Aus der Klinik für Anästhesiologie

der Heinrich-Heine-Universität Düsseldorf

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Der Einfluss des inhalativen Anästhetikums Xenon auf Anästhesie-assoziierte Risiken und die postoperative Erholung

Habilitationsschrift

zur Erlangung der Venia Legendi

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vorgelegt von

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Meiner Frau Henrika und meinem Sohn Oskar, die mir alles bedeuten.

In Andenken an Dr. med. Thomas Artur Werner.

Inhaltsverzeichnis

Präambel und Übersicht der zugrundeliegenden Originalarbeiten

In dieser kumulativen Habilitationsschrift werden Untersuchungsergebnisse aus acht Originalarbeiten diskutiert, die sich mit der Elimination sowie Interaktion des inhalativen Anästhetikums Xenon mit dem kardiovaskulären, respiratorischen und zentralen Nervensystem des Menschen auseinandersetzen. Die wissenschaftlichen Untersuchungen schließen sich inhaltlich unmittelbar an die Dissertation des Verfassers an. [1] Die den Kernaussagen der einzelnen Untersuchungen zugrunde liegenden Ergebnisse werden nachfolgend erörtert. Methodische Details und Ergebnisse sekundärer Zielvariablen sind den einzelnen Originalarbeiten im Anhang zu entnehmen.

1. Schaefer MS, Piper T, Geyer H, Schneemann J, Neukirchen M, Thevis M, Kienbaum P:
Xenon elimination kinetics following brief exposure.
Drug Testing and Analysis 2017; 9:666–670

2. Neukirchen M, Hipp J, Schaefer MS, Brandenburger T, Bauer I, Winterhalter M, Kienbaum P, Werdehausen R:
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3. Neukirchen M, Schaefer MS, Kern C, Brett S, Werdehausen R, Rellecke P, Reyle-Hahn M, Kienbaum P:
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The hip fracture surgery in elderly patients (HIPELD) study to evaluate xenon anaesthesia for the prevention of postoperative delirium: a multicentre, randomized clinical trial. British Journal of Anaesthesia 2018; 120:127–137

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European Journal of Anaesthesiology 2016; 33:750–760

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Paediatric Anaesthesia 2017; 27:1202–1209

Abkürzungsverzeichnis

aOR	adjustiertes Quotenverhältnis
BMI	Body Mass Index
CAM	Confusion Assessment Method
C_{dyn}	Dynamische Compliance
cmH_2O	Zentimeter Wassersäule
C_{stat}	Statische Compliance
CVI	Center of Ventilation Index
η	Dynamische Viskosität
*f*EIT	Funktionelle Elektroimpedanztomographie
GABA	γ-Aminobuttersäure
h	Stunde
kg	Kilogramm
mg	Milligramm
µg	Mikrogramm
min	Minute
mmHg	Millimeter Quecksilbersäule
ms	Millisekunde
NMDA	N-Methyl-D-Aspartat
P_{max}	Inspiratorischer Spitzendruck
POD	Postoperatives Delir
PONV	Postoperative Übelkeit mit oder ohne Erbrechen

POV	Postoperatives Erbrechen
P_{tp}	Transpulmonaler Druck
QTc-Intervall	Frequenzkorrigiertes QT-Intervall
R_{AW}	Atemwegswiderstand
ρ	Dichte
RR	Relatives Risiko
s	Sekunde
TIVA	Totale intravenöse Anästhesie

1. Einleitung

„Das schneidende Messer und der Schmerz sind in der Chirurgie zwei Begriffe, mit denen der Kranke nie einzeln in Berührung kommt“ schrieb 1836 der Pariser Chirurg Louis Valpeau. Neun Jahre später, am 16. Oktober 1846, ließ der Zahnarzt William Thomas Morton im Rahmen einer öffentlichen Vorführung am Bostoner Massachusetts General Hospital im Rahmen einer öffentlichen Operation eines oberflächlichen zervikalen Tumors den Patienten Gilbert Abbott durch Einatmen der Dämpfe eines mit Schwefeläther getränkten Schwamms einschlafen und erst nach erfolgreicher Beendigung der Operation wieder erwachen. Seit dieser ersten öffentlichen Vorführung, die das Dogma von Louis Valpeau widerlegte, war die Allgemeinanästhesie eng mit der Verwendung inhalativer Anästhetika verbunden.

Längst stehen jedoch nicht mehr alleinig die narkotischen Eigenschaften eines Anästhetikums im Zentrum der Aufmerksamkeit. Neben der Steuerbarkeit einer Substanz gilt es nunmehr, Interaktionen mit zentralen Organsystemen wie Kreislaufdepression und Organprotektion zu verstehen. Durch gezielten Einsatz soll eine Senkung der Patientenmorbidität und Erhöhung des Patientenkomforts erreicht werden. Konsequenterweise erweitern sich somit die Anforderungen an moderne Anästhetika, was die Suche nach dem „idealen“ Anästhetikum motiviert.

1.1 Grundlegende Mechanismen des Einflusses inhalativer Anästhetika auf anästhesie-assoziierte Risiken und die postoperative Erholung

1.1.1 Pharmakokinetik

Die pharmakokinetischen Eigenschaften inhalativer Anästhetika bedingen ihre Steuerbarkeit. Dabei bestimmt zunächst die Löslichkeit im Blut die Geschwindigkeit der Aufnahme aus der Lunge. Ist ein inhalatives Anästhetikum nur gering im Blut löslich (niedriger Blut/Gas-Verteilungskoeffizient), so wird die Partialdruckdifferenz zum Alveolarraum während einer Anästhesieeinleitung rasch ausgeglichen. Dies führt gleichzeitig auch im Gehirn zu einem raschen Ausgleich der Partialdruckdifferenzen, da die Löslichkeit im primären Zielorgan bei

den gängigen inhalativen Anästhetika mit der Löslichkeit im Blut korreliert. Neben der Geschwindigkeit des Ausgleichs von Partialdruckdifferenzen zwischen Atemluft und Wirkort ist für den Anästhesiologen im klinischen Alltag die Präzision, d.h. die Variabilität der Aufwachzeiten nach Beendigung der Applikation des Anästhetikums klinisch bedeutsam. Entscheidend hierbei ist eine Kumulation des Anästhetikums im Fettgewebe, die durch Applikationsdauer und Lipophilie der Substanz bestimmt wird. Aufgrund des interindividuell stark variierenden Körperfettgehalts nimmt daher die Präzision einer Anästhesieausleitung mit zunehmender Lipophilie des Anästhetikums deutlich ab. [2,3] Somit erwachen Patienten nach einer Anästhesie mit dem wenig fettlöslichen Desfluran im Vergleich zum lipophileren Sevofluran rascher und präziser aus der Anästhesie. [4] Weiterhin sind die Schutzreflexe der oberen Atemwege unmittelbar nach Extubation bei fast allen Patienten nach Desfluran im Gegensatz zu Sevofluran vollständig wiederhergestellt. [4] Schließlich konnte gezeigt werden, dass Patienten, die noch im Aufwachraum einen eingeschränktem Bewusstseinsstatus aufweisen, ein bis zu 12fach erhöhtes Risiko für Komplikationen wie Hypoxämie und Aspiration aufweisen. [5] Somit könnte der Einsatz rasch eliminierter Anästhetika nicht nur für die Steuerbarkeit einer Anästhesie, sondern auch für die postoperative Morbidität und Patientensicherheit entscheidend sein.

