Xenon Does Not Increase Heart Rate–corrected Cardiac QT Interval in Volunteers and in Patients Free of Cardiovascular Disease

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ABSTRACT

Background: Impaired cardiac repolarization, indicated by prolonged QT interval, may cause critical ventricular arrhythmias. Many anesthetics increase the QT interval by blockade of rapidly acting potassium rectifier channels. Although xenon does not affect these channels in isolated cardiomyocytes, the authors hypothesized that xenon increases the QT interval by direct and/or indirect sympathomimetic effects. Thus, the authors tested the hypothesis that xenon alters the heart rate–corrected cardiac QT (QTc) interval in anesthetic concentrations.

Methods: The effect of xenon on the QTc interval was evaluated in eight healthy volunteers and in 35 patients undergoing abdominal or trauma surgery. The QTc interval was recorded on subjects in awake state, after their denitrogenation, and during xenon monoanesthesia ($F_{et}Xe > 0.65$). In patients, the QTc interval was recorded while awake, after anesthesia induction with propofol and remifentanil, and during steady state of xenon/remifentanil anesthesia ($F_{et}Xe > 0.65$). The QTc interval was determined from three consecutive cardiac intervals on electrocardiogram printouts in a blinded manner and corrected with Bazett formula.

Results: In healthy volunteers, xenon did not alter the QTc interval (mean difference: +0.11 ms [95% CI, −22.4 to 22.7]). In patients, after anesthesia induction with propofol/remifentanil, no alteration of QTc interval was noted. After propofol was replaced with xenon, the QTc interval remained unaffected (417 ± 32 ms *vs.* awake: 414 ± 25 ms) with a mean difference of 4.4 ms (95% CI, −4.6 to 13.5).

Conclusion: Xenon monoanesthesia in healthy volunteers and xenon/remifentanil anesthesia in patients without clinically relevant cardiovascular disease do not increase QTc interval. **(Anesthesiology 2015; 123:542-7)**

ANESTHETIC properties of xenon have been known for more than 50 yr.[1] Because of its very low solubility in blood and brain as well as a lack of metabolism, xenon has been considered to be an almost ideal anesthetic.[2] Because of its low solubility, xenon is characterized by a high minimum alveolar concentration of 50 to 70%, which allows for monoanesthesia before surgery but requires additional analgesia during surgical stimulation.

In contrast to halogenated inhalative anesthetics, xenon maintains sympathetic activity while norepinephrine reuptake is even slightly decreased, so that cardiac output and arterial pressure are stable during xenon-based anesthesia.[3] Because perioperative arterial hypotension is associated with increased morbidity and mortality,[4–6] patients at risk for perioperative cardiovascular events may benefit from xenon-based anesthesia by avoiding arterial hypotension. At the same time, many of these high-risk patients are at risk for critical ventricular arrhythmias. Many anesthetics and/or analgesics may provoke polymorphic ventricular tachycardia such as torsade-de-pointes tachycardia by altering cardiac repolarization. Prolongation of the heart rate–corrected cardiac QT (QTc) interval is a commonly accepted indicator for

What We Already Know about This Topic

- Many anesthetics may provoke polymorphic ventricular tachycardia by altering cardiac repolarization
- Prolongation of the heart rate–corrected cardiac QT (QTc) interval is a commonly accepted indicator of the risk of polymorphic ventricular tachycardia
- Because xenon maintains sympathetic activity and slightly decreases norepinephrine uptake and sympathetic activation in general is thought to increase the QTc interval, the effects of xenon on cardiac repolarization and QTc interval was determined in 8 volunteers and 35 patients

What This Article Tells Us That Is New

- No prolongation of cardiac QT intervals was observed in volunteers during xenon monoanesthesia or in patients without preexisting long QT syndrome during xenon-based anesthesia

This article has been presented at the Annual Meeting of the American Society of Anesthesiologists in Chicago, Illinois, on October 17, 2011 (Xenon-based anesthesia does not alter QT interval), and at the Annual Meeting of the European Society of Anaesthesiology "euroanaesthesia" in Paris, France, on June 12, 2012 (The influence of xenon anesthesia on QTc interval).

