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Multicenter Randomized Comparison of Xenon and Isoflurane on Left Ventricular Function in Patients Undergoing Elective Surgery

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Background: **Volatile anesthetics are commonly used for general anesthesia. However, these can induce profound cardiovascular alterations. Xenon is a noble gas with potent anesthetic and analgesic properties. However, it is uncertain whether xenon alters myocardial function. The aim of this study was therefore to investigate left ventricular function during anesthesia with xenon compared with isoflurane.**

Methods: **The authors performed a randomized multicenter trial to compare xenon with isoflurane with respect to cardiovascular stability and adverse effects in patients without cardiac diseases scheduled for elective surgery. Two hundred fifty-nine patients were enrolled in this trial, of which 252 completed the study according to the protocol. Patients were anesthetized with xenon or isoflurane, respectively. Before administration of the study drugs and at four time points, the effects of both anesthetics on left ventricular function were investigated using transesophageal echocardiography.**

Results: **Global hemodynamic parameters were significantly altered using isoflurane ($P < 0.05$ *vs.* baseline), whereas xenon only decreased heart rate ($P < 0.05$ *vs.* baseline). In contrast to xenon, left ventricular end-systolic wall stress decreased significantly in the isoflurane group ($P < 0.05$ *vs.* baseline). Velocity of circumferential fiber shortening was decreased significantly in the xenon group but showed a more pronounced reduction during isoflurane administration ($P < 0.05$ *vs.* baseline). The contractile index (difference between expected and actually measured velocity of circumferential fiber shortening) as an independent parameter for left ventricular function was significantly decreased after isoflurane ($P < 0.0001$) but unchanged using xenon.**

Conclusions: **Xenon did not reduce contractility, whereas isoflurane decreased the contractile index, indicating that xenon enables favorable cardiovascular stability in patients without cardiac diseases.**

DISEASES of the cardiovascular system are the main causes of death in the industrial nations. Approximately one third of those patients scheduled to undergo noncardiac surgery are at risk for coronary artery disease or have coronary risk factors. It has been hypothesized that approximately 10% of these patients will experience myocardial infarction or cardiac complications perioperatively, leading to a significant reduction in their 2-yr survival rate.[1]

Numerous studies have focused on perioperative concepts to prevent and/or reduce the incidence of perioperative cardiovascular complications and to improve patients' outcome,[2] *e.g.*, prophylaxis using β-adrenoceptor antagonists[3] or α_2-adrenoceptor agonists.[4] The choice of anesthetics may also play an important role regarding cardiovascular stability. On the one hand, clinical results indicate that the volatile anesthetics desflurane and sevoflurane may preserve myocardial function in high-risk patients.[5] On the other hand, volatile anesthetics can alter global hemodynamics and have negative inotropic effects. Therefore, an anesthetic without negative cardiovascular effects would be desirable.

Xenon is a noble gas with potent anesthetic and analgesic properties.[6] Experimental data have shown that xenon had no significant effects on the myocardium,[7] atrioventricular conduction time, or coronary blood flow.[8] Furthermore, xenon does not alter cardiac ion currents[9] or impair the responsiveness of cardiac muscle bundles to inotropic and chronotropic stimulation.[10] Also, *in vivo* experiments demonstrated that xenon anesthesia was associated with a high degree of cardiovascular stability.[11,12]

To date, only a limited number of clinical studies investigating cardiac effects of xenon are available.[13–16] In these studies, it could be demonstrated that xenon enables high cardiovascular stability,[14] associated with a slight decrease in heart rate.[14,15] Furthermore, sedation with xenon in patients after cardiac surgery was

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achieved with minimal cardiovascular effects and enabled rapid recovery characteristics.[16]

Whereas experimental data confirmed that xenon induces only minor cardiovascular changes, clinical trials investigating the effects of xenon with respect to myocardial function in a large patient population are not available yet. Aim of this second multicenter study was to evaluate the effect of xenon anesthesia on left ventricular function, which was investigated by transesophageal echocardiography (TEE), compared with the volatile anesthetic isoflurane.

Materials and Methods

The study was designed as a multicenter, randomized, single-blind trial at six European centers. The protocol was approved by all six institutional ethical committees, and all patients gave written informed consent before participation in this trial.

Patients

The second xenon multicenter study by our group was conducted in a patient population, different from the population of the first multicenter trial.[13] Eligible were adult patients from the departments of surgery, gynecology, urology, traumatology, or orthopedics undergoing elective surgery. Each center recruited their patients in accordance with a pregenerated randomization list (Rancode 3.6 Professional; IDV, Gauting, Germany) using a block design (block size: n = 4) generated on a center-by-center basis. Based on a power analysis, a sample size of n = 90 with the constellation $\alpha = 0.001$ and $\beta = 90\%$ was calculated. Because the number of evaluable TEE cases was unknown before the start of the study, the target number was 32 patients per center (total number = 192). Furthermore, the randomization list enabled to include up to a maximum of 48 patients at each center if video tapes of TEE examination could not be analyzed.

