

Cardiovascular Effects of Sevoflurane Compared with Those of Isoflurane in Volunteers

T. Philip Malan, Jr., Ph.D., M.D.,* James A. DiNardo, M.D.,† R. Joseph Isner, M.D.,* Edward J. Frink, Jr., M.D.,† Mark Goldberg, M.D.,‡ Paul E. Fenster, M.D.,§ Elizabeth A. Brown, B.S.N.,|| Raymond Depa, B.S.,# Leslie C. Hammond, # Heriberto Mata, B.S.#

Background: Sevoflurane is a new inhalational anesthetic with desirable clinical properties. In some clinical situations, an understanding of the detailed cardiovascular properties of an anesthetic is important, so the authors evaluated the hemodynamic effects of sevoflurane in healthy volunteers not undergoing surgery.

Methods: Twenty-one subjects were randomized to receive sevoflurane, isoflurane, or sevoflurane: 60% N₂O. Anesthesia was induced and maintained by inhalation of the designated anesthetic. Hemodynamic measurements were performed before anesthesia, during controlled ventilation, during spontaneous ventilation, and again during controlled ventilation after 5.5 h of anesthesia.

Results: A few subjects became excessively hypotensive at high anesthetic concentrations (2.0 minimum alveolar concentration [MAC] sevoflurane, 1.5 and 2.0 MAC isoflurane), preventing data collection. Sevoflurane did not alter heart rate, but decreased mean arterial pressure and mean pulmonary artery pressure. Cardiac index decreased at 1.0 and 1.5 MAC, but in subjects with mean arterial pressure ≥ 50 mmHg returned to baseline values at 2.0 MAC when systemic vascular resistance decreased. Sevoflurane did not alter echocardiographic indices of ventricular function, but did decrease an index of afterload. Sevoflurane caused a greater decrease in

mean pulmonary artery pressure than did isoflurane, but the cardiovascular effects were otherwise similar. Administration of sevoflurane with 60% N₂O, prolonged administration or spontaneous ventilation resulted in diminished cardiovascular depression.

Conclusions: At 1.0 and 1.5 MAC, sevoflurane was well tolerated by healthy volunteers. At 2.0 MAC, in subjects with mean arterial pressure ≥ 50 mmHg, no adverse cardiovascular properties were noted. Similar to other contemporary anesthetics, sevoflurane caused evidence of myocardial depression. Hemodynamic instability was noted in some subjects at high anesthetic concentrations in the absence of surgical stimulation. The incidence was similar to that with isoflurane. The cardiovascular effects of sevoflurane were similar to those of isoflurane, an anesthetic commonly used in clinical practice since 1981. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: isoflurane; sevoflurane. Blood pressure: drug effects. Heart: echocardiography; myocardial function; vascular pressures.)

SEVOFLURANE is a new inhalational anesthetic with the desirable properties of a low blood-gas partition coefficient¹ and nonpungent character.² Understanding the cardiovascular properties of a new anesthetic is important when evaluating its cardiovascular safety and when applying the agent to clinical situations in which cardiovascular function is an important consideration. The cardiovascular properties of sevoflurane in dogs have been shown to be similar to those of isoflurane, except that heart rate was lower with 1.2 MAC sevoflurane than with isoflurane.³ In surgical patients, heart rate was lower with sevoflurane than with isoflurane from 3–5 min before incision to 60 min after incision, but the cardiovascular properties of the agents were otherwise similar.⁴

In this article, we report the hemodynamic effects of sevoflurane administered to healthy male volunteers. We report the effects of sevoflurane administered in oxygen with ventilation controlled to maintain normocarbica and compare them with the hemodynamic effects of isoflurane administered under identical conditions. Previously studied volatile anesthetics have

* Assistant Professor of Anesthesiology.

† Associate Professor of Anesthesiology.

‡ Fellow in Cardiology.

§ Professor of Internal Medicine (Cardiology).

|| Research Nurse.

Research Assistant.

Received from the Departments of Anesthesiology and Internal Medicine, Cardiology Section, University of Arizona Health Sciences Center, Tucson, Arizona. Submitted for publication November 10, 1994. Accepted for publication June 30, 1995. Supported by a grant from Abbott Laboratories, Abbott Park, Illinois. Presented in part at the Clinical and Scientific Congress of the International Anesthesia Research Society, Orlando, Florida, March 5–9, 1994, and the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 15–19, 1994.

Address reprint requests to Dr. Malan: Department of Anesthesiology, University of Arizona Health Sciences Center, 1501 North Campbell Avenue, Tucson, Arizona 85724. Address electronic mail to: MALAN@CCIT.ARIZONA.EDU.

CARDIOVASCULAR EFFECTS OF SEVOFLURANE

been associated with less cardiovascular depression during spontaneous than during controlled ventilation.⁵⁻⁸ We therefore compare the cardiovascular properties of sevoflurane during spontaneous ventilation with those during controlled ventilation. Similarly, studies of contemporary volatile anesthetics have shown that when each is compared to an equipotent mixture of volatile anesthetic and N₂O, the latter produces less cardiovascular depression.⁹⁻¹² Therefore, we examined the cardiovascular properties of sevoflurane administered in 60% N₂O:40% O₂. Because studies of halothane, enflurane, and desflurane have demonstrated attenuation of cardiovascular effects or cardiovascular stimulation with time,¹³⁻¹⁵ we repeated cardiovascular measurements during controlled ventilation after 5.5 hr of anesthesia.

Materials and Methods

Study Design

Twenty-one subjects were enrolled in a randomized (1:1:1), parallel trial. Using a computer-generated schedule 7 volunteers were randomized to receive sevoflurane in 100% O₂, 7 isoflurane in 100% O₂, and 7 sevoflurane in 60% N₂O:40% O₂. Hemodynamic measurements were performed for each subject before anesthesia, at three anesthetic concentrations during controlled ventilation, at three anesthetic concentrations during spontaneous ventilation and at two anesthetic concentrations during controlled ventilation after 5.5 hr anesthesia.

Subject Selection

After approval from The University of Arizona Human Subjects Committee, informed consent was obtained from 21 healthy, young male volunteers aged 19-34 years. They were of normal weight for height and were healthy by history and physical examination. Specific exclusion criteria included: evidence of cardiovascular, pulmonary, hepatic, or renal disease; use of chronic medications; personal or family history of unusual response to halogenated anesthetics; receipt of a general anesthetic within 6 months; previous use of investigational drugs; use of alcohol or medications within 7 days; and food or drink within 8 hr. Each subject had normal complete blood count, blood chemistry (including sodium, potassium, glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase), urinalysis, electrocardiogram, and diagnostic echocardiogram.

