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Respiratory Mechanics during Xenon Anesthesia in Pigs

Comparison with Nitrous Oxide

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Background: **Because of its high density and viscosity, xenon (Xe) may influence respiratory mechanics when used as an inhaled anesthetic. Therefore the authors studied respiratory mechanics during xenon and nitrous oxide (N_2O) anesthesia before and during methacholine-induced bronchoconstriction.**

Methods: **Sixteen pentobarbital-anesthetized pigs initially were ventilated with 70% nitrogen–oxygen. Then they were randomly assigned to a test period of ventilation with either 70% xenon–oxygen or 70% N_2O–oxygen (n = 8 for each group). Nitrogen–oxygen ventilation was then resumed. Tidal volume and inspiratory flow rate were set equally throughout the study. During each condition the authors measured peak and mean airway pressure (P_{max} and P_{mean}) and airway resistance (R_{aw}) by the end-inspiratory occlusion technique. This sequence was then repeated during a methacholine infusion.**

Results: **Both before and during methacholine airway resistance was significantly higher with xenon–oxygen (4.0 ± 1.7 and 10.9 ± 3.8 cm $H_2O \cdot s^{-1} \cdot l^{-1}$, mean ± SD) when compared to nitrogen–oxygen (2.6 ± 1.1 and 5.8 ± 1.4 cm $H_2O \cdot s^{-1} \cdot l^{-1}$, $P < 0.01$) and N_2O–oxygen (2.9 ± 0.8 and 7.0 ± 1.9, $P < 0.01$). P_{max} and P_{mean} did not differ before bronchoconstriction, regardless of the inspired gas mixture. During bronchoconstriction P_{max} and P_{mean} both were significantly higher with xenon–oxygen (P_{max}, 33.1 ± 5.5 and P_{mean}, 11.9 ± 1.6 cm H_2O) when compared to N_2O–oxygen (28.4 ± 5.7 and 9.5 ± 1.6 cm H_2O, $P < 0.01$) and nitrogen–oxygen (28.0 ± 4.4 and 10.6 ± 1.3 cm H_2O, $P < 0.01$).**

Conclusions: **Airway pressure and resistance are increased during xenon anesthesia. This response is moderate and not likely to assume major importance for the general use of xenon in anesthesia. (Key words: Experimental bronchoconstriction; general anesthesia; lung function.)**

XENON (Xe), because of its high density (ρ_{xe} = 5.9 kg/m^3 at 0°C and 1.013 bar) and viscosity (η_{xe} = 2.3 Pa/s at 25°C and 1 bar), may impair respiratory function when used as an inhaled anesthetic. A need for caution when using xenon in patients with lung disease has been suggested by previous studies of the effects of physical gas properties on pulmonary mechanics[1-5] and gas exchange,[6-13] which revealed that respiratory mechanics in particular are affected by density and viscosity of specific gas mixtures. For example, airway resistance (R_{aw}) is markedly increased when breathing sulfur hexafluoride (SF_6)-oxygen mixtures,[2,4] which are less viscous (η_{SF6} = 1.57) but more dense (ρ_{SF6} = 6.6) than air (η_{air} = 1.83, ρ_{air} = 1.29). Even with xenon ventilation, an increase in R_{aw} related to the inspiratory xenon concentration has been found previously by Zhang *et al.*[14] During experimentally induced bronchoconstriction, however, these authors tested only a lower xenon concentration (50%), which did not produce any significant effect on respiratory mechanics or gas exchange. Furthermore, they performed their measurements in open-chest dogs; *i.e.*, during conditions that are known to affect the impact of methacholine on R_{aw}.[15] In contrast, gas exchange and lung mechanics improve in asthmatic patients during artificial ventilation with helium (He)-oxygen mixtures,[13] which have a low density (ρ_{He} = 0.18) but a higher viscosity (η_{He} = 1.97) when compared to nitrogen (N_2, ρ_{N_2} = 1.25, η_{N_2} = 1.79) and nitrous oxide (N_2O, ρ_{N_2O} = 1.94, η_{N_2O} = 1.46).

The aim of the current investigation was to study

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respiratory mechanics and gas exchange in anesthetized, closed-chest pigs during controlled positive pressure ventilation with an inspiratory mixture composed of either 70% xenon or 70% N_2O + 30% oxygen or with a 70% nitrogen + 30% oxygen.

Materials and Methods

Animals, Anesthesia Technique, and Animal Preparation

The study design was approved by the institutional and federal animal care committee (Tuebingen, Germany). Eighteen pigs (mean body weight 41 ± 4 kg), randomly assigned to receive either N_2O or xenon (n = 9 for each group), were anesthetized with pentobarbital sodium (Nembutal, Sanofi-Wintrop, Munich, Germany; 15 mg/kg induction dose, followed by a continuous infusion of 6–12 mg · kg^{-1} · h^{-1}) supplemented every 4 h and before any surgical or noxious stimuli by 0.3-mg intravenous boluses of buphrenorphine (Temgesic; Boehringer Mannheim, Mannheim, Germany) to prevent an increase in heart rate and blood pressure. The adequacy of this anesthetic procedure has been tested in previous experiments.[16] To eliminate any possible respiratory effort, the animals were paralyzed using alcuronium dichloride (Alloferin, Hoffmann-LaRoche, Basel, Switzerland; 0.25 mg/kg initial dose followed by a continuous application of 0.25 mg · kg^{-1} · h^{-1}) throughout the study period. Depth of anesthesia was controlled by hemodynamic variables and continuous electroencephalographic monitoring (Neurotrac; Interspec Inc., Conshohocken, PA). The spectral edge frequency was always below 15 Hz, and the median power frequency was 5–10 Hz.