Patients were enrolled in this study on the day before the scheduled surgical intervention. The patients had to meet the following inclusion criteria: age ≥ 18 yr, American Society of Anesthesiologists physical status I or II, elective surgery, male sex, or female patients of nonchildbearing potential or with adequate contraception, patients without cardiac disease, and planned duration of anesthesia of approximately 2 h.

Exclusion criteria were refusal of patient to undergo TEE or specific contraindications against TEE, participation at another study, increased intracranial pressure, alcohol or drug abuse, myocardial infarction within 6 months before anesthesia, history of cardiac disease assessed by the revised cardiac risk index,[17] cardiac abnormalities during first TEE examination, stroke within 12 months, adrenal insufficiency, diabetes mellitus, and chronic obstructive pulmonary disease.

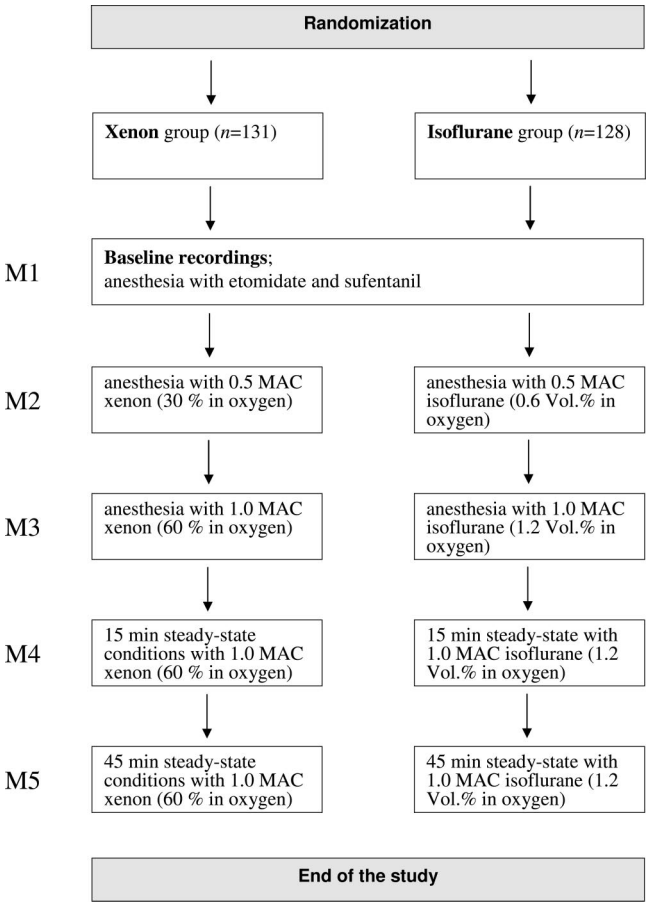

Fig. 1. Flow diagram of the study protocol. MAC = minimum alveolar concentration.

Patients could be withdrawn from the study for the following reasons: impossibility to place the TEE probe or abnormal cardiac findings, unforeseen complications in terms of surgery and/or TEE, withdrawal of consent, intraoperative complications, and/or serious adverse events (*i.e.*, bleeding, pulmonary embolism, death).

Protocol

Patients were premedicated with midazolam 1 h before anesthesia. Using the standard monitoring system of the respective center (continuous registration of electrocardiogram, pulse oximetry, relaxometry, Bispectral Index, and noninvasive measurement of blood pressure every 5 min), anesthesia was induced in all patients using 0.15–0.4 mg/kg etomidate and 0.3–0.5 μg/kg sufentanil. Tracheal intubation was facilitated by 0.1–0.2 mg/kg cisatracurium. Anesthesia was primarily maintained with continuous administration of etomidate in doses ranging between 0.1 and 0.8 $mg \cdot kg^{-1} \cdot h^{-1}$. After tracheal intubation and at least 5 min of steady state conditions, the TEE probe was inserted and the first echocardiographic measurements (baseline; M1) were performed (fig. 1).

After completion of echocardiography, anesthesia was supplemented by 0.5 minimum alveolar concentration

(MAC) xenon (30% in oxygen) or isoflurane (end-tidal concentration, 0.5 MAC [0.6 vol%] isoflurane in oxygen), respectively, using a closed-circuit anesthesia system (Physioflex; Draeger, Lübeck, Germany). Reaching a 5-min steady state (stable concentrations of the respective anesthetic gas) under these conditions, the second TEE examination was performed (M2). Subsequently, anesthesia was deepened by increasing xenon concentrations to 1 MAC (60%) or isoflurane concentration to 1 MAC (1.2 vol%), respectively, and continuous administration of etomidate was stopped. After 5 min of steady state, the next TEE examination was performed (M3), as well as after 15 min (M4) and 45 min (M5).

If maintenance of anesthesia was considered insufficient, as indicated by an increase in systolic blood pressure and heart rate by more than 20% from baseline or Bispectral Index greater than 60, 10 μg sufentanil was intravenously injected, which could be repeated every 3 min.