1.1.2 Interaktion mit dem kardiovaskulären System

Ausnahmslos jedes inhalative Anästhetikum interagiert mit dem kardiovaskulären System [6], wobei das häufigste Symptom die arterielle Hypotension darstellt. Ausmaß und Dauer einer bereits moderaten perioperativen Hypotension sind dabei mit der Höhe einer Troponinfreisetzung als Ausdruck eines myokardialen Schadens assoziiert [7–9]. Patienten mit einem solchen myokardialen Schaden zeigen wiederum eine vierfach erhöhte Letalität innerhalb der ersten 30 postoperativen Tage. [10] Da in einer ersten klinischen Interventionsstudie durch die konsequente individualisierte Behandlung einer intraoperativen arteriellen Hypotension die Inzidenz postoperativer Organfunktionsstörungen reduziert

werden konnte, muss ein kausaler Zusammenhang zwischen Hypotension und Morbidität, sowie bis zum Beweis des Gegenteils auch der postoperativen Sterblichkeit angenommen werden. [11]

Zur Vermeidung einer intraoperativen Hypotension ist das Verständnis der zugrundeliegenden pathophysiologischen Mechanismen essentiell: Es konnte gezeigt werden, dass die gängigen inhalativen Anästhetika wie Desfluran und Sevofluran, die die chemische Struktur eines halogenierten Kohlenwasserstoffs besitzen, die efferente sympathische Nervenaktivität dämpfen. Dadurch wird weniger vasokonstriktorisch wirkendes Noradrenalin freigesetzt und es kommt zu einer systemischen Vasodilatation. Dies sowie die damit einhergehende relative Hypovolämie verursachen regelhaft einen arteriellen Blutdruckabfall. [12] Die Hypotension wird weiterhin dadurch verstärkt, dass die baroreflektorisch vermittelte sympathische Reflexaktivierung gleichermaßen gedämpft und damit ein wesentliches System der kurzfristigen Blutdruckregulation außer Kraft gesetzt wird. [6] Da Hochrisikopatienten mit chronischen Herzerkrankungen ein selbst in Ruhe besonders aktiviertes sympathisches Nervensystem aufweisen, bewirkt die Sympathikushemmung hier häufig profunde Blutdruckabfälle.

Ein zweites relevantes Sicherheitsrisiko stellt die Interaktion des Anästhetikums mit kardialen Ionenkanälen dar: Alle inhalativen Anästhetika interagieren mit myokardialen Kaliumkanälen und beeinflussen dadurch sowohl die Repolarisation kardialer Myozyten als auch Zellen des Reizleitungssystems. [13] Diese Wirkungen können anhand einer Verlängerung der im Oberflächen-Elektrokardiogramm gemessenen QT-Zeit quantifiziert werden. [14–17] Da eine QT-Verlängerung mit lebensbedrohlichen malignen ventrikulären Arrhythmien assoziiert ist [13,18], wird der Einfluss jedes Arzneimittels auf die myokardiale Repolarisation genauestens von den regulierenden Aufsichtsbehörden beobachtet. Somit führten auch in der Anästhesiologie beobachtete, Arzneimittel-assoziierte QT-Verlängerungen in der Vergangenheit zu Warnmeldungen und Einschränkungen von Zulassungen (z.B. Droperidol [19], Haloperidol [20]).

1.1.3 Interaktion mit dem respiratorischen System

Die Vermeidung pulmonaler Komplikationen wie Hypoxie, Aspiration und Pneumonie [21,22] nach einem operativem Eingriff unter Vollnarkose hat in den letzten zwei Jahrzehnten stark an Bedeutung gewonnen: Es konnte gezeigt werden, dass diese signifikant die Intensiv- und Krankenhausverweildauer verlängern [23] und mit einer bis zu zehnfach erhöhten 30-Tages-Letalität assoziiert sind. [24] Eine Vielzahl an Untersuchungen belegen, dass eine Beatmung mit hohem inspiratorischen Spitzendruck (P_{max}) die Entstehung pulmonaler Komplikationen begünstigt. [21,25–30] Durch Limitierung des P_{max} können hohe transpulmonale Drücke (P_{tp}) vermieden werden, die die letztendliche Determinante eines pulmonalen Traumas darstellen. [31,32] Desweiteren beugen Strategien wie die Verwendung eines positiven end-exspiratorischen Drucks und Rekrutierungsmanöver der Entstehung perioperativer Atelektasen [33] vor, die mit postoperativen pulmonalen Komplikationen assoziiert sind. [34,35] Schließlich werden auch direkte lungenprotektive Eigenschaften inhalativer Anästhetika diskutiert: Eine kürzliche Meta-Analyse konnte eine signifikante Reduktion postoperativer pulmonaler Komplikationen bei der intraoperativen Verwendung der inhalativen Anästhetika Sevofluran, Desfluran oder Isofluran im Rahmen kardiochirurgischer Eingriffe nachweisen. [36]

1.1.4 Interaktion mit dem zentralen Nervensystem

Auch nach primärer Elimination des applizierten Anästhetikums und Wiedererlangung des Bewusstseins ist bei zahlreichen Patienten eine anhaltende Beeinträchtigung des zentralen Nervensystems nachweisbar. Klinische Relevanz erlangt hierbei das postoperative Delir (POD) – eine akute, fluktuierende Veränderung des Bewusstseins des Patienten mit Reduktion des bewussten Erlebens sowie Beeinträchtigung der Aufmerksamkeit. [37,38] 40 bis 50% aller Patienten, die wegen einer Hüftfraktur operiert werden, erleiden ein POD. [39–41] Es konnte gezeigt werden, dass dieses mit einer erheblich verlängerten Krankenhausverweildauer [42], sowie einer dreifach erhöhten Letalität [43] assoziiert ist.

