

Myocardial Blood Flow during General Anesthesia With Xenon in Humans

A Positron Emission Tomography Study

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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, $59 \pm 0\%$. Absolute quantification

What We Already Know about This Topic

- Xenon has only minimal hemodynamic effects, but its effects on myocardial blood flow and coronary vascular resistance remain unknown

What This Article Tells Us That Is New

- Xenon had minimal effects on coronary flow dynamics as measured by cardiac positron emission tomography in healthy volunteers

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of MBF was started after the calculated plasma concentration of propofol had decreased to less than $1.5 \mu g \cdot ml^{-1}$.

Results: Compared with baseline ($MBF_{baseline}$, 1.03 ± 0.09 $ml \cdot min^{-1} \cdot g^{-1}$; mean \pm SD), MBF was decreased insignificantly by xenon (MBF_{xenon} , 0.80 ± 0.22 $ml \cdot min^{-1} \cdot g^{-1}$; -21% , $P = 0.11$). Xenon decreased the rate–pressure product (RPP; heart rate \times 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 $ml \cdot g^{-1} \cdot mmHg^{-1}$ vs. $MBF_{corr-baseline}$, 1.60 ± 0.28 $ml \cdot g^{-1} \cdot mmHg^{-1}$, $P = 0.32$). Xenon did not affect the dependency of MBF on the RPP. Coronary vascular resistance did not significantly change ($+15 \pm 23\%$, $P = 0.18$) during xenon anesthesia.

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 effects^{7,9–11} and improves recovery from posts ischemic 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 under-

went 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-

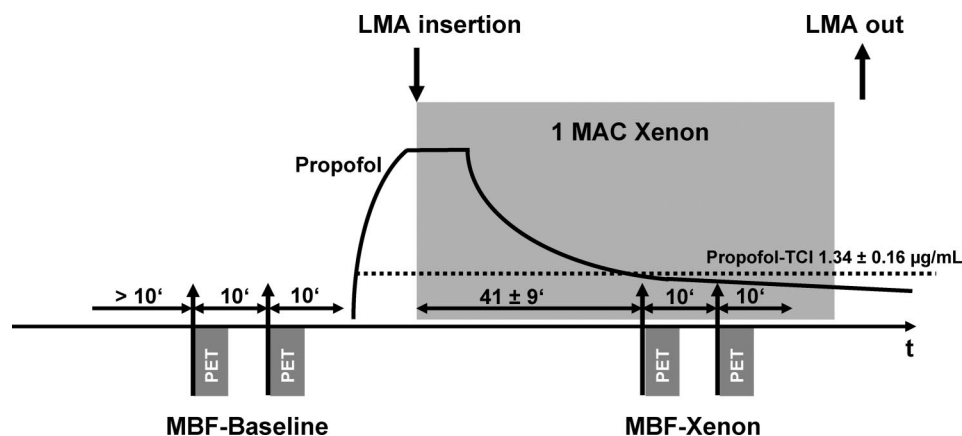


Fig. 1. Experimental procedure. LMA = laryngeal mask airway; MAC = minimum alveolar concentration; MBF = myocardial blood flow; PET = positron emission tomography; TCI = target-controlled infusion.

xygen, nitrogen, carbon dioxide and xenon (Physioflex; Dräger Medical Deutschland GmbH, Lübeck, Germany), electroencephalography using the bispectral index (BIS® A-2000 monitor; Aspect Medical Systems, Leiden, The Netherlands), and intermittent measurements of tympanic temperature. Two intravenous catheters were placed into the antecubital veins on each side, one for administering $H_2^{15}O$, the other for basic fluid substitution ($2-3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ lactated Ringer's solution) and the induction dose of propofol. Two experienced anesthesiologists were present throughout the entire study procedure, and full anesthesia and resuscitation equipment were always available.

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 $10.4 \pm 1.2 \mu\text{g} \cdot \text{ml}^{-1}$ 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.

$H_2^{15}O$ 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 $1.5 \mu\text{g} \cdot \text{ml}^{-1}$ (*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.

$H_2^{15}O$ PET

$H_2^{15}O$ 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 $^{68}\text{Ge}/^{68}\text{Ga}$ transmission scanning. Dynamic PET emission scanning lasting 261 s (frame sequence: $7 \times 3 \text{ s}$, $6 \times 5 \text{ s}$, $6 \times 10 \text{ s}$, $3 \times 20 \text{ s}$, and $3 \times 30 \text{ s}$) started with injection of a target radioactivity dose of 700 megabecquerel $H_2^{15}O$. Injection was performed as a slow bolus using a syringe pump.