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the risk of polymorphic ventricular tachycardia.[7] Although there is lack of evidence of a critical threshold value, prolongation of the QTc interval by more than 20 ms from baseline or absolute values of more than 500 ms are considered clinically relevant.[7–9] Because the effects of xenon on cardiac repolarization and the QTc interval are unknown, we tested the hypothesis that xenon in anesthetic concentrations alters the QTc interval.

Materials and Methods

After obtaining local institutional review board approval (Ethikkommission der Medizinischen Fakultät der Heinrich-Heine Universität, Düsseldorf, Germany, Ref. No.: MO-LKP-394+3386 and Ethikkommission der Ärztekammer Berlin, Germany, Ref. No.: ETH-019/08) and a written informed consent from all participants in the study, xenon-based anesthesia was evaluated in eight healthy volunteers (Eudra CT No.: 2009-012449-48, ClinicalTrials.gov Identifier: NCT01043419), and in a clinical observational study including 35 patients (German Federal Institute for Drugs and Medical Devices [BfArM] study number AL-PMS-01/07GER) subject to xenon-based anesthesia.

Volunteers

The data presented in the study are secondary outcome variables of a previously published clinical trial.[3] Eight nonpremedicated healthy and normotensive volunteers were included in this study in January and February of 2010. Inclusion criteria were age 18 to 65 yr and exclusion of any preexisting disease (American Society of Anesthesiologists class I). None of the subjects was taking prescription or nonprescription drugs. After an overnight fast, all subjects were studied in the supine resting position in the morning. After a resting accommodation period, oxygen was administered for denitrogenation ($F_{IO_2} > 0.95$, $F_{EO_2} > 0.92$) *via* a closed facemask (Classic Star®; Dräger Medical, Germany) without positive end-expiratory pressure. After the subjects' adaptation to facemask and spontaneous breathing in this closed-circuit setting, xenon monoanesthesia was induced with a targeted inspiratory xenon concentration of 70% (LENOXe®; Air Liquide Santé, France) and 30% oxygen. Surface electrocardiogram (ECG) and radial arterial pressure were recorded continuously. For the determination of QTc intervals, ECG printouts were analyzed at three standardized time points: (1) in the awake state, 5 min before denitrogenation, (2) after denitrogenation, after having reached an inspiratory oxygen fraction greater than 95%, and (3) 15 min after xenon introduction and during steady state of xenon monoanesthesia ($F_iXe > 65\%$). After completion of the study protocol, xenon administration was discontinued and subjects awoke from anesthesia.

Patients

Patients included in this postmarketing observational study assessing the safety of xenon-based anesthesia were presumed to be free of cardiovascular disease. The study comprised patients scheduled for abdominal or trauma surgery between April 2009 and February 2011. Inclusion criteria were age 18 to 65 yr, written informed consent about the study enrollment, absence of regional anesthesia, and lack of preexisting pathologic medical conditions relevant to anesthesia in the patients' history (American Society of Anesthesiologists class I to II). After an overnight fast, all subjects were studied in the supine resting position.

After oral premedication with midazolam (75 to 150 μg/kg), general anesthesia was induced and initially maintained by intravenous propofol (initial bolus of 2.5 mg/kg + continuous infusion of 6 mg kg^{-1} min^{-1}), remifentanil (0.2 μg kg^{-1} min^{-1}), and rocuronium (0.6 mg/kg). After denitrogenation ($F_{IO_2} > 0.95$), xenon administration was initiated with 70% xenon (LENOXe®; Air Liquide Santé) in oxygen. After achieving inspiratory fraction of xenon of F_iXe >0.6 and sufficient depth of anesthesia (EEG-based measurement of anesthesia depth [Narcotrend®; Narcotrend Gruppe, Germany] value of ≤30), propofol was discontinued. Noninvasive blood pressure was taken every 3 min, and surface ECG was recorded continuously. For the determination of QTc interval, ECG printouts were analyzed at three standardized time points: (1) in the awake state, 5 min before the beginning of denitrogenation, (2) 10 min after anesthesia induction with propofol and remifentanil, that is, during total intravenous anesthesia, and (3) 15 min after discontinuation of propofol, during steady state of xenon/remifentanil anesthesia (F_iXe >60) and before surgical incision.