Interessanterweise kann die Vermeidung einer zu tiefen Anästhesie die Inzidenz eins PODs um 40 Prozent reduzieren. [44,45] Ob die besondere Empfindlichkeit des Gehirns des alten und kranken Menschen gegenüber Anästhetika lediglich Ausdruck der Erkrankungsschwere ist [46] und ob durch angemessen tiefe Anästhesien auch die Letalität gesenkt werden kann [47], ist bislang noch nicht bewiesen. Pathophysiologisch wird bei der Entstehung eines POD eine Störung kortikaler γ-Aminobuttersäure (GABA)-erger Transmission angenommen [43,48]. Diese wird durch Interaktion mit GABA-ergen Synapsen, die den gängigen inhalativen Anästhetika gemeinsam ist, möglicherweise weiter aggraviert. Weiterhin wird ein Zusammenhang zwischen dem Auftreten eines PODs und einer intraoperativen Hypotension vermutet [49], da Patienten mit instabilen Kreislaufverhältnissen ein erhöhtes Risiko für ein postoperatives Delir aufweisen. [50]

Eine zweite, die eigentliche Anästhesie überdauernde Beeinträchtigung des zentralen Nervensystems durch inhalative Anästhetika ist die postoperative Übelkeit. [51,52] Postoperative Übelkeit mit oder ohne Erbrechen (PONV) ist ein sehr häufiges Ereignis, das mehrere Millionen Menschen jährlich betrifft [53–55] und die Patientenzufriedenheit mit der Anästhesie erheblich beeinflusst. [56] Glücklicherweise kann der Anästhesiologe Hochrisikopatienten identifizieren und die Inzidenz von PONV durch die Gabe einer risikoadaptierten Prophylaxe erheblich senken. In diesem Kontext konnten Apfel und Kollegen weibliches Geschlecht, die Gabe postoperativer Opioide, Nichtraucherstatus sowie bereits stattgehabte PONV oder Reisekrankheit als unabhängige Prädiktoren identifizieren. [57] Zur Prophylaxe stehen eine Reihe effektiver Antiemetika wie Dexamethason, 5-Hydroxytryptamin Typ III-Rezeptorantagonisten und Droperidol zur Verfügung. [58] Weiterhin wird im Rahmen eines internationalen Konsensus der Verzicht auf inhalative Anästhetika und die Durchführung einer totalen intravenösen Anästhesie mit Propofol (TIVA) empfohlen. [59]

In Zusammenschau kann die Auswahl des Anästhetikums die mit seiner Anwendung assoziierten kardialen, pulmonalen und zerebralen Risiken, sowie die postoperative Erholung

beeinflussen. Dies wird durch vier zentrale Eigenschaften der verwendeten Substanz bedingt:

(1) Seiner Pharmakokinetik, welche durch einen niedrigen Blut-Gas-Verteilungskoeffizienten und geringe Lipophilie ein rasches Anfluten und eine präzise Elimination der Substanz bedingen sollte.

(2) Der Interaktion mit dem kardiovaskulären System, das vor Hypotension und Interaktion mit kardialen Ionenkanälen geschützt werden sollte.

(3) Dem Einfluss auf das respiratorische System, wobei durch Vermeidung von hohen Beatmungsdrücken und Atelektasen das Auftreten postoperativer pulmonaler Komplikationen gesenkt werden kann.

(4) Der Interaktion mit dem zentralen Nervensystem, welches auch nach Wiedererlangung des Bewusstseins durch anhaltende Beeinträchtigung mit POD und PONV bedroht ist.

1.2 Das Potential Xenons als inhalatives Anästhetikum

Xenon wurde 1898 vom Chemiker Sir William Ramsay und Morris Travers am University College London entdeckt. [60] 1951 demonstrierten S. Cullen und E. Gross erstmalig am Menschen sein anästhetisches Potential. [61] Als Edelgas kann Xenon nicht kommerziell synthetisiert werden, sondern muss durch fraktionelle Destillation verflüssigter Luft, in der es mit einem sehr niedrigen Volumenanteil von $9x10^{-6}$ Vol-% vorliegt, isoliert werden. Dieser Herstellungsprozess bedingt seine verhältnismäßig hohen Kosten von 15-20€ pro Liter [60,62], wobei für eine durchschnittliche Xenonanästhesie in etwa 15-25 Liter benötigt werden. [63]

Xenon wurde 2000 zunächst in Russland, dann 2005 in Deutschland und schließlich 2007 in Europa als inhalatives Anästhetikum zugelassen und weist mit 0,115 den niedrigsten Blut/Gas-Verteilungskoeffizienten aller bekannten inhalativen Anästhetika auf [64]. Es konnte gezeigt werden, dass Patienten nach Xenonanästhesie deutlich rascher und schneller erwachen und orientiert sind als nach anderen inhalativen Anästhetika. [65–69] Desweiteren ist Xenon mit einem Öl/Gas-Verteilungskoeffizienten von 1,9 deutlich weniger lipophil als Sevofluran und Desfluran [70–72], was selbst bei ausgeprägt adipösen Patienten eine kurze und präzise Zeit bis zum Erwachen bedingt. [73] Dennoch kann Xenon bis zu 24 Stunden in Blut [74] und Urin [75] nachgewiesen werden. Seine terminale Eliminationskinetik, insbesondere im klinischen Alltag, wurde bisher noch nicht beschrieben.

Bereits frühe Untersuchungen zeigten eine ausgeprägte hämodynamische Stabilität während Xenon-basierter Anästhesie. [76–79] Im Rahmen der vorhergehenden Dissertation des Verfassers [1] konnte gezeigt werden, dass Xenon keinen Einfluss auf Muskelsympathikusaktivität und Baroreflexreagibilität ausübt, jedoch signifikant die Plasmakonzentration von Noradrenalin erhöht. Desweiteren beeinflusst Xenon *in vitro* nur unwesentlich myokardiale Kaliumkanäle und könnte somit beim Menschen im Gegensatz zu anderen Anästhetika die kardiale Repolarisation nicht beeinträchtigen. [80]

In tierexperimentellen Untersuchungen konnte nachgewiesen werden, dass Xenon die Lunge vor Schädigungen schützen kann. [81] Im Gegensatz dazu wird im klinischen Alltag jedoch regelhaft ein Anstieg des P_{max} während Xenonanästhesie beobachtet. [82] Unklar ist jedoch, ob dies auch mit einem Anstieg des P_{tp} assoziiert ist und Xenon somit einen Lungenschaden letztendlich begünstigt. Desweiteren ist aufgrund der hohen Viskosität des Edelgases ein Einfluss auf die Lungenbelüftung mit Verminderung anästhesieinduzierter Atelektasen denkbar. [83]

Schließlich konnte für Xenon eine effektive Protektion des zentralen Nervensystems nachgewiesen werden. [84–86] Im Gegensatz zu anderen Anästhetika vermittelt das Edelgas seine anästhetischen Eigenschaften primär nicht über eine Beeinflussung GABAerger Aktivität, sondern per Antagonismus von N-Methyl-D-Aspartat (NMDA)-Rezeptoren [87]. Daher lässt sich mutmaßen, dass die POD-Inzidenz nach Xenon im Gegensatz zu anderen Anästhetika vermindert sein könnte. In der Tat suggerieren erste Untersuchungen an kleinen Patientenkollektiven eine bessere kognitive Funktion in der postoperativen Phase [67] und einen positiven Einfluss auf die Entstehung eines postoperativen Delirs. [88] Die Beantwortung dieser Fragestellung ist letztendlich jedoch nur im Rahmen einer Untersuchung mit adäquater Fallstärke und POD als primärer Zielvariable sicher möglich.

Wie alle anderen inhalativen Anästhetika fördert die Verabreichung von Xenon die Entstehung von PONV. [89] Für eine zielgerichtete medikamentöse Prophylaxe ist somit die Identifikation prädisponierender Risikofaktoren für PONV nach Xenonanästhesie essentiell. Da weiterhin eine Reihe medikamentöser Antiemetika zur Prophylaxe von PONV verfügbar ist [58,59], stellt sich die Frage, ob das emetogene Potential inhalativer Anästhetika durch eine medikamentöse Prophylaxe kompensiert werden kann. Somit müsste bei Patienten mit hohem Risiko für PONV nicht zwangsläufig auf eine inhalative Anästhesie verzichtet werden.