Cardiovascular Measurements

Each volunteer was placed in the left lateral decubitus position. After 20 min rest, a left ventricular short axis two-dimensional echocardiogram was recorded at the mid-papillary muscle level using an echocardiography system (Model CFM 775, Vingmed Sound, Inc., Milpitas, CA) with a 5-MHz transthoracic echocardiography probe (Vingmed Sound, Inc.). The volunteer was then placed supine and peripheral intravenous, radial artery and pulmonary artery catheters were inserted using local anesthesia without sedation. The position of the pulmonary artery catheter was established by the pressure waveform. After 20 min rest, preanesthetic hemodynamic values were measured.

Hemodynamic pressures were measured using transducers (Model T 4812AD-R, Viggo-Spectramed, Oxnard, CA), which had been calibrated using a manometer, and a monitor (Spacelabs 90305 PC2 Bed-side Monitor, Spacelabs, Inc., Redmond, WA) equipped with modules for electrocardiogram, invasive pressure, and cardiac output measurement. Transducers were zeroed at the mid-axillary line. Hemodynamic measurements were made at end-expiration. Pulmonary artery occlusion pressure was not measured for reasons of safety. Cardiac output was determined at end-expiration in triplicate by thermodilution, using a pulmonary artery thermodilution catheter (Edwards Model 93A-931H7.5F, Baxter Healthcare Corp., Irvine, CA) and room-temperature saline.

After induction of anesthesia and intubation of the trachea, a 5-MHz multiplane transesophageal echocardiography probe (Vingmed Sound, Inc.) was positioned in the esophagus at the mid-papillary muscle level and used to record subsequent two-dimensional echocardiograms. Echocardiographic measurements were made at end-expiration.

Customary formulas were used to calculate derived hemodynamic variables. A video analysis system (Vingmed Sound, Inc.) was used to measure left ventricular cross-sectional areas and circumferences. Area ejection fraction was calculated as described by Abel *et al.*¹⁶ Velocity of circumferential fiber shortening was calculated from two-dimensional measurements of left-ventricular circumference as described by Ruschaupt *et al.*¹⁷ and corrected for heart rate as described by Colan *et al.*¹⁸ Meridional left ventricular end-systolic wall stress was calculated as described by Douglas *et al.*¹⁹

Anesthetic Management

Anesthesia was induced by inhalation of the designated anesthetic during spontaneous ventilation. Tracheal intubation was facilitated with vecuronium (0.1 mg/kg). Ventilation was controlled to maintain normocarbia. Cardiovascular measurements were obtained at 1.0 minimum alveolar concentration (MAC), 1.5 MAC, and 2.0 MAC end-tidal anesthetic concentrations after the desired end-tidal anesthetic concentration had been maintained stable for 20 min. Measurements were made in order of increasing anesthetic concentration. If mean arterial pressure (MAP) decreased to less than 50 mmHg, anesthetic concentration was decreased by 0.5 MAC for reasons of safety. Minimum alveolar concentration of sevoflurane was taken as 2.05%,²⁰ MAC of isoflurane was taken as 1.15%,²¹ and MAC of N₂O was taken as 104%.²² Minimum alveolar concentration multiple of sevoflurane was assumed to be additive to that of nitrous oxide. End-tidal anesthetic concentrations were measured at the endotracheal tube orifice by infrared spectroscopy (Datex Capnomac Ultima, Datex Medical Instrumentation, Inc., Tewksbury, MA). Body temperature was maintained at normothermia with a forced-air warming device (Bair Hugger, Augustine Medical, Inc., Eden Prairie, MN). Intravenous fluids were infused as lactated Ringer's solution, using an estimate of basal metabolic rate of $42 \text{ kcal} \cdot \text{m}^{-2} \cdot \text{h}^{-1}$ and assuming a water requirement of 1 ml/kcal expended.²³ The calculated fluid deficit from overnight fasting was replaced before hemodynamic or echocardiographic measurements. Additional saline was administered at three times the amount of blood lost by sampling (approximately 150 ml). Additional fluid was administered if the left ventricular end-diastolic area, as measured using the video analysis system, decreased compared to values obtained after replacement of the calculated deficit and before induction of anesthesia.

Biostatistical Methods

A one-way analysis of variance was used to compare demographic and baseline variables of treatment groups. Cardiovascular data were analyzed to compare anesthetic effects between treatment groups, to examine effects of anesthetic in each treatment group, to compare spontaneous and controlled ventilation and to compare initial measurements with those after 5.5 hr of anesthesia. The change from preanesthesia to each intra-anesthetic measurement was calculated. At each evaluation time, these changes were compared among the three treatment groups with least significant dif-

ference tests within a one-way analysis of variance. The effects of anesthetics within each treatment group were tested using a pooled estimate of error from the analysis of variance. Repeated-measures analysis of variance could not be used because measurements could not be made for all subjects at all anesthetic concentrations. The differences between controlled and spontaneous ventilation or between early and late measurements were analyzed using a paired *t* test.

Results

Of the 21 subjects enrolled in this protocol, 7 received sevoflurane in O₂, 7 sevoflurane in N₂O:O₂, and 6 isoflurane in O₂. One subject randomized to receive isoflurane withdrew from the study prior to anesthetic induction.

The treatment groups were comparable with regard to age, weight, and height (table 1). They were also comparable with regard to baseline values of cardiovascular measurements, except that subjects receiving sevoflurane had higher preanesthetic mean pulmonary artery pressure than did subjects receiving sevoflurane:N₂O or isoflurane and heart rate was lower at baseline in subjects receiving sevoflurane:N₂O than in subjects receiving sevoflurane.

In the 7 subjects receiving sevoflurane during controlled ventilation, MAP was ≥ 50 mmHg during 1.0 and 1.5 MAC anesthetic, whereas in 5 of 7 MAP was ≥ 50 mmHg during 2.0 MAC sevoflurane. All subjects receiving sevoflurane in N₂O tolerated 1.0 and 1.5 MAC, while 6 of 7 tolerated 2.0 MAC. All subjects receiving isoflurane tolerated 1.0 MAC, 4 of 6 tolerated 1.5 MAC, and in 3 of 6 MAP was ≥ 50 mmHg with 2.0 MAC. When the desired MAC level could not be maintained, data for that subject at that MAC multiple were not included in the analysis.

After replacement of the calculated fluid deficit from overnight fasting, left ventricular end-diastolic area was maintained constant by administration of additional fluid, if necessary. The mean total amount of fluid administered, including replacement of the calculated deficit, through the controlled ventilation phase of the protocol (data shown in figs. 1–3) was 1857 ± 181 ml for sevoflurane, 2015 ± 304 ml for isoflurane, and 1757 ± 137 ml for sevoflurane:60% N₂O.

