Myocardial Blood Flow during General Anesthesia with Xenon in Humans

A Positron Emission Tomography Study

Wolfgang Schaefer, M.D., Ph.D.,* Philipp T. Meyer, M.D., Ph.D.,† Rolf Rossaint, M.D., Ph.D.,‡ Jan H. Baumert, M.D., Ph.D., D.E.A.A.,§ Mark Coburn, M.D., Ph.D.,¶ Michael Fries, M.D., Ph.D.,# Steffen Rex, M.D., Ph.D.||

ABSTRACT

Background: Xenon has only minimal hemodynamic side effects and induces pharmacologic preconditioning. Thus, the use of xenon could be an interesting option in patients at risk for perioperative myocardial ischemia. However, little is known about the effects of xenon anesthesia on myocardial blood flow (MBF) and coronary vascular resistance in humans.

Methods: Myocardial blood flow was noninvasively quantified by H$_2^{15}$O positron emission tomography in six healthy volunteers (age: 38 ± 8 yr). MBF was measured at baseline and during general anesthesia induced with propofol and maintained with xenon, 59 ± 0%. Absolute quantification of MBF was started after the calculated plasma concentration of propofol had decreased to less than 1.5 μg · ml$^{-1}$.

Results: Compared with baseline (MBF$_{baseline}$, 1.03 ± 0.09 ml · min$^{-1}$ · g$^{-1}$; mean ± SD), MBF was decreased significantly by xenon (MBF$_{xenon}$, 0.80 ± 0.22 ml · min$^{-1}$ · g$^{-1}$; −21%, P = 0.11). Xenon decreased the rate–pressure product (RPP; heart rate × systolic arterial pressure), an indicator of cardiac work and myocardial oxygen consumption (−15%, P < 0.04). When correcting for the RPP, the decrease in MBF observed during xenon anesthesia was reduced to −9% (MBF$_{corr,xenon}$, 1.42 ± 0.28 ml · g$^{-1}$ · mmHg$^{-1}$ vs. MBF$_{corr,baseline}$, 1.60 ± 0.28 ml · g$^{-1}$ · mmHg$^{-1}$, P = 0.32).

Conclusions: In healthy subjects, xenon has only minimal effects on coronary flow dynamics. These effects are probably of indirect nature, reflecting the decrease in myocardial oxygen consumption induced by the effects of xenon anesthesia on cardiac work.

SINCE the “reintroduction” of xenon into clinical anesthesia by Lachmann and colleagues in 1990,$^{1}$ in experimental and clinical studies xenon repeatedly has been demonstrated to produce only minimal hemodynamic side effects compared with volatile or intravenous anesthetics.$^{2−5}$ These initial observations were confirmed in two European multicenter, randomized controlled trials in which xenon was compared with isoflurane and found to slightly decrease heart rate and preserve or moderately increase arterial pressures.$^{6,7}$ This advantageous hemodynamic profile of xenon anesthesia was also observed in a...
recently published clinical trial in which 160 patients were randomly allocated to anesthesia with xenon or propofol.8

Recent evidence indicates that xenon is virtually devoid of negative inotropic effects7,9–11 and improves recovery from postischemic contractile dysfunction.12,13 Furthermore, and adding to the culminating evidence that noble gases exert organ-protective effects in various conditions,14 xenon was found to induce both early and late pharmacologic preconditioning in experimental models of myocardial ischemia.15–17 Both the favorable hemodynamic profile of xenon anesthesia and its cardioprotective properties could render this noble gas an attractive option for the anesthesia of patients at high risk for perioperative myocardial ischemia. However, little is known about the effects of xenon on myocardial blood flow (MBF) and coronary hemodynamics in humans.

Because animal data suggest that xenon inhalation is associated with only minimal arterial vasodilation18 and has little or no effect on myocardial perfusion,5 we hypothesized that general anesthesia with xenon would have only negligible effects on MBF in man. We tested our hypothesis in healthy volunteers undergoing general anesthesia with 1 minimum alveolar concentration (MAC) xenon. The use of positron emission tomography (PET) allowed us to noninvasively quantify MBF and subsequently coronary vascular resistance.

Materials and Methods

The current study was approved by the institutional review board (Ethik-Kommission, Medical Faculty, Rheinisch-Westfälische Technische Hochschule, Aachen, Germany) and the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz, Salzgitter, Germany). All subjects gave written informed consent after the experimental procedure and possible adverse effects had been explained in detail.