1.3 Fragestellungen

Zusammengenommen zeigt Xenon ein vielversprechendes Wirkprofil: Neben einem (1) sehr niedrigen Blut-/Gas-Verteilungskoeffizienten übt es (2) keinen Einfluss auf das sympathische Nervensystem sowie myokardiale Ionenkanäle *in vitro* aus und reduziert Hypotension durch Steigerung der systemischen Katecholaminspiegel. (3) Es verfügt über lungenprotektive Eigenschaften, erhöht jedoch im klinischen Alltag den P_{max}. (4) Xenon könnte die Inzidenz eines POD senken, induziert jedoch wie alle inhalativen Anästhetika PONV.

Es ergeben sich daher die folgenden Fragestellungen hinsichtlich des Einflusses von Xenon auf anästhesie-assoziierte Risiken und die postoperative Erholung:

Grundlegende Eliminationskinetik:

- Gewährleistet der niedrige Blut/Verteilungskoeffizient und die geringe Lipophilie Xenons eine entsprechend rasche Elimination im klinischen Alltag und wie ist diese charakterisiert?

Interaktion mit dem kardiovaskulären System:

- Ist bei unbeeinflusster efferenter Sympathikusaktivität eine Hemmung der zellulären Katecholaminwiederaufnahme ursächlich für die hämodynamischen Stabilität mit Anstieg der Noradrenalin-Plasmakonzentrationen unter Xenon?
- Trägt eine Nicht-Beeinflussung des kardialen QT-Intervalls zur Sicherheit einer Xenonanästhesie bei?

Interaktion mit dem respiratorischen System:

- Wie modifiziert Xenon die Lungenmechanik und Lungenbelüftung im Patienten?

Interaktion mit dem zentralen Nervensystem:

- Kann eine Xenonanästhesie die Inzidenz eines postoperativen Delirs senken?
- Was sind Prädiktoren für postoperative Übelkeit und Erbrechen nach Xenonanästhesie und sind gebräuchliche prophylaktische Antiemetika effektiv?

- Lassen sich die emetogenen Effekte inhalativer Anästhetika durch eine medikamentöse Prophylaxe kompensieren?

Diese Themenkomplexe werden im Folgenden anhand klinischer Untersuchungen systematisch erörtert.

2. Untersuchungen

2.1 Die Eliminationskinetik von Xenon im Patienten *(Publikation 7.1, Seite 68 ff.)*

Zur Quantifizierung der grundlegenden Eliminationskinetik von Xenon nach Exposition wurden nach positivem Ethikvotum (Registrierungsnummer 4635) und Registrierung unter ClinicalTrials.gov (NCT02105077) Vollblutproben von konsekutiven normalgewichtigen Patienten (74 [66; 77] Jahre), die sich einer routinemäßigen Xenonanästhesie (inspiratorische Xenonkonzentration 60%) für minimalinvasive gefäßchirurgische Eingriffe unterzogen, mittels Gaschromatographie/ Dreifach-Quadrupol-Tandem-Massenspektrometrie auf ihren Xenongehalt hin untersucht. [90] Die Untersuchungen wurden in Zusammenarbeit mit dem Zentrum für präventive Dopingforschung – Institut für Biochemie, Leitung Prof. Dr. rer. nat. Mario Thevis der Deutschen Sporthochschule Köln durchgeführt.

Die maximale Konzentration im Vollblut während Xenonanästhesie betrug 1341 µmol l^{-1} und fiel innerhalb einer Stunde nach Exposition auf 54 [49; 64] µmol l^{-1} ab. Xenon war 24 Stunden in zwei, 32 Stunden in zwei, 40 Stunden in zwei und 48 Stunden in einem weiteren Patienten nachweisebar. Es zeigte sich ein biphasisches Eliminationsprofil (Abbildung 1).

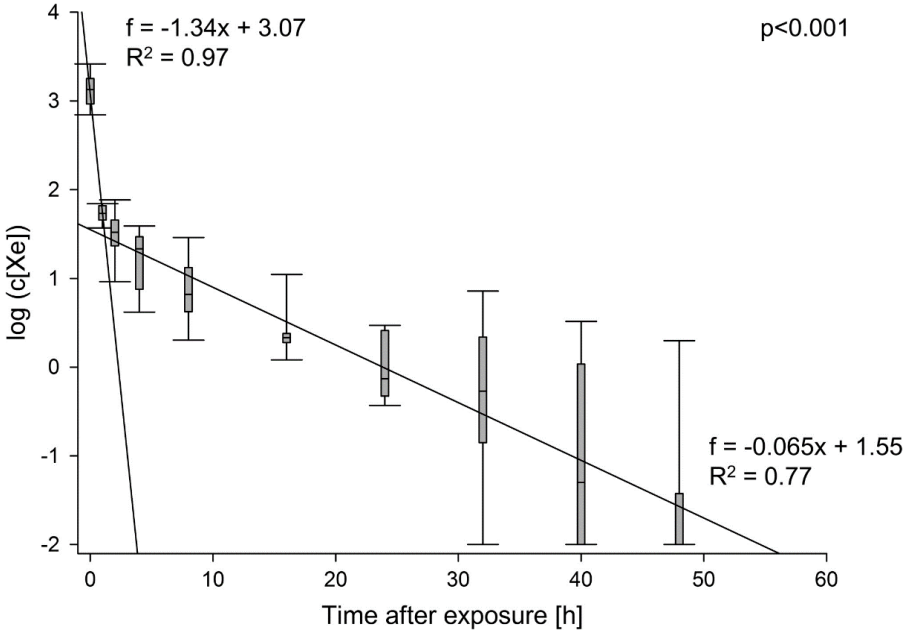

Abbildung 1: Logarithmierte Konzentrationen von Xenon (c[Xe]) im Vollblut nach Beendigung der Xenonzufuhr als Median mit Interquartilenabstand und linearer Regression (schwarze Linien). h: Stunde.

Aus: Schaefer et al. Drug Test Anal 2017; 9:666-670, mit Genehmigung von John Wiley and Sons.