Measurement of the QTc Interval

The QTc interval was determined from three consecutive cardiac intervals of ECG printouts (lead II, feed 50 mm/s) and corrected using the Bazett formula.[10] All analyses were performed by the same board-certified cardiologist (P.R.), who was blinded with respect to the subject and to the time point of ECG recording.

Statistics

Data were collected on logistical concerns in both clinical studies. Accordingly, no *a priori* power calculation was performed.

Statistical analysis was performed using statistical software IBM SPSS Statistics 22 (IBM Deutschland GmbH, Germany) and Stata/IC 10.0 (StataCorp LP, USA). Data are expressed as means ± SD. Differences in means of time point variables were tested by one-way repeated-measures ANOVA followed by the Newman–Keuls *post hoc* test. CIs (95%) were calculated for mean differences of QTc intervals.

The following null hypothesis was tested: means of variables are altered by xenon compared with the awake state or after propofol induction (two tailed). The null hypothesis was rejected in case of an α error of less than 0.05.

Table 1. Volunteers' and Patients' Characteristics

	Volunteers (n = 8)	Patients (n = 35)
Sex (male/female)	6/2	18/17
Age (yr)	25 ± 2	44 ± 11
BMI (kg/m^2)	23.5 ± 1.8	26.7 ± 1.8
ASA status	I	I + II

ASA = American Society of Anesthesiologists; BMI = body mass index.

Results

General cohort data of volunteers and patients are summarized in table 1.

Volunteers

All enrolled participants completed the study protocol. Denitrogenation (F_{IO_2} > 0.95) did not alter their arterial pressure or heart rate. As previously reported, xenon monoanesthesia with 63 ± 6% end-tidal concentration increased mean arterial pressure (93 ± 5 mmHg at rest *vs.* 107 ± 6 mmHg under xenon anesthesia) without any effect on the heart rate (64 ± 10 min^{-1} *vs.* 70 ± 10 min^{-1}, respectively).[3] Xenon did not change the QTc interval at any measurement time point (awake subjects: 398 ± 42 ms *vs.* after denitrogenation: 409 ± 45 ms [P = 0.55] and *vs.* xenon anesthesia: 409 ± 30 ms [P = 0.43] when compared with awake patients; fig. 1). Mean difference in QTc interval length between denitrogenation and xenon anesthesia period was +0.11 ms (95% CI, −22.4 to 22.7). All volunteers were breathing spontaneously achieving arterial normocarbia (45 ± 6 mmHg) and an arterial oxygen partial pressure of 173 ± 19 mmHg. Two of the eight volunteers experienced short-lasting nausea and vomiting immediately after awakening. Both volunteers reported a history of nausea after general anesthesia. No other adverse events were observed.

Patients

All patients enrolled in the study completed the protocol. Induction of anesthesia with propofol, remifentanil, and rocuronium decreased arterial pressure (systolic/diastolic: from 129 ± 13 mmHg/70 ± 8 mmHg to 97 ± 8 mmHg/51 ± 6 mmHg, P < 0.001) as well as heart rate (from 69 ± 11 min^{-1} to 61 ± 12 min^{-1}, P < 0.001). Administration of xenon (end-tidal concentration: 65 ± 5%) and discontinuation of propofol significantly increased arterial pressure (to: systolic/diastolic: 113 ± 13 mmHg/62 ± 8 mmHg, P < 0.001 *vs.* propofol/remifentanil) and further decreased heart rate (to: 58 ± 10 min^{-1}, P = 0.04 *vs.* propofol/remifentanil).

The average QTc interval was unchanged during propofol/remifentanil anesthesia (P = 0.06) with a mean difference of −8.5 ms (95% CI, −15.2 to −1.8). Xenon did not change the QTc interval compared with the preanesthetic baseline level (417 ± 32 ms *vs.* awake: 414 ± 25 ms, P = 0.3; fig 2), and the mean difference in individual patients being +4.4 ms (95% CI, −4.6 to 13.5).