After induction of anesthesia, the pigs were intubated with a cuffed endotracheal tube (8.5 mm ID), and their lungs were mechanically ventilated while in the supine position using a semiclosed circuit anesthesia machine (Cicero; Drägerwerk AG, Lübeck, Germany) with a carbon dioxide absorber placed in the inspiratory limb of the breathing circuit. A central venous catheter and a thermistor-tipped pulmonary artery flotation catheter (model 93A 754 7F; Baxter Healthcare, Irvine, CA) were placed through an external jugular vein into the superior vena cava and into a pulmonary artery, respectively, for drug infusion, monitoring, and data sampling of hemodynamics and gas exchange. A 4-French catheter was inserted into a femoral artery for hemodynamic monitoring and arterial blood gas sampling. Mixed venous and arterial blood samples were analyzed for oxygen tension (P_{O_2}) and carbon dioxide tension (P_{CO_2}), using an IL 1306 blood gas analyzer (Instrumentation Laboratory, Lexington, MA), and for arterial and mixed venous hemoglobin oxygen saturation (Sa_{O_2} and Sv_{O_2}) and total hemoglobin concentration by means of the Co-Oximeter IL 282 (Instrumentation Laboratory), which was precalibrated for pig blood.

The Cicero anesthesia machine, which was modified to provide xenon application, performs mechanical ventilation by means of a motor-driven piston pump, which provides constant inspiratory flow. Ventilator settings throughout the experiment were as follows: tidal volume (V_T) = 12–14 ml/kg (adjusted to achieve a Pa_{CO_2} between 37 and 43 mmHg); frequency (f) = 12/min; inspiratory time (T_i) = 1.5 s; inspiration hold = 1 s; expiratory time (T_e) = 2.5 s; and positive end-expiratory pressure (PEEP) = 5 cm H_2O. The inspiratory oxygen fraction (FI_{O_2}) was kept constant at 30%, regardless of the inspiratory mixture actually used (N_2O–oxygen, xenon–oxygen, or nitrogen–oxygen, see fig. 1) and was continuously measured in the inspiratory limb of the ventilator circuit by the machine-integrated oxygen monitor (a fuel cell sensor with an accuracy of ± 2%) calibrated before each experiment. Fresh gas supply of the anesthesia circuit was set to one half the minute ventilation throughout the experiment. Density and viscosity of the gas mixtures for the experimental conditions (37°C, 1 bar) were ρ_{Xe/O_2} = 3.95, η_{Xe/O_2} = 2.4, ρ_{N_2O}/O_2 = 1.57, η_{N_2O}/O_2 = 1.67, ρ_{N_2}/O_2 = 1.13, and η_{N_2}/O_2 = 1.93. Airway pressure (P_{aw}) was measured through a port placed between the endotracheal tube and Y piece with a pressure transducer (142PC01G; Honeywell, Plymouth, MN) with a range of 70 cm H_2O, a linearity of 0.75%, and a precision of 0.25%. Flow was measured with a heated pneumotachograph (Fleisch No. 2; Fleisch, Lausanne, Switzerland) connected to a differential pressure transducer (PC 500; PasCal, Schwerin, Germany) and calibrated for each gas mixture using a 1-l supersyringe. Expiratory P_{CO_2} was analyzed with the side-stream infrared carbon dioxide analyzer integrated in the anesthesia machine. Gas sampling rate was 200 ml/min, the delay between flow and carbon dioxide signal was corrected using values determined separately for gas mixtures containing 70% nitrogen, N_2O, or xenon in 30% oxygen ($Delay_{N_2}$ = 185 ms, $Delay_{N_2O}$ = 175 ms and $Delay_{Xe}$ = 240 ms. For recording P_{aw}, Flow, and P_{CO_2} signals on a personal computer we used the DaqBoard 216 A/D converter system (IOtech, Cleveland, OH) and the data acquisition software DASYLab (Datalog, Mönchengladbach, Germany).

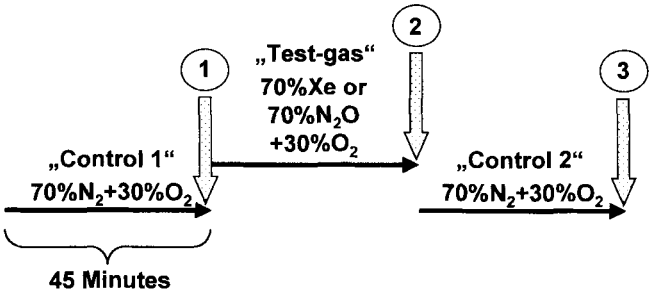

Fig. 1. Both phases of our experiments, *i.e.*, before and during bronchoconstriction, were subdivided into three 45-min periods of ventilation with either control gas (70% nitrogen + 30% oxygen) or test gas (70% xenon or 70% N_2O + 30% oxygen). Measurements were performed at the end of each period, as shown by the white dotted arrows in chronologic order.