After completion of the study protocol, anesthesia was maintained in the respective groups with the randomized anesthetics (isoflurane or xenon, respectively). All measurements were performed before initiating the surgical procedure.

Transesophageal Echocardiography

Primary target criterion for assessment of the left ventricular contractility before and during administration of the respective anesthetics was the so-called contractile index (CI), evaluated using TEE.[18] After a routine cardiac examination to exclude cardiac diseases, a transgastric transducer position was used to image the left ventricle (LV) at midpapillary level in a short axis view with a transducer position of 0°. Meticulous care was taken to obtain an almost circular shape of the LV with clear visualization of the endocardial and epicardial borders. At least five consecutive heartbeats of the LV cross-sectional view were documented for subsequent analysis. After recording the short axis view, the image plane of the transducer was rotated to 110°–140° to image the LV outflow tract. A continuous wave Doppler was directed parallel to the direction of blood flow through the LV outflow tract to measure blood velocity. The Doppler profile was recorded for at least five consecutive beats. Both transgastric recordings were obtained at the above described time points.

Left ventricular end-systolic and end-diastolic frames were analyzed to obtain the variables specified below. Each measurement was performed three times using three cardiac cycles in both echocardiographic core centers (total of six measurements for each variable). Values for each variable are expressed as mean values calculated from all six measurements.

The endocardial borderline was traced at the end of systole and of diastole in between the endocardial borderzone; the papillary muscles were excluded. Left ventricular end-systolic area (LVESA) and left ventricular end-diastolic area (LVEDA) were measured in units of cm^2, whereas the end-systolic and end-diastolic circumference (LVESC and LVEDC) were measured in cm.

Total left ventricular area (AT; cm^2) was measured at the end of systole as the total area included by the epicardial border. Cardiac cycle length (RR; ms) and LV ejection time (LVET; ms) were measured in the Doppler tracings obtained in the LV outflow tract. Using these measurements, the following parameters were calculated:

$$\text{FAC} = \text{fractional area contraction} = \frac{\text{LVEDA} - \text{LVESA}}{\text{LVEDA}} \cdot 100 \quad [\%]$$

$$\text{CFS} = \text{circumferential fiber shorting} = \frac{\text{LVEDC} - \text{LVESC}}{\text{LVEDC}} \cdot 100 \quad [\%]$$

$$\text{LVESWS} = \text{left ventricular end systolic wall stress} = 1.35 \cdot \text{RR}_{\text{sys}} \cdot \frac{\text{LVESA}}{\text{AT} - \text{LVESA}} \quad [\text{g}/\text{cm}^2]$$

$$\text{VCFc} = \text{rate corrected velocity of fiber shortening} = \frac{\text{LVEDC} - \text{LVESC} \cdot \sqrt{\text{RR}/40}}{\text{LVEDC} \cdot \text{LVET}/40} \quad [\text{circ}/\text{s}]$$

Left ventricular contractility was evaluated by analyzing the relation between VCFc and LVESWS for both treatment groups. Using the data of M1, a linear regression equation between VCFc and LVESWS was calculated separately for both treatment groups:

$$\text{VCFc} = a \cdot \text{LVESWS} + b$$

The regression analysis for isoflurane ($a = -0.0012$; $b = 0.2956$; and $r = 0.539$) as well as xenon ($a = -0.0011$; $b = 0.2901$; and $r = 0.539$) showed significant results ($P < 0.0001$).

The VCFc/LVESWS data obtained at measurement times M2–M5 were compared with this line of regression obtained at baseline. For each LVESWS value measured at times M2–M5, the expected VCFc value was calculated according to the following formula:

$$\text{VCFc}_{\text{expected}} = a \cdot \text{LVESWS} + b$$

The difference between actual VCFc and $\text{VCFc}_{\text{expected}}$ was calculated as follows:

$$\Delta\text{VCFc} = \text{VCFc} - \text{VCFc}_{\text{expected}}$$

$$\Delta\text{VCFc} \ \% = \frac{\Delta\text{VCFc}}{\text{VCFc}_{\text{expected}}} \cdot 100 \quad [\%]$$

For both groups, the following equations were used to calculate ΔVCFc:

$$\text{Isoflurane}: \Delta\text{VCFc} = \text{VCFc} - \left(-0.0012 \cdot \text{LVESWS} + 0.2956\right)$$

$$\text{Xenon}: \Delta\text{VCFc} = \text{VCFc} - \left(-0.0011 \cdot \text{LVESWS} + 0.2901\right)$$

A positive ΔVCFc value indicates an increase in LV contractility (as compared with baseline measurements), whereas a negative ΔVCFc value shows a decrease. Therefore, ΔVCFc was interpreted as CI with respect to the baseline measurements.