Cardiovascular Effects of Sevoflurane

The effects of sevoflurane on selected hemodynamic variables are shown in figure 1. Sevoflurane did not

CARDIOVASCULAR EFFECTS OF SEVOFLURANE

Table 1. Physical Characteristics and Baseline Values of Volunteers

	Volunteers Receiving Sevoflurane (n = 7)	Volunteers Receiving Isoflurane (n = 6)	Volunteers Receiving Sevoflurane:N ₂ O (n = 7)
Age (yr)	26 ± 2	24 ± 2	24 ± 1
Height (cm)	178 ± 2	185 ± 3	178 ± 3
Weight (kg)	72 ± 4	82 ± 4	83 ± 4
Temperature (°C)	36.6 ± 0.4	36.8 ± 0.3	36.7 ± 0.5
HR (beats/min)	72 ± 4	62 ± 4	58 ± 4*
MAP (mmHg)	92 ± 3	85 ± 3	88 ± 3
MPAP (mmHg)	16 ± 1	12 ± 1*	15 ± 1
CVP (mmHg)	5.7 ± 0.8	3.8 ± 0.8	6.1 ± 0.8
CI (L · min ⁻¹ · m ⁻²)	3.8 ± 0.2	4.0 ± 0.2	3.8 ± 0.2
SVR (dyne · s · cm ⁻⁵)	974 ± 65	823 ± 70	881 ± 65
LVEDA (cm ²)	18 ± 1	20 ± 1	18 ± 1
LVEF (%)	41 ± 3	43 ± 3	36 ± 3
V _{cls} (circ/s)	0.63 ± 0.08	0.71 ± 0.09	0.62 ± 0.09
SWS (g/cm ²)	123 ± 16	120 ± 17	126 ± 17
S _{vo2} (%)	78 ± 2	76 ± 1	74 ± 2

Data are mean ± SEM.

HR = heart rate; MAP = mean arterial blood pressure; MPAP = mean pulmonary arterial blood pressure; CVP = central venous pressure; CI = cardiac index; SVR = systemic vascular resistance; LVEDA = left ventricular end-diastolic cross-sectional cavity area; LVEF = left ventricular area ejection fraction; V_{cls} = velocity of circumferential fiber shortening; SWS = systolic wall stress; S_{vo2} = mixed venous oxyhemoglobin saturation.

* $P < 0.05$ versus volunteers receiving sevoflurane.

alter heart rate compared to awake values. Sevoflurane decreased MAP, mean pulmonary artery pressure, and stroke volume index at all anesthetic concentrations. Cardiac index decreased compared to awake measurements at 1.0 and 1.5 MAC, but not at 2.0 MAC where systemic vascular resistance decreased. Central venous pressure decreased slightly compared to awake values at 1.5 MAC, but not at 1.0 or 2.0 MAC. Mixed venous hemoglobin saturation increased at all anesthetic concentrations, while total body oxygen consumption decreased at all anesthetic concentrations. Arterial base-excess was unchanged. Sevoflurane did not alter left ventricular area ejection fraction, or velocity of circumferential fiber shortening (figure 2). Systolic wall stress decreased at all anesthetic concentrations. Left ventricular end-diastolic area was unchanged, as dictated by the experimental protocol.

Cardiovascular Effects of Sevoflurane Compared with Those of Isoflurane

The effects of isoflurane on cardiovascular variables are shown in figures 1 and 2. Isoflurane increased heart rate at 1.5 and 2.0 MAC. Cardiac index decreased compared to awake measurements at 1.0 MAC, but not at 1.5 and 2.0 MAC where systemic vascular resistance decreased. Mean arterial pressure, stroke volume index,

and systolic wall stress decreased at all anesthetic concentrations. Mixed venous hemoglobin saturation increased at all isoflurane concentrations, while total body oxygen consumption decreased at 1.5 and 2.0 MAC. Other measured variables were unchanged.

When treatment groups were compared directly, sevoflurane caused a greater decrease in mean pulmonary artery pressure at 1.0 and 1.5 MAC than did isoflurane. No other differences between treatment groups were noted.

Cardiovascular Effects of Sevoflurane: N₂O Compared to Those of Sevoflurane

The cardiovascular effects of sevoflurane administered in 60% N₂O:40% O₂ during controlled ventilation were compared directly to those of sevoflurane in 100% O₂ (figs. 1 and 2). Mean arterial pressure decreased less at 1.0 MAC and mean pulmonary artery pressure decreased less at 1.0 and 1.5 MAC with sevoflurane:N₂O than with sevoflurane. Mixed venous oxyhemoglobin saturation increased less with sevoflurane:N₂O than with sevoflurane at all anesthetic concentrations.

Cardiovascular Effects of Sevoflurane during Spontaneous Ventilation

During sevoflurane, sevoflurane:N₂O, or isoflurane anesthesia in spontaneously ventilating subjects, arte-

