Isoflurane and Desflurane Impair Right Ventricular–Pulmonary Arterial Coupling in Dogs

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Background: Halogenated anesthetics depress left ventricular function, but their effects on the right ventricle have been less well studied. Therefore, the authors studied the effects of isoflurane and desflurane on pulmonary arterial (PA) and right ventricular (RV) properties at baseline and in hypoxia.

Methods: Right ventricular and PA pressures were measured by micromanometer catheters, and PA flow was measured by an ultrasonic flow probe. PA mechanics were assessed by flow–pressure relations and by impedance spectra derived from flow and pressure waves. RV contractility was assessed by end-systolic elastance (Ees), RV afterload was assessed by effective PA elastance (Ea), and RV–PA coupling efficiency was assessed by the Ees:Ea ratio. Anesthetized dogs were randomly assigned to increasing concentrations (0.5, 1, and 1.5 times the minimum alveolar concentration) of isoflurane (n = 7) or desflurane (n = 7) in hyperoxia (fraction of inspired oxygen, 0.4) and hypoxia (fraction of inspired oxygen, 0.1).

Results: Isoflurane and desflurane had similar effects. During hyperoxia, both anesthetics increased PA resistance and characteristic impedance, increased Ea (isoflurane, from 0.82 to 1.44 mmHg/ml; desflurane, from 0.86 to 1.47 mmHg/ml), decreased Ees (isoflurane, from 1.09 to 0.66 mmHg/ml; desflurane, from 1.10 to 0.72 mmHg/ml), and decreased Ees:Ea (isoflurane, from 1.48 to 0.52; desflurane, from 1.52 to 0.54) in a dose-dependent manner (all *P* < 0.05). Hypoxia increased PA resistance, did not affect characteristic impedance, increased afterload, and increased contractility. During hypoxia, isoflurane and desflurane had similar ventricular effects as during hyperoxia.

Conclusions: Isoflurane and desflurane markedly impair RV–PA coupling efficiency in dogs, during hyperoxia and hypoxia, both by increasing RV afterload and by decreasing RV contractility.

SINCE the introduction of halothane nearly 40 yr ago, inhalational halogenated agents have been widely used. Many studies have reported their depressant effect on left ventricular myocardial contractility, due to a decrease in intracellular calcium availability and sensitivity.[1-6] Authors also noted a better preservation of left ventricular performance with isoflurane than with halothane.[2,4] The effects of inhalational anesthetics on right

ventricular (RV) contractility have been studied much less,[7-11] but at least two studies reported different effects on right and left ventricular performance and afterload.[8,11] Desflurane is a recent halogenated anesthetic, with short duration of action due to its low tissue solubility and negligible biotransformation.[12] Its effects on left ventricular function are similar to those of isoflurane, the anesthetic most used in clinical practice.[1-3,5,13] No study has assessed the effects of desflurane on the right ventricle.

Therefore, we undertook a study to investigate more completely the effects of isoflurane and desflurane at clinically relevant concentrations (0.5, 1.0, and 1.5 times the minimum alveolar concentration [MAC]) on pulmonary circulation and RV function in absence and in presence of hypoxia. To better identify and quantify the pulmonary arterial (PA) and RV components of the observed changes, we assessed pulmonary circulation by PA flow–pressure curves and PA impedance[14,15] and ventricular function by RV end-systolic elastance and RV–PA coupling efficiency.[16] We hypothesized that isoflurane and desflurane would impair RV–PA coupling by decreasing ventricular contractility and perhaps increasing PA resistance, elastance, or both.

Materials and Methods

All experiments were approved by the Animal Ethics Committee of the Brussels Free University School of Medicine (Brussels, Belgium) and were done in accordance with the *Guide of the Care and Use of Laboratory Animals* of the National Academy of Science.

Preparation

The study included 14 mongrel dogs (mean weight, 25 kg) premedicated with 20 mg/kg intramuscular ketamine, anesthetized with 0.15 mg/kg intravenous midazolam and 0.5 μg/kg intravenous sufentanil followed by 0.15 mg · kg^{-1} · h^{-1} midazolam and 2 μg · kg^{-1} · h^{-1} sufentanil, and paralyzed with 0.2 mg/kg and 0.2 mg · kg^{-1} · h^{-1} intravenous pancuronium bromide. Additional sufentanil was given occasionally as to reverse increases of heart rate during thoracotomy, mainly at the time of rib spreader insertion. The dogs were ventilated with a fraction of inspired oxygen (F$_{IO_2}$) of 0.40, a PEEP of 5 cm H_2O, and a tidal volume of 20 ml/kg. Other details of our preparation have been published previously.[15,16] A thermistor-tipped catheter (131H 7-French; Baxter Edwards, Irvine, CA) was inserted into a branch

