

Effects of Desflurane and Sevoflurane on Length-dependent Regulation of Myocardial Function in Coronary Surgery Patients

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Background: Desflurane and sevoflurane have negative inotropic effects. The current study investigated whether these effects resulted in an altered left ventricular response to increased cardiac load and affected length-dependent regulation of myocardial function. Length-dependent regulation of myocardial function refers to the ability of the heart to improve its performance when preload is increased.

Methods: A high-fidelity pressure catheter was positioned in the left ventricle and left atrium in 20 coronary surgery patients with a preoperative ejection fraction greater than 40%. Studies were performed before the initiation of cardiopulmonary bypass. Left ventricular response to increased cardiac load, obtained by leg elevation, was assessed during control conditions and during increasing concentrations of desflurane (2, 4, and 6% end tidal; n = 10) or sevoflurane (1, 2, and 3% end tidal; n = 10). Effects on contraction were evaluated by analysis of changes in maximal rate of pressure development. Effects on relaxation were assessed by analysis of changes in minimum rate of pressure development and by analysis of the load dependence of myocardial relaxation (R = slope of the relation between time constant τ of isovolumic relaxation and end-systolic pressure). Peak left atrial-left ventricular pressure gradients were analyzed during early left ventricular filling.

Results: With both desflurane and sevoflurane, maximal and minimum rates of pressure development decreased while τ increased. Peak left atrial-left ventricular pressure gradients remained unchanged. The hemodynamic effects of leg elevation were similar at the different concentrations. Changes in parameters of contraction and relaxation during leg elevation were coupled and were not altered by desflurane or sevoflurane.

Conclusions: Despite their negative inotropic and lusitropic effects, neither desflurane nor sevoflurane adversely affect length-dependent regulation of left ventricular function. In the conditions of our study, the ability of the left ventricle to respond to increased cardiac load is not altered by the use of desflurane or sevoflurane.

EVALUATION of changes in left ventricular (LV) function during an alteration in cardiac load allows dynamic evaluation of LV contractile reserve and assessment of the ability of the myocardium to recruit the length-dependent regulation mechanism.^{1,2} Length-dependent

regulation of myocardial function refers to the ability of the heart to improve its performance when preload is increased. In the nonfailing heart, an increase in diastolic volume is associated with improved cardiac function,^{3,4} but when a failing left ventricle is subjected to an additional load, it appears to be unable to recruit the Frank-Starling mechanism and to improve its function.^{5,6} In coronary surgery patients with a baseline ejection fraction greater than 40%, an increase in cardiac load by leg elevation resulted in a variable response of LV function. Some patients showed improvement, whereas others showed either no change or even impairment of LV function. The latter response was related to a deficient length-dependent regulation of myocardial function, which is characterized by a decrease in stroke volume and maximal rate of pressure development (dp/dt_{max}) and a delayed myocardial relaxation with enhanced load dependence of LV pressure decrease.^{1,2}

Reductions in myocardial contractility adversely modify load dependence of myocardial relaxation.^{7,8} Volatile anesthetics produce direct negative inotropic effects and may therefore exacerbate load dependence of LV relaxation.⁹ This may result in further deterioration of LV function, especially in patients with impaired length-dependent regulation of myocardial function. The hemodynamic effects of desflurane and sevoflurane have been well documented in animals¹⁰⁻¹⁵ and healthy humans¹⁶⁻¹⁸ but not in patients with coronary artery disease. Both agents produce a dose-dependent decrease in myocardial contractility and a prolongation of myocardial relaxation. Because of these properties, we hypothesized that desflurane and sevoflurane would impair length-dependent regulation of myocardial function. We tested this hypothesis in patients scheduled for elective coronary artery surgery. The effects of an increase in cardiac load by leg elevation on LV function were analyzed in the presence of increasing concentrations of desflurane and sevoflurane.

Methods

Patient Population

The study was performed in 20 patients scheduled for elective coronary bypass surgery. The study was approved by the Institutional Ethical Committee (University Hospital Antwerp, Edegem, Belgium), and informed consent was obtained. Patients with a preoperative ejection fraction of more than 40% were included. Patients

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undergoing repeat coronary surgery, concurrent valve repair, or aneurysm resection were excluded. Patients with unstable angina or with valve insufficiency were also excluded. Patients were randomly allocated to receive either sevoflurane or desflurane.