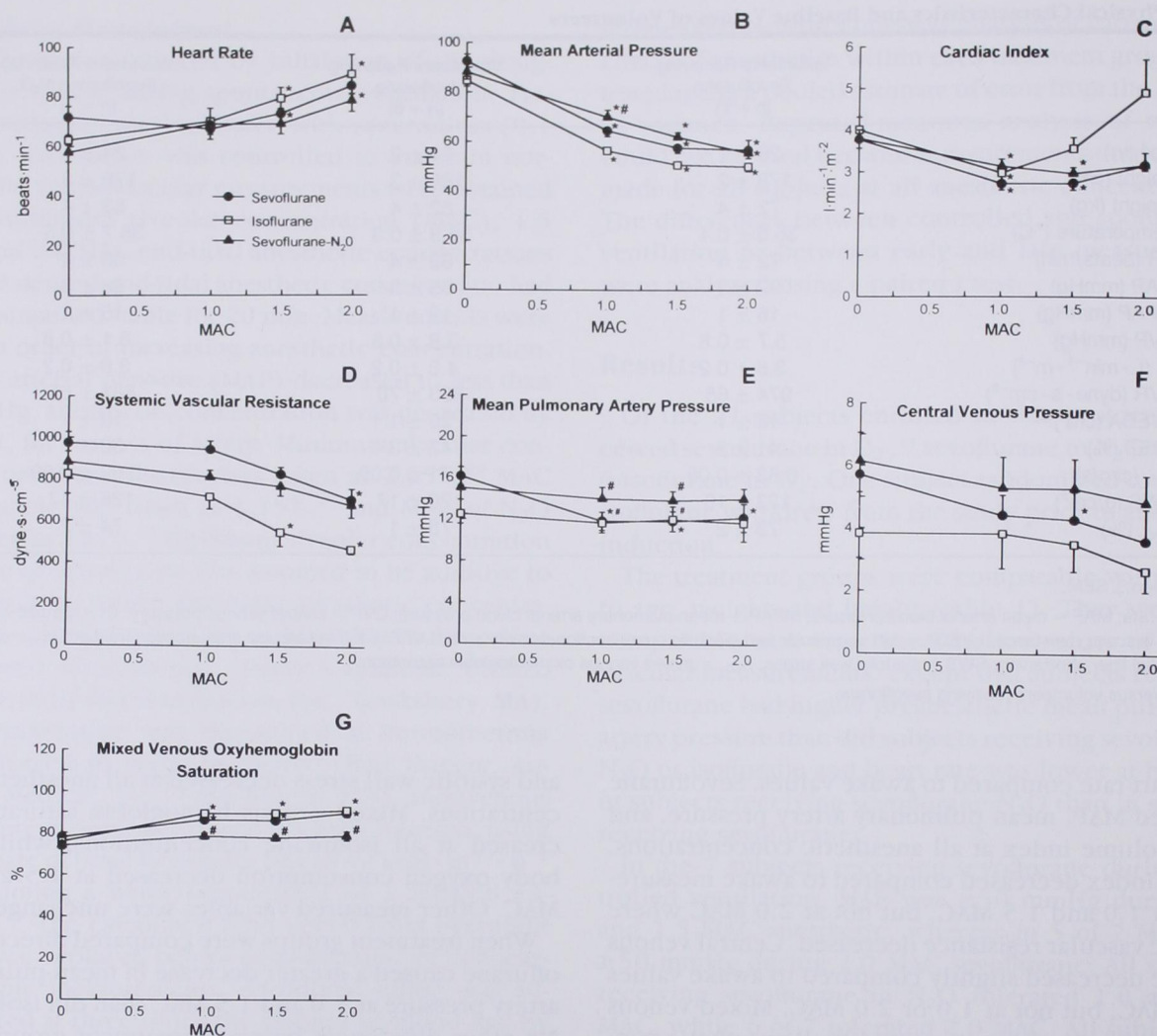


Fig. 1. (A-G) Hemodynamic indices of the cardiovascular effects of sevoflurane, sevoflurane:N₂O, or isoflurane anesthesia in healthy men during controlled ventilation. Zero MAC value refers to preanesthetic measurement. Data are expressed as mean \pm SEM. * $P < 0.05$ versus preanesthetic value. # $P < 0.05$ compared to sevoflurane. See table 1 for definitions of abbreviations. Data could not be collected for some subjects at higher anesthetic concentrations because of intolerable hypotension. Before anesthesia and at 1.0 MAC, $n = 7$ for sevoflurane and sevoflurane:N₂O and $n = 6$ for isoflurane. At 1.5 MAC, $n = 7$ for sevoflurane and sevoflurane:N₂O and $n = 4$ for isoflurane. At 2.0 MAC, $n = 5$ for sevoflurane, $n = 6$ for sevoflurane:N₂O and $n = 3$ for isoflurane.

rial partial pressure of carbon dioxide increased compared to preanesthetic values (fig. 3). At each MAC multiple, PaCO₂ values did not differ among treatment groups.

All subjects receiving sevoflurane during spontaneous ventilation tolerated 1.0 and 1.5 MAC, while in 1 of 7 subjects MAP fell below 50 mm Hg at 2.0 MAC. Heart rate and stroke volume index were higher during spontaneous than during controlled ventilation at 1.0 and 1.5 MAC (table 2). Mean arterial pres-

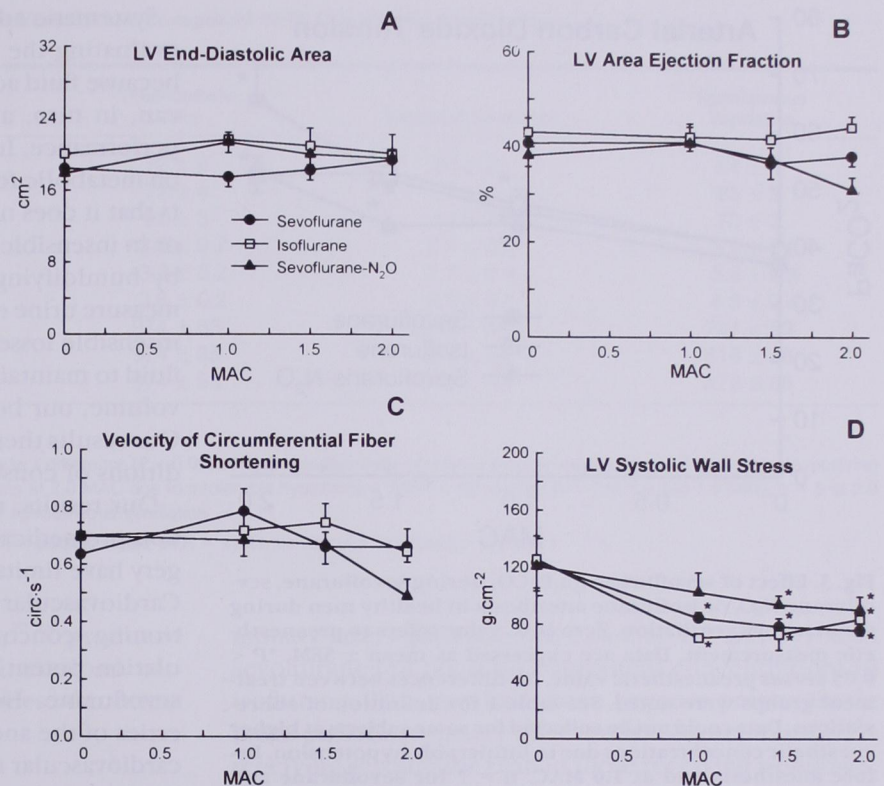
sure was higher during spontaneous ventilation at 1.0 MAC. Cardiac index was higher and systemic vascular resistance lower during spontaneous ventilation at all anesthetic concentrations. Velocity of circumferential fiber shortening was higher during spontaneous ventilation at 1.5 MAC.

Cardiovascular Effects of Prolonged Anesthesia

All subjects receiving sevoflurane after 5.5 hr of anesthesia tolerated 1.0 MAC, while 3 of 7 subjects devel-

CARDIOVASCULAR EFFECTS OF SEVOFLURANE

Fig. 2. (A–D) Echocardiographic indices of the cardiovascular effects of sevoflurane, sevoflurane:N₂O, or isoflurane anesthesia in healthy men during controlled ventilation. Zero MAC value refers to preanesthetic measurement. Data are expressed as mean \pm SEM. * $P < 0.05$ versus preanesthetic value. No difference between treatment groups was noted. See table 1 for definition of abbreviations. Data could not be collected for some subjects at higher anesthetic concentrations because of intolerable hypotension. Before anesthesia and at 1.0 MAC, $n = 7$ for sevoflurane and sevoflurane:N₂O and $n = 6$ for isoflurane. At 1.5 MAC, $n = 7$ for sevoflurane and sevoflurane:N₂O and $n = 4$ for isoflurane. At 2.0 MAC, $n = 5$ for sevoflurane, $n = 6$ for sevoflurane:N₂O, and $n = 3$ for isoflurane.



opened intolerable hypotension (MAP < 50 mmHg) at 2.0 MAC. At 1.0 MAC heart rate, cardiac index, stroke volume index, and mixed venous oxygen saturation were higher after 5.5 hr of sevoflurane anesthesia than during the first 150 min of anesthesia (table 3). Systemic vascular resistance was less in the later period at both 1.0 and 2.0 MAC.

