General anesthesia with sevoflurane decreases myocardial blood volume and hyperemic blood flow in healthy humans

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Chapter 3

Abstract

Preservation of myocardial perfusion during general anesthesia is likely important in patients at risk for perioperative cardiac complications. Data related to the influence of general anesthesia on the normal myocardial circulation are limited. In this study, we investigated myocardial microcirculatory responses to pharmacological vasodilation and sympathetic stimulation during general anesthesia with sevoflurane in healthy humans immediately before surgical stimulation. Six female and 7 male subjects (mean age 43 years, range 28–61) were studied at baseline while awake and during the administration of 1 minimum alveolar concentration sevoflurane. Using myocardial contrast echocardiography, myocardial blood flow (MBF) and microcirculatory variables were assessed at rest, during adenosine-induced hyperemia, and after cold pressor test–induced sympathetic stimulation. MBF was calculated from the relative myocardial blood volume multiplied by its exchange frequency ($\beta$) divided by myocardial tissue density ($\rho_T$), which was set at 1.05 g·mL$^{-1}$. During sevoflurane anesthesia, MBF at rest was similar to baseline values (1.05 ± 0.28 vs 1.05 ± 0.32 mL·min$^{-1}$·g$^{-1}$; $P = 0.98$; 95% confidence interval [CI], −0.18 to 0.18). Myocardial blood volume decreased ($P = 0.0044$; 95% CI, 0.01–0.04) while its exchange frequency ($\beta$) increased under sevoflurane anesthesia when compared with baseline. In contrast, hyperemic MBF was reduced during anesthesia compared with baseline (2.25 ± 0.5 vs 3.53 ± 0.7 mL·min$^{-1}$·g$^{-1}$; $P = 0.0003$; 95% CI, 0.72–1.84). Sympathetic stimulation during sevoflurane anesthesia resulted in a similar MBF compared to baseline (1.53 ± 0.53 and 1.55 ± 0.49 mL·min$^{-1}$·g$^{-1}$; $P = 0.74$; 95% CI, −0.47 to 0.35). In otherwise healthy subjects who are not subjected to surgical stimulation, MBF at rest and after sympathetic stimulation is preserved during sevoflurane anesthesia despite a decrease in myocardial blood volume. However, sevoflurane anesthesia reduces hyperemic MBF, and thus MBF reserve, in these subjects.
Introduction
Myocardial blood flow (MBF) is meticulously matched to oxygen demand by complex interactions of metabolic, endothelial, and neural factors. General anesthesia may interfere with this regulatory process by influencing the determinants of MBF, such as coronary vascular resistance (CVR), myocardial oxygen consumption, or perfusion pressure. Understanding the mechanisms of myocardial perfusion regulation during general anesthesia is important in patients at risk for perioperative cardiac complications, particularly those with coronary artery disease. Experimental research has demonstrated that volatile anesthetics are coronary vasodilators with different effects on hemodynamic variables and myocardial perfusion. Clinical studies are ambiguous, reporting either increases or decreases in CVR and overall myocardial perfusion after exposure to inhaled anesthetics.

Until recently, the lack of noninvasive, bedside imaging techniques impeded investigation of MBF in the perioperative setting. Accepted techniques such as single-photon emission computed tomography or positron-emission tomography are nonportable and involve exposure to radiation. Myocardial contrast echocardiography (MCE) is a safe, noninvasive bedside tool that may provide a unique opportunity to investigate myocardial microvascular responses during general anesthesia. The technique has been validated under experimental conditions and against the aforementioned “gold standards” for MBF measurements. MCE enables quantification of absolute MBF from its microvascular constituents, the relative myocardial blood volume (rBV), and its exchange frequency (β) that corresponds to the capillary blood exchange rate. Because 90% of the myocardial blood volume resides within the capillary network, rBV mainly represents the blood volume at the capillary level.

Regulation of MBF and microvascular function may be evaluated by 2 contrasting interventions. Pharmacological coronary vasodilation allows assessment of the vascular smooth muscle-dependent increase in MBF whereas sympathetic stimulation by the cold pressor test (CPT) evaluates the endothelium-dependent increase in MBF. In this study, we investigated myocardial microcirculatory responses to pharmacological vasodilation and sympathetic stimulation during general anesthesia with sevoflurane in healthy humans immediately before surgical stimulation.