Study Design

Measurements were performed at the end of three sequential 45-min periods of ventilation with either nitrogen–oxygen (periods 1 and 3 designated as control 1 and control 2) or anesthetic gas (xenon–oxygen or N_2O–oxygen, depending on the random order of the experiment, period 2, designated as test-gas period) before and during methacholine infusion (fig. 1). At each point of measurement, we recorded the P_{aw}, Flow, and P_{CO_2} signals for three sequential 2-min periods of continuous measure at a frequency of 100 Hz for subsequent off-line analysis. Additionally, we registered heart rate, mean arterial pressure, central venous pressure, mean pulmonary artery pressure, pulmonary artery occlusion pressure, and cardiac output. Methacholine infusion was started with a dosage of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which was increased stepwise (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) every 3–5 min, until R_{aw} had approximately doubled when compared to the value measured with baseline conditions before methacholine infusion. Then, the study protocol was repeated identically and analogous to the previous series of measurements.

Calculations

Pulmonary mechanics were assessed according to the method described by Bates *et al.*[17] The same technique was also used to separately determine the resistance of the endotracheal tube (R_{tube}) for each experimental gas mixture over a flow range between 0.1 and 1.0 l/s. For this purpose, the tip of the cuffed endotracheal tube was positioned at the distal end of an artificial trachea, which was connected to a 3-l bag.

The two prerequisites for using the occlusion technique described by Bates *et al.*,[17] namely, continuous inspiratory flow and sudden flow interruption at the end of inspiration, are met during volume-controlled ventilation with the CICERO anesthesia machine. In contrast to previous investigations using this technique, the sudden flow interruption is not obtained by occluding the inspiratory valve, as occurs when using intensive care unit ventilators, but by the sudden arrest of the piston pump. Nevertheless, a square flow pattern is achieved regardless of the interruption mode. According to previous descriptions of this occlusion technique, we determined the peak airway pressure (P_{max}), and the airway pressures registered both immediately after end-inspiratory flow interruption (P_1) and after an occlusion period of 6 s (P_2) from each occluded breath. By subtraction of the pressure component imposed by the resistance of the endotracheal tube (calculated by multiplying R_{tube} and inspiratory flow) from P_{max} we obtained an estimation of the peak pressure within the trachea (P_{max}'). The correction proposed by Bates *et al.*,[18] which consists of extrapolating the pre- and postocclusion pressure signals to the point in time when the inspiratory valve is semiclosed, was used for determining P_{max} and P_1, to account for the finite time of flow interruption. For this purpose, the postocclusion pressure decay, which is caused by the stress relaxation of the lung tissue and by gas redistribution, was analyzed with a logarithmic function determined by the least-squares fit technique as described by Marquardt.[19] This logarithmic fit was back-extrapolated to the time of flow interruption to obtain P_1. Inspiratory resistance was then determined as R_{min} and R_{max} by the equations

$$R_{min} = ((P_{max} - P_1)/Flow) \quad (1)$$

$$R_{max} = ((P_{max} - P_2)/Flow) \quad (2)$$

Because R_{min} equals the sum of R_{aw} and R_{tube}, R_{aw} was obtained by subtraction of R_{tube} from R_{min}. ΔR was then calculated as

$$\Delta R = R_{max} - R_{min} \quad (3)$$

The total inspiratory pressure drop over the bronchial tree (ΔP) was calculated for each gas mixture as

$$\Delta P = P_{max} - P_1 \quad (4)$$

and the ΔP ratio of two different gas mixtures x and y was calculated as $\Delta P_x/\Delta P_y$.

Static and dynamic compliances (C_{st} and C_{dyn}) were calculated by the equations

$$C_{st} = V_T/(P_2 - PEEP_i) \quad (5)$$

$$C_{dyn} = V_T/(P_1 - PEEP_i) \quad (6)$$

where $PEEP_i$ is the intrinsic positive end-expiratory pressure, determined by the end-expiratory occlusion maneuver, *i.e.*, P_{aw} 10 s after occlusion. Representative original P_{aw} and Flow curves registered during baseline conditions and during methacholine infusion, which further explain these calculations, are shown in figures 2A and B, respectively.

The carbon dioxide expirograms were analyzed for the alveolar carbon dioxide slope (S_{CO_2}), which was calculated according to Fletcher *et al.*[20] and Meyer *et al.*[21,22] by linear fit of the expiratory P_{CO_2} plotted as a function of expired volume plot between 70 and 95% of expiration, which yields the change of P_{CO_2} normalized for mixed expired P_{CO_2} per unit of expired volume. In addition, series dead space was computed using the method described by Fletcher *et al.*[20] The expired volume was calculated by integration of the flow signal.

Dead space ventilation (V_D/V_T) and venous admixture (Q_S/Q_T) were calculated from blood gas data and mixed expired carbon dioxide pressure (PE_{CO_2}) using the standard equations

$$V_D/V_T(\%) = (Pa_{CO_2} - PE_{CO_2})/(Pa_{CO_2} \times 100) \quad (7)$$

$$Q_S/Q_T(\%) = (Cc_{O_2} - Ca_{O_2})/(Cc_{O_2} - Cv_{O_2}) \times 100 \quad (8)$$

where Ca_{O_2} and Cv_{O_2} are the arterial and mixed venous oxygen content, respectively, and Cc_{O_2} is the capillary oxygen content derived from the alveolar P_{O_2} (PA_{O_2}) calculated by the simplified alveolar gas equation[23] as

$$PA_{O_2} = (P_B - P_{H_2O}) \times FI_{O_2} - Pa_{CO_2}/RQ \quad (9)$$

where P_B is the barometric pressure, P_{H_2O} is water-vapor pressure, FI_{O_2} is the inspiratory oxygen concentration, and RQ is the respiratory quotient assumed to be 0.8. Arterial to alveolar oxygen difference was then calculated as $PA_{O_2} - Pa_{O_2}$.