Discussion

We evaluated the hemodynamic effects of sevoflurane in healthy volunteers not undergoing surgery. The use of volunteers allows detailed measurement of cardiovascular variables under controlled conditions without confounding factors common in surgical patients.

Study Limitations

Cardiovascular measurements could not be performed on some subjects receiving high anesthetic concentrations because of unacceptable hypotension. These data were not available for inclusion in the statistical analysis. This introduces a bias in the analysis of the response of MAP and possibly of other cardiovascular variables to 1.5 or 2.0 MAC anesthetic. This

bias is significant because data from subjects with the greatest hemodynamic response to anesthetic were not available for analysis. In addition to creating a possible bias in averaged data, inability to include data from some subjects decreases statistical power and may cause cardiovascular effects of higher anesthetic concentrations to go undetected. It was possible, however, to collect data for all subjects at 1.0 MAC sevoflurane, sevoflurane:N₂O, and isoflurane. Therefore, comparisons are valid at this anesthetic concentration. It is likely that the effects of isoflurane on MAP at higher anesthetic concentrations were underestimated to an equal or greater extent than were those of sevoflurane and sevoflurane:N₂O because a greater number of measurements were unable to be performed during isoflurane anesthesia than during anesthesia induced by the other agents. The effects on other hemodynamic variables of the loss of data from some subjects at higher anesthetic concentrations cannot be accurately predicted.

We administered anesthetics in increasing concentrations so that if adverse hemodynamic events occurred at lower concentrations, higher concentrations with more adverse consequences would not be attempted.

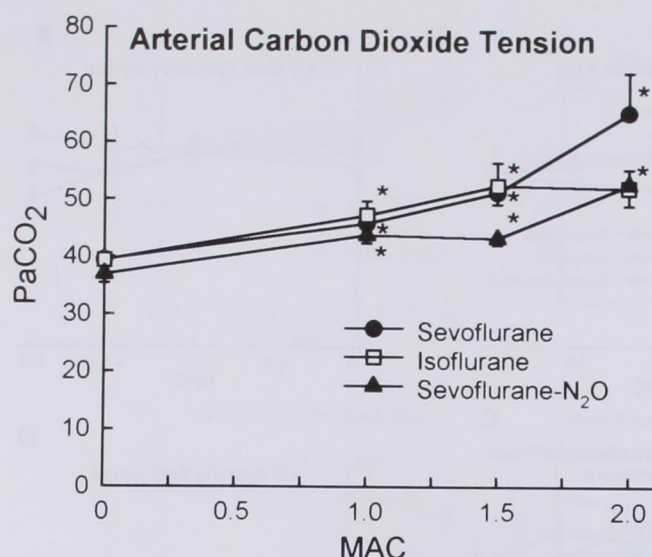


Fig. 3. Effect of sevoflurane on PaCO_2 during sevoflurane, sevoflurane: N_2O , or isoflurane anesthesia in healthy men during spontaneous ventilation. Zero MAC value refers to preanesthetic measurement. Data are expressed as mean \pm SEM. * $P < 0.05$ versus preanesthetic value. No differences between treatment groups were noted. See table 1 for definition of abbreviations. Data could not be collected for some subjects at higher anesthetic concentrations due to intolerable hypotension. Before anesthesia and at 1.0 MAC, $n = 7$ for sevoflurane and sevoflurane: N_2O and $n = 6$ for isoflurane. At 1.5 MAC, $n = 7$ for sevoflurane and sevoflurane: N_2O and $n = 4$ for isoflurane. At 2.0 MAC, $n = 5$ for sevoflurane, $n = 6$ for sevoflurane: N_2O , and $n = 3$ for isoflurane.

This also raises a possible confounding factor (the effect of anesthetic duration) when different anesthetic concentrations are compared.

Examination of our data reveals some apparent physiologic inconsistencies. For example, left ventricular end-diastolic volume and left ventricular area ejection fraction were unchanged, whereas stroke volume decreased. Also, at 2.0 MAC sevoflurane, cardiac index and heart rate were unchanged, whereas stroke volume decreased. This is probably because changes in some related variables did not achieve statistical significance owing to the small number of subjects enrolled. In addition, two-dimensional echocardiographic indices of ventricular volume are likely to be relatively insensitive to small changes in volume. Therefore, caution should be used in drawing detailed physiologic conclusions from our data. These data are more appropriately used descriptively to anticipate the changes in the same variables when patients are anesthetized with these agents.

Systematic administration of fluid is important when evaluating the cardiovascular effects of a medication, because fluid administration can affect preload. Preload can, in turn, affect other measures of cardiovascular performance. In this study, we administered fluid based on metabolic formulas. The limitation of this approach is that it does not account for variation in urine output or in insensible losses. We minimized respiratory losses by humidifying inspired gasses; however we did not measure urine output and were unable to measure other insensible losses. We therefore administered additional fluid to maintain constant left ventricular end-diastolic volume, our best measure of left ventricular preload. Our results therefore most accurately apply under conditions of constant preload.

Our results, which are measured in healthy, young, non-premedicated male subjects not undergoing surgery have limitations when applied to surgical patients. Cardiovascular disease, age, gender, physical conditioning, concomitant medications, and surgical stimulation potentially affect cardiovascular responses to sevoflurane. However, because cardiovascular properties of the anesthetic are a significant determinant of cardiovascular responses during surgery, understanding these properties enables the clinician to anticipate possible cardiovascular responses to the variety of clinical situations faced. Most importantly, the detailed cardiovascular responses to sevoflurane are nearly identical to those of isoflurane, an anesthetic with which most clinicians are familiar.