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of the pulmonary artery, and a balloon catheter (Percor Stat-DL 10.5-French; Datascope, Paramus, NJ) was advanced into the inferior vena cava to produce a titratable decrease in cardiac output by reducing venous return. Temperature was maintained between 36° and 38°C with an electrical heating pad. Thrombus formation was prevented by 100 U/kg intravenous heparin given before insertion of the balloon catheter. A left lateral thoracotomy was performed, and a 16- to 20-mm nonconstricting ultrasonic flow probe (T206; Transonic Systems, Ithaca, NY) was positioned around the main pulmonary artery for measurement of instantaneous flow. A 5F manometer-tipped catheter (SPC 350; Millar Instruments, Houston, TX) was introduced through the right ventricle into the pulmonary artery, and its tip was positioned just distal to the flow probe. A second 5-French manometer-tipped catheter was positioned in the right ventricle. The chest was closed, pleural air was evacuated, and the lungs were expanded with several large insufflations.

Protocol

Dogs were randomly assigned to receive isoflurane or desflurane that was administered at 0.5, 1.0, and 1.5 MAC with separate vaporizers. Inspired and expired anesthetic concentrations were measured by infrared spectrophotometry (Ultima II; Datex, Helsinki, Finland). After 30 min of postoperative stabilization, one group (n = 7) received isoflurane at target end-tidal concentrations of 0.7, 1.4, and 2.1%[17] for periods of 60 min. The other group (n = 7) received desflurane at target end-tidal concentrations of 3.6, 7.2, and 10.8%[18] for periods of 60 min. Actual end-tidal concentrations (mean ± SD) were 0.70 ± 0.05, 1.49 ± 0.09, and 2.13 ± 0.07% for isoflurane and 3.58 ± 0.12, 7.14 ± 0.09, and 10.78 ± 0.16% for desflurane. Different concentrations were delivered in random sequence. At each concentration, the animals were ventilated for 30 min in hyperoxia (F_{IO_2}, 0.40) and for 30 min in hypoxia (F_{IO_2}, 0.10), in a random sequence. Flow and pressures were collected at the end of each 30 min period, at steady state for calculations of impedance and RV–PA coupling, and during a brief flow reduction for determination of flow–pressure relations. At the end of the study, animals were killed by intravenous potassium chloride during deep anesthesia.

Data Analysis

The instantaneous pressure and flow signals were sampled at 200 Hz and stored on a personal computer for off-line analysis. PA resistance was assessed by flow–pressure relations obtained by rapid flow reduction.[15] The relations looked rectilinear and were analyzed by linear regression. PA pressure values were interpolated at flows of 2 and 4 $1 \cdot min^{-1} \cdot m^{-2}$ from individual regressions and were averaged to obtain composite flow–pressure plots. PA impedance was calculated from Fourier series expressions of pressure and flow.[15] Total

resistance or 0 Hz impedance (Zo) and characteristic impedance (Zc) were derived from the impedance spectra. Zc was computed as the average of moduli between 2 and 15 Hz. PA compliance was calculated by the pulse pressure method.[19] Total work was computed as the integration of the instantaneous flow–pressure product over time, steady state work was computed as the mean flow by mean pressure product, and oscillatory work was computed as the difference between total and steady state work. RV contractility and RV–PA coupling were assessed from steady state RV pressure–volume curves using our single-beat method.[16] RV end-systolic elastance (Ees) was computed as the slope of the end-systolic pressure–volume line, PA effective elastance (Ea) was computed as the absolute slope of the end-systolic to end-diastolic line, and ventriculoarterial coupling efficiency was computed as the Ees:Ea ratio.[16]

Statistical Analysis

Data are expressed as mean ± SD. Results were first submitted to analysis of variance, allowing identification of the effects of isoflurane *versus* desflurane and hyperoxia *versus* hypoxia. The anesthetic dose–response relations were submitted to trend analyses, corrected by the Sidak-Holm procedure. Two-tailed *P* values less than 0.05 were accepted as significant.

Results

Effects of Isoflurane and Desflurane

Isoflurane and desflurane caused similar dose-related decreases in cardiac output, systemic arterial pressure, and PA pressure (table 1). Flow–pressure curves were shifted to higher pressures (fig. 1). Impedance showed an increase in Zo and in Zc (table 2 and fig. 2). Both anesthetics decreased steady state and oscillatory work and decreased the ratio of oscillatory to total work. Isoflurane and desflurane progressively increased Ea from approximately 0.85 to 1.45 mmHg/ml, decreased Ees from approximately 1.10 to 0.70 mmHg/ml, and markedly decreased Ees:Ea from approximately 1.50 to 0.50 (all *P* < 0.05).