Anesthesia and Surgery

All preoperative cardiac medication was continued until the morning of surgery. Patients received routine monitoring in the operating room, including five-lead electrocardiogram, radial and pulmonary artery catheters with continuous cardiac output measurement, pulse oximetry, capnography, and blood and urine bladder temperature monitoring. Anesthesia was induced with 20 $\mu\text{g/kg}$ fentanyl, 0.1 mg/kg diazepam, and 0.1 mg/kg pancuronium bromide. An additional dose of 10 $\mu\text{g/kg}$ fentanyl was administered before sternotomy. Standard median sternotomy and pericardiotomy were performed, and the aortic canula was secured in place. No volatile agents were administered during the preparation period.

Experimental Preparation

In each patient, two sterilized electronic tipmanometers (MTCP3Fc catheter, Dräger Medical Electronics, Best, The Netherlands; frequency response = 100 kHz) were inserted. One catheter was positioned in the left atrium through the right superior pulmonary vein, and the other catheter was positioned in the LV cavity through the apical dimple. Both catheters were connected to a Hewlett Packard monitor (HP78342A, Hewlett Packard, Brussels, Belgium). Both catheters were electronically zeroed after insertion. The output signals of the pressure transducer system were digitally recorded together with the electrocardiogram signals at 1-ms intervals (Cudas, DataQ, Akron, OH). Zero and gain setting of the tipmanometers were also checked against a high-fidelity pressure gauge (Druck Ltd., Leicester, United Kingdom) after removal.

Experimental Protocol

Heart rate was kept constant by atrioventricular sequential pacing at a rate of 90 beats/min. LV end-diastolic pressure was kept constant to ensure stable conditions of filling pressures throughout by slow administration of the priming fluid through the aortic canula whenever necessary. All measurements were obtained with the ventilation suspended at end expiration. The measurements consisted of recordings of consecutive electrocardiographic and LV pressure tracings during an increase of systolic and diastolic pressures obtained by raising the caudal part of the surgical table by 45°, resulting in raising of the legs. Leg elevation resulted in a rapid beat-to-beat increase in LV pressures.

After recording the data during control conditions (control condition 1), the patients were randomly allo-

cated to receive increasing doses of either desflurane (2, 4, and 6% end-tidal concentrations) or sevoflurane (1, 2, and 3% end-tidal concentrations). A stabilization period of 5 min was allowed at each concentration before the recordings were made. After the recordings at the highest concentration, administration of the volatile agents was discontinued. When end-tidal concentrations were returned to zero, a new recording was obtained after a stabilization period of 5 min (control condition 2) to assess a possible time effect.

Data Analysis

End-diastolic pressure was timed at the peak of the R wave on the electrocardiogram. The effects of leg elevation in the different conditions on LV load and function were evaluated by the changes in end-diastolic pressure, peak LV pressure, LV pressure at dP/dt_{\min} (end-systolic pressure [ESP]), and dP/dt_{\max} . Effects of leg elevation on rate of LV pressure decrease were evaluated by dP/dt_{\min} and the time constant τ of isovolumic relaxation. τ was calculated based on the monoexponential model with nonzero asymptote using LV pressure values from dP/dt_{\min} to mitral valve opening. The following equation was used: $\ln P_t = \ln P_0 - \text{time}/\tau$. Time constant τ was linearly fit to the corresponding ESP, and the slope R (milliseconds per millimeters of mercury) of this relation was calculated. R quantified changes in τ induced by the changes in ESP and quantified afterload dependence of the rate of LV pressure decrease.⁸ At least 10 consecutive beats were taken for the calculation of R. Sample correlation coefficients of the ESP- τ relations yielded values of r greater than 0.92 in all patients.

The gradient between left atrial and LV pressure during early ventricular filling was evaluated by calculation of the peak pressure gradient between the left atrium and the left ventricle in the period between mitral valve opening and the next pressure crossover.