Subjects

Six adult male volunteers (age: 38 ± 8 yr, height: 188 ± 6 cm, weight: 90 ± 7 kg) were recruited through the internet and flyers. Before admittance to the study, all subjects underwent a careful medical examination and were found to be in excellent medical condition (American Society of Anesthesiologists physical status 1). None had a clinical history of myocardial infarction, evidence of valvular or primary myocardial disease, or history of diabetes or systemic hypertension. All subjects were nonsmokers. Drug abuse was excluded with a toxicologic urine test. All volunteers received financial compensation for their participation.

Study Protocol

Subjects fasted for at least 8 h and refrained from caffeine and alcohol for 24 h before undergoing the PET examination. All PET studies were performed at low ambient noise and dimmed light. During the scans done while the volunteers were awake, the volunteers were instructed to lie motionless, relax, and close their eyes while breathing room air.

The PET scans were performed as previously described (fig. 1).19,20 In brief, each subject twice underwent two PET scans in a fixed order: The first two PET scans were performed during wakefulness (assessment of baseline MBF), the subsequent two PET scans were acquired during general anesthesia with 1 MAC xenon (assessment of MBF during xenon anesthesia). MBF was measured using $^{15}$O-labeled water ($H_2^{15}O)$, which is a commonly used, freely diffusible PET tracer. Because of the relatively high noise level of $H_2^{15}O$ PET, scans were performed in duplicate for statistical reasons. The two PET scans in the waking state and during xenon anesthesia, respectively, were acquired with an interscan interval of 10 min, which is sufficient for virtually complete radioactive decay of the remaining radioactivity of the preceding scan given the short half-life of $^{15}O$ (122 s). The delay between the awake scans and anesthesia scans resulted from the induction of xenon anesthesia and washout of propofol (see Anesthesia).

Physiologic and apparatus monitoring during each scan consisted of a three-lead electrocardiogram, pulse oximetry, intermittent oscillometric noninvasive blood pressure measurements (all Datex Ohmeda GmbH, Duisburg, Germany), continuous measurement of inspired and expired ox-
Anesthesia

After denitrogenization with 100% oxygen, anesthesia was induced with propofol using a target-controlled infusion (Pilot Anesthesia syringe pump with a Master Target-Controlled Infusion unit; Becton Dickinson, Heidelberg, Germany) (fig. 1). The pump was controlled by the Diprifusor target-controlled infusion software algorithm (AstraZeneca, Macclesfield, United Kingdom). Anesthesia was induced with a target plasma concentration of 10.4 ± 1.2 μg·ml⁻¹ propofol to enable the insertion of a laryngeal mask airway. The propofol infusion was stopped once the airway had been instrumented. Anesthesia was then maintained with 1 MAC xenon using a closed-circuit anesthesia machine (Physioflex; Dräger Medical Deutschland GmbH). Subjects were ventilated with pressure control maintaining normocapnia.

H₂¹⁵O was administered once a deep level (suggested by a bispectral index lower than 35)²¹,²² and steady state of general anesthesia with 1 MAC xenon was achieved and once the calculated propofol plasma concentrations were less than 1.5 μg·ml⁻¹ (i.e., in a subanesthetic range).²³ Both criteria were achieved within 41 ± 9 min of xenon anesthesia.

After the last myocardial PET scan, three PET scans for the assessment of cerebral perfusion were performed; the results of those scans have been published by our group.²⁰

Administration of xenon was stopped and the laryngeal mask airway removed after spontaneous breathing had resumed. After subjects emerged from anesthesia, they were monitored for stable vital signs for at least 1 h and discharged in accordance with the standards of our department for outpatient anesthesia.

H₂¹⁵O PET

H₂¹⁵O was synthesized online using an ODS 111 cyclotron (Siemens/CTI, Knoxville, TN). PET examinations were done on an ECAT 922/47 scanner (Siemens/CTI) in two-dimensional mode. Subjects were positioned under laser guidance. Attenuation correction was performed by ⁶⁸Ge/⁶⁸Ga transmission scanning. Dynamic PET emission scanning lasting 261 s (frame sequence: 7 × 3 s, 6 × 5 s, 6 × 10 s, 3 × 20 s, and 3 × 30 s) started with injection of a target radioactivity dose of 700 megabecquerel H₂¹⁵O. Injection was performed as a slow bolus using a syringe pump.