Effects of Hypoxia

Acute hypoxia decreased arterial oxygen tension and increased heart rate, cardiac output, and PA pressure (table 1). Flow–pressure curves were shifted to higher pressures (fig. 1). Hypoxia increased Zo and did not affect Zc (table 2 and fig. 2). Hypoxia increased steady state and oscillatory work and decreased the ratio of oscillatory to total work. Hypoxia markedly increased Ea from 0.85 to 1.55 mmHg/ml, increased Ees from approximately 1.10 to 1.60 mmHg/ml, and decreased the Ees:Ea ratio from approximately 1.50 to 1.10 (table 2).

Table 1. Effects of Isoflurane and Desflurane on Standard Hemodynamics and Blood Gases

	F$_{IO_2}$ 0.40					F$_{IO_2}$ 0.10					
	0 MAC	0.5 MAC	1.0 MAC	1.5 MAC	P	0 MAC	0.5 MAC	1.0 MAC	1.5 MAC	P	P
HR, beats/min											
Isoflurane	129 ± 19	116 ± 15	130 ± 20	130 ± 13		167 ± 24	156 ± 18	150 ± 5	148 ± 7	*	†
Desflurane	125 ± 24	125 ± 23	133 ± 23	129 ± 19		155 ± 25	166 ± 20	149 ± 18	143 ± 22	*	†
CI, l · min^{-1} · m^{-2}											
Isoflurane	4.8 ± 0.6	3.9 ± 0.2	3.3 ± 0.6	2.8 ± 0.3	*	5.7 ± 1.1	5.3 ± 0.6	4.2 ± 0.6	2.9 ± 0.5	*	†
Desflurane	4.4 ± 0.9	3.9 ± 1.0	3.2 ± 0.7	2.5 ± 0.8	*	5.8 ± 1.4	5.5 ± 0.9	4.3 ± 1.1	3.1 ± 1.1	*	†
Psa, mmHg											
Isoflurane	114 ± 7	114 ± 7	86 ± 10	55 ± 9	*	124 ± 27	99 ± 23	71 ± 14	55 ± 18	*	
Desflurane	113 ± 17	106 ± 15	74 ± 12	53 ± 12	*	113 ± 16	102 ± 11	82 ± 14	63 ± 14	*	
Ppa, mmHg											
Isoflurane	19 ± 3	18 ± 2	17 ± 3	14 ± 2	*	33 ± 8	33 ± 7	26 ± 6	22 ± 3	*	†
Desflurane	18 ± 3	18 ± 3	16 ± 2	16 ± 2	*	35 ± 8	29 ± 5	25 ± 5	22 ± 3	*	†
Pra, mmHg											
Isoflurane	6 ± 3	7 ± 2	6 ± 2	7 ± 1		6 ± 2	7 ± 1	7 ± 2	7 ± 2		
Desflurane	6 ± 1	7 ± 2	7 ± 1	8 ± 1	*	6 ± 1	7 ± 2	7 ± 1	8 ± 2	*	
Ppao, mmHg											
Isoflurane	9 ± 2	9 ± 2	9 ± 2	9 ± 1		10 ± 2	10 ± 1	10 ± 2	10 ± 2		
Desflurane	9 ± 1	10 ± 2	9 ± 2	10 ± 2	*	9 ± 2	11 ± 1	11 ± 2	12 ± 2	*	
PVR, dyn · s · cm^{-5} · m^2											
Isoflurane	165 ± 29	188 ± 64	181 ± 90	189 ± 103		299 ± 75	321 ± 112	302 ± 103	336 ± 129		
Desflurane	184 ± 42	188 ± 75	191 ± 83	208 ± 60		288 ± 107	281 ± 106	288 ± 142	299 ± 99		
pHa											
Isoflurane	7.43 ± 0.03	7.42 ± 0.05	7.43 ± 0.04	7.41 ± 0.06		7.45 ± 0.05	7.44 ± 0.02	7.45 ± 0.03	7.45 ± 0.02		†
Desflurane	7.41 ± 0.04	7.41 ± 0.04	7.41 ± 0.04	7.39 ± 0.02		7.44 ± 0.04	7.44 ± 0.03	7.43 ± 0.04	7.45 ± 0.04		†
Paco$_2$, mmHg											
Isoflurane	36 ± 3	33 ± 3	34 ± 3	34 ± 5		35 ± 3	33 ± 2	33 ± 3	33 ± 4		
Desflurane	36 ± 2	36 ± 4	37 ± 2	35 ± 3		33 ± 3	35 ± 2	36 ± 3	33 ± 2		†
Pao$_2$, mmHg											
Isoflurane	191 ± 52	168 ± 47	156 ± 44	161 ± 50		35 ± 4	32 ± 5	34 ± 4	33 ± 6		†
Desflurane	193 ± 60	158 ± 39	156 ± 47	163 ± 21		33 ± 4	34 ± 9	30 ± 5	34 ± 11		†

Values are presented as mean ± SD.