Myocardial blood flow was quantified from the attenuation-corrected dynamic $H_2^{15}O$ 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. K_1 estimates were multiplied by the density of myocardial tissue ($1.04 \text{ ml} \cdot \text{g}^{-1}$), equaling absolute MBF in $\text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$.^{26,27}

To account for the changes in MBF produced by cardiac workload, MBF was corrected for the RPP (RPP = heart rate \times systolic blood pressure), an index of myocardial oxygen consumption,²⁸ using the formula: $\text{MBF}_{\text{corr}} = (\text{MBF}/\text{RPP}) 10^4$.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, MBF_{corr} , 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 \times 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 \pm 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% ($\text{RPP}_{\text{baseline}}, 6,680 \pm 1,090 \text{ mmHg} \cdot \text{min}^{-1}$ vs. $\text{RPP}_{\text{xenon}}, 5,559 \pm 780 \text{ mmHg} \cdot \text{min}^{-1}$, *P* = 0.04).

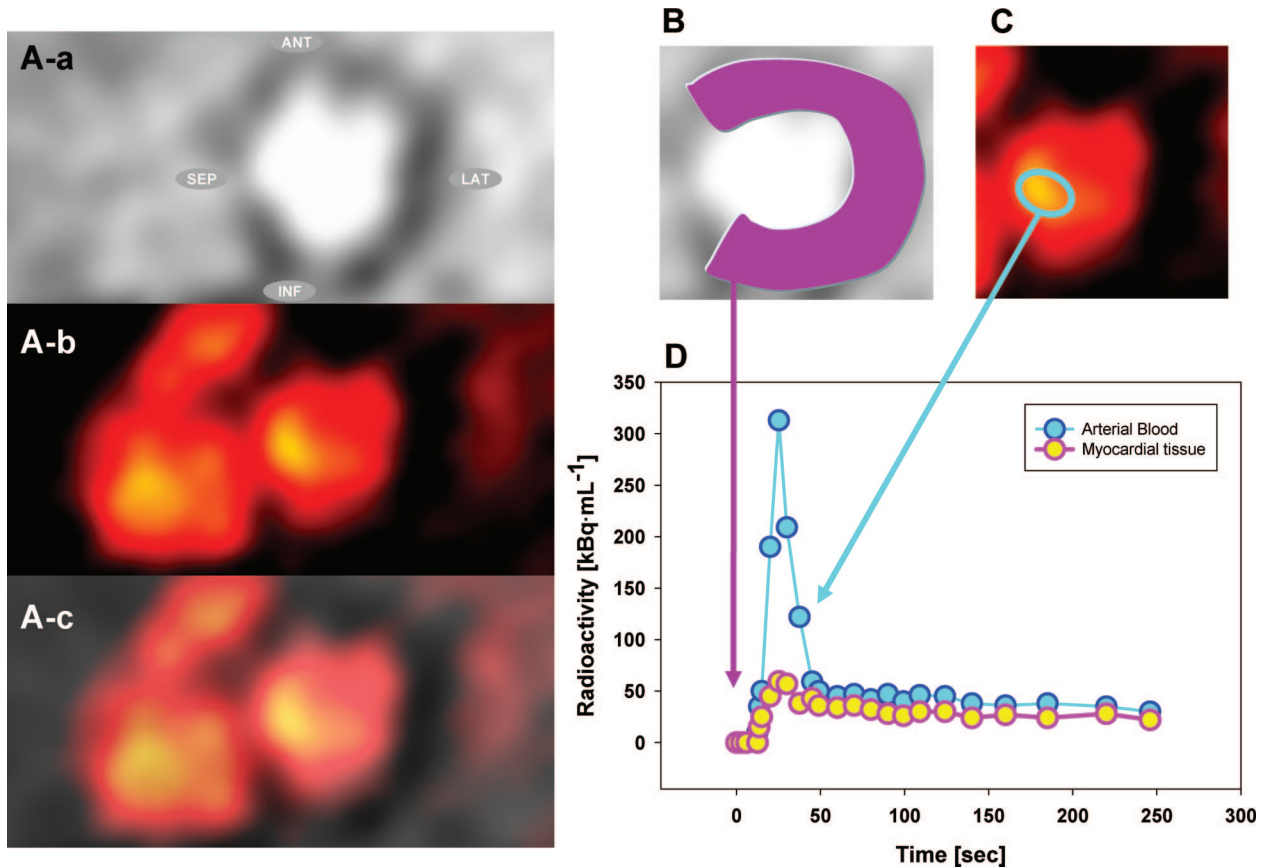


Fig. 2. Schematic illustration of the assessment of myocardial blood flow by positron emission tomography. Images of left ventricular myocardium (A-a) and blood pool (A-b) were generated using factor analysis and were used as anatomic references; an overlay of both images was used to control the proper calculation of the factorial images (A-c). Regions of interest were drawn on basal to midventricular short-axis slices (excluding the septum) to obtain time–activity curves of myocardial tissue (B), and within the base of the left ventricle, to obtain arterial blood time–activity curves as input function (C). Arterial and myocardial tissue time–activity curves are then fit to a validated, single-tissue compartment model, resulting in the absolute quantification of myocardial blood flow (D). For details, see Materials and Methods: H_2^{15}O PET. ANT = anterior; LAT = lateral; INF = inferior; SEP = septal.