Statistical Analysis

All data were controlled for normal distribution. The data before and after leg elevation at the different concentrations were then compared using a two-way analysis of variance for repeated measurements. Interaction analysis revealed whether effects of leg elevation were different with desflurane and sevoflurane. Posttest analysis was performed using the Bonferroni-Dunn test. Relations in hemodynamic parameters were analyzed using linear regression analysis computing the Pearson correlation coefficient. Slopes and intercepts of the different relations were compared using the t test.¹⁹ Preoperative patient data were compared using contingency table analysis and unpaired t test analysis where appropriate. Statistical significance was accepted at $P < 0.05$.

Table 1. Preoperative Data of the Patients Included in the Desflurane and Sevoflurane Groups

	Desflurane (n = 10)	Sevoflurane (n = 10)
Male/female ratio	8/2	8/2
Age (yr)	65 ± 8	67 ± 11
Length (cm)	171 ± 10	170 ± 10
Weight (kg)	82 ± 13	76 ± 12
Diabetes	2	2
COPD	1	2
Previous AMI	3	2
Hypertension	10	10
Ejection fraction (%)	53 ± 7	57 ± 9
Medication		
β-Blocking agents	10	10
ACE Inhibitors	2	3
Calcium channel blockers	6	5
Nitrates	6	6

Data are mean ± SD.

COPD = chronic obstructive pulmonary disease; AMI = acute myocardial infarction; ACE = angiotensin converting enzyme.

Results

Table 1 summarizes the preoperative demographic data of the patients in the desflurane and sevoflurane groups. There was no difference in any of the variables. None of the patients developed myocardial ischemia or hemodynamic instability during the period of the study.

Figure 1 illustrates in an individual patient the effects of leg elevation in control conditions (control) and at approximately 1 minimum alveolar concentration (MAC) of desflurane (fig. 1, top) and sevoflurane (fig. 1, bottom). During both conditions, leg elevation resulted in an increase in LV and left atrial pressures when compared with baseline.

Table 2 summarizes the effects of increasing concentrations of desflurane on left atrial and LV hemodynamic data at baseline and after leg elevation. At baseline, left atrial pressures (peak A and V waves) and LV end-diastolic pressure remained unchanged with increasing end-tidal concentrations. Peak LV pressure and LV pressure at dP/dt_{min} (ESP) decreased with higher concentrations. dP/dt_{max} and dP/dt_{min} also decreased in a dose-dependent way. Time constant of isovolumic relaxation (τ) increased with higher concentrations. Peak left atrial-LV pressure gradient during early ventricular filling remained unchanged throughout (7 ± 3 mmHg at baseline and 6 ± 2 , 6 ± 3 , and 7 ± 3 mmHg at 2, 4, and 6% desflurane, respectively). Thermodilution cardiac index was 2.9 ± 0.6 l · min⁻¹ · m⁻² at control and was unaltered with increasing concentrations of desflurane (2.7 ± 0.5 , 2.8 ± 0.6 , and 2.6 ± 0.4 l · min⁻¹ · m⁻², respectively). Changes in left atrial and LV hemodynamic data after leg elevation were similar in control conditions and with increasing concentrations of desflurane. Load dependence of relaxation was not altered.

Table 3 summarizes the effects of increasing concentrations of sevoflurane on left atrial and LV hemody-

