or more platinum wires that are heated under constant current mode or, more commonly, constant temperature mode [8]. Constant current anemometers relate flow rate to changes in wire temperature and resistivity, whereas constant temperature anemometers relate flow rate to fluctuations in the current needed to maintain the temperature of the hot wire. When electrical energy dissipation in the wire and convective heat transfer from the wire to the gas are balanced, the heat transfer coefficient h between the wire and gas is given by [10]:

$$h = \frac{i_w^2 R_w}{A_w (T_w - T_g)} \quad (2)$$

where i_w is the wire current, R_w the resistance of the wire, A_w is the surface area of heat exchange, and T_w and T_g are the temperatures of the heated wire and the ambient gas, respectively. For a constant temperature HWA, $\dot{V}_{HWA}$ is empirically related to h according to King's Law [11]:

$$\dot{V}_{HWA} = \left(\frac{h - A}{B} \right)^2 \quad (3)$$

where

$$A = \frac{0.42}{d_w} (k^4 c_p \mu)^{\frac{1}{5}} \quad (4)$$

$$B = \frac{0.57}{\sqrt{A_{cs} d_w}} \left(\frac{k^2 c_p}{\sqrt{\mu}} \right)^{\frac{1}{3}} \sqrt{\rho} \quad (5)$$

The A_{cs} is the cross-sectional area of gas flow, d_w is the diameter of the wire, k is the thermal conductivity of the gas, and c_p is the specific heat capacity of the gas [9, 14]. Fluctuation in i_w can thus be converted to a corresponding gas velocity using Eqs. 2–5, since A and B will be constant for a given mixture [9, 11]. However A and B may not be constant

if there are substantial changes in gas composition following HWA calibration. Rather $\dot{V}_{HWA}$ for a specified h will be inversely proportional to changes in B^2 , such that:¹

$$\dot{V}_{HWA} = \left(\frac{1}{\rho} \right) \left(\frac{h C_{w1}}{k^{0.67} c_p^{0.33} \mu^{-0.17}} - \frac{C_{w2}}{k^{-0.13} c_p^{-0.47} \mu^{-0.57}} \right)^2 \quad (6)$$

where C_{w1} and C_{w2} are coefficients determined by the geometrical properties of the HWA (i.e., A_{cs} , d_w) and are assumed constant for a given HWA. Therefore $\dot{V}_{HWA}$ depends on h , as well as several physical properties of the gas mixture (i.e. ρ , μ , k , and c_p). Equation 6 is in contrast to (Eq. 1, for which only μ is the dominant physical gas property influencing the $\dot{V}$ estimated by the PNT).

3 Methods

3.1 Experimental protocol

A Fabius GS anesthesia machine (Drägerwerk, Lübeck, Germany) and an S/5 ADU Carestation anesthesia machine (General Electric, Fairfield, CT) were used to ventilate a spring-loaded mechanical test lung (IngMar Medical, Ltd., Pittsburgh, PA) with $\dot{V}$ measured at the Y-piece using a PNT measurement system (4700A and RSS100-HR, Hans Rudolph, Shawnee, KS) in series with a constant temperature HWA (Florian, Acutronic Medical Systems, Hirzel, Switzerland). Breathing circuit compliance and leak tests were performed with the anesthesia machine in standby mode, according to the manufacturer's specifications. Both the PNT and HWA were calibrated separately with room air using a 3 L super syringe, according to the flow-integration method [15]. A schematic of the experimental configuration is shown in Fig. 1. The electronically transduced $\dot{V}$ waveforms from both devices were low-pass filtered at 10 Hz (Frequency Devices Inc., 90IP, Ottawa, IL) and sampled at 40 Hz using a 12-bit analog-to-digital converter (USB-6008, National Instruments, Austin, TX). Custom-written data acquisition software (LabVIEW 2011, National Instruments) provided real-time monitoring of $\dot{V}$ and V_T on a breath-by-breath basis for each device.

The mechanical test lung was ventilated in volume control mode, with a fresh gas flow rate of 6 L min⁻¹ compressed air. Volatile anesthetics were delivered using individual vaporizers for isoflurane (Aladin Cassette with S/5 ADU Carestation, General Electric), sevoflurane (Vapor 2000 with Fabius GS, Drägerwerk), and desflurane (D-Vapor with Fabius GS, Drägerwerk). Anesthetic concentrations of 1.2, 2.0, and 6.0% corresponded to the minimum alveolar concentration (MAC) for isoflurane, sevoflurane, and desflurane, respectively. Delivered MAC was monitored at the Y-piece using a side-stream gas analyzer (Capnomac Ultima, Datex-Engstrom, Finland), with measuring ranges of 0–5% (isoflurane), 8% (sevoflurane), and 18% (desflurane) and corresponding accuracies of 0.2, 0.2, and 1.0 vol.%, respectively [16]. Ventilator rates of 8, 10, and 12 min⁻¹, and V_T of 400, 600, and 800 mL were used with compressed air and increasing anesthetic concentrations of 1.0, 1.5,