Statistical Analysis

All data are presented as mean ± SD. After normal distribution was confirmed by the Kolmogorov-Smirnov test, a two-way analysis of variance of repeated measures of one repeated factor, followed, when significant, by the Tukey test, was used to compare the data obtained within both groups (repeated factor) during the nitrogen-control periods and during the phases of xenon and N_2O ventilation, before and after methacholine, respectively, and to further compare the differences between the two groups (not repeated factor) during xenon and N_2O inhalation. Statistical significance was assumed at $P < 0.05$.

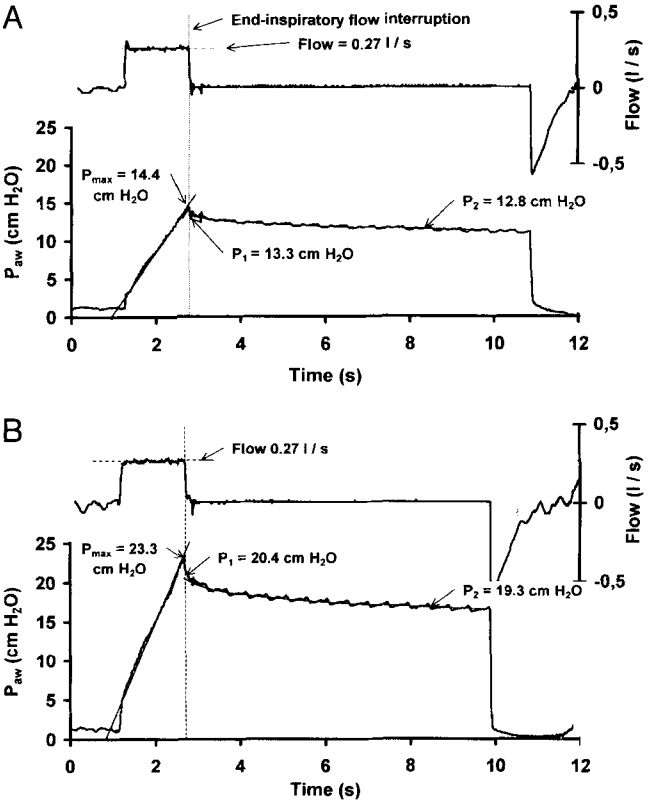

Fig. 2. (*A*) Original airway pressure (P_{aw}) and flow curves registered during control conditions (inspiratory gas mixture composed by 70% nitrogen and 30% oxygen, no methacholine infusion). Note the rectangular flow pattern that results from the constant inspiratory flow and the simultaneous linear increase in P_{aw}. After inspiratory flow decreases sharply to zero at the end of inspiration, a sudden drop is observed in the P_{aw} tracing. According to Bates *et al.*,[18] peak airway pressure (P_{max}) is determined by linear extrapolation of the P_{aw} signal preceding flow interruption up to the point in time when flow has reached one half the inspiratory value (this point is indicated by the vertical dotted line). Correspondingly, P_1 is determined by back extrapolation of the logarithmic postocclusion pressure decay to the same point. The preinterruption linear and postinterruption logarithmic fit are shown superimposed to the corresponding parts of the P_{aw} curve. P_2 was determined as the P_{aw} after 6 s of flow interruption. (*B*) P_{aw} and flow curves registered in the same animal during methacholine infusion. Inspiratory flow pattern remain unchanged, but the P_{aw} increased more steeply and the postinterruption pressure drop, as well as the decay, from P_1 to P_2 is more pronounced.

Results

The results of our experiments are summarized in figure 3 and in tables 1 and 2. In each group, the first

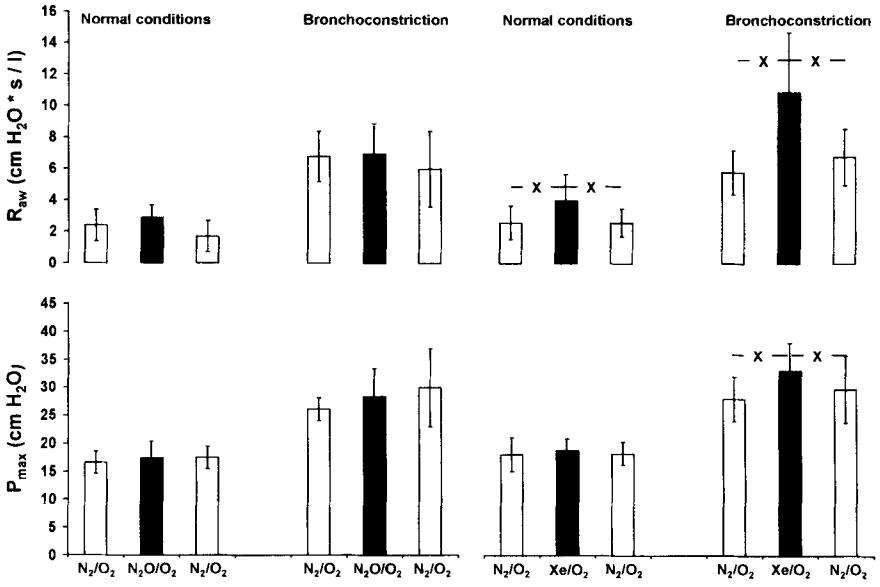

Fig. 3. The charts show the results concerning airway resistance (R_{aw}) and peak airway pressure (P_{max}) with all experimental conditions. Data are mean ± SD, X = significant difference between xenon–oxygen and nitrogen–oxygen. The white bars indicate the values obtained during nitrogen–oxygen ventilation, the dark ones those during xenon–oxygen or N_2O–oxygen ventilation, respectively. Note that during xenon–oxygen ventilation R_{aw} was significantly higher both before and during bronchoconstriction when compared to the corresponding nitrogen–oxygen controls. A statistically significant increase in P_{aw}, however, was found during xenon–oxygen ventilation during bronchoconstriction only.