Myocardial blood flow was quantified from the attenuation-corrected dynamic H₂¹⁵O PET data using pixel-wise modeling software (PMOD, Zürich, Switzerland). First, images of myocardium and blood pool were generated using factor analysis.²⁴ These images were then used as anatomic references. Myocardial regions of interest were drawn on basal to midventricular short-axis slices excluding the septum (fig. 2). Regions of interest were also drawn within the base of the left ventricle to obtain arterial blood time–activity curves as input function.²⁵ Myocardial tissue time–activity curves were fitted by a standard one-tissue compartment model using the arterial time–activity curve as input. K₁ estimates were multiplied by the density of myocardial tissue (1.04 ml·g⁻¹), equaling absolute MBF in ml·g⁻¹·min⁻¹.²⁶,²⁷

To account for the changes in MBF produced by cardiac workload, MBF was corrected for the RPP (RPP = heart rate systolic blood pressure), an index of myocardial oxygen consumption,²⁸ using the formula: MBFcorr = (MBF/RPP) 10⁻⁴.²⁹ Coronary vascular resistance was calculated as the mean arterial blood pressure to MBF ratio.²⁹

Statistical Analysis

Statistical analysis was performed using JMP® 8 (SAS Institute, Cary, NC). All data were checked for normal distribution using the Shapiro–Wilk W test. The effects of xenon on MBF, RPP, coronary vascular resistance, MBFcorr, and other physiologic variables were then compared using Student t test for paired samples. Linear regression analysis and the calculation of Pearson product-moment correlation (r) were used to analyze the correlation between MBF and RPP. The Spearman rank correlation coefficient was used to describe the correlation between absolute and percentage changes in MBF and RPP that were induced by xenon anesthesia. To assess whether xenon anesthesia might affect the regression slope (RPP × condition interaction) between MBF and RPP, we performed an analysis of covariance with MBF as a dependent variable and RPP (continuous variable) and the condition (wakefulness/xenon; categorical) being independent variables. In each case, a two-sided P value of less than 0.05 was considered statistically significant. Data are presented as mean ± SD.

Results

Administration of approximately 1 MAC xenon was associated with a deep state of anesthesia, as estimated by clinical signs and suggested by the decrease in the bispectral index (table 1). No participant reported an episode of awareness after emerging from anesthesia.

Although heart rate did not change throughout the study period, we observed a slight decrease in mean arterial pressure after steady state of xenon anesthesia was reached (table 1), resulting in a decrease in RPP by 15% (RPPbaseline 6,680 ± 1,090 mmHg·min⁻¹ vs. RPPxenon 5,559 ± 780 mmHg·min⁻¹, P = 0.04).
During xenon anesthesia (MBF\textsubscript{xenon}, 0.80 ± 0.22 ml \cdot min\textsuperscript{-1} \cdot g\textsuperscript{-1}) we found a nonsignificant decrease in MBF (−21%, P = 0.11) compared with baseline (MBF\textsubscript{baseline}, 1.03 ± 0.09 ml \cdot min\textsuperscript{-1} \cdot g\textsuperscript{-1}) (fig. 3). When we corrected for RPP, the decrease in MBF observed during xenon anesthesia was reduced to 9% (MBF\textsubscript{corr-xenon}, 1.42 ± 0.28 ml \cdot g\textsuperscript{-1} \cdot mmHg\textsuperscript{-1} vs. MBF\textsubscript{corr-baseline}, 1.60 ± 0.28 ml \cdot g\textsuperscript{-1} \cdot mmHg\textsuperscript{-1}, P = 0.32). Coronary vascular resistance was increased by 15 ± 23% (P = 0.18) during xenon anesthesia (fig. 3); however, this did not reach statistical significance.

Linear correlation analysis showed a close correlation of MBF with RPP (r = 0.68, P = 0.015) (fig. 4) and for the absolute changes of MBF and RPP that were induced by xenon (Spearman R = 0.89, P = 0.018). Likewise, percentage changes in RPP were closely paralleled by percentage changes in MBF (Spearman R = 0.88, P = 0.019). Analysis of covariance revealed that the dependency of MBF on RPP was not changed by xenon. Only RPP exhibited a significant effect on MBF (P = 0.028); this correlation was not affected by the condition (wakefulness/xenon; P = 0.15) or the interaction RPP \times condition (P = 0.10; i.e., testing the difference in regression slopes for the association of MBF and RPP between both conditions).

One subject showed a different behavior as his MBF increased during xenon anesthesia, but his heart rate was stable and arterial pressure slightly decreased, as occurred in the other participants. However, even when excluding this subject from the analysis, MBF\textsubscript{corr} was still not significantly affected by xenon anesthesia.