¹Equation 6 is derived according to Eqs. 2–5, using Matlab R2014b Symbolic Math Tool box 6.1.

and 2.0 MAC for each agent. Several breaths were collected for 1 min during each measurement condition, with the first seven breaths used in the analysis. Delivered V_T at the airway opening was estimated on a breath-by-breath basis using trapezoidal integration of the sampled $\dot{V}_{PNT}$ waveform, and averaging the inspired and exhaled V_T . The set V_T on the anesthesia machine ventilator was adjusted to yield the desired V_T as reported by the calibrated PNT. Between each measurement period, the test lung was ventilated with compressed air to washout the previous anesthetic.

3.2 Flow compensation

Since the PNT assumes an inverse relationship between $\dot{V}$ and μ (Eq. 1), the addition of volatile anesthetics in clinically relevant concentrations will have a negligible influence on effective gas viscosity [12, 17]. By contrast, a more complicated relationship exists between $\dot{V}_{HWA}$ and several other properties of the gas [9, 10]. Based on previous findings [4, 12], we assumed that changes in gas density were primarily responsible for changes in $\dot{V}_{HWA}$ during measurement with anesthetic gas mixtures. Thus we adjusted $\dot{V}_{HWA}$ using a compensation factor accounting for changes in gas mixture density (ρ_{mix}) relative to the density of the gas used for the calibration of the HWA (ρ_{cal}):

$$\dot{V}'_{HWA} = \left(\frac{\rho_{cal}}{\rho_{mix}} \right) \dot{V}_{HWA} \quad (7)$$

where $\dot{V}'_{HWA}$ is the compensated estimate of HWA flow. Estimates of gas density for individual species were based on molecular weights and ideal gas behavior at 23 °C and 1 atm. (Table 1). The resultant densities of the various mixtures used in this protocol were calculated from molar fractions of the individual species (“Appendix”).

4 Statistical analysis

Comparisons between the HWA and PNT estimates of V_T were performed using correlation and Bland–Altman plots. Percent difference between the estimated tidal volumes from the HWA ($V_{T,HWA}$) and the PNT ($V_{T,PNT}$) was computed as:

$$\%Difference = 100\% \times \frac{V_{T,HWA} - V_{T,PNT}}{0.5 \times (V_{T,HWA} + V_{T,PNT})} \quad (8)$$

Four-way analysis of variance (ANOVA) was used to compare percent differences in estimates of V_T with the HWA and PNT, accounting for effects of individual anesthetic agent (AA), agent concentration (AC), respiratory rate (RR), and V_T . If significance was obtained with ANOVA, *post hoc* analysis on anesthetic agent (the only categorical factor) was performed using the Tukey HSD criterion. Paired t-tests were used to compare differences between uncompensated and compensated estimates of V_T (Eq. 7). $P < 0.05$ was considered statistically significant. All analyses were performed using MATLAB R2014b

(The Mathworks, Inc., Natick, MA) and SigmaPlot 12.3 (Systat Software, Inc., San Jose, CA).

5 Results

Figure 2 shows the correlation and Bland–Altman plots for the various ventilator settings and anesthetic concentrations used in the protocol. Estimates of $V_{T,PNT}$ and uncompensated $V_{T,HWA}$ demonstrated close agreement under baseline conditions with dry compressed air. By contrast, we observed progressively less agreement between the PNT and HWA with increasing concentrations of isoflurane, sevoflurane and desflurane, especially at high V_T . For the GE Carestation machine using isoflurane, we also observed some minor deviation between the $V_{T,PNT}$ and the desired V_T after data processing. Ventilation with isoflurane, sevoflurane, and desflurane yielded percent differences of 6.3 ± 3.0 , 10.0 ± 7.3 , and $25.8 \pm 17.2\%$, respectively, when averaged over the ranges of anesthetic concentrations, ventilator frequencies, and tidal volumes. Statistical comparisons are summarized in Table 2. Four-way ANOVA determined five effects significantly contributed to the absolute value of percent difference in estimated V_T : all involving agent concentration as either a main effect or an interaction term (Table 2). Increasing agent concentration resulted in increasing discrepancies between $V_{T,HWA}$ and $V_{T,PNT}$. *Post hoc* comparisons of agent using the Tukey HSD criterion demonstrated that sevoflurane yielded a significantly larger percent difference compared to isoflurane ($P < 0.001$), and that desflurane yielded a significantly larger percent difference compared to sevoflurane ($P < 0.001$). Positive correlations were observed between the percent differences with respect to both respiratory rate and V_T when anesthetic agent concentration was greater than zero. Thus anesthetic agent and concentration were the strongest predictors of variation for the observed differences between $V_{T,HWA}$ and $V_{T,PNT}$, with additional minor influences from respiratory rate and V_T at non-zero anesthetic agent concentrations.