animal had to be discarded from statistical analysis because of a lethal complication during induction of bronchoconstriction in one case (N_2O group) and because of insufficient effect of methacholine in the second case (xenon group). Comparing the data obtained during the two control periods of each series, *i.e.*, the periods of nitrogen-oxygen ventilation before and after each test gas period, we found a statistically significant decrease in C_{st} and C_{dyn} and increases in P_{max}, P_1, P_2, and P_{mean} in the N_2O group during methacholine infusion only. There were no statistically significant differences between the two controls for any of the other conditions. The effects of methacholine infusion were validated by comparing the data related to airway pressure and resistance before and during bronchoconstriction during the nitrogen-oxygen control periods: all these values (except for R_{tube}) significantly increased during methacholine infusion ($P < 0.01$); C_{st} and C_{dyn} simultaneously decreased ($P < 0.01$). The methacholine dosage necessary for induction of bronchoconstriction was similar in both groups (40.5 ± 42.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the xenon group and 36.1 ± 10.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the N_2O group). The large SD in the xenon group is caused by two single animals that required a relatively high (143.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and low (12 $\mu g \cdot kg^{-1} \cdot min^{-1}$) dosage, respectively.

Substitution of xenon for nitrogen significantly increased R_{min}, R_{max}, R_{aw}, and R_{tube} before and during methacholine infusion ($P < 0.01$). These parameters also were increased when comparing the xenon and N_2O group with both study conditions ($P < 0.01$). In contrast, they were not affected when nitrogen was replaced by N_2O. During methacholine-induced bronchoconstriction P_{max} and P_{mean} were significantly higher with xenon-oxygen ventilation when compared to the nitrogen-oxygen controls ($P < 0.01$). In contrast, there were no statistically significant differences in P_{max} or P_{mean} during xenon-oxygen and nitrogen-oxygen ventilation before bronchoconstriction or during N_2O-oxygen and nitrogen-oxygen ventilation during baseline conditions and during bronchoconstriction. During bronchoconstriction, P_{mean}, but not P_{max}, was significantly higher with xenon-oxygen when compared to the N_2O group ($P < 0.01$). In the xenon group, but not in the N_2O group, the ΔP ratio was higher during bronchoconstriction when compared to baseline.

Generally, $PEEP_i$ was low and did not change significantly when replacing nitrogen with xenon or with N_2O, regardless of the experimental condition, but increased during bronchoconstriction when compared to baseline conditions.

Regardless of the inspiratory gas mixture, pulmonary gas exchange was impaired during methacholine infusion, as shown by the lower Pa_{O_2}, the higher Pa_{CO_2}, the Q_S/Q_T, the alveolar-arterial difference in partial pressure of oxygen ($PA_{O_2} - Pa_{O_2}$), and the total dead space (V_{Dtot}) when compared to baseline conditions (table 2). However, before, and during, bronchoconstriction, gas exchange parameters did not differ between the xenon-oxygen and N_2O-oxygen groups, or between nitrogen-oxygen controls and either test gas. In both groups, S_{CO_2} was higher with bronchoconstriction when compared