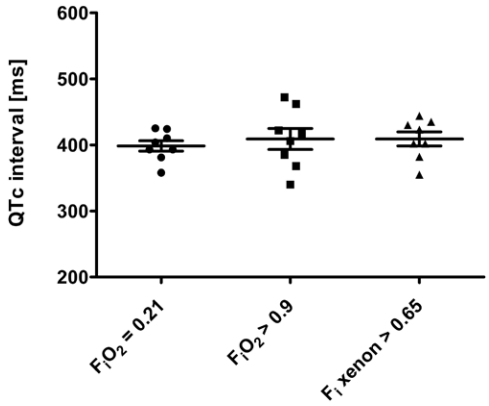

Fig. 1. Depicted are *data points* from each individual volunteer (n = 8), means and SD of heart rate–corrected cardiac QT interval awake, after denitrogenation before xenon and during xenon monoanesthesia. F_{IO_2} = inspiratory oxygen fraction; $F_I$xenon = inspiratory xenon fraction; QTc interval = heart rate–corrected cardiac QT interval.

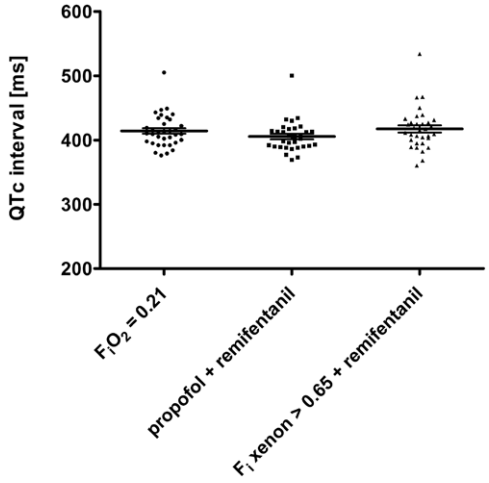

Fig. 2. Depicted are *data points* from each individual patient (n = 35), means and SD of heart rate–corrected cardiac QT interval awake, during general anesthesia with propofol/remifentanil before xenon and during xenon/remifentanil anesthesia. F_{IO_2} = inspiratory oxygen fraction; $F_I$xenon = inspiratory xenon fraction; QTc interval = heart rate–corrected cardiac QT interval.

Noteworthy was a further increase of an initially pathological QTc interval before anesthesia from 505 to 534 ms (+29 ms) in one patient during xenon/remifentanil anesthesia. The patient showed no signs of cardiac arrhythmia (fig. 2).

Postoperative nausea and vomiting occurred in 6 of the 35 patients (17%). No other adverse events were observed.

Discussion

The current study is the first to demonstrate that xenon monoanesthesia does not alter QTc interval in healthy volunteers. Moreover, our data indicate that in patients with normal QTc interval, xenon-based anesthesia does not

increase the QTc interval as compared with the awake baseline values. In summary, xenon does not prolong a normal QTc interval. Of interest is also that we did not observe any ventricular arrhythmias associated with xenon administration throughout the study.

The anesthetic effect of xenon has been discovered more than 50 yr ago, and it might be considered as an almost ideal anesthetic.[11,12] In contrast to other inhalational anesthetics, sympathetic activity is maintained during xenon anesthesia while norepinephrine reuptake even decreases slightly, which results in increased plasma norepinephrine concentrations.[3,13] This contributes to stable cardiac output and arterial pressure during xenon-based anesthesia. Although no definitive proof of arterial hypotension as a cause of increased perioperative morbidity/mortality has been scientifically demonstrated so far, hypotension is commonly considered to be an undesired side effect during an anesthetic.[4–6] Xenon-based anesthesia may facilitate achieving this goal. Whether this favorable pharmacodynamic profile of xenon is able to improve patient outcome is a matter of current investigation.[14] Both general and regional anesthetics are still an unavoidable independent risk factor of any surgical and in particular major surgical procedures. Therefore, it is of great importance to analyze potential problems and side effects of anesthetic drugs. The knowledge of potential side effects allows us to minimize the risks they pose on our patients. However, taking into consideration a comparably high and variable surgical risk, it is not trivial to demonstrate the beneficial effects of modern anesthetics (*e.g.*, desflurane) or anesthetic techniques (*e.g.*, thoracic epidurals) although clinical advantages appear obvious.[15,16] More than 3 decades after the introduction of droperidol into anesthesia practice, drug-induced long QT syndromes have been reported in association with administration of droperidol. In those cases, abnormal cardiac repolarization could be identified by a prolonged QTc interval more than 440 ms in the surface ECG.[17] Patients suffering from inherited long QT syndrome are characterized by a QTc interval longer than 500 ms.[18,19] The associated risk of critical ventricular arrhythmias and reports of several deaths after administration of more than 5 mg droperidol led to a black box warning by the U.S. Food and Drug Administration and withdrawal of droperidol from the European market.[20] Interestingly, large retrospective trials indicate that low-dose droperidol used for the treatment of postoperative nausea and vomiting in the surgical population was not associated with an increased incidence of polymorphic ventricular tachycardia or increased mortality,[21,22] most likely because of the low-dose use of droperidol. This case demonstrates the necessity to detect and recognize the effects of drugs on repolarization of cardiomyocytes, particularly in patients without cardiovascular disease and in those with preexisting repolarization abnormalities. Although large preclinical and clinical studies of the anesthetic drugs' impact on human body have clear advantages, smaller studies with well-defined outcome variables may help to identify unknown anesthetic risk factors.