Methods
Subjects
This prospective, observational clinical study was approved by the local Human Subjects Ethics Committee of the VU University Medical Center, Amsterdam, The Netherlands (www.clinicaltrials.gov; NCT00866801). All 13 included subjects (6 women, 7 men; mean age
43 ± 11 years) were scheduled for general anesthesia and gave written informed consent. Exclusion criteria were a history of cardiac or pulmonary disease, hypertension, hypercholesterolemia, diabetes mellitus, and allergic reactions to echocardiographic contrast agents. All patients were ASA class I and had a normal physical examination and resting electrocardiogram (ECG). None of the subjects received medications known to interfere with MBF measurements. Routine transthoracic echocardiography (TTE) revealed no abnormalities except for mild asymptomatic aortic insufficiency in 1 patient. Standard cardiovascular autonomic function tests (heart rate variability at rest and during deep breathing, heart rate, and arterial blood pressure response to the Valsalva maneuver and postural change) were performed to exclude the presence of autonomic dysfunction.(18)

**Study Protocol**

All subjects were scheduled for an extra visit to our hospital for screening and baseline MBF measurements. These were performed several days before the surgical procedure to avoid surgery-related anxiety and stress that might influence the results. On the day of surgery, MBF measurements were repeated after induction of anesthesia and before the start of the surgical procedure. All subjects refrained from caffeine and xanthine derivatives 12 hours before MBF measurements.

**Assessment of MBF**

TTE was used to perform MCE for measurement of MBF at rest and after adenosine-induced hyperemia and CPT-induced sympathetic stimulation. A sulfur hexafluoride-filled, phospholipid-coated ultrasound contrast agent with a mean microbubble diameter of 2.5 μm (Sonovue, Bracco Imaging, Milan, Italy) was used for flow measurements. Microbubbles were infused continuously at a rate of 0.5 to 0.7 mL·min⁻¹.(19) After a steady and homogenous distribution of contrast was reached, rest perfusion sequences were acquired from transthoracic apical 4-, 2-, and 3-chamber views. Subsequently, hyperemia was induced by a continuous infusion of adenosine (0.14 mg·kg⁻¹·min⁻¹). Two minutes after starting the adenosine infusion, another series of perfusion sequences was obtained. Five minutes after discontinuing the adenosine infusion, sympathetic stimulation was provoked by the CPT, which is performed by immersing the patient's hand in ice water (2°C–4°C) for 3 minutes. A similar series of perfusion sequences was captured directly after the CPT. Heart rate, arterial blood pressure, and ECG were obtained at predetermined times throughout the protocol.
Anesthetic Procedure

On arrival in the operating room, patients received standard hemodynamic monitoring (pulse oximetry, ECG, and noninvasive blood pressure measurement). All subjects were administered 0.02 mg·kg\(^{-1}\) midazolam via an IV cannula inserted in a forearm vein. Anesthesia was induced by inhalation of sevoflurane (Abbott B.V., Hoofddorp, The Netherlands) and maintained at 1.0 minimum alveolar concentration (MAC) during the study period, which took on average 20 minutes. After insertion of a laryngeal mask airway, MBF measurements were performed in left lateral position during spontaneous breathing without positive airway pressure and a Fio2 of 100%. End-tidal CO2 was observed to be between 35 and 45 mm Hg. After the study protocol, anesthesia and the surgical procedure were continued according to standard of care.

Myocardial Contrast Echocardiography

Acquisition

Real-time MCE was performed using an iE33 ultrasound scanner equipped with a S5-1 sector array transducer and contrast-specific software (Power modulation, Philips Medical Systems, Best, The Netherlands). Settings included a mechanical index (MI; the acoustic intensity of an ultrasound beam) of 0.17 for microbubble detection, MI of 0.64 for microbubble destruction, dynamic range of 47 dB, and linear postprocessing for minimal distortion of the original input values.(19) MBF was calculated from a destruction-replenishment sequence consisting of 5 cardiac cycles of low-MI imaging (steady state), followed by a short burst (0.5 seconds) of high-MI for complete myocardial contrast destruction. Subsequently, 15 cardiac cycles of low-MI images were acquired to allow myocardial contrast replenishment. All data were stored for offline analysis.