Table 1. Respiratory Mechanics Values at Each Point of Measurement

	P_{max}' (cm H_2O)	P_{mean} (cm H_2O)	P_1 (cm H_2O)	P_2 (cm H_2O)	ΔP ratio	R_{min} (cm H_2O*s/L)	R_{max} (cm H_2O*s/L)	R_{tube} (cm H_2O*s/L)	ΔR (cm H_2O*s/L)	PEEPi (cm H_2O)	C_{st} (ml/cm H_2O)	C_{dyn} (ml/cm H_2O)
Baseline conditions												
N_2/O_2	17.6 ± 3.0‡	7.7 ± 1.5‡	16.9 ± 3.1‡	16.0 ± 2.9‡		4.4 ± 0.7‡	7.5 ± 1.6‡	1.8 ± 0.6	3.0 ± 1.5‡	2.4 ± 1.3	33.0 ± 9.9‡	31.2 ± 9.5‡
Xe/O_2	18.1 ± 2.8‡	7.3 ± 0.9‡	17.0 ± 2.8‡	16.0 ± 2.6‡	1.55 ± 0.17†‡	6.8 ± 0.9*†‡	10.1 ± 1.9*†‡	2.7 ± 1.0*†	3.3 ± 1.3‡	1.8 ± 0.4†‡	32.4 ± 9.9‡	30.4 ± 9.3‡
N_2/O_2	17.8 ± 2.4‡	7.2 ± 0.7‡	17.0 ± 2.4‡	16.3 ± 2.4‡		4.6 ± 0.7‡	6.9 ± 1.4‡	1.9 ± 0.5	2.3 ± 0.7‡	1.8 ± 0.2‡	31.8 ± 7.7‡	30.3 ± 7.3‡
N_2/O_2	16.1 ± 2.8‡	6.3 ± 0.9‡	15.4 ± 2.7‡	14.8 ± 2.6‡		4.2 ± 0.6‡	6.4 ± 1.4‡	1.8 ± 0.6	2.2 ± 0.8‡	1.5 ± 0.3‡	32.3 ± 5.7‡	30.9 ± 5.6‡
N_2O/O_2	16.8 ± 3.1‡	6.4 ± 1.1‡	16.0 ± 3.2‡	15.4 ± 3.0‡	1.23 ± 0.15†	4.7 ± 0.7†‡	6.6 ± 1.3†‡	1.6 ± 0.5†	1.9 ± 0.7‡	1.2 ± 0.4†‡	30.4 ± 5.9‡	29.2 ± 5.8‡
N_2/O_2	16.9 ± 2.7‡	6.8 ± 1.0‡	16.4 ± 2.7‡	15.7 ± 2.5‡		3.7 ± 0.9‡	6.2 ± 1.2‡	1.9 ± 0.5	2.6 ± 0.9‡	1.7 ± 0.5	30.7 ± 5.6‡	29.2 ± 5.5‡
Bronchoconstriction												
N_2/O_2	27.4 ± 4.2‡	10.6 ± 1.3‡	25.7 ± 4.2‡	24.2 ± 4.1‡		7.6 ± 1.3‡	13.2 ± 2.4‡	1.8 ± 0.6	5.6 ± 1.5‡	2.8 ± 1.5	22.1 ± 8.2‡	20.4 ± 7.3‡
Xe/O_2	32.1 ± 5.4*‡	11.9 ± 1.6*†	28.9 ± 5.9‡	26.6 ± 5.5‡	1.90 ± 0.27†‡	14.0 ± 3.1*†‡	21.8 ± 4.7*†‡	3.1 ± 1.2*†	7.8 ± 2.7‡	3.3 ± 1.0†‡	21.5 ± 8.4‡	19.5 ± 7.8‡
N_2/O_2	29.3 ± 6.0‡	10.8 ± 1.8‡	27.6 ± 6.4‡	25.8 ± 6.3‡		7.9 ± 1.7‡	14.1 ± 2.8‡	1.8 ± 0.6	6.2 ± 2.1‡	2.6 ± 0.6‡	20.6 ± 8.3‡	19.1 ± 7.6‡
N_2/O_2	25.5 ± 2.6‡§	9.3 ± 0.9‡§	23.6 ± 2.8‡§	22.0 ± 2.4‡§		8.7 ± 1.5‡	14.2 ± 2.0‡	1.9 ± 0.6	5.5 ± 2.2‡	2.3 ± 0.3‡	22.6 ± 3.7‡§	21.0 ± 3.6‡§
N_2O/O_2	27.8 ± 5.4‡	9.5 ± 1.6†‡	25.7 ± 5.7‡	24.0 ± 5.1‡	1.16 ± 0.18†	8.7 ± 2.1†‡	14.3 ± 3.9†‡	1.7 ± 0.5†	5.6 ± 3.0‡	1.8 ± 0.7†‡	20.8 ± 4.6‡	19.3 ± 4.4‡
N_2/O_2	29.5 ± 6.7‡§	10.4 ± 1.9‡§	27.7 ± 7.1‡§	25.8 ± 6.7‡§		7.8 ± 2.6‡	14.7 ± 3.7‡	1.8 ± 0.5	6.9 ± 3.3‡	2.4 ± 1.0	20.1 ± 5.0‡§	18.5 ± 4.6‡§

P_{max}' = estimated peak tracheal pressure; P_{mean} = mean airway pressure; P_1 = airway pressure immediately after flow interruption; P_2 = airway pressure after 6 s of flow interruption; ΔP ratio = ratio of the total inspiratory pressure drop over the airways with Xe/O_2 and N_2O/O_2 *versus* the corresponding N_2/O_2 controls; R_{min} = minimum inspiratory resistance; R_{max} = maximum inspiratory resistance; R_{tube} = inspiratory endotracheal tube resistance; $\Delta R = R_{max} - R_{min}$; PEEPi = intrinsic positive end-expiratory pressure; C_{st} = static compliance of thorax and lung; C_{dyn} = dynamic compliance of thorax and lung.

* $P < 0.01$, control *versus* Xe or control *versus* N_2O.

† $P < 0.01$, Xe *versus* N_2O.

‡ $P < 0.05$, baseline conditions *versus* bronchoconstriction.

§ $P < 0.05$, control 1 *versus* control 2.