Cardiovascular Effects of Sevoflurane

The decrease in cardiac index or systemic vascular resistance, combined with the unchanged filling pressures and heart rate observed with sevoflurane indicates decreased myocardial contractility. The pattern of unchanged echocardiographic ejection-phase indices of left ventricular function (left ventricular area ejection fraction and velocity of circumferential fiber shortening) with unchanged preload (left ventricular end-diastolic area) and decreased afterload (systolic wall stress) also indicates decreased myocardial contractility. The ejection-phase indices would be expected to increase in the face of decreasing afterload if contractility were maintained.^{24,25} Sevoflurane-induced myocardial depression is consistent with the work of Pagel *et al.*,²⁶ who showed that sevoflurane administered to chronically instrumented dogs decreases preload-recruitable stroke work slope, a reliable index of myocardial contractility. In addition, isoflurane, an anes-

CARDIOVASCULAR EFFECTS OF SEVOFLURANE

Table 2. Differences Noted with Spontaneous Ventilation Compared with Controlled Ventilation during Sevoflurane Anesthesia

Variable	MAC	Preanesthetic Value	Controlled Ventilation	Spontaneous Ventilation
HR (beats/min)	1.0	72 ± 4	67 ± 2	84 ± 4
	1.5	72 ± 4	73 ± 3	83 ± 3
MAP (mmHg)	1.0	92 ± 3	64 ± 2	70 ± 3
	1.5	92 ± 3	64 ± 2	70 ± 3
CI (L · min ⁻¹ · m ⁻²)	1.0	3.8 ± 0.2	2.7 ± 0.2	3.9 ± 0.2
	1.5	3.8 ± 0.2	2.7 ± 0.2	3.8 ± 0.3
	2.0	3.8 ± 0.2	3.2 ± 0.1	4.5 ± 0.4
SVR (dyne · s · cm ⁻⁵)	1.0	974 ± 65	948 ± 41	741 ± 59
	1.5	974 ± 65	832 ± 34	618 ± 48
	2.0	974 ± 65	712 ± 53	478 ± 56

Data are mean ± SEM.

Variables included in this table are those for which there was a difference ($P < 0.05$) between mechanically ventilated and spontaneously ventilated subjects receiving sevoflurane. Data could not be collected for some subjects at 2.0 MAC due to intolerable hypotension (MAP < 50 mmHg); $n = 7$ at 1.0 and 1.5 MAC, $n = 5$ at 2.0 MAC for controlled ventilation, and $n = 6$ at 2.0 MAC for spontaneous ventilation.

HR = heart rate; MAP = mean arterial blood pressure; CI = cardiac index; SVR = systemic vascular resistance.

thetic known to decrease contractility,^{27,28} produced a similar pattern of changes in preload, afterload, cardiac index, and echocardiographic indices of contractility.

Cardiovascular Effects of Sevoflurane Compared with Those of Isoflurane

In our comparative study, the cardiovascular effects of sevoflurane were qualitatively and quantitatively similar to those of isoflurane. When cardiovascular measurements during anesthesia were compared to baseline values, some differences between anesthetics were suggested. However, when the effects of sevoflurane and isoflurane were compared directly, sevoflurane differed from isoflurane only in that mean pul-

monary artery pressure decreased at 1.0 and 1.5 MAC sevoflurane but not with equipotent concentrations of isoflurane. This may have been because preanesthetic mean pulmonary artery pressure was higher in subjects receiving sevoflurane than in those receiving isoflurane.

Comparison with Previous Studies of Cardiovascular Effects of Volatile Anesthetics

Our measurements during isoflurane anesthesia correspond well to those of Stevens *et al.*²⁹ Four differences were noted, however. First, in our study, heart rate increased only at 1.5 and 2.0 MAC, not at 1.0 MAC as observed by Stevens *et al.* Second, in our study, systemic vascular resistance was maintained at 1.0 MAC and decreased only at higher end-tidal isoflurane concentra-

Table 3. Differences Noted with Prolonged Sevoflurane Administration

Variable	MAC	Preanesthetic Value	Early Value	Late Value
HR (beats/min)	1.0	72 ± 4	67 ± 2	83 ± 3
CI (L · min ⁻¹ · m ⁻²)	1.0	3.8 ± 0.2	2.7 ± 0.2	3.8 ± 0.3
SVR (dyne · s · cm ⁻⁵)	1.0	974 ± 65	948 ± 41	712 ± 76
	2.0	974 ± 65	712 ± 53	373 ± 0
SVI (ml/m ²)	1.0	57 ± 4	41 ± 2	47 ± 3
S _{VO₂} (%)	1.0	78.0 ± 1.8	86.3 ± 1.1	90.2 ± 0.6

Data are mean ± SEM.

Variables included in this table are those for which there was a difference ($P < 0.05$) between the early and late values. Early value is that obtained during first 150 min of anesthesia. Late value is that obtained after 320–400 min of anesthesia. Data could not be collected for some subjects at 2.0 MAC due to intolerable hypotension (MAP < 50 mmHg); $n = 7$ at 1.0 MAC, $n = 5$ at 2.0 MAC in the early period, and $n = 4$ at 2.0 MAC in the later period.

HR = heart rate; CI = cardiac index; SVR = systemic vascular resistance; SVI = stroke volume index; S_{VO₂} = mixed venous oxyhemoglobin saturation.

tions. Third, our data show isoflurane's effect on cardiac index to be biphasic; in subjects with MAP ≥ 50 mmHg at all anesthetic concentrations, cardiac index decreased at 1.0 MAC, but returned to preanesthetic values at higher isoflurane concentrations as systemic vascular resistance decreased. Fourth, the increased right atrial pressure observed by Stevens *et al.* was not found. The reasons for these differences are not clear. The subjects of Stevens *et al.* displayed a higher baseline systemic vascular resistance, possibly contributing to the observed differences in this variable between the two studies. It is possible that the subjects of Stevens *et al.* were relatively hypervolemic compared to our subjects, leading to increased right atrial pressure. Stevens *et al.* did not describe the protocol used for fluid administration, whereas our echocardiographic data demonstrate constant preload.

The cardiovascular effects of sevoflurane are similar to those of previously studied volatile anesthetics, with a few exceptions. During sevoflurane anesthesia, cardiac index is maintained as systemic vascular resistance decreases, whereas during halothane anesthesia, cardiac index falls as systemic vascular resistance is maintained.¹³ The response of cardiac index to sevoflurane differed from that with halothane, enflurane, and desflurane. With sevoflurane, in subjects who tolerated all three anesthetic concentrations, cardiac index decreased at 1.0 and 1.5 MAC, but returned to preanesthetic values at 2.0 MAC as systemic vascular resistance fell.¹³⁻¹⁵ In this study, we observed this biphasic response of cardiac index with isoflurane as well, suggesting methodologic differences between our protocol and those of previous investigators. Sevoflurane also differed from previously studied volatile anesthetics in that central venous pressure did not increase. Echocardiographic measurements during sevoflurane anesthesia yielded similar results to those obtained during desflurane anesthesia by Weiskopf *et al.*¹⁵

Cardiovascular Effects of Sevoflurane N₂O Compared with Those of Sevoflurane

Sevoflurane administered in 60% N₂O:40% O₂ caused a smaller decrease in MAP at 1.0 MAC than did an equipotent concentration of sevoflurane in 100% O₂. Better maintenance of arterial pressure with N₂O mixtures has also been observed with previously studied volatile anesthetics.⁹⁻¹² Although neither cardiac index nor systemic vascular resistance independently was higher with sevoflurane:N₂O than with sevoflurane alone, both tended to be higher at 1 MAC sevoflurane:N₂O than at

1 MAC sevoflurane and may have contributed to better maintenance of MAP. Of previously studied volatile anesthetics, isoflurane:N₂O and desflurane:N₂O caused higher systemic vascular resistance, while halothane:N₂O and enflurane:N₂O caused higher cardiac index than did the volatile anesthetics alone.⁹⁻¹² Sevoflurane:N₂O decreased mean pulmonary artery pressure less than did sevoflurane alone. No difference in mean pulmonary artery pressure was noted with desflurane:N₂O compared to desflurane alone.¹² The increased pulmonary artery pressures observed with desflurane:N₂O,¹² were not observed with sevoflurane:N₂O.