Data Analysis

Quantification of MBF was performed as described previously.(19) In short, perfusion sequences were analyzed using custom-designed software with manual tracking of region of interest (ROI) (Figure. 1). Using only end-systolic frames, ROIs were drawn in accordance with the vascular territories of the coronary arteries in the mid-inferoseptal and mid-anterolateral wall (apical 4-chamber view); in the mid-inferior and mid-anterior wall (apical 2-chamber view); and in the mid-inferolateral and mid-antero septal wall (apical 3-chamber view) of the myocardium. Additional ROIs were drawn in the left ventricular cavity, adjacent to the myocardial ROI. Subsequently, the obtained signal intensities were linearized by removing logarithmic compression, and intensity data were expressed in arbitrary units. Myocardial steady-state intensity \(A_{myo}\) was calculated by averaging the myocardial intensity data extracted from the end-systolic frames before contrast destruction. Left ventricular
intensity $A_{LV}$ was determined by averaging all ventricular intensities except in the end-systolic frames during and the first 2 after contrast destruction. Dividing plateau intensity $A_{myo}$ by the left ventricular intensity $A_{LV}$ yielded the rBV. Finally, $\beta$ (min$^{-1}$) was derived from fitting of the refill equation $y(t) = A_{myo}(1 - e^{-\beta t})$ by Wei et al. (13) to the myocardial intensity data after microbubble destruction. The capillary exchange rate $\beta$ provides an estimate of the speed of erythrocytes through the capillary system. A slower or faster capillary passage, indicated by a decrease or increase in $\beta$, is consistent with arteriolar vasoconstriction or dilation respectively.

**Figure 1.** Example of a destruction-replenishment sequence analysis obtained with real-time myocardial contrast echocardiography (apical 4-chamber view, zoomed in on left ventricle). Signal intensities are determined by myocardial (red) and ventricular (blue) regions of interest. A, Steady-state concentration of microbubbles during low-mechanical index (MI) impulse; B, complete myocardial contrast destruction directly after high-MI impulse; C, D, replenishment of myocardial contrast during low-MI imaging. ALV = average left ventricular intensity; Amyo = average myocardial steady-state intensity; $\beta$ = rate constant; AU = arbitrary units. For further details, see Methods.

**Calculated Variables**

Absolute MBF in mL·min$^{-1}$·g$^{-1}$ was calculated using the quantification algorithm of Vogel et al. (14)

$$MBF = rBV \cdot \frac{\beta}{\rho T} = \frac{A_{myo}}{A_{LV}} \cdot \frac{\beta}{\rho T}$$
General anesthesia decreases myocardial blood volume and hyperemic blood flow

(tissue density $\rho_T$ was set to 1.05 g·mL$^{-1}$). Increases in MBF in response to adenosine and the CPT were expressed as percentage from MBF at rest (100%). Another calculated variable was the rate-pressure product (RPP), which is an estimate of myocardial oxygen consumption or myocardial work and is calculated by heart rate $\times$ systolic blood pressure. An index of CVR was derived from the ratio of mean arterial blood pressure to MBF.

**Measurement of Catecholamines**

The systemic response to the CPT at baseline and during the administration of sevoflurane was evaluated by determination of levels of circulating norepinephrine. In venous blood samples taken before the start and 2 minutes into the CPT, plasma levels of norepinephrine were measured by high-performance liquid chromatography with electrochemical detection.

**Statistical Analysis**

All data are represented as mean values ± SD unless indicated otherwise. In healthy subjects, MBF increases 200% to 300% in response to adenosine and about 30% to 40% in response to sympathetic stimulation by the CPT.(20) Considering a 25% change in myocardial perfusion as relevant, power analysis revealed that 13 patients should be included to detect this difference with a power of 0.9. Using SPSS statistical software version 15.0 (SPSS Inc., Chicago, IL), an unpaired t test was used to compare catecholamine levels before and after CPT and percent increase in MBF after adenosine and CPT at baseline versus sevoflurane anesthesia. For each unpaired t test, a Shapiro-Wilk normality test was applied to residuals and all $P > 0.1042$.

As stated previously, hemodynamic and myocardial perfusion variables ($\beta$, rBV, MBF) were repeatedly obtained at baseline and during sevoflurane anesthesia. Differences were calculated and changes in hemodynamic and myocardial perfusion variables were analyzed using a Linear Mixed model with an unstructured covariance matrix in Statistical Analysis Software version 9.2 (SAS Institute Inc., Cary, NC). This procedure accounts for the repeated measurements of MBF and hemodynamic variables. The main assumption of the Linear Mixed model was checked by generating residual plots to see whether these were normally distributed. $P < 0.05$ was considered to be statistically significant.