All videotapes were reviewed by two independent cardiologists in the echocardiographic core centers (Hamburg and Aachen) with respect to overall image quality and evaluability. During the complete process of data analysis, the echocardiographic core centers were blinded against the used anesthetics and to the results of each other. If two-dimensional image quality did not allow an adequate delineation of endocardial and epicardial boundaries (at end-diastole and end-systole) or if Doppler tracings did not allow determination of onset and offset of blood flow through the LV outflow tract, the corresponding patient was excluded from the study. In case of different opinions of the echocardiographic core centers, videotapes were reviewed together by both cardiologists for a second time to come to a unanimous decision. All videotapes that did not meet the above quality criteria were excluded from the evaluation.

The quantities of administered anesthetic agents as well as hemodynamic and respiratory parameters were chosen as secondary endpoints. In addition, the incidences of adverse events were documented. An adverse event was defined as any undesirable and unintended medical event, such as alterations in cardiovascular functions (*e.g.*, severe hypotension, arrhythmia, ST elevation), postoperative nausea and vomiting, hyperthermia, shivering, and so on. Hypertension was defined as an increase in systolic blood pressure greater than 20% despite three boluses of 10 μg sufentanil concomitant with a stable heart rate and no other signs of low depth of anesthesia, such as sweating. Hypotension and bradycardia were defined as a change of greater than 20% from baseline.

Statistical Analysis

The analysis of data ensued by means of the double-entry procedure (data entry by two independent assistants into two separate databases, followed by a subsequent computerized examination), to ensure a high level of data integrity.

With exception for the primary endpoint, all tests, either between-group or within-group comparisons, were classified as exploratory and therefore did not undergo any α adjustments or potential multiple testing. The following test methods were used for the between-group comparisons: interval/proportional scales: Peto–Wilcoxon tests for the stratified situation (centers as strata), Wilcoxon–Mann–Whitney U test; ordinal scales: Mantel–Haenszel test; nominal scales: 2 × 2 tables with continuity correction. All test results were interpreted two-sided. Apart from *P* values, confidence intervals (95%) were used to interpret the results.

Table 1. Biometric Data

	Xenon (n = 131)	Isoflurane (n = 128)	*P* Value
Age, yr	47.6 ± 13.9	46.9 ± 13.1	0.6238
Height, cm	172 ± 9	172 ± 9	0.5917
Weight, kg	75 ± 13	75 ± 14	0.4347
Sex, male/female	63/68	62/66	0.9435
ASA physical status, I/II	71/60	63/65	0.4567
Intubation time, min	6.3 ± 3.4	6.1 ± 2.7	0.5176
Incision time, min	63.0 ± 33.4	63.1 ± 32.0	0.9102
Duration of anesthesia, min	127.9 ± 74.0	119.7 ± 79.0	0.2112

Data are shown as mean ± SD.

ASA = American Society of Anesthesiologists; incision time = time from induction of anesthesia to start of operation; intubation time = time from induction of anesthesia to endotracheal intubation.

Results

From July 2000 to September 2001, a total of 259 patients were enrolled in this clinical trial, of which 252 completed the study according to the protocol. Seven patients were withdrawn from the study because of impossible TEE measurements (n = 5; 2 in the xenon group and 3 in the isoflurane group), withdrawal of consent before the study (n = 1 in the xenon group), and one serious adverse event (xenon group, details under "Adverse Events").

Patients' characteristics showed no significant differences regarding age, height, weight, sex distribution, or American Society of Anesthesiologists physical status (table 1). Furthermore, the times to intubation and incision as well as the duration of anesthesia were comparable in both groups. The anesthetic requirement was greater in the xenon group, with the xenon group requiring significantly more sufentanil than the isoflurane group (0.82 ± 0.40 *vs.* 0.62 ± 0.24 μg/kg; $P < 0.0001$).

Cardiovascular Effects of Xenon and Isoflurane

Baseline recordings of hemodynamic parameters showed comparable results for systolic blood pressure as well as heart rate in both groups (table 2). Systolic blood pressure decreased significantly during isoflurane administration ($P < 0.0001$), whereas in the xenon group, a biphasic course was observed. After a slight but signifi-