Figure 3 shows the percent differences between $V_{T,HWA}$ and $V_{T,PNT}$ as a function of ρ_{mix} as estimated for the baseline conditions and increasing anesthetic concentrations (Appendix). Differences between the two flowmeters increased linearly with ρ_{mix} ($R^2 = 0.989$). The use of a density-compensation factor (Eq. 7) for isoflurane, sevoflurane, and desflurane significantly reduced the percent difference observed between $V_{T,HWA}$ and $V_{T,PNT}$ at all non-zero concentrations of anesthetic agent, as shown in Fig. 4.

6 Discussion

In this study, we demonstrate that changes in volatile anesthetic concentration yield systematic differences between pneumotachographic and anemometric estimates of tidal volume. We used these two flow measuring devices to simultaneously measure flow at the airway opening of a mechanical test lung during ventilation with three commonly used anesthetic agents over a range of clinically relevant concentrations, ventilator rates, and tidal volumes. Our main findings include: (1) differences in estimates of V_T occur for isoflurane, sevoflurane, and desflurane compared with baseline conditions; (2) these differences in V_T increase with increases in anesthetic concentration; and (3) a simple compensation factor

accounting for changes in the delivered gas mixture density significantly reduces the observed differences between flowmeters.

Previously, Habre et al. [12] characterized changes in the physical properties of gas mixtures for various concentrations of volatile anesthetics, and concluded that clinically relevant concentrations significantly affected estimates of ρ (*i.e.*, up to 48% deviation compared to room air), but only marginally affected estimates of μ (*i.e.*, less than 4% deviation compared to room air). Following these principal findings, Miyaji et al. [4] demonstrated that ventilation with sevoflurane and desflurane altered delivered V_T for feedback-control conditions determined using a variable orifice flow sensor. Their findings are similar to our observations that increasing concentrations of less potent anesthetic agents yield considerable differences in estimated V_T between the PNT and HWA (Fig. 2). However, the variable orifice flow sensor relies on turbulent flow across a movable flap, which they demonstrated is sensitive to differences in the measured P due to variations in ρ between gas mixtures, in contrast to the $\dot{V}$ measuring devices used in this study. Our results therefore not only support previous findings that mechanical ventilation with volatile anesthetics affects the accuracy of $\dot{V}$ measurement, but also suggest that the corresponding changes in gas mixture yield device-specific biases in estimated V_T . The underlying mechanism for such biases may arise from the different physical principles of $\dot{V}$ measurement for the PNT and HWA.

The PNT is commonly used in research settings for accurate flow measurement during mechanical ventilation [12, 17–19]. The PNT measures a differential pressure across a calibrated resistive element, and assumes that the relationship between P and $\dot{V}$ is linear and dependent on μ , but not on other gas properties such as ρ , k , and c_p [12, 17]. By contrast, the HWA operates on the principle of convective heat transfer from a current-carrying wire immersed in a flowing gas. Equations 2–3 describe how the flow rate of the gas is related to current through the heated wire. The parameters for this relationship will not be identical for all gas mixtures, but may be described in terms of additional physical properties, such as ρ (Eqs. 4–5). This is in contrast to the PNT, which estimates a flow that is inversely proportional to μ (Eq. 1).

Given the differences between the physical principles of measurement for the PNT and HWA, combined with the influence of volatile anesthetics on gas mixture density, it is apparent why device-specific biases would occur for variations in gas composition. The observed differences in estimates of V_T between the PNT and HWA are linearly correlated to the calculated density of the gas mixture for isoflurane, sevoflurane, and desflurane (Fig. 3). Accordingly, *post hoc* compensation for changes in ρ_{mix} reduced the average observed measurement bias to 3% or less for all concentrations of the anesthetic agents. Our findings indicate that increases in ρ_{mix} during ventilation with volatile anesthetics lead to the detection of larger V_T for the HWA compared to the PNT. The effectiveness of this compensation, along with the lack of available data quantifying the thermal conductivity and specific heat capacity for volatile anesthetics, suggest that it is reasonable to assume that measurement error associated with anemometry is primarily dependent on the $\rho_{\text{mix}}/\rho_{\text{cal}}$ ratio. Although statistically significant, the higher order interaction terms between anesthetic agent concentration, respiratory rate, and V_T predict variations in percent difference that are an

order of magnitude smaller than those predicted by changes in density. The physical mechanism underlying these interaction terms may be related to nonlinear effects that become enhanced at higher flow rates and anesthetic agent concentrations. Nevertheless, differences between the HWA and PNT are effectively minimized simply by accounting for changes in ρ_{mix} for the corresponding anesthetic concentration.