**Results**

In all 13 patients, MBF measurements were completed successfully on both occasions except for 1 baseline CPT, which was stopped due to patient discomfort during immersion of the hand. Table 1 shows the baseline characteristics of the study population.
Table 1. Baseline Characteristics of Study Population (n = 13)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>43 (28-61)</td>
</tr>
<tr>
<td>Female/male, n</td>
<td>6/7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78 ± 16</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.5 ± 4.4</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>120 ± 16</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>73 ± 6</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.6 ± 0.8</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.4 ± 0.5</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.6 ± 0.7</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>8.5 (6.7-9.7)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Ear, nose and throat</td>
<td>5</td>
</tr>
<tr>
<td>Urology</td>
<td>2</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>2</td>
</tr>
<tr>
<td>General (cholecystectomy, ganglion)</td>
<td>4</td>
</tr>
</tbody>
</table>

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

* Age and haemoglobin are given as mean (range).

Baseline Measurements

At baseline, resting MBF was 1.05 ± 0.32 mL·min⁻¹·g⁻¹, which increased to 3.53 ± 0.75 mL·min⁻¹·g⁻¹ during adenosine-induced hyperemia (P < 0.0001; 95% confidence interval [CI] 2.03–2.93; Table 2 and Figure 2). In response to adenosine, both rBV (0.099 ± 0.021 mL·mL⁻¹ to 0.143 ± 0.025 mL·mL⁻¹; P = 0.0001; 95% CI, 0.03–0.06) and β (11.1 ± 2.5 min⁻¹ to 25.8 ± 5.8 min⁻¹; P < 0.0001; 95% CI, 11.74–17.69) increased compared with rest. Heart rate and RPP increased with infusion of adenosine whereas blood pressure remained similar (Table 2). During sympathetic stimulation by the CPT, MBF increased to 1.53 ± 0.5 mL·min⁻¹·g⁻¹ (P = 0.0012 compared with rest; 95% CI, 0.25–0.76). An increase in heart rate
and blood pressure, and a decrease in CVR were also observed compared with rest. Circulating norepinephrine levels did not increase during baseline CPT (Table 3).

### Table 2. Hemodynamics and Echocardiographic Data at Baseline and During Sevoflurane Anesthesia

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Rest</th>
<th>Adenosine</th>
<th>Cold pressor test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>64 (58–69)</td>
<td>91 (83–99)*</td>
<td>69 (64–74)*</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>116 (108–124)</td>
<td>122 (113–130)</td>
<td>132 (119–144)*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>87 (83–91)</td>
<td>91 (87–94)</td>
<td>96 (89–104)*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72 (68–77)</td>
<td>75 (71–79)</td>
<td>79 (73–84)*</td>
</tr>
<tr>
<td>RPP, min⁻¹ · mm Hg</td>
<td>7382 (6096–8669)</td>
<td>11,098 (9741–12,455)*</td>
<td>9061 (7951–10,170)</td>
</tr>
<tr>
<td>CVR, mm Hg·mL⁻¹·min⁻¹·g⁻¹</td>
<td>92 (72–112)</td>
<td>27 (23–30)*</td>
<td>65 (50–80)*</td>
</tr>
<tr>
<td>β, min⁻¹</td>
<td>11.1 (9.6–12.6)</td>
<td>25.8 (22.3–29.3)*</td>
<td>14.6 (12.2–16.9)*</td>
</tr>
<tr>
<td>rBV, mL·mL⁻¹</td>
<td>0.099 (0.086–0.112)</td>
<td>0.143 (0.128–0.158)*</td>
<td>0.102 (0.083–0.121)</td>
</tr>
<tr>
<td>MBF, mL·min⁻¹·g⁻¹</td>
<td>1.05 (0.85–1.24)</td>
<td>3.53 (3.08–3.98)*</td>
<td>1.53 (1.19–1.86)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, min⁻¹</td>
<td>72 (65–80)§</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>100 (92–109)‖</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>71 (65–78)‖</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>57 (51–63)‖</td>
</tr>
<tr>
<td>RPP, min⁻¹ · mm Hg</td>
<td>7262 (6294–8231)</td>
</tr>
<tr>
<td>CVR, mm Hg·mL⁻¹·min⁻¹·g⁻¹</td>
<td>72 (59–85)</td>
</tr>
<tr>
<td>β, min⁻¹</td>
<td>14.6 (12.3–17.0)‖</td>
</tr>
<tr>
<td>rBV, mL·mL⁻¹</td>
<td>0.076 (0.067–0.085)‖</td>
</tr>
<tr>
<td>MBF, mL·min⁻¹·g⁻¹</td>
<td>1.05 (0.88–1.22)</td>
</tr>
</tbody>
</table>