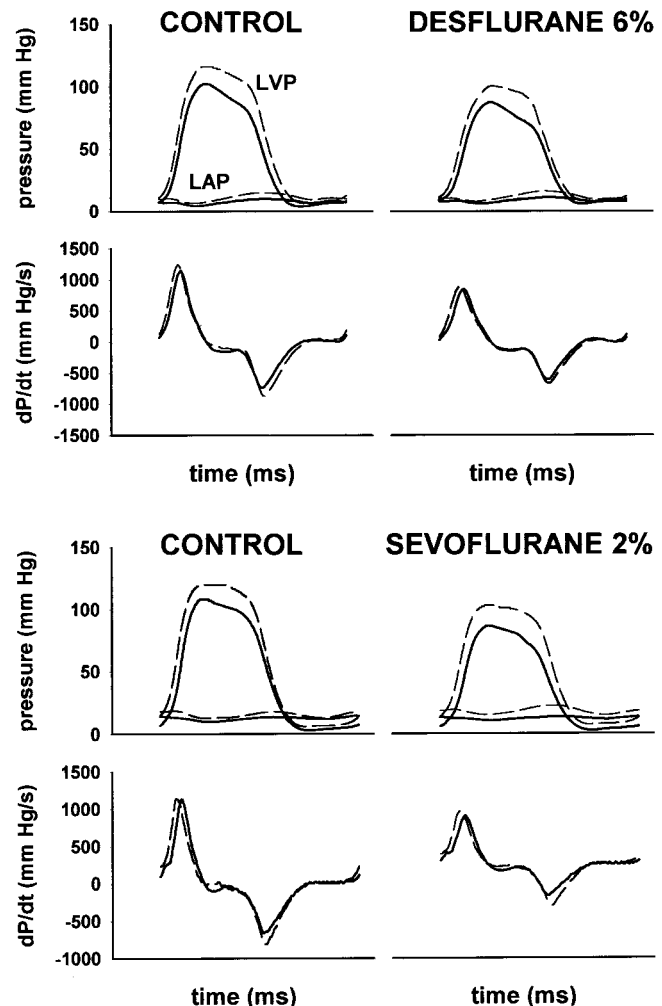


Fig. 1. Representative example of the effects on left ventricular pressure (LVP), left atrial pressure (LAP), and dP/dt tracings of leg elevation in control conditions (control) and at approximately 1 minimal alveolar concentration of desflurane (top) and sevoflurane (bottom). In both conditions, leg elevation (dashed lines) resulted in an increase in left ventricular and left atrial pressures when compared with baseline (solid lines).

namic data at baseline and after leg elevation. At baseline, left atrial pressures and LV end-diastolic pressure remained unchanged with increasing end-tidal concentrations. Peak LV pressure, ESP, dP/dt_{max} , and dP/dt_{min} decreased in a dose-dependent way. Time constant of isovolumic relaxation (τ) increased with higher concentrations. Peak left atrial-LV pressure gradient during early ventricular filling did not change throughout (6 ± 2 mmHg at baseline and 5 ± 1 , 6 ± 2 , and 6 ± 3 mmHg at 1, 2, and 3% sevoflurane, respectively). Thermodilution cardiac index was 2.7 ± 0.4 l · min⁻¹ · m⁻² at control and was unaltered with increasing concentrations of sevoflurane (2.8 ± 0.5 , 2.6 ± 0.4 , and 2.6 ± 0.5 l · min⁻¹ · m⁻², respectively). Changes in left atrial and LV hemodynamic data after leg elevation were similar in control conditions and with increasing concentrations of sevoflurane. Load-dependence of relaxation was not altered.

Table 2. Left Ventricular and Left Atrial Hemodynamic Data at Different Concentrations of Desflurane

	Control Condition 1	Desflurane			Control Condition 2
		2%	4%	6% (~1 MAC)	
Baseline					
Peak A wave (mmHg)	10 ± 3	10 ± 3	10 ± 2	10 ± 3	10 ± 3
Peak V wave (mmHg)	13 ± 4	12 ± 4	12 ± 2	14 ± 5	13 ± 4
EDP (mmHg)	9 ± 3	9 ± 4	8 ± 3	9 ± 2	9 ± 3
Peak LVP (mmHg)	101 ± 9	101 ± 11	91 ± 7*	84 ± 6*	99 ± 12
ESP (mmHg)	59 ± 7	56 ± 9	54 ± 7*	49 ± 8*	59 ± 9
dP/dt _{max} (mmHg/s)	1,022 ± 109	984 ± 118	931 ± 99*	826 ± 119*	1,043 ± 98
dP/dt _{min} (mmHg/s)	775 ± 119	771 ± 118	692 ± 118*	623 ± 118*	738 ± 95
τ (ms)	58 ± 6	58 ± 6	61 ± 6	63 ± 5*	56 ± 6
Effects of leg elevation					
Δ Peak A wave (mmHg)	4 ± 2	4 ± 2	4 ± 3	4 ± 3	4 ± 2
Δ Peak V wave (mmHg)	7 ± 4	7 ± 3	7 ± 3	7 ± 4	7 ± 4
Δ EDP (mmHg)	4 ± 2	4 ± 2	5 ± 3	4 ± 3	4 ± 2
Δ Peak LVP (mmHg)	14 ± 7	15 ± 7	15 ± 5	14 ± 6	14 ± 5
Δ ESP (mmHg)	12 ± 6	10 ± 5	11 ± 6	12 ± 6	11 ± 6
Δ dP/dt _{max} (mmHg/s)	59 ± 75	39 ± 67	42 ± 57	39 ± 64	50 ± 71
Δ dP/dt _{min} (mmHg/s)	107 ± 70	105 ± 65	104 ± 62	115 ± 73	120 ± 74
Δ τ (ms)	3 ± 2	3 ± 3	4 ± 3	4 ± 3	3 ± 2
R (ms/mmHg)	0.344 ± 0.428	0.427 ± 0.137	0.358 ± 0.307	0.414 ± 0.337	0.388 ± 0.205