Previous studies have shown that propofol does not alter QTc interval. Inhalational anesthetics, thiopental and several opioids, however, might be associated with an increase in the cardiac QT interval duration.[7] For instance, sevoflurane was shown to prolong the QTc interval in both children (414 ± 21 ms *vs.* 433 ± 28 ms, $P < 0.01$)[23,24] and adults (413 ± 19 ms *vs.* 444 ± 24 ms; $P < 0.05$).[25] The underlying mechanism is presumably a blockade of the fast-acting component of the cardiac delayed rectifier potassium channel, which is believed to be responsible for cardiac repolarization.[26,27] In contrast to high doses of fentanyl and sufentanil, remifentanil administered in doses comparable with the ones that our patients received significantly decreased the cardiac QT interval and prevented its increase in response to tracheal intubation.[28] Thus, remifentanil may mask QT interval–prolonging effects of other anesthetics. However, because xenon did not alter the QTc interval in our volunteers when given alone, it is very unlikely that such effects occur in patients. Our results are in accordance with previously published data showing no effects of xenon on those channels either in human atrial myocytes or in isolated guinea pig hearts.[29,30]

In our patient cohort, we accidentally detected a patient with a preexisting long QT syndrome and a baseline QTc interval of 505 ms. His QT interval increased further under xenon/remifentanil anesthesia. He did not have history of a cardiovascular or any other anesthesia-relevant preexisting pathological condition, did not take any regular medication, and did not develop bradycardia during xenon/remifentanil anesthesia. Unfortunately, the patient refused genetic testing, so that we were unable to find out whether his long QT interval was the result of mutation of any of the genes typically associated with the syndrome. Although xenon does not alter a normal QTc interval, this finding suggests that further studies are warranted to evaluate the potential influence of xenon on the QTc interval in patients experiencing inherited or acquired long QT syndromes.

Although sympathetic activation in general is thought to increase the QTc interval[31] and xenon is known to increase norepinephrine plasma concentrations,[3] we did not observe prolonged QTc intervals in volunteers during xenon monoanesthesia or in patients without preexisting long QT syndrome during xenon-based anesthesia. These results also suggest that indirect sympathetic activation does not increase QTc interval through a norepinephrine-dependent mechanism.

In summary, our data from both healthy volunteers and patients free of cardiovascular disease and without preexisting long QT syndrome provide clinically based support to previous *in vitro* electrophysiological findings that xenon does not alter cardiac repolarization.

Limitations of the Study

In the current study, we analyzed the effects of xenon on the QT interval in healthy volunteers and patients presumably free of cardiovascular disease. Our data cannot be directly extrapolated to predict the effects of xenon on patients with preexisting cardiac repolarization pathology.

Second, the effects of xenon on the QT interval were studied at 65% end-tidal xenon concentration only. However, it is conceivable that the effect of xenon on the QTc interval could be dose dependent and this was not analyzed in our study. Accordingly, one cannot exclude the possibility of an effect of xenon on cardiac repolarization at lower end-tidal xenon concentrations.

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Competing Interests

Dr. Reyle-Hahn has received fees for lectures from Air Liquide Medical, Düsseldorf, Germany. Dr. Kienbaum has been consulting for Air Liquide Medical, and Baxter Deutschland GmbH, Unterschleissheim, Germany. The other authors declare no competing interests.

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