During xenon anesthesia ($\text{MBF}_{\text{xenon}}$, $0.80 \pm 0.22 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$) we found a nonsignificant decrease in MBF (-21% , $P = 0.11$) compared with baseline ($\text{MBF}_{\text{baseline}}$, $1.03 \pm 0.09 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$) (fig. 3). When we corrected for RPP, the decrease in MBF observed during xenon anesthesia was reduced to -9% ($\text{MBF}_{\text{corr-xenon}}$, $1.42 \pm 0.28 \text{ ml} \cdot \text{g}^{-1} \cdot \text{mmHg}^{-1}$ vs. $\text{MBF}_{\text{corr-baseline}}$, $1.60 \pm 0.28 \text{ ml} \cdot \text{g}^{-1} \cdot \text{mmHg}^{-1}$, $P = 0.32$). Coronary vascular resistance was increased by $15 \pm 23\%$ ($P = 0.18$) 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 $\text{RPP} \times \text{condition}$ ($P = 0.10$; *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_{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).

Table 1. Apparative and Physiologic Variables

	Awake	Xenon
Xe _{insp.} (%)	—	59 ± 0
TCl _{Prop} (μg · mL ⁻¹)	—	1.34 ± 0.16
FiO ₂ —	0.21 ± 0	0.28 ± 0.01*
V _T (mL)	—	581 ± 69
RR (min ⁻¹)	—	13 ± 3
P _{insp} (cm H ₂ O)	—	16 ± 2
BIS —	97 ± 1	34 ± 1*
HR (min ⁻¹)	57 ± 8	54 ± 5
MAP (mmHg)	87 ± 8	74 ± 7*
SpO ₂ (%)	97 ± 2	96 ± 1
ETCO ₂ (mmHg)	41 ± 1	40 ± 1
T (°C)	36.3 ± 0	36.2 ± 0

Data are mean ± SD. All parameters are averaged for the two acquisition periods, each during wakefulness and xenon anesthesia.

* P < 0.05 vs. awake.

BIS = bispectral index; ETCO₂ = end-tidal carbon dioxide concentration; FiO₂ = fraction of inspired oxygen; HR = heart rate; MAP = mean arterial pressure; P_{insp} = inspiratory airway pressure; RR = respiratory rate; SpO₂ = partial oxygen saturation; T = temperature; TCl_{Prop} = calculated propofol plasma concentration; V_T = tidal volume; Xe_{insp.} = inspiratory xenon concentration.

In the left ventricle, coronary artery flow is mainly dependent upon myocardial oxygen demand.³⁰ 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%