Die zweite Phase der Elimination wurde durch eine einfach-exponentielle, Zweifaktorenfunktion hinreichend beschrieben (R^2 0,83) und wies eine Eliminationskinetik erster Ordnung mit einer Halbwertszeit von 2,7 Stunden auf (Abbildung 2):

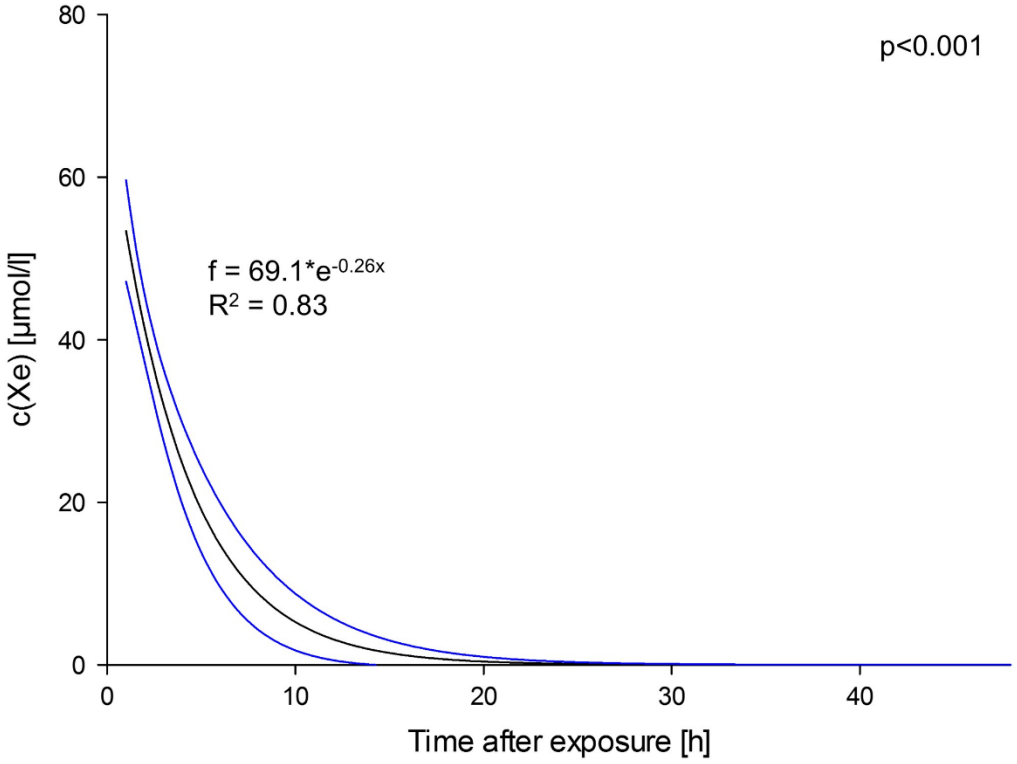

Abbildung 2: Eliminationskinetik 1. Ordnung der zweiten Elimiantionsphase. Nicht-lineare Regression (schwarze Linie) mit 95%-Konfidenzintervall (blaue Linien). c(Xe): Xenonkonzentration im Vollblut; h: Stunde.

Aus: Schaefer et al. Drug Test Anal 2017; 9:666-670, mit Genehmigung von John Wiley and Sons.

Zusammenfassend fallen die Xenonkonzentrationen im Blut von Patienten innerhalb von einer Stunde nach Exposition auf 4% der während Exposition gemessenen Konzentrationen. Die weitere Elimination verläuft entsprechend einer Kinetik erster Ordnung. Xenon ist 24 bis 48 Stunden in geringen Konzentrationen im Blut von Patienten nachweisbar.

2.2 Beeinflussung des kardiovaskulären Systems *(Publikation 7.2 & 7.3, Seite 73 ff.)*

Zur Untersuchung eines Effekts von Xenon auf die zelluläre Katecholaminaufnahme wurden humane Nierenepithel- (HEK239) und Neuroblastomzellen (SH-SY5Y) mit einem Gasgemisch aus 65% Xenon oder 65% Stickstoff, 30% Sauerstoff und 5% Kohlendioxid inkubiert. [91] Während die HEK239-Zellen lediglich den humanen Noradrenalintransporter exprimieren, verfügen die SH-SY5Y Neuroblastomzellen zusätzlich über den humanen NMDA-Rezeptor. Zusätzlich wurde der spezifische NMDA-Antagonist MK-801 (2µmol l^{-1}), NMDA und sein Co-Agonist Glycin (25 und 10µmol l^{-1}) oder ein Vehikel der Zellflüssigkeit zugegeben. Die Katecholaminaufnahme in die Zellen wurde anhand eines Fluoreszenzsubstrats detektiert [92]. In den HEK293 hNET-Zellen hemmte Ketamin ($p<0,01$), aber nicht Xenon, MK-801 oder NMDA mit Glycin signifikant die Noradrenalinaufnahme. Xenon, MK-801 sowie Ketamin und NMDA mit Glycin reduzierten jedoch signifikant die Noradrenalinaufnahme in NMDA-Rezeptor exprimierenden SH-SY5Y-Zellen. Die Gabe von MK-801, NMDA und Glycin sowie Ketamin zu Xenon hatte keinen additiven Effekt (Abbildung 3).

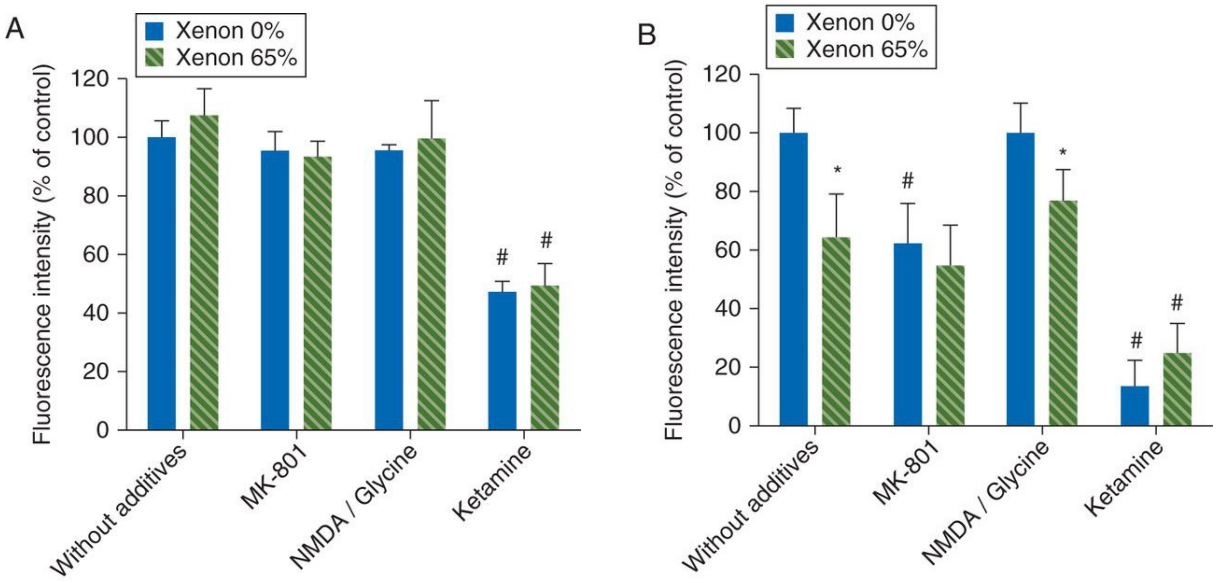

Abbildung 3 Fluoreszenzintensität (MW ±SD) als Parameter für die zelluläre Noradrenalinaufnahme für 65% Stickstoff (blau) versus 65% Xenon (grün) in Abhängigkeit verschiedener kompetitiver Substrate. (A) Aufnahme in HEK293 Zellen, die lediglich den humanen Noradrenalintransporter exprimieren und (B) Aufnahme in humane Neuroblastomzellen (SH-SY5Y), die zusätzlich den humanen NMDA-Rezeptor exprimieren. *$p<0,01$ versus Xenon 0%, #$p<0,01$ versus ohne Zusätze. *Aus: Neukirchen et al. Br J Anaesth 2012; 109:887-896, Elsevier, vorbehaltenes Recht des Autors*