* Statistically significant for $P < 0.05$ compared with control condition 1.

During the alteration in cardiac load by leg elevation, changes in parameters of contraction and relaxation were coupled. Figure 2 (top) illustrates the relation between afterload dependence of LV pressure decrease (R) and individual changes in dP/dt_{max} with leg elevation during control conditions and at approximately 1 MAC desflurane. The relation between the changes in dP/dt_{max} and the individual R values at control ($y = 0.66 - 0.007 \cdot x$; $r = 0.87$; $P < 0.001$) and at 6% desflurane ($y = 0.64 - 0.008 \cdot x$; $r = 0.85$; $P < 0.001$) were similar during both condi-

tions. The same observation was made when comparing approximately 1 MAC sevoflurane with control conditions (fig. 2, bottom; control: $y = 0.63 - 0.006 \cdot x$, $r = 0.84$, $P < 0.001$; 2% sevoflurane: $y = 0.52 - 0.006 \cdot x$, $r = 0.79$, $P < 0.001$). Contraction-relaxation coupling was therefore not affected by desflurane or sevoflurane.

When the effects of desflurane and sevoflurane on left atrial and LV hemodynamic data at baseline and after leg elevation were compared at equipotent concentrations (1 MAC: desflurane approximately 6%, sevoflurane ap-

Table 3. Left Ventricular and Left Atrial Hemodynamic Data at Different Concentrations of Sevoflurane

	Control Condition 1	Sevoflurane			Control Condition 2
		1%	2% (~1 MAC)	3%	
Baseline					
Peak A wave (mmHg)	12 ± 2	11 ± 2	11 ± 2	11 ± 2	11 ± 2
Peak V wave (mmHg)	13 ± 3	12 ± 4	12 ± 4	12 ± 4	12 ± 4
EDP (mmHg)	10 ± 4	9 ± 3	10 ± 4	9 ± 4	9 ± 4
Peak LVP (mmHg)	103 ± 11	96 ± 10	87 ± 8*	81 ± 9*	101 ± 10
ESP (mmHg)	60 ± 12	57 ± 9	52 ± 7*	48 ± 9*	59 ± 7
dP/dt _{max} (mmHg/s)	994 ± 98	945 ± 87	875 ± 82*	813 ± 76*	1002 ± 79
dP/dt _{min} (mmHg/s)	766 ± 103	712 ± 95	635 ± 100*	591 ± 84*	745 ± 98
τ (ms)	59 ± 4	60 ± 4	63 ± 4*	65 ± 4*	59 ± 3
Effects of leg elevation					
Δ Peak A wave (mmHg)	4 ± 2	5 ± 2	4 ± 1	4 ± 2	4 ± 2
Δ Peak V wave (mmHg)	7 ± 4	8 ± 2	7 ± 2	7 ± 2	7 ± 3
Δ EDP (mmHg)	5 ± 2	5 ± 2	5 ± 3	5 ± 2	4 ± 2
Δ Peak LVP (mmHg)	13 ± 6	14 ± 7	13 ± 4	13 ± 5	12 ± 5
Δ ESP (mmHg)	11 ± 6	11 ± 5	11 ± 4	11 ± 5	12 ± 5
Δ dP/dt _{max} (mmHg/s)	35 ± 56	21 ± 48	21 ± 38	28 ± 52	51 ± 42
Δ dP/dt _{min} (mmHg/s)	97 ± 53	111 ± 55	94 ± 58	103 ± 61	105 ± 59
Δ τ (ms)	4 ± 3	3 ± 3	3 ± 3	4 ± 2	3 ± 3
R (ms/mmHg)	0.378 ± 0.296	0.415 ± 0.221	0.395 ± 0.268	0.401 ± 0.352	0.399 ± 0.276

Data are mean ± SD.