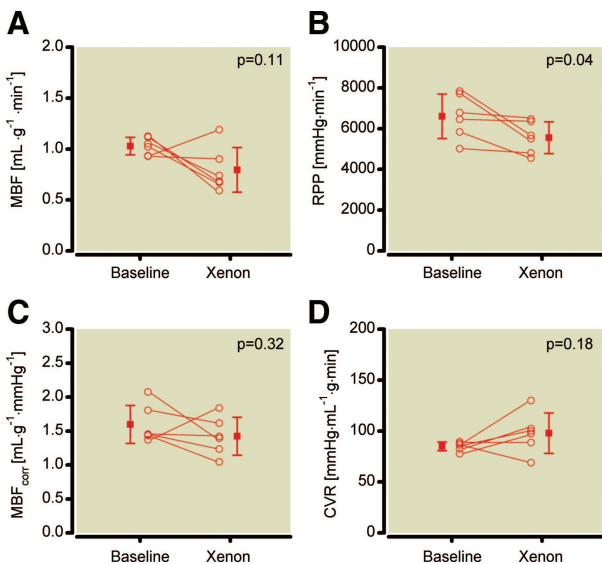


Fig. 3. Effects of xenon on myocardial blood flow (MBF) (A), rate pressure product (RPP) (B), MBF corrected for RPP (MBF_{corr}) (C), and coronary vascular resistance (CVR) (D). The data are presented as mean (squares) ± SD. Individual values are depicted as open circles (two scans under each condition; data points represent average values of the respective condition).

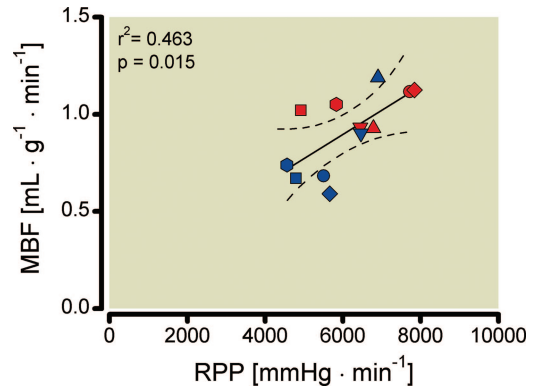


Fig. 4. Linear correlation analysis of the relationship between myocardial blood flow (MBF) and rate pressure product (RPP). Data from six healthy volunteers studied by H₂¹⁵O positron emission tomography under resting wakefulness (red symbols) and xenon anesthesia (blue symbols) (two scans under each condition; data points represent average values of the respective condition). Each individual is represented by separate symbols. Solid line = linear regression line; dotted lines = 95% confidence interval of the regression line.

to the metabolic demands of the ventricle.³⁰ 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.^{28,31,32} 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.^{29,33} 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.⁵ These findings might be explained by xenon having minimal or no vasodilating effects in the arterial system.¹⁸ 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.³⁴ Moreover, the latter agents increased coronary flow despite a decrease in cardiac work and thus myocardial oxy-

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.^{26,27,35} 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 did not mask xenon-related effects on MBF to any relevant extent because therapeutic concentrations of propofol have been demonstrated not to affect coronary blood flow.³⁶ Moreover, we carefully avoided hyperoxia throughout the experimental procedure. This allowed us to ensure the administration of nearly 1 MAC of xenon and avoid potentially counteracting effects of hyperoxia and xenon on coronary vasomotor tone. Hyperoxia has been shown to induce a coronary vasoconstriction mediated by the closure of adenosine triphosphate-sensitive potassium channels,³⁷ whereas xenon has been reported to activate the neuronal type of these channels.³⁸

In summary, we demonstrated that in healthy volunteers (*i.e.*, those without coronary artery disease) xenon anesthesia

has only minimal effects on coronary flow dynamics, most probably reflecting the decrease in myocardial oxygen consumption induced by the effects of general anesthesia on cardiac work. Xenon's lack of intrinsic effects on MBF could render it 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