Table 2. Hemodynamic Data

	Group	M1	M2	M3	M4	M5
Heart rate, beats/min	Xenon (n = 131)	65 ± 11	57 ± 9*	53 ± 9*	52 ± 9*	56 ± 12*
	Isoflurane (n = 128)	68 ± 16	63 ± 11*†	67 ± 13†	64 ± 11*†	65 ± 10†
RR systolic, mmHg	Xenon (n = 131)	128 ± 19	119 ± 19*	117 ± 19*	126 ± 20	138 ± 21*
	Isoflurane (n = 128)	126 ± 23	106 ± 18*†	97 ± 15*†	95 ± 15*†	99 ± 18*†
LVESA, cm^2	Xenon (n = 87)	7.8 ± 2.3	8.0 ± 2.3	8.5 ± 2.7*	8.7 ± 2.7*	8.7 ± 2.5*
	Isoflurane (n = 90)	7.7 ± 2.6	7.8 ± 2.4	8.4 ± 2.6*	8.5 ± 2.7*	8.2 ± 2.5*
LVEDA, cm^2	Xenon (n = 87)	17.1 ± 4.0	17.2 ± 3.8	18.0 ± 4.5*	18.3 ± 4.2*	19.3 ± 6.5*
	Isoflurane (n = 90)	17.0 ± 4.3	17.0 ± 4.0	17.0 ± 4.2	17.4 ± 4.3	17.6 ± 3.8
CFS, %	Xenon (n = 87)	32.6 ± 6.1	32.3 ± 6.0	32.1 ± 5.9	31.9 ± 6.7*	32.3 ± 5.7
	Isoflurane (n = 90)	33.2 ± 6.4	33.0 ± 6.4	30.5 ± 5.7*	31.0 ± 6.2*	32.3 ± 6.3*
FAC, %	Xenon (n = 87)	54.3 ± 8.0	53.5 ± 8.6	53.0 ± 7.9*	52.7 ± 8.6*	54.1 ± 8.0
	Isoflurane (n = 90)	54.8 ± 8.8	54.0 ± 7.5	51.0 ± 8.0*	51.7 ± 8.4*	53.5 ± 8.2
LVESWS, g/cm^2	Xenon (n = 87)	69.2 ± 22.4	64.6 ± 18.6	67.2 ± 20.5	73.4 ± 24.7	77.8 ± 23.3*
	Isoflurane (n = 90)	66.2 ± 20.7	57.8 ± 17.7*†	56.0 ± 18.5*†	55.0 ± 17.5*†	54.6 ± 15.8*†
VCFc, circ/s	Xenon (n = 87)	0.213 ± 0.046	0.216 ± 0.039	0.212 ± 0.038	0.203 ± 0.044*	0.203 ± 0.038*
	Isoflurane (n = 90)	0.214 ± 0.047	0.212 ± 0.042	0.193 ± 0.039*	0.197 ± 0.043*	0.198 ± 0.041*
ΔVCFc	Xenon (n = 87)	ND	−0.0036 ± 0.035	−0.0048 ± 0.029	−0.0065 ± 0.034	0.0016 ± 0.034
	Isoflurane (n = 90)	ND	−0.014 ± 0.037*†	−0.036 ± 0.033*†	−0.033 ± 0.037*†	−0.032 ± 0.034*†

Data are shown as mean ± SD.

* $P < 0.05$ *vs.* M1. † $P < 0.0.5$ *vs.* xenon.

CFS = circumferential fiber shorting; FAC = fractional area change; LVEDA = left ventricular end-diastolic area; LVESA = left ventricular end-systolic area; LVESWS = left ventricular end-systolic wall stress; ND = not defined; RR = blood pressure; VCFc = velocity of fiber shortening; ΔVCFc = contractile index.

cant decrease at M2 and M3, systolic blood pressure increased at the end of the investigation significantly. Heart rate showed a different pattern as it decreased significantly only in the xenon group ($P < 0.0001$). In the xenon group, significantly more cases of bradycardia and hypertension were observed ($P < 0.05$) compared with the isoflurane group (table 3).

All TEE records were analyzed by two independent, blinded cardiologists who decided whether the videotapes met sufficient evaluation criteria as described above. Both cardiologists completely agreed on the evaluable videotapes, and based on their decisions, 82 of 259 patients were finally excluded because of technically inadequate examinations (for criteria, see Materials and Methods). Using this procedure, all enclosed TEE examinations fulfilled the same high level of quality. The number of patients enrolled in this study and the number of TEE recordings usable for evaluation are shown for each center in table 4.

Left ventricular end-systolic area as well as LVEDA areas were comparable in both groups at M1 (table 2). Left ventricular end-systolic area increased in both groups significantly to the same extent. LVEDA increased slightly during isoflurane administration, whereas patients treated with xenon showed a continuous and significant increase ($P < 0.0001$).

Circumferential fiber shorting decreased significantly in the xenon patients from M1 to M4 ($P < 0.0383$) and reached the baseline level again at M5. In contrast, the decrease of circumferential fiber shorting was more pronounced in the isoflurane group ($P < 0.0001$ at M3). FAC showed only a slight decrease up to M4 in the xenon group but reached baseline levels again at M5. In patients anesthetized with isoflurane, FAC decreased significantly from M1 to a minimum at M3 ($P < 0.0001$). At M4 and M5, FAC increased but did not reach baseline values.

Left ventricular end-systolic wall stress was comparable in both groups at M1. In the xenon group, a significant increase at M5 was noted ($P < 0.0001$). In contrast, during administration of isoflurane, LVESWS

Table 3. Adverse Events

	Xenon (n = 131)	Isoflurane (n = 128)
PONV	36*	16
Hypertension	19*	6
Hypotension	2*	74
Bradycardia	8*	4
Shivering	11	12

Data are shown as number of patients with adverse events.

* $P < 0.05$ *vs.* isoflurane.