* Statistically significant for $P < 0.05$ compared with control condition 1.

MAC = minimum alveolar concentration; EDP = end-diastolic pressure; LVP = left ventricular pressure; ESP = end-systolic pressure.

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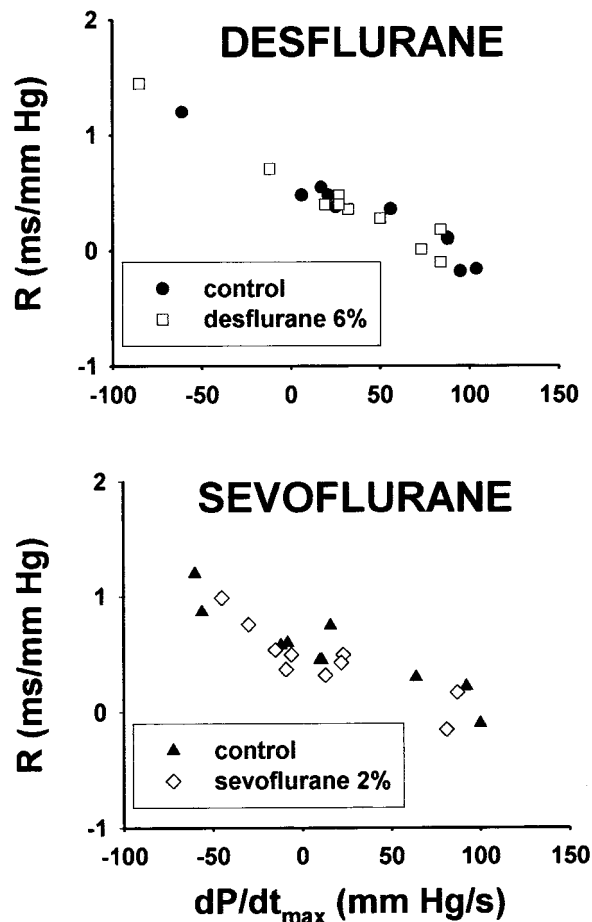


Fig. 2. Plots relating individual values of afterload dependence of LV pressure decrease (R) to corresponding changes in maximal rate of pressure development (dP/dt_{\max}) with leg elevation during control conditions (filled icons) and at approximately 1 minimum alveolar concentration (MAC) desflurane (top, filled dots) and approximately 1 MAC sevoflurane (bottom, filled triangles). With leg elevation, load dependence of myocardial relaxation (R) was coupled with changes in parameters of contraction (dP/dt_{\max}). This relation was not altered by desflurane or sevoflurane.

proximately 2% end-tidal concentration), no significant difference between the two agents were observed. Data during control conditions 1 and 2 were similar (tables 2 and 3), excluding a possible time effect in the current observations.

Discussion

Despite their negative inotropic effects, neither desflurane nor sevoflurane adversely affected the ability of the left ventricle to respond to an increased cardiac load in the current study population of coronary artery surgery patients with a baseline preoperative ejection fraction greater than 40%. Assessment of baseline hemodynamic data, but should also inform about how the ventricle deals with an additional cardiac load; hence, it should

inform about functional cardiac reserve. All patients in the current study had a baseline cardiac function that could be qualified as near normal. Nevertheless, a number of patients developed impairment of LV function when subjected to an increase in cardiac load. These patients developed a decrease in dP/dt_{\max} and a delayed myocardial relaxation with enhanced load dependence of LV pressure decrease. The latter response is indicative of a deficient length-dependent regulation of myocardial function,² indicating that despite their normal values of baseline ejection fraction, these patients had impaired LV function.