Table 2. Gas Exchange with Each Study Condition

	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	Q_S/Q_T (%)	AaD_{O_2} (mmHg)	$V_{Dseries}$ (ml)	V_{Dtot} (ml)	SC_{O_2} (l^{-1})	HR (min^{-1})	MAP (mmHg)	MPAP (mmHg)	CVP (mmHg)	PAOP (mmHg)	CO (l/min)
Baseline conditions													
N_2/O_2	123 ± 18	36 ± 1*	20 ± 7*	52 ± 17	167 ± 38	171 ± 38	0.85 ± 0.40*	102 ± 14	98 ± 7*	24 ± 2*	6 ± 2	13 ± 3	5.7 ± 1.1
Xe/O_2	126 ± 19*	35 ± 1*	18 ± 5*	51 ± 18*	154 ± 35	167 ± 36*	0.86 ± 0.31*	92 ± 7	90 ± 10*	24 ± 3	8 ± 2	11 ± 3	5.4 ± 1.2*
N_2/O_2	120 ± 12*	34 ± 2*	21 ± 5	58 ± 11*	171 ± 32	176 ± 27*	0.99 ± 0.46	93 ± 9	88 ± 10*	22 ± 2*	8 ± 3	10 ± 2	5.8 ± 1.3
N_2/O_2	126 ± 16	36 ± 2	22 ± 6	47 ± 16	149 ± 29	146 ± 20*	1.01 ± 0.33	113 ± 18	85 ± 5*	21 ± 2*	7 ± 3	10 ± 4	5.2 ± 1.5
N_2O/O_2	134 ± 18*	37 ± 2*	14 ± 5*	38 ± 18*	163 ± 31	156 ± 19*	0.94 ± 0.36	90 ± 10	82 ± 8*	22 ± 4*	7 ± 2	9 ± 3	4.6 ± 1.1
N_2/O_2	127 ± 15*	35 ± 2*	16 ± 6*	48 ± 15*	172 ± 37	175 ± 44*	0.92 ± 0.25*	97 ± 20	82 ± 7*	22 ± 3	7 ± 2	10 ± 3	5.0 ± 1.1
Bronchoconstriction													
N_2/O_2	96 ± 35	42 ± 5*	36 ± 12*	76 ± 33	180 ± 30	197 ± 33	1.60 ± 0.81*	101 ± 26	67 ± 13*	32 ± 3*	11 ± 4	13 ± 2	4.4 ± 0.9
Xe/O_2	85 ± 28*	42 ± 5*	32 ± 14*	87 ± 25*	174 ± 36	223 ± 52*	1.66 ± 0.72*	94 ± 13	60 ± 10*	28 ± 4	10 ± 3	11 ± 2	4.1 ± 1.2*
N_2/O_2	83 ± 22*	40 ± 4*	33 ± 13	90 ± 20*	185 ± 40	224 ± 41*	1.69 ± 0.72	100 ± 21	67 ± 13*	29 ± 4*	9 ± 2	12 ± 2	4.5 ± 1.1
N_2/O_2	102 ± 29	42 ± 5	29 ± 13	65 ± 25	186 ± 28	213 ± 15*	1.34 ± 0.42	122 ± 30	59 ± 10*	30 ± 5*	10 ± 2	14 ± 5	5.5 ± 1.7
N_2O/O_2	94 ± 31*	46 ± 6*	32 ± 13*	72 ± 27*	192 ± 29	222 ± 46*	1.48 ± 0.62	106 ± 26	59 ± 12*	30 ± 3*	11 ± 2	13 ± 2	5.2 ± 1.4
N_2/O_2	88 ± 28*	43 ± 6*	32 ± 14*	79 ± 24*	204 ± 32	241 ± 43*	1.59 ± 0.35*	112 ± 25	57 ± 13*	26 ± 6	11 ± 3	13 ± 3	6.1 ± 1.7

Pa_{O_2} = arterial oxygen partial pressure; Pa_{CO_2} = arterial carbon dioxide partial pressure; Q_S/Q_T = venous admixture; AaD_{O_2} = alveolar–arterial oxygen content difference; $V_{Dseries}$ = series dead space; V_{Dtot} = total dead space; SC_{O_2} = slope of the expired alveolar carbon dioxide partial pressure; HR = heart rate; MAP = mean systemic arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; CO = cardiac output.

* $P < 0.05$, baseline conditions *versus* methacholine.

to baseline conditions but did not differ between control and test-gas ventilation.

No changes in hemodynamic variables were induced by the different gases used in our experiment, whereas metacholine infusion, when compared to the baseline conditions before bronchoconstriction, significantly decreased mean arterial pressure, concomitant with a simultaneous increase in mean pulmonary artery pressure in both groups. There were no statistically significant differences regarding heart rate, central venous pressure, pulmonary artery occlusion pressure between baseline conditions, and bronchoconstriction. During xenon ventilation, but not during N_2O ventilation, cardiac output decreased significantly with bronchoconstriction.

Discussion

The aim of this investigation was to compare pulmonary mechanics and gas exchange in mechanically ventilated pigs during xenon-oxygen and N_2O-oxygen anesthesia before and during continuous intravenous methacholine. The main result was that R_{aw} and pressure increased during xenon-oxygen ventilation. In terms of absolute values, these changes were moderate before methacholine infusion, as suggested by the unchanged P_{max}, despite the increased resistance, but more pronounced during intravenous methacholine.

Lung Mechanics

Our results agree with previous data regarding the effect of physical gas properties on respiratory mechanics.[2,4] They also confirm data regarding pulmonary resistance in dogs during 70% xenon and 70% N_2O anesthesia, previously published by Zhang *et al.*[14]; however, in our study, the relative change in R_{aw} produced by xenon was more pronounced (1.54 before and 1.88 during bronchoconstriction compared to 1.35 as measured by Zhang *et al.*[14]). With inspiratory xenon concentrations of 50%, as tested by these authors during methacholine-induced bronchoconstriction, they did not find any significant difference between xenon and nitrogen or N_2O. The discrepancy in our data during bronchoconstriction may be caused by the maintenance of the anesthetic concentration at 70% even during this condition. This is crucial for xenon because, due to the particularly high density and viscosity of this noble gas, the effects of a xenon-oxygen mixture on respiratory mechanics are markedly sensitive to changes of the inspired xenon concentration. Moreover, it must be taken into account that baseline R_{aw} values measured by Zhang *et al.*[14] in dogs were lower when compared to our data, suggesting larger airway dimensions in this species. Finally, Zhang *et al.*[14] performed their measurements in open-chest animals, a condition that affects the response to methacholine.[15]