1. Lachmann B, Armbruster S, Schairer W, Landstra M, Trouwborst A, Van Daal GJ, Kusuma A, Erdmann W: Safety and efficacy of xenon in routine use as an inhalational anaesthetic. *Lancet* 1990; 335:1413-5
2. Boomsma F, Ruprecht J, Man in 't Veld AJ, de Jong FH, Dzoljic M, Lachmann B: Haemodynamic and neurohumoral effects of xenon anaesthesia. A comparison with nitrous oxide. *Anaesthesia* 1990; 45:273-8
3. Hettrick DA, Pagel PS, Kersten JR, Tessmer JP, Bosnjak ZJ, Georgieff M, Wartier DC: Cardiovascular effects of xenon in isoflurane-anesthetized dogs with dilated cardiomyopathy. *ANESTHESIOLOGY* 1998; 89:1166-73
4. Preckel B, Schlack W, Heibel T, Rütten H: Xenon produces minimal haemodynamic effects in rabbits with chronically compromised left ventricular function. *Br J Anaesth* 2002; 88:264-9
5. Preckel B, Ebel D, Müllenheim J, Fräsdorf J, Thämer V, Schlack W: The direct myocardial effects of xenon in the dog heart *in vivo*. *Anesth Analg* 2002; 94:545-51
6. Rossaint R, Reyle-Hahn M, Schulte Am Esch J, Scholz J, Scherpereel P, Vallet B, Giunta F, Del Turco M, Erdmann W, Tenbrinck R, Hammerle AF, Nagele P, Xenon Study Group: Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. *ANESTHESIOLOGY* 2003; 98:6-13
7. Wappler F, Rossaint R, Baumert J, Scholz J, Tonner PH, van Aken H, Berendes E, Klein J, Gommers D, Hammerle A, Franke A, Hofmann T, Schulte Esch J, Xenon Multicenter Study Research Group: Multicenter randomized comparison of xenon and isoflurane on left ventricular function in patients undergoing elective surgery. *ANESTHESIOLOGY* 2007; 106:463-71
8. Coburn M, Kunitz O, Baumert JH, Hecker K, Haaf S, Zühlsdorff A, Beeker T, Rossaint R: Randomized controlled trial of the haemodynamic and recovery effects of xenon or propofol anaesthesia. *Br J Anaesth* 2005; 94:198-202
9. Schroth SC, Schotten U, Alkanoglu O, Reyle-Hahn MS, Hanrath P, Rossaint R: Xenon does not impair the responsiveness of cardiac muscle bundles to positive inotropic and chronotropic stimulation. *ANESTHESIOLOGY* 2002; 96:422-7
10. Hüneke R, Jüngling E, Skasa M, Rossaint R, Lückhoff A: Effects of the anesthetic gases xenon, halothane, and isoflurane on calcium and potassium currents in human atrial cardiomyocytes. *ANESTHESIOLOGY* 2001; 95:999-1006
11. Baumert JH, Hein M, Hecker KE, Satlow S, Neef P, Rossaint R: Xenon or propofol anaesthesia for patients at cardiovascular risk in non-cardiac surgery. *Br J Anaesth* 2008; 100:605-11
12. Preckel B, Müllenheim J, Moloschavij A, Thämer V, Schlack W: Xenon administration during early reperfusion reduces infarct size after regional ischemia in the rabbit heart *in vivo*. *Anesth Analg* 2000; 91:1327-32
13. Hartlage MA, Berendes E, Van Aken H, Fobker M, Theisen M, Weber TP: Xenon improves recovery from myocardial stunning in chronically instrumented dogs. *Anesth Analg* 2004; 99:655-64
14. Oei GT, Weber NC, Hollmann MW, Preckel B: Cellular effects