* $P < 0.05$ when increasing minimum alveolar concentration (MAC) (by trend analysis). † $P < 0.05$ hypoxia *vs.* hyperoxia (by factor analysis). No significant difference was found between isoflurane and desflurane.

CI = cardiac index; HR = heart rate; Paco$_2$ = arterial carbon dioxide tension; Pao$_2$ = arterial oxygen tension; pHa = arterial pH; Ppa = mean pulmonary arterial pressure; Ppao = mean occluded pulmonary arterial pressure; Pra = mean right atrial pressure; Psa = mean systemic arterial pressure; PVR = pulmonary vascular resistance.

Effects of Isoflurane and Desflurane in Hypoxia

During hypoxia, isoflurane and desflurane again caused similar decreases in cardiac output, systemic arterial pressure, and PA pressure (table 1). Flow–pressure curves were shifted to higher pressures, but less than in hyperoxia (fig. 1). Impedance spectra showed an increase in Zo but no change in Zc (table 2 and fig. 2). Both anesthetics decreased steady state and oscillatory work, with the ratio of oscillatory to total work decreasing nonsignificantly. Isoflurane and desflurane increased Ea nonsignificantly from approximately 1.55 to 1.90 mmHg/ml, decreased Ees from approximately 1.60 to 1.00 mmHg/ml, and markedly decreased Ees:Ea from approximately 1.10 to 0.50 ($P < 0.05$)

Discussion

The current results show that isoflurane and desflurane exert similar and dose-related effects on PA hemodynamics, RV function, and RV-PA coupling efficiency. The results were obtained in dogs, after thoracotomy and
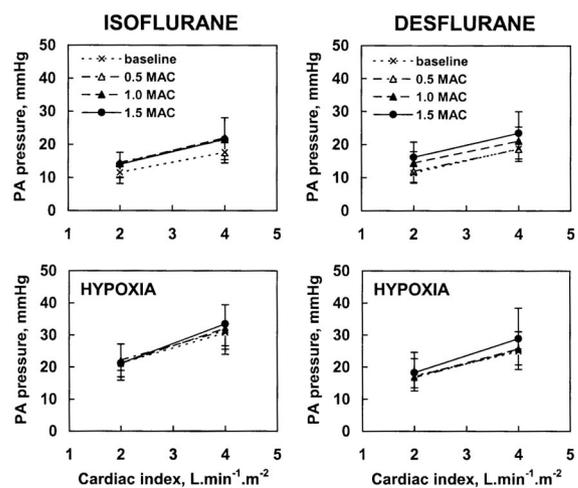
Fig. 1. Effects of isoflurane and desflurane on mean pulmonary arterial (PA) pressure–*versus*–cardiac output relations, in hyperoxia (*top*) and in hypoxia (*bottom*). Values are presented as mean ± SDs. No significant difference was found between isoflurane and desflurane. Both anesthetics shifted the flow–pressure curves up to higher pressures during hyperoxia ($P < 0.05$ by trend analysis) and during hypoxia ($P < 0.05$ for isoflurane). MAC = minimal alveolar concentration.

Table 2. Effects of Isoflurane and Desflurane on Pulmonary Arterial Impedance and Right Ventricular–Pulmonary Arterial Coupling