PONV = postoperative nausea and vomiting.

Table 4. Numbers of Patient Recruitment and of Evaluable TEE Recordings

Center	Patient Recruitment, n	TEE Recordings, n
Aachen	39	32
Hamburg	48	30
Kiel	37	28
Münster	39	30
Rotterdam	48	31
Vienna	48	26
Total	259	177

TEE = transesophageal echocardiography.

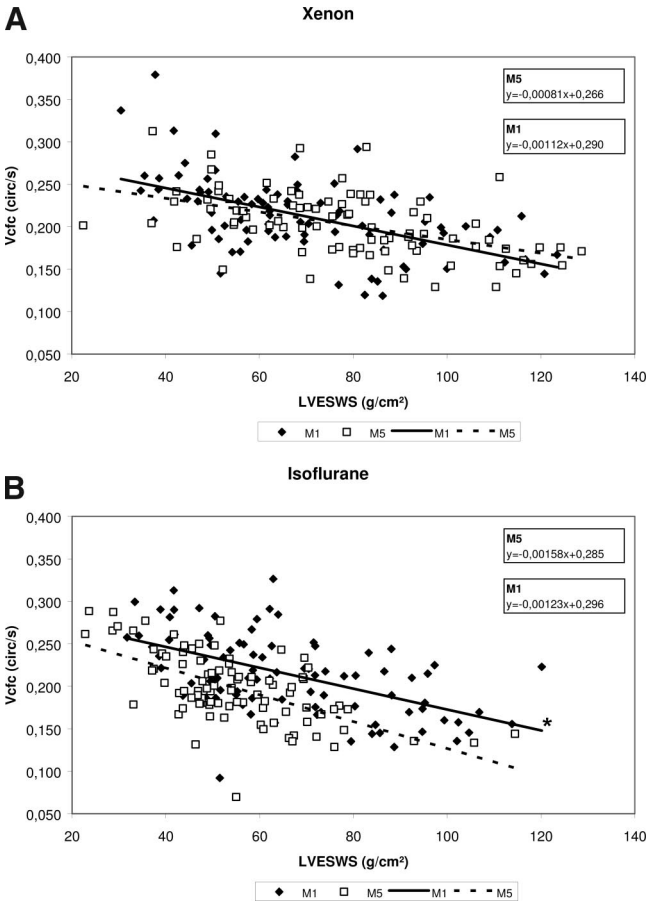

Fig. 2. Correlations between velocity of circumferential fiber shortening (VCFc) and left ventricular end-systolic wall stress (LVESWS) at time M1 (baseline; immediately after induction of anesthesia, 5 min of steady state) and M5 (administration of xenon (*A*) or isoflurane (*B*), respectively, for 45 min in a concentration of 60%) in patients anesthetized with xenon (*A*) or isoflurane (*B*), respectively. * $P < 0.0001$ M5 *versus* M1.

decreased significantly ($P < 0.0001$). VCFc showed no differences between both groups at M1. After xenon, a significant decrease at M4 and M5 was observed. In the isoflurane patients, VCFc was significantly decreased at M3–M5 compared with baseline values.

According to the regression equation at baseline, each LVESWS value during either isoflurane or xenon corresponds to an expected VCFc value. The difference between expected VCFc and actually measured VCFc was interpreted as the contractile index (ΔVCFc). During administration of xenon, ΔVCFc was stable, indicating an unaltered contractility of the LV throughout the study period (fig. 2A shows the results at M5). In contrast, the line of regression between VCFc and LVESWS shifted downward with respect to the baseline measurements during administration of isoflurane (fig. 2B shows the results at M5). The CI in the isoflurane group was significantly decreased at all time points compared with the baseline and xenon values ($P < 0.0001$) (fig. 3).

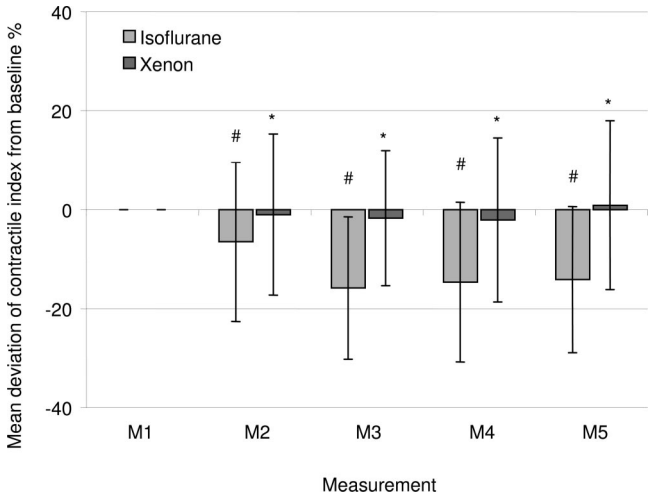

Fig. 3. Contractile index (Δ of velocity of circumferential fiber shortening [ΔVCFc]), shown as deviation from baseline at time points M2–M5 in percent (for definition of time points, see table 1). M2: Anesthesia with 0.5 minimum alveolar concentration (MAC) xenon (30% in oxygen) or 0.5 MAC isoflurane (0.6 vol% in oxygen), respectively. M3: Anesthesia with 1 MAC xenon (30% in oxygen) or 1 MAC isoflurane (1.2 vol% in oxygen). M4: 15 min steady state conditions with 1 MAC xenon or isoflurane. M5: 45 min steady state conditions with 1 MAC xenon or isoflurane. * $P < 0.0001$ *versus* isoflurane. # $P < 0.0001$ *versus* M1.