Der Einfluss von Xenonanästhesie auf die kardiale Repolarisation, gemessen anhand des frequenzkorrigierten QT-Intervalls (QTc), wurde 1. an acht freiwilligen erwachsenen Probanden (25 ±2 Jahre) ohne Vorerkrankungen und ohne Medikamenteneinnahme sowie 2. 35 Patienten (44 ±11 Jahre), die sich einer Xenonanästhesie im Rahmen eines elektiven operativen Eingriffs an der Uniklinik Düsseldorf unterzogen, untersucht (MO-LKP-394+3386, Ethikkommission der Medizinischen Fakultät der Heinrich-Heine Universität sowie ETH-019/08 der Ärztekammer Berlin). [93] Die Messungen des QTc-Intervalls fanden jeweils zu drei Zeitpunkten statt: 1. Während einer initialen Ruhephase, 2. während Sauerstoffatmung (Probanden) bzw. nach Anästhesieeinleitung mit Propofol/Remifentanil (Patienten) sowie 3. während Xenonanästhesie.

Xenon erhöhte signifikant den systolischen Blutdruck (Probanden: 93 ±5 versus 107 ±6 mmHg, p<0,01; Patienten: 97 ±8 versus 113 ±13 mmHg, p<0,001). Das QTc-Intervall änderte sich im Vergleich zum wachen Zustand während Sauerstoffatmung/nach Anästhesieeinleitung sowie unter Xenonanästhesie bei den gesunden Probanden nicht (398 ±42 versus 409 ±45 versus 409 ±30 ms, p=0,55 und 0,43 zum wachen Zustand, mittlere Änderung +0,11 [95% Konfidenzintervall -22,4; 22,7] ms, Abbildung 4)

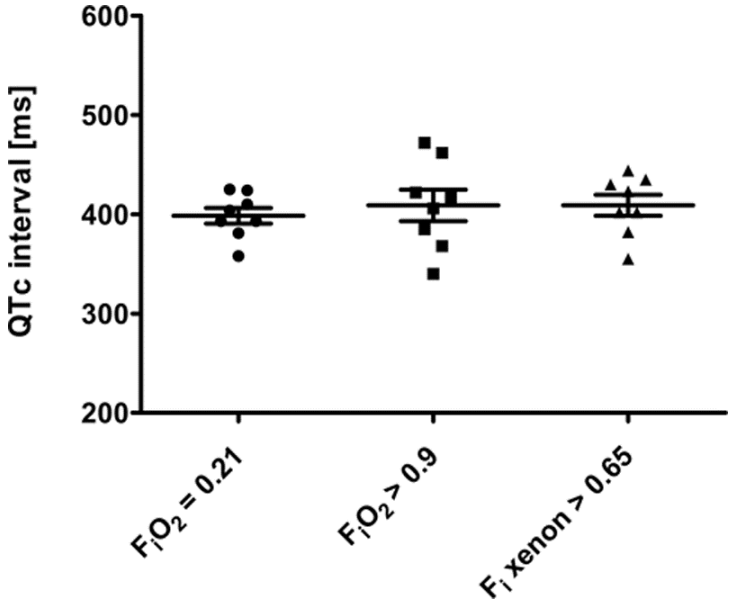

Abbildung 4 Herzfrequenzkorrigiertes QT-Intervalls (QTc, MW ±SD) gesunder Probanden unter initialer Atmung von Raumluft, anschließender Atmung reinen Sauerstoffs sowie mindestens 65% Xenon in Sauerstoff. FiO_2: Inspiratorische Sauerstoffkonzentration

Aus: Neukirchen et al. Anesthesiology 2015; 123:542-547, Genehmigung Wolters Kluwer Health, Inc.

Ebenfalls zeigte sich keine Änderung des QTc-Intervalls in der Patientenkohorte (414 ±25 versus 417 ±32 ms, p=0,3, mittlere Änderung +4,4 [-4,6; 13,5] ms, Abbildung 5).

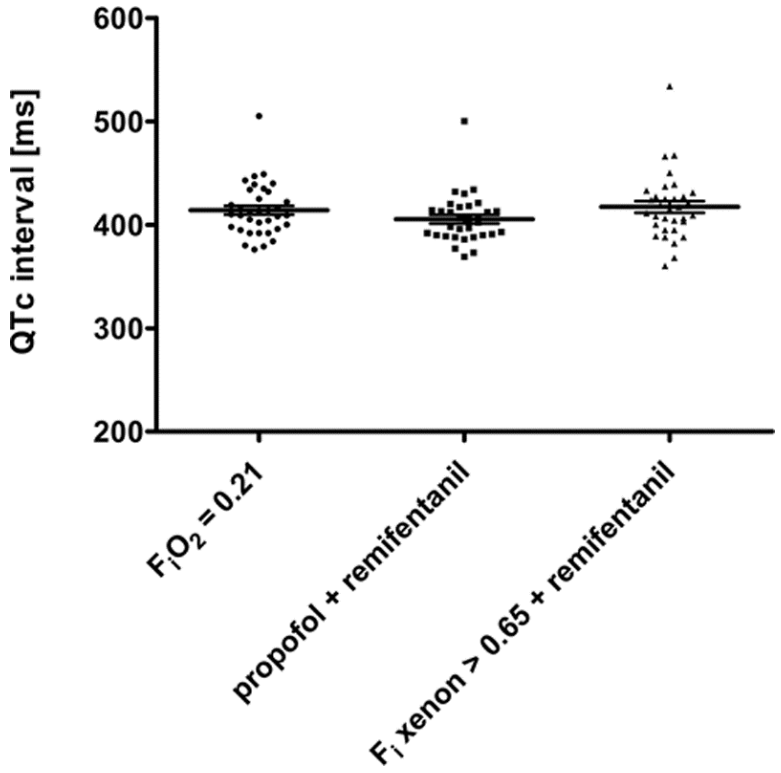

Abbildung 5 Herzfrequenzkorrigiertes QT-Intervalls (QTc, MW ±SD) von Patienten unter initialer Atmung von Raumluft, anschließender Anästhesie mit Propofol und Remifentanil sowie Anästhesie mit Xenon und Remifentanil. FiO_2: Inspiratorische Sauerstoffkonzentration

Aus: Neukirchen et al. Anesthesiology 2015; 123:542-547, Genehmigung Wolters Kluwer Health, Inc.

Xenon bewirkt somit in Abhängigkeit vom NMDA-Rezeptor eine Hemmung der Noradrenalinwiederaufnahme und trägt damit zur unter Xenonanästhesie beobachteten Kreislaufstabilität bei. Es zeigt weiterhin weder bei gesunden Probanden noch bei Patienten einen Einfluss auf das QTc-Intervall.