	F_{IO_2} 0.40					F_{IO_2} 0.10					
	0 MAC	0.5 MAC	1.0 MAC	1.5 MAC	P	0 MAC	0.5 MAC	1.0 MAC	1.5 MAC	P	P
Zo, dyn · s · cm^{-5} · m^2											
Isoflurane	338 ± 48	403 ± 51	403 ± 33	506 ± 59	*	510 ± 106	561 ± 75	551 ± 140	654 ± 185	*	†
Desflurane	360 ± 90	426 ± 150	431 ± 122	574 ± 159	*	519 ± 156	578 ± 135	550 ± 214	675 ± 207	*	†
Zc, dyn · s · cm^{-5} · m^2											
Isoflurane	82 ± 22	93 ± 29	99 ± 31	113 ± 27	*	79 ± 9	90 ± 31	96 ± 14	90 ± 33		
Desflurane	83 ± 35	111 ± 33	110 ± 41	121 ± 37	*	90 ± 19	93 ± 25	100 ± 23	101 ± 25		
C, ml/mmHg											
Isoflurane	76 ± 10	72 ± 11	73 ± 16	78 ± 14		68 ± 19	66 ± 21	70 ± 21	70 ± 18		
Desflurane	72 ± 9	67 ± 14	68 ± 14	70 ± 20		62 ± 17	60 ± 18	65 ± 19	57 ± 18		
Wst, mW											
Isoflurane	218 ± 64	183 ± 25	124 ± 30	93 ± 9	*	448 ± 111	392 ± 93	239 ± 69	136 ± 23	*	†
Desflurane	179 ± 45	150 ± 45	115 ± 17	88 ± 34	*	412 ± 148	368 ± 73	245 ± 62	160 ± 71	*	†
Wosc, mW											
Isoflurane	69 ± 21	55 ± 14	37 ± 7	27 ± 5	*	119 ± 44	107 ± 58	50 ± 15	29 ± 9	*	†
Desflurane	56 ± 11	40 ± 17	29 ± 13	23 ± 11	*	100 ± 52	91 ± 37	66 ± 29	35 ± 22	*	†
Wosc/Wtot, %											
Isoflurane	25 ± 4	22 ± 4	23 ± 4	22 ± 3		21 ± 5	21 ± 7	17 ± 3	17 ± 4		†
Desflurane	24 ± 3	21 ± 4	19 ± 5	20 ± 3	*	19 ± 5	19 ± 5	20 ± 5	18 ± 4		†
Ea, mmHg/ml											
Isoflurane	0.82 ± 0.32	1.02 ± 0.43	1.31 ± 0.33	1.44 ± 0.51	*	1.55 ± 0.38	1.72 ± 0.53	1.75 ± 0.17	1.94 ± 0.90		†
Desflurane	0.86 ± 0.36	1.13 ± 0.46	1.40 ± 0.43	1.47 ± 0.47	*	1.54 ± 0.82	1.62 ± 0.22	1.79 ± 0.77	1.91 ± 0.66		†
Ees, mmHg/ml											
Isoflurane	1.09 ± 0.16	1.01 ± 0.26	0.85 ± 0.17	0.66 ± 0.20	*	1.53 ± 0.29	1.40 ± 0.33	1.25 ± 0.31	1.11 ± 0.38	*	†
Desflurane	1.10 ± 0.30	0.93 ± 0.28	0.88 ± 0.22	0.72 ± 0.14	*	1.68 ± 0.72	1.51 ± 0.28	1.14 ± 0.22	0.84 ± 0.13	*	†
Ees/Ea											
Isoflurane	1.48 ± 0.50	1.09 ± 0.40	0.68 ± 0.23	0.52 ± 0.25	*	1.04 ± 0.34	0.91 ± 0.38	0.73 ± 0.26	0.62 ± 0.20	*	
Desflurane	1.52 ± 0.89	1.19 ± 0.88	0.76 ± 0.51	0.54 ± 0.19	*	1.14 ± 0.15	0.96 ± 0.24	0.77 ± 0.41	0.44 ± 0.20	*	

Values are presented as mean ± SD.

* $P < 0.05$ when increasing minimum alveolar concentration (MAC) (by trend analysis). † $P < 0.05$ hypoxia *vs.* hyperoxia (by factor analysis). No significant difference was found between isoflurane and desflurane.

C = compliance; Ea = pulmonary artery effective elastance; Ees = right ventricular end-systolic elastance; Wosc = oscillatory work; Wst = steady state work; Wtot = total work; Zc = characteristic impedance; Zo = total resistance.

during background anesthesia with midazolam and sufentanil, and therefore should be extended only with caution to other species or conditions. The number of experiments was limited and possibly insufficient to detect additional more subtle effects of isoflurane or desflurane.