Differences between sevoflurane:N₂O and sevoflurane alone may have been due to the specific cardiovascular properties of N₂O or may have been caused when sevoflurane was replaced in part by an agent with fewer cardiovascular effects. Our study design does not allow us to distinguish between these possibilities. Forty percent N₂O alone, when administered to healthy volunteers, did not affect MAP.³⁰ It did increase total peripheral resistance, one factor that may have contributed to the observed increase in MAP when N₂O was added to sevoflurane. Forty percent N₂O alone did cause a decrease in heart rate and in central venous pressure.³⁰ We did not observe these changes when sevoflurane:N₂O was compared to sevoflurane alone.

Sevoflurane in 60% N₂O:40% O₂ resulted in lower values of mixed venous oxyhemoglobin saturation than did sevoflurane in 100% O₂. This may have resulted from a lower inspired oxygen concentration and lower arterial oxygen content leading to decreased venous oxygen content. Even during sevoflurane:N₂O anesthesia this index was higher than before anesthesia.

Kikura and Ikeda studied the cardiovascular properties of sevoflurane with 60% N₂O in surgical patients.³¹ In contrast to our results, they found no increase in heart rate compared to preanesthetic values, although they did find a decrease in blood pressure at all anesthetic concentrations. Systolic wall stress decreased from the lowest (0.9 MAC) to the highest (1.6 MAC) sevoflurane concentration used. Velocity of circumferential fiber shortening, fractional area change, and end-diastolic area did not change with anesthetic concentration. It is not possible to determine changes in echocardiographic variables from the preanesthetic state, because preanesthetic values were not measured in the group of patients studied during anesthesia.

The cardiovascular effects of sevoflurane administered with 60% N₂O are similar enough to those of equipotent concentrations of sevoflurane that the decision to add

CARDIOVASCULAR EFFECTS OF SEVOFLURANE

nitrous oxide to sevoflurane should be based on factors other than hemodynamic considerations.

Effects of Spontaneous Ventilation during Sevoflurane Anesthesia

We observed diminished cardiovascular depression when sevoflurane was administered during spontaneous ventilation compared to controlled ventilation. The cardiovascular effects of sevoflurane administered during spontaneous ventilation are likely to be a combination of direct anesthetic effects and effects of anesthetic-induced hypercapnia. In addition, comparison of cardiovascular effects of anesthetics in normocapnic and hypercapnic subjects is typically complicated by the hemodynamic effects of mechanical ventilation. Our study design does not allow separation of these confounding effects. The cardiovascular effects of sevoflurane during spontaneous ventilation are generally similar to those during normocarbic controlled ventilation, suggesting that direct anesthetic effects play a major role in determining cardiovascular performance in both conditions.

Many of the quantitative differences between the cardiovascular effects of sevoflurane administered during spontaneous ventilation and those during mechanical ventilation may be due to the effects of hypercarbia. In conscious, healthy, mechanically ventilated volunteers, hypercarbia increased heart rate, cardiac index, and stroke volume.³² Hypercarbia decreased systemic vascular resistance. These results parallel the observed differences in cardiovascular properties of sevoflurane during controlled and spontaneous ventilation.

Weiskopf *et al.* suggested that spontaneous ventilation improves the safety of inhaled anesthetic administration, because the concentration of previously studied volatile anesthetics producing cardiovascular collapse exceeds that producing apnea.³³ Spontaneous ventilation during sevoflurane anesthesia results in higher MAP, cardiac index, and stroke volume index than does controlled ventilation. This diminished cardiovascular depression may result in increased cardiovascular safety.

Effects of Prolonged Anesthesia

We observed evidence of cardiovascular stimulation during prolonged sevoflurane anesthesia. This was manifested by increased heart rate and cardiac index and decreased systemic vascular resistance and stroke volume index at 1.0 MAC after 5.5 hr of sevoflurane compared to the earlier period. At 2.0 MAC, the only

difference noted with prolonged anesthesia was that systemic vascular resistance was lower during the later period. This pattern of changes was similar to those observed with halothane, enflurane, and desflurane.¹³⁻¹⁵ The most notable difference in our study compared to the referenced studies was a decrease in stroke volume index with prolonged anesthesia, whereas stroke volume was unchanged over time with desflurane and increased over time with 1% halothane and 1 MAC enflurane.¹³⁻¹⁵ We cannot exclude the possibility that the hemodynamic changes noted with prolonged anesthesia occurred because the later period followed a period of spontaneous ventilation in which changes in heart rate, cardiac index, systemic vascular resistance, and stroke volume index were also noted.

Conclusions

Sevoflurane was well tolerated by healthy volunteers at 1.0 and 1.5 MAC end-tidal anesthetic concentrations. Hemodynamic instability (MAP < 50 mmHg) was noted in some subjects at 2.0 MAC end-tidal concentrations in the absence of surgical stimulation. The incidence of intolerable hypotension with sevoflurane was similar to that seen with isoflurane. At 2.0 MAC, in subjects with MAP \geq 50 mmHg no adverse cardiovascular effects of sevoflurane were noted. When administered with 60% N₂O, sevoflurane caused a smaller decrease in MAP than did sevoflurane alone. Spontaneous ventilation during sevoflurane anesthesia or prolonged sevoflurane administration resulted in diminished cardiovascular depression. The cardiovascular effects of sevoflurane are similar to those of isoflurane, an anesthetic commonly used in clinical practice since 1981.

The authors thank Burnell R. Brown, Jr., M.D., Ph.D., F.R.C.A., and Robert G. Merin, M.D., for advice and editorial assistance. They also thank Tailiang Xie, Ph.D., for advice regarding statistical analysis, and Suzanne Causbie, for administrative and clerical assistance.