2.3 Beeinflussung des respiratorischen Systems *(Publikation 7.4, Seite 89 ff.)*

Die Untersuchungen zur Beeinflussung der Lungenmechanik und Lungenbelüftung wurden an nach Body Mass Index (BMI) stratifizierten Patienten (53 ±18 Jahre, 10 Patienten mit einem BMI ≤25 und 10 Patienten ≥30 kg m^{-2}) ohne pulmonale Vorerkrankungen, die sich einer Xenon-basierten Anästhesie im Rahmen eines elektiven operativen Eingriffs unterzogen, durchgeführt (Ethikvotum 5161R; ClinicalTrials.gov NCT02682758). [94] Es wurden 1. während initialer Propofolanästhesie und 2. nach Beendigung des Xenon-Einwaschvorgangs der P_{tp} sowie P_{max}, $R_{AW,}$ dynamische (C_{dyn}) und statische (C_{stat}) Compliance des respiratorischen Systems ermittelt. Weder im Gesamtkollektiv, noch in den Subgruppen der Patienten mit einem BMI <25 und >30 kg m^{-2} zeigte Xenon einen Einfluss auf den P_{tp} (Abbildung 6).

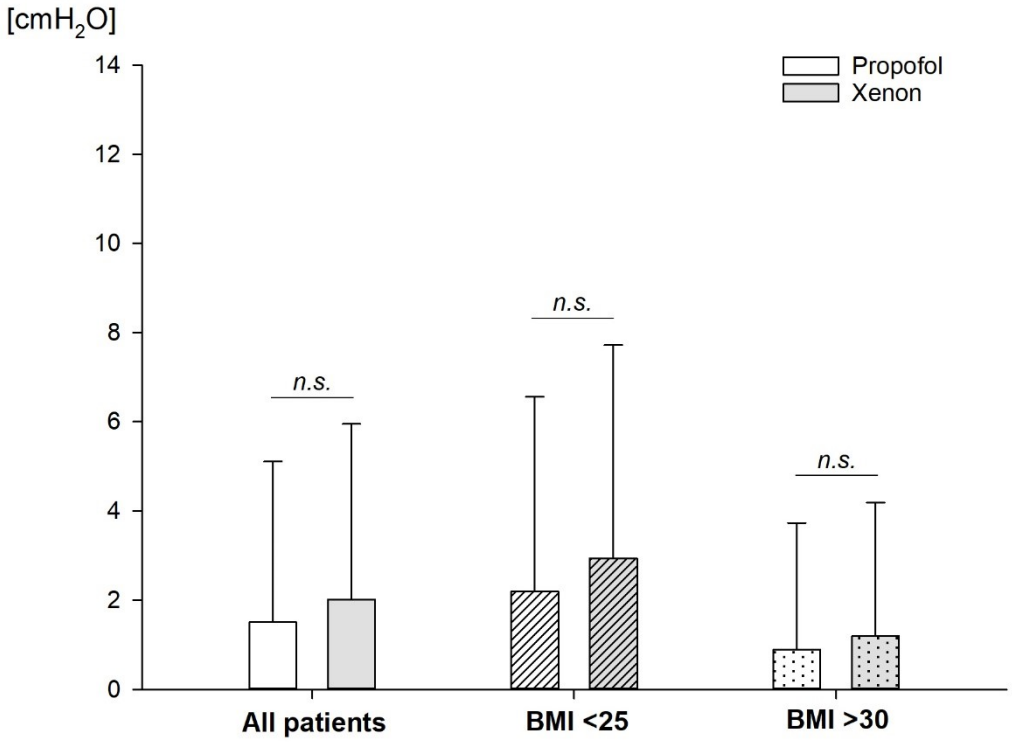

Abbildung 6 Transpulmonaler Druck (MW ±SD) unter Propofol-basierter Anästhesie (weiß) und anschließender Xenonanästhesie (grau), jeweils mit Remifentanil, für alle Patienten (links) sowie in den zwei Subgruppen nicht-adipöser Patienten (Mitte, schraffiert) und adipöser Patienten (rechts, gepunktet). cmH_2O: Zentimeter Wassersäule; n.s.: nicht signifikant; BMI: Body Mass Index. *Aus: Schaefer et al. Br J Anaesth 2018; 120:1394-1400, Elsevier, vorbehaltenes Recht des Autors*

Xenon erhöhte signifikant den P_{max} von 20,8 ±3 auf 22,6±3 cm H_2O (p<0,001). Desweiteren steigerte Xenon den R_{AW} um 54 ±25% und C_{dyn} um 8 ±8%, ohne C_{stat} zu beeinträchtigen (Abbildung 7).

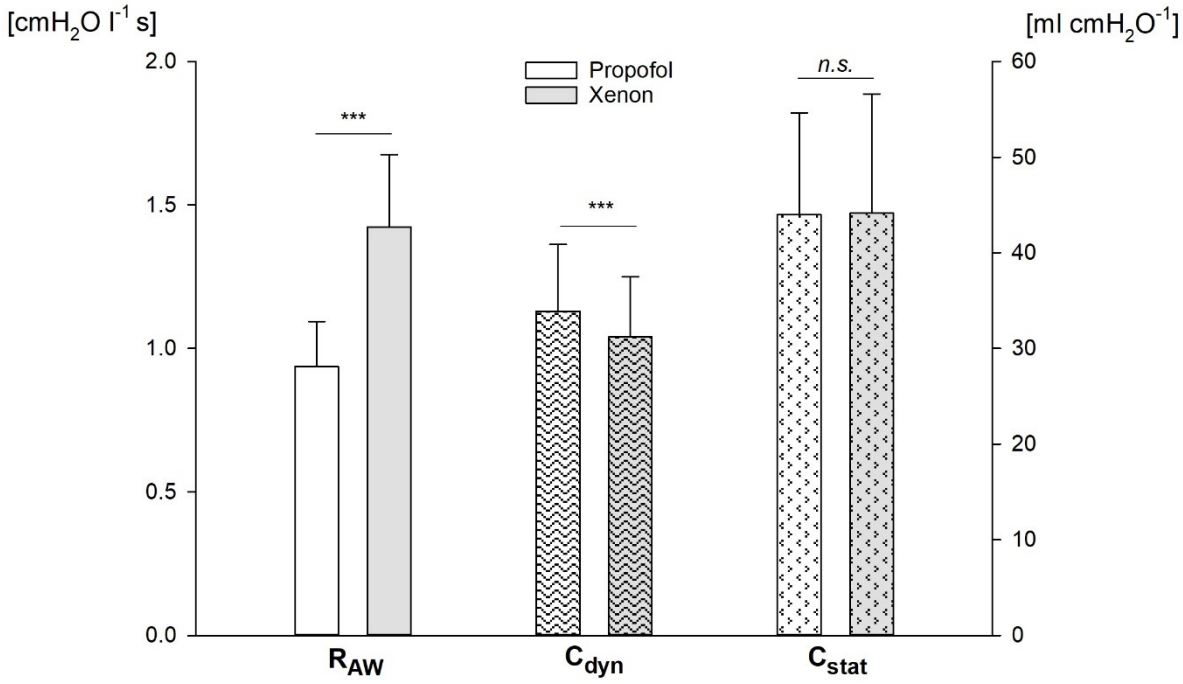

Abbildung 7 Atemwegswiderstand (R_{AW}), dynamische (C_{dyn}, schraffiert) und statische (C_{stat}, Pfeile) Compliance des respiratorischen Systems unter Propofol (weiß) und anschließender Xenonanästhesie (grau). Alle Werte verstehen sich als Mittelwert mit Standardabweichung. *** p<0,001; n.s.: nicht signifikant. cmH_2O: Zentimeter Wassersäule.
Aus: Schaefer et al. Br J Anaesth 2018; 120:1394-1400, Elsevier, vorbehaltenes Recht des Autors