Pulmonary vascular mechanics are commonly described by PA pressure and calculated pulmonary vascular resistance, but these variables are flow dependent and do not take into account the pulsatile nature of circulation. Flow–pressure relations better discriminate between passive (flow-induced) changes and active (tone-induced) changes in PA pressure and permit detection of more subtle changes in vascular tone.[14,20] Flow–pressure curves here were generated with transient flow reductions (< 10 s) to prevent cardiovascular responses due to sympathetic activation.[15] Pulmonary vascular impedance allows for the quantification of the three components that oppose blood ejection from the ventricle into the artery, *i.e.*, resistance due to small distal vessels, elastance due to large proximal vessels, and reflected waves that increase pressure and decrease forward flow.[21] In previous studies, isoflurane was found to cause some increase or no change in pulmonary vascular tone.[10,17,20,22] Heerdt *et al.*[11] reported that PA resistance and elastance were increased with isoflurane, in contrast with aortic resistance that decreased and aortic elastance that remained unchanged. In the current study, isoflurane and desflurane reduced PA pressure. The reduction was clearly flow related, because flow–pressure curves showed an absence of change at lower doses and an increase in resistance at higher doses. These results again confirm the confounding effect of flow changes when interpreting changes in PA pressure or in pulmonary vascular resistance. Hydraulic work decreased together with flow and pressure, whereas oscillatory work (the proportion of work "wasted" into pulsatility) decreased at lower pressure. Impedance data mainly showed a dose-related increase in Zc. Zc may increase as a result of higher pressure, decreased diameter, or increased elastance.[15,21] Pressure and thus diameter decreased, so that the increase in Zc here may reflect the decrease in diameter or an increase in vessel elastance (higher stiffness). The unchanged compliance despite lower pressure suggests that vessel elastance did increase. Isoflurane and desflurane thus increased the
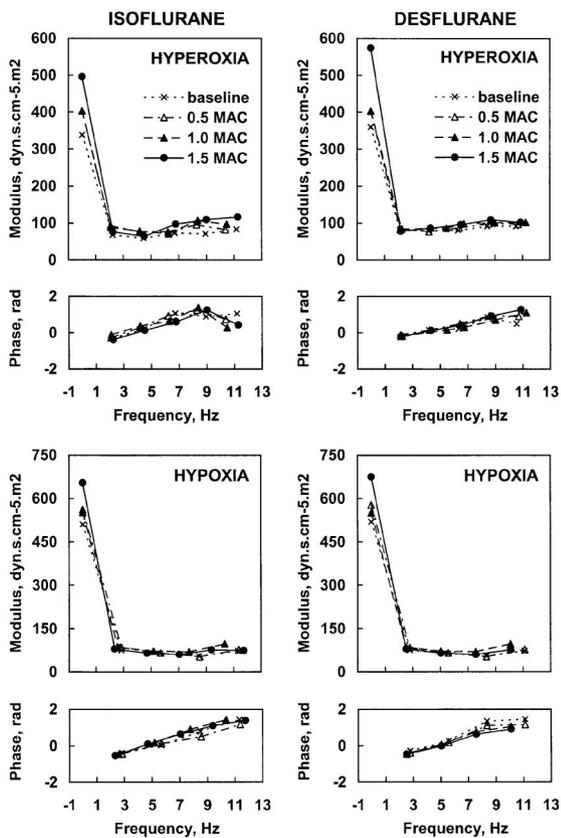
Fig. 2. Effects of isoflurane and desflurane on pulmonary arterial impedance spectra, in hyperoxia (*top*) and in hypoxia (*bottom*). Values are presented as mean (SDs not shown for clarity). No significant difference was found between isoflurane and desflurane. Both anesthetics increased total resistance in hyperoxia and in hypoxia and increased characteristic impedance only in hyperoxia ($P < 0.05$ by trend analysis). MAC = minimal alveolar concentration; rad = radians.

afterload by increasing both the resistance and elastance of pulmonary vessels. The right ventricle can normally adapt to such increase in afterload and maintain cardiac output, so that the decrease in cardiac output observed with isoflurane and desflurane already suggests a concomitant decrease in RV contractility.

Right ventricular function in whole animals or humans is commonly assessed by RV ejection fraction or dP/dt, but both variables are critically dependent on preload and afterload.[16,23,24] Ventricular contraction is better investigated by ventricular pressure–volume curves and by end-systolic pressure–volume relations that are essentially load independent in physiologic ranges of preload and afterload.[16,23] In that approach, contractility is directly quantified by Ees, afterload by Ea, and ventriculo-arterial coupling efficiency by the Ees:Ea ratio.[23,25,26] The ability of Ees and Ees:Ea to measure RV contractility and coupling efficiency, in normal conditions or during pulmonary hypertension and RV failure, has been shown in several studies.[16,27–29] Previous studies reported that halothane, enflurane, and isoflurane decreased RV contractility in a dose-related manner.[7,9,11] Isoflurane dete-

riorated RV function more than LV function because it decreased LV afterload but did not affect RV afterload.[8,11] In a previous study, we noted that dogs receiving propofol during pulmonary embolism tolerated the procedure, whereas those receiving isoflurane had RV failure and died.[10] In the current study, isoflurane and desflurane caused a marked and dose-dependent decrease in RV contractility. Unfortunately, the decrease in RV contractility occurred in addition to the above-mentioned increase in RV afterload. As a result of this combination, RV–PA coupling efficiency decreased by 65% to reach approximately 0.50 at the highest anesthetic dose. Ees:Ea values well below 1 denote an advanced degree of uncoupling and predict an inability to maintain flow.[22] Cardiac output actually decreased markedly, despite the normal baseline cardiovascular status of these experimental animals.