References

1. Wallin RF, Regan BM, Napoli MD, Stern IJ: Sevoflurane: A new inhalational anesthetic agent. *Anesth Analg* 54:758-765, 1975
2. Holaday DA, Smith FR: Clinical characteristics and biotransformation of sevoflurane in human volunteers. *ANESTHESIOLOGY* 54:100-106, 1981
3. Bernard J-M, Wouters PF, Doursout M-F, Florence B, Chelly JE, Merin R: Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. *ANESTHESIOLOGY* 72:659-662, 1990

4. Frink EJ, Malan TP, Atlas M, Dominguez LM, DiNardo JA, Brown BR Jr: Clinical comparison of sevoflurane and isoflurane in healthy patients. *Anesth Analg* 74:241-245, 1992
5. Bahlman SH, Eger EI II, Halsey MJ, Stevens WC, Shakespeare TF, Smith NT, Cromwell TH, Fourcade H: The cardiovascular effects of halothane in man during spontaneous ventilation. *ANESTHESIOLOGY* 36:494-502, 1972
6. Calverly RK, Smith NT, Jones CW, Prys-Roberts C, Eger EI II: Ventilatory and cardiovascular effects of enflurane anesthesia during spontaneous ventilation in man. *ANESTHESIOLOGY* 57:610-618, 1978
7. Cromwell TH, Stevens WC, Eger EI II, Shakespeare TF, Halsey MJ, Bahlman SH, Fourcade HE: The cardiovascular effects of compound 469 (Forane) during spontaneous ventilation and CO₂ challenge in man. *ANESTHESIOLOGY* 35:17-25, 1971
8. Weiskopf RB, Cahalan MK, Ionescu P, Eger EI II, Yasuda N, Lockhart SH, Rampil IJ, Laster M, Freire B, Peterson N: Cardiovascular effects of desflurane with and without nitrous oxide during spontaneous ventilation in humans. *Anesth Analg* 73:165-174, 1991
9. Bahlman SH, Eger EI II, Smith NT, Stevens WC, Shakespeare TF, Sawyer DC, Halsey MJ, Cromwell TH: The cardiovascular effects of nitrous oxide-halothane anesthesia in man. *ANESTHESIOLOGY* 35:274-285, 1971
10. Smith NT, Claverly RK, Prys-Roberts C, Eger EI II, Jones CW: Impact of nitrous oxide on the circulation during enflurane anesthesia in man. *ANESTHESIOLOGY* 48:345-349, 1978
11. Dolan WM, Stevens WC, Eger EI II, Cromwell TH, Halsey MJ, Shakespeare TH, Miller RD: The cardiovascular and respiratory effects of isoflurane-nitrous oxide anaesthesia. *Can Anaesth Soc J* 21:557-567, 1974
12. Cahalan MK, Weiskopf RB, Eger EI II, Yasuda N, Ionescu P, Rampil IJ, Lockhart SH, Freire B, Peterson NA: Hemodynamic effects of desflurane/nitrous oxide anesthesia in volunteers. *Anesth Analg* 73:157-164, 1991
13. Eger EI II, Smith NT, Stoelting RK, Cullen DJ, Kadis LB, Whitcher CE: Cardiovascular effects of halothane in man. *ANESTHESIOLOGY* 32:396-409, 1970
14. Calverly RK, Smith NT, Prys-Roberts C, Eger EI II, Jones CW: Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. *Anesth Analg* 57:619-628, 1978
15. Weiskopf RB, Cahalan MK, Eger EI II, Yasuda N, Rampil IJ, Ionescu P, Lockhart SH, Johnson BH, Freire B, Kelley S: Cardiovascular effects of desflurane in normocarbic volunteers. *Anesth Analg* 73:143-156, 1991
16. Abel MD, Nishimura RA, Callahan MJ, Rehder K, Ilstrup DM, Tajik AJ: Evaluation of intraoperative transesophageal two-dimensional echocardiography. *ANESTHESIOLOGY* 66:64-68, 1987
17. Ruschaupt DG, Sodt P, Hutcheon NA, Arcilla RA: Estimation of circumferential fiber shortening velocity by echocardiography. *J Am Coll Cardiol* 2:77-84, 1983
18. Colan SD, Borrow KM, Neumann A: Left ventricular end-systolic wall stress velocity of circumferential fiber shortening relation: A load-independent index of myocardial contractility. *J Am Coll Cardiol* 4:715-724, 1984
19. Douglas PS, Reichek N, Plappert T, Muhammad A, St. John Sutton MG: Comparison of echocardiographic methods for assessment of left ventricular shortening and wall stress. *J Am Coll Cardiol* 9:945-951, 1987
20. Scheller MS, Saidman LJ, Partridge BL: MAC of sevoflurane in humans and the New Zealand white rabbit. *Can J Anaesth* 35:153-156, 1988
21. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, deJong RH, Elashoff RM: Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *ANESTHESIOLOGY* 42:197-205, 1975
22. Hornbein TF, Eger EI II, Winter PM, Smith G, Wetstone D, Smith KH: The minimum alveolar concentration of nitrous oxide in man. *Anesth Analg* 61:553-556, 1982
23. Tonnesen AS: Crystalloids and colloids, Anesthesia. Edited by Miller RD. New York, Churchill Livingstone, 1990, p 1443
24. Andersen K, Vik-Mo H: Increased left ventricular emptying at maximal exercise after reduction in afterload. *Circulation* 69:492-496, 1984
25. Quinones MA, Gaasch WH, Alexander JK: Influence of acute changes in preload, afterload, contractile state and heart rate on ejection and lusitropic indices of myocardial contractility in man. *Circulation* 53:293-302, 1976
26. Pagel PS, Kersten JR, Hettrick DA, Wartier DL: Negative inotropic and lusitropic actions of sevoflurane in chronically instrumented dogs. *Anesth Analg* 78:S332, 1994
27. Merin RG, Basch S: Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane or enflurane? *ANESTHESIOLOGY* 55:398-408, 1981
28. Pagel PS, Kampine JP, Schmeling WT, Wartier DC: Influence of volatile anesthetics on myocardial contractility in vivo: Desflurane versus isoflurane. *ANESTHESIOLOGY* 74:900-907, 1991
29. Stevens WC, Cromwell TH, Halsey MJ, Eger EI II, Shakespeare TF, Bahlman SH: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. *ANESTHESIOLOGY* 35:8-16, 1971
30. Eisele JH, Smith NT: Cardiovascular effects of 40 percent nitrous oxide in man. *Anesth Analg* 51:956-962, 1972
31. Kikura M, Ikeda K: Comparison of effects of sevoflurane/nitrous oxide and enflurane/nitrous oxide on myocardial contractility in humans. *ANESTHESIOLOGY* 79:235-243, 1993
32. Cullen DJ, Eger EI II, Gregory GA: The cardiovascular effects of carbon dioxide in man, conscious and during cyclopropane anesthesia. *ANESTHESIOLOGY* 31:407-413, 1969
33. Weiskopf RB, Holmes MA, Rampil IJ, Johnson BH, Yasuda N, Targ AG, Eger EI II: Cardiovascular safety and actions of high concentrations of I-653 and isoflurane in swine. *ANESTHESIOLOGY* 70:793-798, 1989