Recent anesthesia machine models have incorporated flow compensation features to correct estimates of delivered tidal volume. For example, the Dräger Fabius GS uses a simple correction factor to adjust its integrated HWA flowmeter calibration when the user indicates that desflurane is being used [20]. Such compensation is currently only available for desflurane, and not in all anesthesia machine models. For applications that require high accuracy of measured flow in the presence of other volatile agents, such as isoflurane and sevoflurane, our results indicate that a relatively simple compensation technique (Eq. 7) may also be used. [17, 19].

One limitation of this study is the fact that absolute measurement errors for the PNT and HWA are not determined (instead the relative error is used), and that we report measurements using a single HWA. Previous studies [12, 17] have reported negligible effects of volatile anesthetics on $\dot{V}$ as measured with a PNT calibrated on room air, which would suggest that it is sufficient to compare the relative discrepancies between the two techniques as presented here. Measurement error may be introduced by variations in gas mixture properties caused by changes in temperature, pressure, and humidity relative to the conditions of the gas mixture during flowmeter calibration. The impact of gas temperature and humidity on measurement error have been characterized for orifice-type flowmeters [21, 22], although such factors minimally influence HWA measurement error [23]. Although gas saturated with water vapor at 37 °C may more closely mimic delivered gases used in clinical practice, the use of humidified gas in our experimental protocol would not alter the general conclusions presented here. Rather, the addition of water vapor as a constituent of the gas mixture would introduce another source of variability in ρ , μ , k , and c_p . Furthermore, while there may exist slight operational differences between constant-temperature and constant-current mode anemometers, our data and the presented theory suggest that changes in gas composition likely yield similar effects on anemometric measurement of flow. Despite the use of two different anesthesia machines (isoflurane was delivered via the General Electric S/5 ADU Carestation, yet sevoflurane and desflurane via the Dräger Fabius GS), the linear relationship between gas mixture density and relative error between the HWA and PNT volume measurements was consistent across all anesthetic agents and concentrations (Fig. 3). This study expands upon previous work to include the effects of the more potent anesthetic isoflurane while also characterizing differences across a range of clinically relevant concentrations, ventilator rates, and V_T .

In summary, we have shown that volatile anesthetics at clinically relevant concentrations can have a significant impact on flow measurement and flow-derived estimates of tidal volume. Such device-specific biases depend primarily on the choice and concentration of anesthetic agent, but do not depend heavily on ventilator rate nor on delivered volume. Systematic differences in estimates of tidal volume between the pneumotachograph and hot-wire anemometer can be effectively compensated by accounting for changes in the density of the

delivered gas mixture. These findings provide new insight for facilitating accurate flow measurement and tidal volume monitoring during mechanical ventilation with volatile anesthetics.

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Appendix

Density (ρ) for a homogeneous gas is expressed as the mass contained within a given volume:

$$\rho = \frac{nM}{V} \quad (9)$$

where n is the number of moles in a given volume V , and M is the molecular weight of the particular gas species. For an ideal gas this expression can be re-written as:

$$\rho = \frac{PM}{\mathcal{R}T} \quad (10)$$

where P is absolute pressure, T is absolute temperature, and $\mathcal{R}$ is the universal gas constant. In a mixture of N ideal gases, the mole fraction (x_i) of each species is given by the ratio of the number of moles of each species (n_i) relative to the total number of moles (n_{mix}):

$$x_i = \frac{n_i}{n_{\text{mix}}} \text{ where } n_{\text{mix}} = \sum_{i=1}^N n_i \quad (11)$$