Adverse Events

The overall incidence of adverse events was 72% in all patients, without differences between the total rates in both groups (table 3). Only in one case was a serious adverse event documented (transient decrease of oxygen saturation); this patient had received xenon according to the study protocol. Significantly more cases of postoperative nausea and vomiting were observed in the xenon group ($P < 0.05$). In contrast, in the isoflurane patients, significantly more hypotensive episodes were registered compared with xenon ($P < 0.05$).

Discussion

The results of this multicenter trial demonstrate that in patients without cardiac diseases who are undergoing elective noncardiac surgery, xenon enables favorable conditions for anesthesia compared with the volatile anesthetic isoflurane. Global hemodynamic as well as echocardiographic parameters of xenon patients were more stable throughout the study than in patients anesthetized with isoflurane. Furthermore, in patients receiving isoflurane, the contractile index, as an independent indicator of LV contractility, decreased significantly, whereas the CI was unaltered in the xenon group.

Volatile anesthetics present numerous side effects, such as alterations in cardiovascular function or respiratory depression. Xenon, in contrast, was considered to be cardiovascularly inert.[13] Although the anesthetic properties of xenon have been known for more than 50 yr,[19] an increasing interest has emerged since 1990,

when the effects of xenon on the circulatory and respiratory systems were investigated for the first time.[20] In this latter study, changes in blood pressure were significantly greater throughout the study period in the nitrous oxide group than in the xenon group, and xenon patients required less analgesic supplementation, indicating that xenon is a potent and effective anesthetic. Furthermore, it could be demonstrated that plasma adrenaline and cortisol levels increased in the nitrous oxide group but did not change in the xenon group, underlining the favorable hemodynamic effects of the latter.[14]

Numerous experimental studies have focused on the hemodynamic effects of xenon. In isolated rat hearts, the effects of xenon, nitrous oxide, and nitrogen on cardiac function were compared.[7] Gas exposure in all groups significantly decreased oxygen delivery, coronary perfusion pressure, and LV pressure. However, neither xenon nor nitrous oxide caused further cardiac depressant effects compared with nitrogen.

Furthermore, in guinea pig heart preparations, atrioventricular conduction time, LV pressure, and cardiac efficiency were not altered by xenon.[8] In isolated cardiomyocytes, the amplitudes of the Na^+, the L-type Ca^{2+}, and inward-rectifier K^+ channels remained unchanged over a range of voltages during administration of xenon, indicating that xenon has no important physiologic effects on the heart. In human atrial myocytes, volatile anesthetics exhibited inhibitory effects on voltage-gated cardiac Ca^{2+} and K^+ currents, which are likely of pathophysiologic relevance.[9] In contrast, xenon exerts no effect on Ca^{2+} currents and only slightly inhibited transient K^+ outward currents. In ventricular muscle bundles from guinea pig hearts, it could be demonstrated that in contrast to volatile anesthetics, xenon does not affect myocardial contractility or physiologic responses to inotropic and chronotropic stimuli.[10]

In pigs anesthetized with xenon, global hemodynamic responses as well as plasma concentrations of dopamine and noradrenaline remained within normal limits, whereas adrenaline concentrations were reduced.[11] Direct effects on myocardial function during global and regional administration of xenon were examined in the dog heart *in vivo*.[12] No changes of global hemodynamics, coronary blood flow, and regional myocardial function in the left anterior descending coronary artery–dependent myocardium were observed. Regional administration of 50% xenon to the left anterior descending coronary artery–dependent myocardium had no significant effect on regional myocardial function. However, 70% xenon reduced systolic wall thickening and mean velocity of systolic wall thickening in the area perfused by the left anterior descending coronary artery significantly, indicating a small direct negative inotropic effect. In the comparative group of dogs receiving isoflurane, global hemodynamic parameters were significantly altered. Furthermore, the negative inotropic effect on the myocardium was more pronounced compared with xenon.

Volatile anesthetics can protect myocardial tissue against reperfusion injury. *In vivo* investigations showed that also xenon, when administered during early reperfusion after occlusion of a coronary artery, significantly reduced the infarct size.[21] Therefore, the authors speculated that xenon might be beneficial especially in patients with cardiac diseases and/or undergoing cardiac surgery.