Hypoxia was associated with the expected pulmonary vasoconstriction. PA resistance increased, reflecting smooth muscle contraction in small distal vessels.[20] Zc did not change, indicating a balance between the opposite effects of higher pressure and higher diameter due to passive dilation of proximal arteries from distal vasoconstriction and possible effects of elastance changes.[15] RV afterload thus increased markedly. RV contractility also increased, as a result of adrenergic stimulation and of the Anrep effect.[16] Ees:Ea decreased moderately, and cardiac output was maintained. Previous studies have shown that the right ventricle can adapt to pulmonary hypertension by an increase in contractility (homeometric autoregulation) and maintain cardiac output.[16,27,30,31] The current study confirms that the decreased cardiac output observed with isoflurane and desflurane does not result from an isolated increase in RV afterload but also from a decrease in RV contractility.

Isoflurane and desflurane had different effects on the pulmonary circulation in hypoxia than in hyperoxia. Resistance increased somewhat less, suggesting a weakening of hypoxic pulmonary vasoconstriction (HPV). This change is consistent with previous reports that isoflurane preserves HPV at a lower dose but reduces HPV at a higher dose.[17,20,22,32,33] This reduction of HPV also explains why arterial carbon dioxide tension is lower with isoflurane or desflurane than at baseline. Elastance did not increase with isoflurane or desflurane in hypoxia, suggesting that anesthetics do not further affect elastance when proximal vessels are already dilated by HPV-induced hypertension and activated by hypoxia-induced adrenergic stimulation.[15] Isoflurane and desflurane had similar deleterious effects on Ea and Ees as in hyperoxia, resulting in a similar dramatic decrease in coupling efficiency.

We conclude (1) that isoflurane and desflurane have similar, dose-related effects on pulmonary hemodynamics and ventricular function in hyperoxic and hypoxic dogs and (2) that isoflurane and desflurane markedly

impair RV–PA coupling efficiency, both by increasing RV afterload and by decreasing RV contractility.

References

1. Merin RG, Bernard JM, Doursout MF, Cohen M, Chelly JE: Comparison of the effects of isoflurane and desflurane on cardiovascular dynamics and regional blood flow in the chronically instrumented dog. ANESTHESIOLOGY 1991; 74:568–74

2. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Comparison of the systemic and coronary hemodynamic actions of desflurane, isoflurane, halothane, and enflurane in the chronically instrumented dog. ANESTHESIOLOGY 1991; 74:539–51

3. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Influence of volatile anesthetics on myocardial contractility *in vivo*: Desflurane *versus* isoflurane. ANESTHESIOLOGY 1991; 74:900–7

4. Kawasaki T, Hoka S, Okamoto H, Okuyama T, Takahashi S: The difference of isoflurane and halothane in ventriculoarterial coupling in dogs. Anesth Analg 1994; 79:681–6

5. Hettrick DA, Pagel PS, Warltier DC: Desflurane, sevoflurane, and isoflurane impair canine left ventricular–arterial coupling and mechanical efficiency. ANESTHESIOLOGY 1996; 85:403–13

6. Housmans PR, Wanek LA, Carton EG, Bartunek AE: Effects of halothane and isoflurane on the intracellular calcium transient in ferret cardiac muscle. ANESTHESIOLOGY 2000; 93:189–201

7. Mote PS, Pruett JK, Gramling ZW: Effects of halothane and enflurane on right ventricular performance in hearts of dogs anesthetized with pentobarbital sodium. ANESTHESIOLOGY 1983; 58:53–60

8. Priebe HJ: Differential effects of isoflurane on regional right and left ventricular performances, and on coronary, systemic, and pulmonary hemodynamics in the dog. ANESTHESIOLOGY 1987; 66:262–72

9. Heerdt PM, Pleimann BE: The dose-dependent effects of halothane on right ventricular contraction pattern and regional inotropy in swine. Anesth Analg 1996; 82:1152–8

10. Ewalenko P, Brimioulle S, Delcroix M, Lejeune P, Naeije R: Comparison of the effects of isoflurane with those of propofol on pulmonary vascular impedance in experimental embolic pulmonary hypertension. Br J Anaesth 1997; 79:625–30

11. Heerdt PM, Gandhi CD, Dickstein ML: Disparity of isoflurane effects on left and right ventricular afterload and hydraulic power generation in swine. Anesth Analg 1998; 87:511–21