The gas mixture density (ρ_{mix}) is then given by modifying (Eq. 9) to obtain:

$$\rho_{\text{mix}} = \frac{1}{V} \sum_{i=1}^N n_i M_i = \frac{n_{\text{mix}}}{V} \sum_{i=1}^N x_i M_i \quad (12)$$

where M_i is molecular weight of each species. Again assuming ideal gas behavior:

$$\rho_{\text{mix}} = \frac{P}{\mathcal{R}T} \sum_{i=1}^N x_i M_i \quad (13)$$

which is equivalent to the weighted average of individual species densities at the same reference temperature and pressure:

$$\rho_{mix} = \sum_{i=1}^N x_i \rho_i \quad (14)$$

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Glossary

μ	Gas viscosity
ρ	Gas density
ρ_{mix}	Density of gas mixture
ρ_{cal}	Density of gas used for calibration
n	Number of moles of gas
N	Number of ideal gas species in gas mixture
n_{mix}	Total number of moles of gas in mixture
P	Absolute pressure
M	Molecular weight of gas
T	Temperature of gas
V	Volume of gas
i	Gas species index
x_i	Molar fraction of gas species i
$\mathcal{R}$	Universal gas constant
$\dot{V}$	Flow
$\dot{V}_{\text{PNT}}$	Flow estimated using PNT
$\dot{V}_{\text{HWA}}$	Flow estimated using HWA
$\dot{V}'_{\text{HWA}}$	Compensated estimate of flow from the HWA

V_T	Tidal volume
$V_{T,HWA}$	Estimated tidal volume from the HWA
$V_{T,PNT}$	Estimated tidal volume from the PNT
PNT	Pneumotachograph
HWA	Hot-wire anemometer
MAC	Minimum alveolar concentrations
ANOVA	Analysis of variance
P	Differential pressure across PNT resistive element
C_m	Coefficient from PNT mesh screen geometrical properties
α	Viscous resistance coefficient for PNT mesh screen
h	Heat transfer coefficient between gas and HWA wire
T_w	Temperature of HWA wire
T_g	Temperature of ambient gas
A_w	Surface area of heat exchange on HWA wire
R_w	Resistance of HWA wire
i_w	Current through the HWA wire
A, B	Calibration constants of King's Law
A_{cs}	Cross-sectional area of the gas flow in HWA
d_w	Diameter of HWA wire
C_{w1}, C_{w2}	Coefficients from HWA geometrical properties
k	Thermal conductivity of gas
c_p	Specific heat capacity

Fig. 1.

Schematic of experimental set-up, demonstrating serial arrangement of the pneumotachograph (PNT) and hot-wire anemometer (HWA) for simultaneous measurement of flow during ventilation of a mechanical test lung with the anesthesia machine

Fig. 2.

a Correlation for HWA and PNT estimated V_T during ventilation with isoflurane (purple), sevoflurane (yellow), and desflurane (blue). Solid lines indicate lines of identity. **b** Bland-Altman plots for HWA and PNT estimates of V_T ; solid lines represent mean, dashed lines represent ± 1.96 SD. Legend included for symbols and colors of corresponding tested conditions. Data points represent the mean for all breaths at each measurement condition

Fig. 3. Relationship between density of the gas mixture (ρ_{mix}) and percent difference for HWA and PNT estimates of V_T , with a *straight dashed line* fitted to the data ($R^2 = 0.989$). *Darker shading* corresponds to increasing MAC for each agent. *Data* presented as average percent difference across all ventilator rates and V_T , *error bars* represent standard deviation

Fig. 4.

Comparison of percent difference between HWA and PNT estimates of V_T before and after density compensation for **a** isoflurane, **b** sevoflurane, and **c** desflurane. Each *bar* represents absolute values for average percent difference across all ventilator rates and V_T , *error bars* represent standard deviation. *Asterisks* indicates statistically significant differences ($P < 0.05$) before and after compensation

Table 1

Densities of gas species

Species	Density (kg m ⁻³)
N ₂	1.153
Ar	1.645
O ₂	1.318
CO ₂	1.820
Isoflurane	7.592
Sevoflurane	8.232
Desflurane	6.915

Reference values obtained from NIST WTT for dry conditions at 23 °C and 1 atm

Table 2

Significance levels for four-way ANOVA of V_T absolute percent difference, and post hoc pairwise comparisons using the Tukey HSD criterion

Factor / Comparison	P value
ANOVA	
AC · AA	<0.001
AC	<0.001
AC · V_T	<0.001
AC · RR	<0.001
AC · V_T · RR	0.003
V_T · RR	0.079
V_T	0.083
RR	0.147
AA	0.688
AA · RR	0.773
AA · V_T	0.799
AC · AA · V_T · RR	0.813
AC · AA · RR	0.868
AA · V_T · RR	0.944
AC · AA · V_T	0.975
<i>Post-hoc</i> Tukey HSD	
Isoflurane–Sevoflurane	<0.001
Sevoflurane–Desflurane	<0.001
Isoflurane–Desflurane	<0.001

AA Anesthetic agent, AC anesthetic concentration, V_T set tidal volume, RR respiratory rate