According to the theoretical approaches proposed by Pedley *et al.*,[24,25] Olson *et al.*,[26] and Jaffrin and Kesic,[27] which were more recently reviewed by Pedley and Drazen,[28] both the high viscosity and the density of xenon are probably responsible for the results of our experiment. Briefly, these authors applied laws of fluid mechanics to complex systems of branching tubes such as the bronchial airways. Their model calculations showed how gas flow, despite laminar throughout the bronchial system, is disturbed at branching sites, resulting in blunted flow velocity profiles. A specific distance (called "entrance length"), which depends on airway diameter and the Reynold number (and hence on viscosity and density of the gas mixture), has to be covered by the bulk flow at each generation of the bronchial tree until the typical parabolic velocity profile of fully developed laminar flow is reestablished. Because this is an energy-consuming process, previous predictions of total pressure drop over the bronchial system based on the assumption of overall fully developed laminar flow,[29] which only depends on the viscosity of the inspiratory gas mixture, resulted in underestimation of experimental data.[30,31] This is also the case for our results insofar as both ratios $\eta_{Xe/O_2}/\eta_{N_2}/O_2$ (1.25 at 37°C) and $\eta_{N_2O}/O_2/\eta_{N_2}/O_2$ (0.87 at 37°C) were lower than $\Delta P_{Xe/O_2}/\Delta P_{N_2}/O_2$ (1.55 before and 1.90 during bronchoconstriction) and $\Delta P_{N_2O}/O_2/\Delta P_{N_2}/O_2$ (1.23 before and 1.16 during bronchoconstriction). In contrast, ΔP ratios calculated according to Pedley *et al.*,[25] *i.e.*, $\Delta P_x/\Delta P_y = (\rho_x * \eta_x)^{1/2}/(\rho_y * \eta_y)^{1/2}$, which yields theoretical values for $\Delta P_{Xe/O_2}/\Delta P_{N_2}/O_2 = 2.08$ and for $\Delta P_{N_2O}/O_2/\Delta P_{N_2}/O_2 = 1.1$, more closely approximated the measured $\Delta P_{Xe/O_2}/\Delta P_{N_2}/O_2$ and $\Delta P_{N_2O}/O_2/\Delta P_{N_2}/O_2$ ratios. However, $\Delta P_{Xe/O_2}/\Delta P_{N_2}/O_2$ before methacholine infusion was overestimated by Pedley's formula. According to Ingram and Pedley[32] and Wood *et al.*,[4] the presence of flow conditions equivalent to fully developed laminar flow in the more peripheral sections of the bronchial system (bronchial diameters < 4 mm) partially may have caused this overestimation. These flow conditions are not explained by the theory of Pedley *et al.*[25] and tend to reduce the measured pressure drop over the distal airways when compared to the predicted values, in particular by the

use of high-density gases. We can exclude an airway narrowing effect of xenon as a possible further cause of the increased R_{aw} observed in our experiment when considering the data for ΔR, C_{st}, and C_{dyn}: neither of these changed with respect to the different inspiratory gas mixtures as one would expect if airway smooth muscle tone was raised.

The different effect of xenon on R_{aw} and airway pressure is caused by the fact that airway pressure is determined by both a resistive and an elastic component. During xenon anesthesia resistance, consequently, the resistive pressure component only, was increased, but not compliance.

Gas Exchange and Hemodynamics

In contrast to respiratory mechanics, xenon and N_2O did not affect gas exchange or hemodynamics. Even the methacholine-induced deterioration in gas exchange, as documented by the Pa_{O_2}; Q_S/Q_T; $PA_{O_2} - Pa_{O_2}$; Pa_{CO_2}; and V_D/V_T, was of similar degree, regardless of the composition of the inspiratory gas. In addition, the S_{CO_2} was unaffected by the different inspiratory gas mixtures, suggesting that the properties of the gas species used in our experiment did not significantly affect the V_A/Q distribution in the lung. The alveolar slope of the expired P_{CO_2} is considered as an indicator of the nonhomogenous V_A/Q distribution.[21] Interpreting this test, however, is particularly difficult, because the alveolar P_{CO_2} slope is determined by both the series and the parallel nonhomogeneity of the V_A/Q ratio,[22] and these two components cannot be analyzed separately.

Our gas exchange data agree fairly well with previously published investigations of the effects of gas mixtures with different physical properties on V_A/Q matching. In fact, in three of these studies,[7,10,11] $PA_{O_2} - Pa_{O_2}$ even decreased with increasing gas density, but the changes were only subtle and probably of no clinical relevance. In contrast, in two other studies, $PA_{O_2} - Pa_{O_2}$ was uninfluenced or even slightly increased with higher gas density. In line with these results, investigations by Schumacker *et al.*[12] and Schulz *et al.*[33] showed only a slight relation between gas density and intrapulmonary gas distribution, gas distribution being more homogeneous in high-density atmospheres.

In summary, airway mechanics in pigs are affected during xenon anesthesia. This response is moderate with baseline conditions but more pronounced during bronchoconstriction. The results of our findings, however, probably assume only minor importance for the general anesthetic use of xenon for the following reasons: (1) during mechanical ventilation, as usual during general anesthesia, the ventilator but not the patient has to overcome the increased inspiratory resistance caused by the high density and viscosity of xenon. (2) The consequent effects on airway pressure are probably of minor relevance because they are negligible in healthy conditions and only moderate during bronchoconstriction. Furthermore, the increment in airway pressure is likely to be less accentuated in more peripheral lung regions and to disappear at the alveolar level because it is caused by the physical properties of xenon but not by an increase in airway muscle tone that would narrow the airway diameter and increase lung compliance. (3) Gas exchange does not deteriorate during xenon anesthesia, and, therefore, xenon is unlikely to impair oxygenation even during bronchoconstriction.

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