**Discussion**

In the current study, we demonstrated that general anesthesia with xenon has only minimal effects on MBF. We found a nonsignificant decline in MBF that most likely was caused by a decrease of myocardial oxygen consumption induced by xenon anesthesia. Moreover, we observed that xenon does not affect the close relationship between MBF and myocardial oxygen consumption (as estimated by RPP).
In the left ventricle, coronary artery flow is mainly dependent upon myocardial oxygen demand. Coronary vasomotor tone and vascular diameter are regulated by a sophisticated network of various interacting factors, allowing MBF to increase during exercise and meet metabolic demands. It is estimated that heart rate accounts for 60% of myocardial oxygen consumption, whereas contractility and cardiac work (mainly determined by afterload) each contribute 15–25% to the metabolic demands of the ventricle. Combining these determinants of myocardial oxygen demand, the product of heart rate and systolic arterial pressure (i.e., the RPP) has been validated and established as a noninvasive estimate of myocardial oxygen consumption. Importantly, we confirmed the close relationship between MBF and RPP in the study volunteers. In our study, xenon anesthesia resulted in a nonsignificant decrease in MBF. However, we suggest that these effects were mainly imposed by the fact that xenon anesthesia was associated with a modest decrease in arterial pressure, whereas heart rate was preserved. This leads to a decrease in cardiac work and consequently myocardial oxygen requirements, as reflected by the decrease in RPP. To account for the changes in MBF produced by the decrease in cardiac workload and independent of the direct effects of xenon on coronary flow, we corrected MBF for RPP. With this approach, we found xenon to be virtually devoid of intrinsic effects on MBF. This conclusion is corroborated by the results of the analysis of covariance, which indicate that the association between MBF and RPP is not affected by xenon anesthesia, either alone or in interaction with RPP.

Our observations are in accordance with previous findings in the dog heart, in which global and even regional administration of xenon did not alter coronary blood flow in the left anterior descending and the left circumflex coronary artery. These findings might be explained by xenon having minimal or no vasodilating effects in the arterial system. In contrast, other anesthetics known to induce vasodilation (thereby decreasing vascular resistance) have been found to increase coronary flow in a concentration-dependent manner, as has been demonstrated for isoflurane and sevoflurane. Moreover, the latter agents increased coronary flow despite a decrease in cardiac work and thus myocardial oxygen consumption, whereas contractility and cardiac work (mainly determined by afterload) each contribute 15–25% to the metabolic demands of the ventricle. Combining these determinants of myocardial oxygen demand, the product of heart rate and systolic arterial pressure (i.e., the RPP) has been validated and established as a noninvasive estimate of myocardial oxygen consumption. Importantly, we confirmed the close relationship between MBF and RPP in the study volunteers. In our study, xenon anesthesia resulted in a nonsignificant decrease in MBF. However, we suggest that these effects were mainly imposed by the fact that xenon anesthesia was associated with a modest decrease in arterial pressure, whereas heart rate was preserved. This leads to a decrease in cardiac work and consequently myocardial oxygen requirements, as reflected by the decrease in RPP. To account for the changes in MBF produced by the decrease in cardiac workload and independent of the direct effects of xenon on coronary flow, we corrected MBF for RPP. With this approach, we found xenon to be virtually devoid of intrinsic effects on MBF. This conclusion is corroborated by the results of the analysis of covariance, which indicate that the association between MBF and RPP is not affected by xenon anesthesia, either alone or in interaction with RPP.

Our observations are in accordance with previous findings in the dog heart, in which global and even regional administration of xenon did not alter coronary blood flow in the left anterior descending and the left circumflex coronary artery. These findings might be explained by xenon having minimal or no vasodilating effects in the arterial system. In contrast, other anesthetics known to induce vasodilation (thereby decreasing vascular resistance) have been found to increase coronary flow in a concentration-dependent manner, as has been demonstrated for isoflurane and sevoflurane. Moreover, the latter agents increased coronary flow despite a decrease in cardiac work and thus myocardial oxygen consumption, whereas contractility and cardiac work (mainly determined by afterload) each contribute 15–25% to the metabolic demands of the ventricle. Combining these determinants of myocardial oxygen demand, the product of heart rate and systolic arterial pressure (i.e., the RPP) has been validated and established as a noninvasive estimate of myocardial oxygen consumption. Importantly, we confirmed the close relationship between MBF and RPP in the study volunteers. In our study, xenon anesthesia resulted in a nonsignificant decrease in MBF. However, we suggest that these effects were mainly imposed by the fact that xenon anesthesia was associated with a modest decrease in arterial pressure, whereas heart rate was preserved. This leads to a decrease in cardiac work and consequently myocardial oxygen requirements, as reflected by the decrease in RPP. To account for the changes in MBF produced by the decrease in cardiac workload and independent of the direct effects of xenon on coronary flow, we corrected MBF for RPP. With this approach, we found xenon to be virtually devoid of intrinsic effects on MBF. This conclusion is corroborated by the results of the analysis of covariance, which indicate that the association between MBF and RPP is not affected by xenon anesthesia, either alone or in interaction with RPP.