Values are presented as mean (95% confidence interval). The MIXED procedure was used for statistical analysis. SBP = systolic blood pressure; MAP = mean arterial blood pressure; DBP = diastolic blood pressure; RPP = rate-pressure product; CVR = coronary vascular resistance; rBV = relative blood volume; MBF = myocardial blood flow. * P < 0.0001 versus corresponding value at rest; † P < 0.01 versus corresponding value at rest; ‡ P < 0.05 versus corresponding value at rest. § P < 0.05 versus corresponding baseline value; || P < 0.01 versus corresponding baseline value; ‖ P < 0.0001 versus corresponding baseline value.
Table 3. Levels of Circulating Catecholamines at Rest and During the Cold Pressor Test

<table>
<thead>
<tr>
<th>Catecholamine</th>
<th>Rest</th>
<th>Cold pressor test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (nmol/L)</td>
<td>2.7 ± 1.1</td>
<td>3.1 ± 1.2</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>1.4 ± 0.3</td>
<td>1.5 ± 0.4</td>
</tr>
</tbody>
</table>

An unpaired t test was used for statistical analysis

Sevoflurane Measurements

During sevoflurane anesthesia, resting MBF was similar compared with baseline (1.05 ± 0.28 vs 1.05 ± 0.32 mL·min⁻¹·g⁻¹; P = 0.98; 95% CI, −0.18 to 0.18). However, the rBV was lower during anesthesia (0.076 ± 0.015 mL·mL⁻¹ vs 0.099 ± 0.021 mL·mL⁻¹ at baseline; P = 0.0044; 95% CI, 0.01–0.04). MBF was preserved because of an increased β (14.6 ± 3.9 min⁻¹ vs 11.1 ± 2.5 min⁻¹ at baseline; P = 0.0005; 95% CI, −5.18 to −1.89). Resting blood pressure decreased and heart rate increased compared with baseline values. CVR was statistically similar for both conditions (P = 0.06; 95% CI, −1.1 to 40.6).

Adenosine infusion during anesthesia increased MBF to 2.25 ± 0.53 mL·min⁻¹·g⁻¹, which was significantly lower than at baseline (P = 0.0003; 95% CI, 0.72–1.84). Consequently, a lower percent increase was observed compared with baseline (228% vs 375%; P = 0.0087; 95% CI, 40.8–253.5; Figure 3). In contrast with baseline results, blood pressure and RPP decreased during hyperemia. CVR decreased to a similar level as baseline.

The CPT during sevoflurane anesthesia increased MBF, and the magnitude of flow increase was similar compared with baseline (153% vs 152%; P = 0.96; 95% CI, −44.2 to 42.2; Figure 3). Also, during CPT, the rBV was lower when compared with baseline (P = 0.03; 95% CI, 0.01 – 0.05). However, MBF was maintained by an increased β. Interestingly, the hemodynamic response to the CPT was different from baseline. A decrease in blood pressure and in RPP was observed, and the CVR was reduced compared with baseline. Also, circulating norepinephrine levels did not increase during sevoflurane anesthesia.

Discussion

Sevoflurane anesthesia preserves MBF at rest and during sympathetic stimulation. However, hyperemic MBF during 1.0 MAC sevoflurane was lower compared with baseline values without sevoflurane.
General anesthesia decreases myocardial blood volume and hyperemic blood flow

Figure 2. Myocardial perfusion variables at rest, during adenosine-induced hyperemia and after the cold pressor test (CPT). A, Myocardial blood flow (MBF); B, capillary exchange rate (β); C, relative blood volume (rBV). Data presented as mean ± SD. The MIXED procedure was used for statistical analysis. *P < 0.05 versus corresponding value at rest; †P < 0.01 versus corresponding value at rest; ‡P < 0.0001 versus corresponding value at rest; §P < 0.05 versus corresponding baseline value; ¶P < 0.01 versus corresponding baseline value.

Figure 3. Percent increases in myocardial blood flow (MBF) in response to adenosine-induced hyperemia (A) and the cold pressor test (B) at baseline and during sevoflurane anesthesia. Data presented as mean ± SD. An unpaired t-test was used for statistical analysis. *P = 0.0087 versus baseline.