- of helium in different organs. *ANESTHESIOLOGY* 2010; 112:1503-10
15. Weber NC, Toma O, Wolter JI, Obal D, Müllenheim J, Preckel B, Schlack W: The noble gas xenon induces pharmacological preconditioning in the rat heart *in vivo* via induction of PKC-epsilon and p38 MAPK. *Br J Pharmacol* 2005; 144:123-32
 16. Weber NC, Frässdorf J, Ratajczak C, Grueber Y, Schlack W, Hollmann MW, Preckel B: Xenon induces late cardiac preconditioning *in vivo*: A role for cyclooxygenase 2? *Anesth Analg* 2008; 107:1807-13
 17. Baumert JH, Hein M, Gerets C, Baltus T, Hecker KE, Rossaint R: The effect of xenon anesthesia on the size of experimental myocardial infarction. *Anesth Analg* 2007; 105:1200-6
 18. Fukuda T, Nakayama H, Yanagi K, Mizutani T, Miyabe M, Ohshima N, Toyooka H: The effects of 30% and 60% xenon inhalation on pial vessel diameter and intracranial pressure in rabbits. *Anesth Analg* 2001; 92:1245-50
 19. Rex S, Schaefer W, Meyer PH, Rossaint R, Boy C, Setani K, Büll U, Baumert JH: Positron emission tomography study of regional cerebral metabolism during general anesthesia with xenon in humans. *ANESTHESIOLOGY* 2006; 105:936-43
 20. Rex S, Meyer PT, Baumert JH, Rossaint R, Fries M, Büll U, Schaefer WM: Positron emission tomography study of regional cerebral blood flow and flow-metabolism coupling during general anaesthesia with xenon in humans. *Br J Anaesth* 2008; 100:667-75
 21. Fahlenkamp AV, Krebber F, Rex S, Grottko O, Fries M, Rossaint R, Coburn M: Bispectral index monitoring during balanced xenon or sevoflurane anaesthesia in elderly patients. *Eur J Anaesthesiol* 2010; 27:906-11
 22. Fahlenkamp AV, Peters D, Biener IA, Billoet C, Apfel CC, Rossaint R, Coburn M: Evaluation of bispectral index and auditory evoked potentials for hypnotic depth monitoring during balanced xenon anaesthesia compared with sevoflurane. *Br J Anaesth* 2010; 105:334-41
 23. Fiset P, Paus T, Daloz T, Plourde G, Meuret P, Bonhomme V, Hajj-Ali N, Backman SB, Evans AC: Brain mechanisms of propofol-induced loss of consciousness in humans: A positron emission tomographic study. *J Neurosci* 1999; 19:5506-13
 24. Hermansen F, Ashburner J, Spinks TJ, Kooner JS, Camici PG, Lammertsma AA: Generation of myocardial factor images directly from the dynamic oxygen-15-water scan without use of an oxygen-15-carbon monoxide blood-pool scan. *J Nucl Med* 1998; 39:1696-702
 25. Iida H, Rhodes CG, de Silva R, Araujo LI, Bloomfield PM, Lammertsma AA, Jones T: Use of the left ventricular time-activity curve as a noninvasive input function in dynamic oxygen-15-water positron emission tomography. *J Nucl Med* 1992; 33:1669-77
 26. Iida H, Kanno I, Takahashi A, Miura S, Murakami M, Takahashi K, Ono Y, Shishido F, Inugami A, Tomura N: Measurement of absolute myocardial blood flow with H₂¹⁵O and dynamic positron-emission tomography. Strategy for quantification in relation to the partial-volume effect. *Circulation* 1988; 78:104-15
 27. Araujo LI, Lammertsma AA, Rhodes CG, McFalls EO, Iida H, Rechavia E, Galassi A, De Silva R, Jones T, Maseri A: Noninvasive quantification of regional myocardial blood flow in coronary artery disease with oxygen-15-labeled carbon dioxide inhalation and positron emission tomography. *Circulation* 1991; 83:875-85
 28. Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y: The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation* 1978; 57:549-56
 29. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG: Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med* 1994; 330:1782-8
 30. Duncker DJ, Bache RJ: Regulation of coronary blood flow during exercise. *Physiol Rev* 2008; 88:1009-86
 31. Czernin J, Müller P, Chan S, Brunken RC, Porenta G, Krivokapich J, Chen K, Chan A, Phelps ME, Schelbert HR: Influence of age and hemodynamics on myocardial blood flow and flow reserve. *Circulation* 1993; 88:62-9
 32. Rex S, Missant C, Claus P, Buhre W, Wouters PF: Effects of inhaled iloprost on right ventricular contractility, right ventriculo-vascular coupling and ventricular interdependence: A randomized placebo-controlled trial in an experimental model of acute pulmonary hypertension. *Crit Care* 2008; 12:R113
 33. Schaefer WM, Koch KC, Nowak B, Noth J, Buell U, Weiss PH: Dipyridamole/ aspirin combination in secondary stroke prevention: Effects on absolute myocardial blood flow and coronary vascular resistance. *Int J Clin Pharmacol Ther* 2006; 44:319-25
 34. Graf BM, Vicenzi MN, Bosnjak ZJ, Stowe DF: The comparative effects of equimolar sevoflurane and isoflurane in isolated hearts. *Anesth Analg* 1995; 81:1026-32
 35. Bergmann SR, Fox KA, Rand AL, McElvany KD, Welch MJ, Markham J, Sobel BE: Quantification of regional myocardial blood flow *in vivo* with H₂¹⁵O. *Circulation* 1984; 70:724-33
 36. Mouren S, Baron JF, Albo C, Szekely B, Arthaud M, Viars P: Effects of propofol and thiopental on coronary blood flow and myocardial performance in an isolated rabbit heart. *ANESTHESIOLOGY* 1994; 80:634-41
 37. Ouattara A, Boccara G, Lecomte P, Souktani R, Le Cosquer P, Mouren S, Coriat P, Riou B: Amplification by hyperoxia of coronary vasodilation induced by propofol. *Anesth Analg* 2004; 98:595-603
 38. Bantel C, Maze M, Trapp S: Noble gas xenon is a novel adenosine triphosphate-sensitive potassium channel opener. *ANESTHESIOLOGY* 2010; 112:623-30