Our observations are in accordance with previous findings in the dog heart, in which global and even regional administration of xenon did not alter coronary blood flow in the left anterior descending and the left circumflex coronary artery. These findings might be explained by xenon having minimal or no vasodilating effects in the arterial system. In contrast, other anesthetics known to induce vasodilation (thereby decreasing vascular resistance) have been found to increase coronary flow in a concentration-dependent manner, as has been demonstrated for isoflurane and sevoflurane. Moreover, the latter agents increased coronary flow despite a decrease in cardiac work and thus myocardial oxygen consumption, whereas contractility and cardiac work (mainly determined by afterload) each contribute 15–25% to the metabolic demands of the ventricle. Combining these determinants of myocardial oxygen demand, the product of heart rate and systolic arterial pressure (i.e., the RPP) has been validated and established as a noninvasive estimate of myocardial oxygen consumption. Importantly, we confirmed the close relationship between MBF and RPP in the study volunteers. In our study, xenon anesthesia resulted in a nonsignificant decrease in MBF. However, we suggest that these effects were mainly imposed by the fact that xenon anesthesia was associated with a modest decrease in arterial pressure, whereas heart rate was preserved. This leads to a decrease in cardiac work and consequently myocardial oxygen requirements, as reflected by the decrease in RPP. To account for the changes in MBF produced by the decrease in cardiac workload and independent of the direct effects of xenon on coronary flow, we corrected MBF for RPP. With this approach, we found xenon to be virtually devoid of intrinsic effects on MBF. This conclusion is corroborated by the results of the analysis of covariance, which indicate that the association between MBF and RPP is not affected by xenon anesthesia, either alone or in interaction with RPP.

Our observations are in accordance with previous findings in the dog heart, in which global and even regional administration of xenon did not alter coronary blood flow in the left anterior descending and the left circumflex coronary artery. These findings might be explained by xenon having minimal or no vasodilating effects in the arterial system. In contrast, other anesthetics known to induce vasodilation (thereby decreasing vascular resistance) have been found to increase coronary flow in a concentration-dependent manner, as has been demonstrated for isoflurane and sevoflurane. Moreover, the latter agents increased coronary flow despite a decrease in cardiac work and thus myocardial oxygen consumption, whereas contractility and cardiac work (mainly determined by afterload) each contribute 15–25% to the metabolic demands of the ventricle.
gen consumption, resulting in an uncoupling of coronary flow from metabolic needs. In contrast, we observed in our study that xenon did not affect the close coupling between MBF and myocardial oxygen consumption (RPP).

In experimental conditions, coronary blood flow is primarily measured by the use of coronary flow probes; this approach is not feasible in humans because of its invasiveness. However, several groups have shown that PET can be used to absolutely quantitate regional MBF in an accurate and noninvasive manner. Therefore, PET has become the clinical gold standard in the quantitative assessment of MBF. To the best of our knowledge, the current study is the first in humans using PET to investigate the effects of anesthesia on MBF.

The results of this study should be interpreted within the constraints of several potential limitations. First, given the small number of study subjects, our results have to be considered largely observational, but they are in line with evidence from laboratory findings. Second, we investigated only healthy volunteers without any clinical evidence of coronary disease. An extrapolation of our results to patients with coronary artery stenoses is purely speculative. Thus, our observations are hypothesis-generating and warrant further investigation with respect to the unknown effects of xenon on coronary flow reserve in patients with coronary artery stenoses. Third, the precise effects of an anesthetic on intrinsic coronary vasomotor tone are difficult to assess in vivo because of concomitant changes in systemic vascular resistance, myocardial contractility, baroreflex activity, and central nervous system activity evoked by anesthesia. On the other hand, the complex interaction of these determinants and thus the more indirect effects of an anesthetic on MBF appear to be of particular relevance for clinical practice. Finally, anesthesia was induced with high doses of propofol to allow the insertion of a laryngeal mask airway in healthy subjects who had not been premedicated. In an attempt to minimize confounding the influences of propofol on MBF, the propofol infusion was stopped immediately after insertion of the laryngeal mask airway, and PET measurements were started only after the calculated propofol plasma concentration had decreased to a subanesthetic range. We suggest that the use of propofol alone is an interesting option in the care of patients at risk for perioperative myocardial ischemia, a hypothesis that should be tested in an adequately powered, randomized clinical trial.

References

14. Oei GT, Weber NC, Hollmann MW, Preckel B: Cellular effects...
of helium in different organs. Anesthesiology 2010; 112: 1503–10