Resting Myocardial Perfusion During Sevoflurane Anesthesia

The effects of volatile anesthetics on myocardial perfusion in humans have not been well described. One clinical study showed a decrease in MBF and oxygen consumption during halothane anesthesia in only 7 healthy patients.(21) A more recent study reported no difference in resting MBF during xenon anesthesia in 6 healthy subjects.(22) Available data on actions of sevoflurane are based on animal studies. Several investigators have reported coronary vasodilation with sevoflurane both in vitro and in vivo.(4, 23, 24) Furthermore, several studies showed a reduced coronary blood flow during sevoflurane anesthesia, attributed to a decrease in myocardial oxygen consumption and perfusion pressure.(25-27) Instrumented rats demonstrated no alterations in hemodynamics and coronary blood flow in response to sevoflurane administration.(28, 29) In contrast, increases in coronary blood flow were reported in dogs when perfusion pressure was kept constant during measurements.(24) In our population, sevoflurane administration resulted in arteriolar vasodilation reflected by an increase in the exchange frequency (β).(30) The lower myocardial blood volume during
sevoflurane anesthesia compared with baseline is an interesting finding. It has been shown that, under physiological circumstances, myocardial blood volume remains stable when arteriolar vasomotion is intact. (31, 32) Ninety percent of the myocardial blood volume is located in the capillaries, which have a constant length and cannot dilate or constrict due to a lack of smooth muscle. It follows that the myocardial blood volume can only decrease if capillaries are functionally occluded. (33) Whether sevoflurane alone, or in combination with other perioperative factors causes derecruitment of capillaries remains to be elucidated.

**Adenosine-Induced Hyperemia During Sevoflurane Anesthesia**

During adenosine-induced hyperemia, active vasomotor influences are eliminated and MBF is mainly dependent on perfusion pressure. (34) At baseline, perfusion pressure remained unaltered and coronary vasodilation resulted in an average MBF increase of 375%. On average, a 3- to 5-fold increase in MBF is observed in healthy humans. (2) A significantly lower perfusion pressure was the result of the joint administration of sevoflurane and adenosine. Interestingly, an average 228% increase in MBF during sevoflurane anesthesia was observed, suggesting preservation of a substantial vasodilator capacity. In contrast with our data, Gilbert et al. (35) demonstrated that the reactive hyperemic response after brief coronary artery occlusion was unaffected by increasing concentrations of isoflurane up to 1.5 MAC, despite reductions in arterial pressure. In the same study, halothane exhausted the vasodilator capacity expressed as the coronary flow reserve (ratio of MBF$_{hyperemia}$/MBF$_{rest}$) at concentrations of 1.25 to 1.5 MAC, also after correcting for lower perfusion pressures. The mechanism behind the decrease in coronary flow reserve with halothane in that study is difficult to interpret due to the absence of awake measurements and the lack of separate resting and peak flows. Verrier et al. (36) reported a greater coronary flow reserve in dogs anesthetized with low concentrations of halothane compared with nitrous oxide. The lower flow reserve with nitrous oxide may be the result of the higher heart rate and contractility found in that group, changes that are known to alter coronary flow reserve. (37, 38) Furthermore, resting coronary blood flow was significantly lower in the halothane group, which increases the maximal achievable flow reserve. However, the mechanism behind reactive hyperemia is complex as other mediators, besides adenosine, are involved as well. (39)

In our population, the decrease in perfusion pressure is a plausible explanation for the lower hyperemic MBF. This hypothesis is supported by Hickey et al., (40) studying the effect of 1.0 MAC halothane, enflurane, and isoflurane on coronary vascular reserve in chronically instrumented dogs. Hyperemia was induced with adenosine, and diastolic pressures were kept constant. The investigators showed that coronary vascular reserve was not changed by any of the tested anesthetics. Larach and Schuler, (4) investigating coronary flow reserve
during sevoflurane administration in isolated rat hearts, confirmed our finding in part. At a constant perfusion pressure, hyperemic coronary blood flow remained unchanged during different sevoflurane concentrations. Also, a comparable degree of coronary vasodilation, indicated by the CVR, was observed at baseline and during anesthesia in our population. This further supports our hypothesis that the reduction in perfusion pressure and the subsequent decrease in rBV are responsible for the decrease in hyperemic MBF. It remains unclear whether this reduction is purely a consequence of the indirect effects of sevoflurane on hemodynamic variables or also the result of a direct, blunting effect on the recruitment capacity of the capillary network during hyperemia.