Although the inotropic properties of desflurane and sevoflurane have been extensively studied, the effects of these agents on diastolic function remain poorly defined in coronary artery patients. All volatile anesthetics, including desflurane and sevoflurane, produce a dose-related prolongation of isovolumic relaxation.^{10,12-14,20} Slowing of isovolumic relaxation was associated with a decline in early ventricular filling, but this was probably not of sufficient magnitude to alter chamber stiffness.⁹ The current study evaluated the effects of both agents on some of the determinants of diastolic function, *i.e.*, myocardial relaxation and left atrial-LV pressure gradients. Desflurane and sevoflurane caused a similar increase in τ and a comparable decrease in dP/dt_{\min} , indicating a delay in the isovolumic relaxation phase of diastole. τ depends on heart rate, ventricular loading conditions, and inotropic state.²¹ In the current study, heart rate was carefully controlled, excluding this element as possible confounding factor. Both inotropic state and ventricular loading conditions are altered by desflurane and sevoflurane. Whether the increase in τ is caused by change in afterload, a decrease in inotropic state, or reflects a direct myocardial negative lusitropic effect cannot be elucidated with the current observations. During the diastolic phase, the early ventricular filling is not only affected by relaxation rate, but also depends on the gradient between left atrial and LV pressures.²¹⁻²³ In the conditions of our study, this gradient was not modified by desflurane or sevoflurane. This suggested that the reported effects of sevoflurane on early ventricular filling¹⁵ are probably mainly related to a decrease in relaxation rate.

Despite their negative inotropic and lusitropic effects, desflurane and sevoflurane did not impair length-dependent regulation of myocardial function. The clinical implication of this observation is that, in patients with coronary artery disease, desflurane and sevoflurane impair LV inotropy, but improvement of myocardial function by the Frank-Starling mechanism remains preserved. This observation might be attributed to the maintenance of an optimal LV-arterial coupling as a result of the combined effects of desflurane and sevoflurane on myocardial contractility and ventricular afterload. In an open-chest dog model, Hettrick *et al.*¹⁴ demonstrated that

volatile anesthetics preserve optimum LV-arterial coupling and efficiency at end-tidal anesthetic concentrations less than 0.9 MAC. The physiologic importance of this close interaction between myocardial contractility and ventricular loading conditions in the assessment of dynamic cardiac functional reserve fits in the concept of relative cardiac load.^{24,25} Based on this concept, it might be hypothesized that improved LV function with leg elevation indicates a left ventricle operating at low relative load, whereas impairment of LV function with leg elevation is indicative of a left ventricle operating at high relative load. The combined effects of desflurane and sevoflurane on myocardial contractility and LV loading conditions did not modify relative cardiac load, and, therefore, the response of the left ventricle to leg elevation was not altered.

The MAC in oxygen has been reported to be 6.0 ± 0.3 (mean \pm SD) for desflurane²⁶ and 1.71 ± 0.07 (mean \pm SEM) for sevoflurane.²⁷ The concentration range examined in the current study therefore allowed comparison of nearly equipotent doses of desflurane and sevoflurane (approximately 1 MAC). Both agents had similar effects on the LV hemodynamics and on the ability of the left ventricle to respond to an increased load. Concentrations higher than 6% for desflurane and 3% for sevoflurane were not evaluated because of the obvious possible deleterious effects on hemodynamics in the current study population.

Because both anesthetic agents affect ventricular loading conditions, myocardial contractility and central nervous system activity, the observed changes in hemodynamics may vary according to the experimental set-up. In our study, all patients received chronic preoperative β -blocking medication. They underwent anesthesia based on high-dose opioids combined with benzodiazepines. These two factors will result in a depression of autonomic nervous system reflexes. Myocardial contractility was evaluated by $LV\ dp/dt_{max}$, which represents an isovolumic index of contractile state that is heart rate- and preload-dependent.²⁸ The current results were obtained in a clinical model with a fixed-paced heart rate and at constant LV filling pressures. This implies that any effect secondary to a change in heart rate or LV filling pressure was obviated. The observed negative inotropic effects of desflurane and sevoflurane are in line with previous observations using similar^{13,15,29} and other indices of myocardial contractile function.^{9-14,17,18} The similar degree of depression of myocardial inotropy with equipotent doses of desflurane and sevoflurane in the current group of patients with coronary artery disease also confirms previous observations in experimental study designs.^{12,13,30}

In conclusion, despite their negative inotropic effects, neither desflurane nor sevoflurane adversely affected the

ability of the left ventricle to respond to an increased cardiac load in coronary surgery patients with baseline ejection fraction greater than 40%. The clinical implication of this finding is that, in this particular subset of patients, desflurane and sevoflurane impair LV function but do not alter regulation of myocardial function by the Frank-Starling mechanism.

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