12. Patel SS, Goa KL: Desflurane: A review of its pharmacodynamic and pharmacokinetic properties and its efficacy in general anesthesia. Drugs 1995; 50:742–67

13. Warltier DC, Pagel PS: Cardiovascular and respiratory actions of desflurane: Is desflurane different from isoflurane? Anesth Analg 1992; 75:S17–31

14. Lodato RF, Michael JR, Murray PA: Multipoint pulmonary vascular pressure-cardiac output plots in conscious dogs. Am J Physiol 1985; 249:H351–7

15. Brimioulle S, Maggiorini M, Stephanazzi J, Vermeulen F, Lejeune P, Naeije R: Effects of low flow on pulmonary vascular flow-pressure curves and pulmonary vascular impedance. Cardiovasc Res 1999; 42:183–92

16. Brimioulle S, Wauthy P, Ewalenko P, Rondelet B, Vermeulen F, Kerbaul F, Naeije R: Single-beat estimation of right ventricular end-systolic pressure-volume relationship. Am J Physiol Heart Circ Physiol 2003; 284:H1625–30

17. Ewalenko P, Stefanidis C, Holoye A, Brimioulle S, Naeije R: Pulmonary vascular impedance vs. resistance in hypoxic and hyperoxic dogs: effects of propofol and isoflurane. J Appl Physiol 1993; 74:2188–93

18. Doorley BM, Waters SJ, Terrell RC, Robinson JL: MAC of I-653 in beagle dogs and New Zealand white rabbits. ANESTHESIOLOGY 1988; 69:89–91

19. Segers P, Brimioulle S, Stergiopulos N, Westerhof N, Naeije R, Maggiorini M, Verdonck P: Pulmonary arterial compliance in dogs and pigs: The three-element windkessel model revisited. Am J Physiol 1999; 277:H725–31

20. Naeije R, Lejeune P, Leeman M, Melot C, Deloof T: Pulmonary arterial pressure-flow plots in dogs: Effects of isoflurane and nitroprusside. J Appl Physiol 1987; 63:969–77

21. Milnor WR: Pulsatile blood flow. N Engl J Med 1972; 287:27–34

22. Eisenkraft JB: Effects of anaesthetics on the pulmonary circulation. Br J Anaesth 1990; 65:63–78

23. Sagawa K: The end-systolic pressure-volume relationship of the ventricle: definition, modifications and clinical use. Circulation 1981; 63:1223–7

24. Robotham JL, Takata M, Berman M, Harasawa Y: Ejection fraction revisited. ANESTHESIOLOGY 1991; 74:172–83

25. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K: Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983; 245:H773–80

26. Burkhoff D, Sagawa K: Ventricular efficiency predicted by an analytical model. Am J Physiol 1986; 250:R1021–7

27. Wauthy P, Pagnamenta A, Vassalli F, Naeije R, Brimioulle S: Right ventricular adaptation to pulmonary hypertension: An interspecies comparison. Am J Physiol Heart Circ Physiol 2004; 286:H1441–7

28. Wauthy P, Abdel Kafi S, Mooi WJ, Naeije R, Brimioulle S: Inhaled nitric oxide versus prostacyclin in chronic shunt-induced pulmonary hypertension. J Thorac Cardiovasc Surg 2003; 126:1434–41

29. Kerbaul F, Rondelet B, Motte S, Fesler P, Hubloue I, Ewalenko P, Naeije R, Brimioulle S: Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. Crit Care Med 2004; 32:1035–40

30. de Vroomen M, Lopes Cardoso RH, Steendijk P, van Bel F, Baan J: Improved contractile performance of right ventricle in response to increased RV afterload in newborn lambs. Am J Physiol Heart Circ Physiol 2000; 278:H100–5

31. Hon JK, Steendijk P, Khan H, Wong K, Yacoub M: Acute effects of pulmonary artery banding in sheep on right ventricle pressure-volume relations: Relevance to the arterial switch operation. Acta Physiol Scand 2001; 172:97–106

32. Kerbaul F, Bellezza M, Guidon C, Roussel L, Imbert M, Carpentier JP, Auffray JP: Effects of sevoflurane on hypoxic pulmonary vasoconstriction in anaesthetized piglets. Br J Anaesth 2000; 85:440–5

33. Kerbaul F, Guidon C, Stéphanazzi J, Bellezza M, Le Dantec P, Longeon T, Aubert M: Sub MAC concentrations of desflurane do not inhibit hypoxic pulmonary vasoconstriction in anesthetized piglets. Can J Anaesth 2001; 48:760–7