**Myocardial Perfusion in Response to Sympathetic Stimulation**

Sympathetic stimulation by the CPT activates α- and β-adrenergic receptors in the heart. Furthermore, pain sensation will induce an increase in adrenomedullary catecholamine release followed by an increase in heart rate, blood pressure, and oxygen demand. The net effect of these alterations is coronary vasodilation and an average increase of 40% in MBF in healthy humans. Our results indicate that during sevoflurane anesthesia, MBF increases in response to sympathetic stimulation despite a decrease in blood pressure and RPP and similar catecholamine levels. Acceleration of erythrocyte passage (increased β) and reduction of CVR indicates arteriolar vasodilation, probably due to adrenergic stimulation via thermal receptors in the skin. The administration of sevoflurane itself and the subsequent decrease in perfusion pressure may have further contributed to the decrease in CVR. The lack of increase in estimated myocardial work in response to sympathetic stimulation might be explained by the blunting effect of sevoflurane on pain sensation. Moffitt and Sethna showed a decrease in coronary blood flow and oxygen demand after sternotomy. In contrast, Kirnö et al. reported an increase in great cardiac vein flow and oxygen demand during sternotomy. Also, measurements were performed in patients with coronary artery disease and during different anesthesia techniques, limiting possible comparison with our results.

**Limitations**

The following limitations should be considered in the interpretation of our results. In this *in vivo* study, interpretation of the exact mechanism behind changes in myocardial perfusion during general anesthesia is limited by the simultaneous influence of sevoflurane on the myocardial vasculature as well as on left ventricular contractility, systemic vascular resistance, and sympathetic nerve activity. In this study, we did not control hemodynamic variables during the measurements. In addition, patients were breathing spontaneously via a laryngeal mask, which may have reduced the accuracy of end-tidal CO2 values because
of possible leaks. The reduced sympathetic response of laryngeal mask insertion compared with endotracheal intubation may limit generalized translation of our results. Also, it would have been preferable to measure myocardial oxygen consumption directly from the coronary sinus. The noninvasive RPP used in this study is a simplifi index of myocardial metabolism with limited reliability. It remains, however, widely used in clinical studies with a noninvasive character.

Myocardial perfusion is a dynamic process that is dependent on many physiologic and psychological factors. Therefore, correct timing of experiments is crucial. Unfortunately, due to logistical reasons it was not always possible to perform baseline measurements on the same day before surgery. The variation of several days between patients may have influenced our results. However, possible bias was minimized by performing all experiments early in the morning after overnight fasting and in the same order (autonomic function tests, ECG, TTE, perfusion measurements). Also, experiments during sevoflurane anesthesia were always performed at 8:00am since these patients were scheduled as first on the surgery schedule of that day. For logistical reasons, we did not repeat resting MCE after adenosine-induced hyperemia and before CPT-induced sympathetic stimulation.

The CPT is a widely used method for evoking sympathetic stimulation in awake patients but its effects under anesthesia are less well defined. Our results indicate that changes occur on a microvascular level compared with the resting situation, which led to an increase in MBF. Changes in hemodynamic variables are, however, different from what would be expected and cannot be explained in the current study design.

Finally, the cardiovascular status of the study population was confirmed by physical examination, laboratory investigation, ECG, and routine TTE. Due to the invasive nature, coronary angiography was not performed, and therefore we cannot exclude the presence of mild atherosclerosis. However, it is unlikely that unknown atherosclerosis affected our results because of the absence of cardiovascular risk factors and the normal baseline myocardial flow reserves.

**Conclusion**

Our data show that myocardial perfusion at rest is unaffected by sevoflurane anesthesia, despite an apparent decrease in myocardial blood volume. Furthermore, hyperemic MBF (representing myocardial flow reserve), is reduced during anesthesia, most likely caused by a decrease in perfusion pressure. Finally, sympathetic stimulation during sevoflurane resulted in a similar increase in MBF compared with baseline. Whether the observed changes are the result of a direct effect of sevoflurane on the myocardial vasculature, or purely a consequence of indirect hemodynamic alterations, remains to be elucidated in future studies.
References


General anesthesia decreases myocardial blood volume and hyperemic blood flow.