In an early clinical study in healthy patients, short-term administration of xenon showed that the FAC of the LV remained unchanged.[15] In this investigation, FAC was used as an indicator for global LV function. However, most TEE parameters are dependent on heart rate, preload, or afterload, respectively. Therefore, it is necessary to stabilize all variables that might influence myocardial function and also necessary to build up a parameter that is independent from other variables. To avoid the abovementioned influences, we designed an independent parameter, the so-called CI, which is defined as the difference between the expected VCFc and measured VCFc (ΔVCFc). During isoflurane administration, there was a significant decrease of the CI by 15.8% compared with a decrease of only 1.7% in the xenon group. Therefore, isoflurane significantly decreases LV contractility, whereas contractility is virtually unchanged during xenon administration. Furthermore, hemodynamic parameters such as mean arterial pressure remained stable in the xenon group, whereas using isoflurane, mean arterial pressure decreased significantly. Only heart rate showed a significant reduction in the xenon group compared with the isoflurane group. This effect of xenon was explained by an enhanced baroreflex-mediated increase of the vagal tone and/or a reduced activation of the adrenal medullary system.[14] These results underline the findings from the first multicenter trial on xenon.[13] In this trial, it has been shown that hemodynamics and respiratory parameters remained stable throughout administration of both xenon and isoflurane, with unambiguous advantages for the xenon group. In both multicenter trials, patients without an increased cardiac risk were investigated. However, regarding the results from this study, it could be clearly demonstrated that xenon has no negative effect on myocardial function. Therefore, it could be hypothesized that xenon would also enable a high grade of cardiovascular stability in patients with cardiac diseases, as has been shown in a case report.[22]

However, until now only limited data regarding this question have been available. In rabbits with chronically compromised LV function, xenon produced a slight negative inotropic action, but this effect was minor compared with isoflurane.[23] In isoflurane-anesthetized dogs

with dilated cardiomyopathy, administration of xenon did not alter myocardial function.[24]

Whether xenon enables hemodynamic stability in patients with cardiac diseases was first tested in patients who had undergone aortocoronary bypass surgery.[16] However, in this study, xenon was used only for sedation in the postoperative period. Under these conditions, xenon enabled cardiovascular stability, but concentrations administered in these patients were approximately 27%, which is far below anesthetic requirements.

In a recent study, patients with heart failure who were scheduled to undergo implantation of a cardioverter–defibrillator were anesthetized with xenon.[25] Xenon provided stable hemodynamics in this study, and in contrast to propofol, LV afterload increased without decreasing the ejection fraction. The authors speculated that xenon might be a promising anesthetic for patients with LV dysfunction; which had to be proved in larger trials. In contrast, in high-risk patients undergoing elective aortic surgery, no significant differences regarding myocardial performance, myocardial contractility, or laboratory parameters were found between xenon and total intravenous anesthesia.[26]

The overall rate of adverse events was comparable between both groups. Whereas cardiovascular alterations were increased during isoflurane administration, postoperative nausea and vomiting (PONV) occurred distinctly more frequently in the xenon group, and it must be questioned whether xenon *per se* increases the risk for PONV. However, PONV has a multifactorial origin with an incidence of approximately 30%.[27] Several risk factors are known that can lead to higher PONV rates, such as surgery-, anesthesia-, and patient-related problems. Interestingly, the differences in the PONV rates between both study groups are in contrast to the results from the first multicenter trial, where no differences were observed.[13] This might be explained by the fact that in the current study, xenon patients received higher doses of sufentanil, and significant side effects of opioids are nausea and vomiting.[28] Furthermore, epidemiologic studies on the incidence of PONV require a much larger number of patients to be included as well as a more defined study population.

A relevant limitation of this study might be a difference in the depth of anesthesia. Thus, patients of the xenon group required significantly higher doses of sufentanil than patients receiving isoflurane. This might have induced an increased liberation of endogenous catecholamines leading to an improved myocardial contractility. However, heart rate was lower during xenon administration, and Bispectral Index levels during anesthesia were comparable in both groups (32.3 *vs.* 34.7).

In contrast to the first multicenter study of our group,[13] patients from the xenon group received significantly more sufentanil than patients from the isoflurane group. In the current study, supplemental sufentanil administration was permitted by decision of the anesthesiologist in case of insufficient anesthesia based on clinical parameters such as a decrease in mean arterial pressure. However, in the first multicenter trial, significantly lower concentrations of isoflurane (in combination with nitrous oxide) were administered; under these conditions, a lower incidence of hypotensive events was observed. Regarding the much higher rates of hypotension in the isoflurane group in this study, it is therefore tempting to speculate that the respective anesthesiologists used lower doses of sufentanil to avoid a further reduction of blood pressure.

The results of this multicenter trial indicate that in patients without cardiovascular diseases, administration of xenon provides hemodynamic stability and does not reduce contractility. In contrast, the volatile anesthetic isoflurane led to a significant decrease of the contractile index. Therefore, xenon enables favorable anesthetic conditions in healthy patients, and future studies should prove whether xenon might be also beneficial in patients with myocardial dysfunction.

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