Ferner wurde der Einfluss von Xenonanästhesie auf die Lungenbelüftungen mittels elektrischer Impedanztomographie [33,95] 1. vor Anästhesieeinleitung sowie parallel zu den zwei Messzeitpunkten der Lungenmechanik ermittelt und anhand des *Center of Ventilation Index* (CVI) quantifiziert. [33,95,96]

Anästhesieeinleitung bewirkte eine signifikante Verminderung der ventilierten Lungenfläche in der dorsalen Hälfte des Bildes der funktionellen Elektroimpedanztomographie (*f*EIT, 153 ±41 versus 95 ±63 Pixel, p<0,001), die von einer Erhöhung des CVI in Richtung ventraler Lungenregionen begleitet wurde. Xenonanästhesie hatte keinen Einfluss auf den CVI im Gesamtkollektiv oder in der Subgruppe der Patienten mit einem BMI<25 kg m^{-2}. Allerdings

zeigte sich bei Patienten mit einem BMI>30 kg m^{-2} eine signifikante Reduktion des CVI um 1,0 ±0,6% (Abbildung 9).

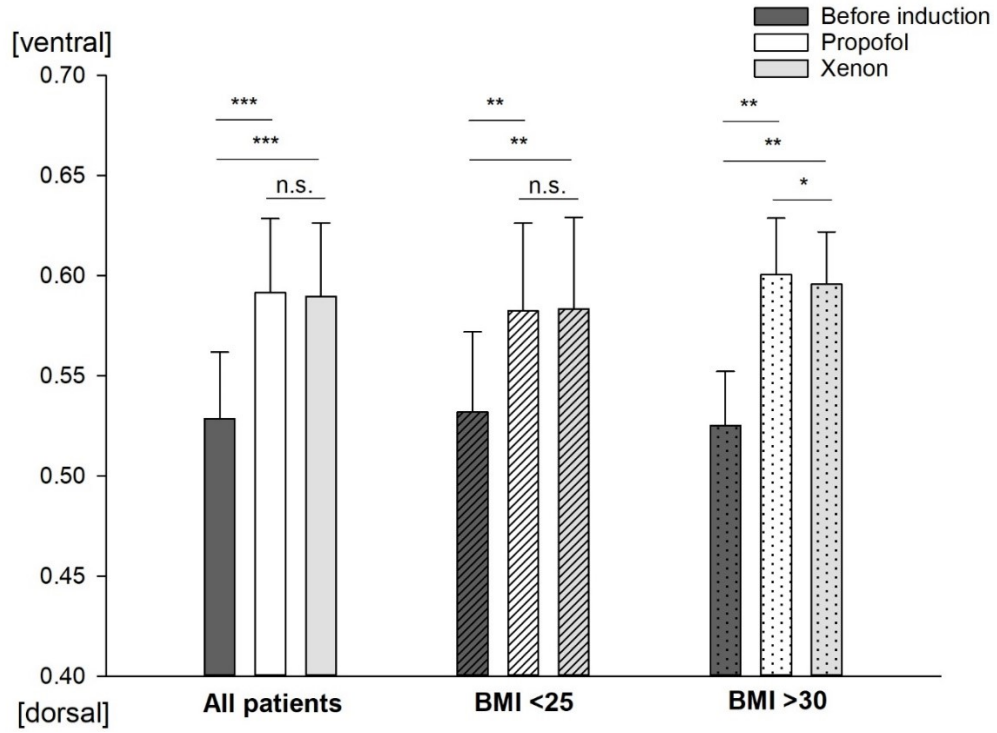

Abbildung 9 *Center of Ventilation Index* (MW ±SD) unter Spontanatmung vor Anästhesieeinleitung (dunkelgrau), Propofolanästhesie (weiß) und anschließender Xenonanästhesie (hellgrau) für alle Patienten (links) sowie nicht-adipöse (Mitte, schraffiert) und adipöse Patienten (rechts, gepunktet). ***p<0,001; **p<0,01; *p<0,05.
Aus: Schaefer et al. Br J Anaesth 2018; 120:1394-1400, Elsevier, vorbehaltenes Recht des Autors

Desweiteren fand sich keine Änderung der ventilierten Lungenfläche durch Xenon weder im gesamten *fEIT*-Bild (288 ±85 versus 289 ±86 Pixel, p=0,99), noch in der dorsalen Hälfte des Bildes (95 ±63 versus 97 ±62 Pixel, p=0,41).

Diese Befunde bedeuten in Zusammenschau, dass Xenon den P_{max} steigert, ohne den P_{tp} zu erhöhen. Xenon erhöht weiterhin den R_{AW}. Es zeigt keinen Einfluss auf die Verteilung und Homogenität der Lungenbelüftung, mit Ausnahme eines marginalen Effekts im Sinne einer Re-Dorsalisierung der Lungenbelüftung bei adipösen Patienten.

2.4 Beeinflussung des zentralen Nervensystems

Einfluss auf ein postoperatives Delir (Publikation 7.5 Seite 96 ff.)

Die Inzidenz eines POD nach Xenon- versus einer Kontrollgruppe mit Sevoflurananästhesie wurde im Rahmen einer multizentrischen, randomisierten, doppelt verblindeten Phase-II-Studie nach Arzneimittelgesetz an 256 Patienten (mittleres Alter 84 Jahre), die sich einer operativen Versorgung einer Hüftgelenksfraktur unterzogen, untersucht (Ethikvotum MC-522, ClinicalTrials.gov NCT01199276, EudraCT 2009-017153-35). [97] Der Leiter der klinischen Prüfung war Herr Prof. Dr. Mark Coburn, Aachen. An unserem Studienzentrum wurden 42 der 256 Patienten eingeschlossen.

Die Anästhesie wurde entweder mit Xenon (Ziel-Fi_{Xe} 60% in 35-45% O_2) oder Sevofluran (altersadjustierte minimale alveoläre Konzentration 1,0) und Remifentanil unter Kontrolle der Anästhesietiefe mittels Bispektralem Index (BIS VISTA™, Aspect Medical Systems, Norwood, USA) durchgeführt. Das Auftreten eines POD innerhalb der ersten vier Tage nach Operation wurde mittels des „Confusion Assessment Method“ (CAM) [98] erhoben. A *priori* wurde die benötigte Fallzahl anhand einer in Voruntersuchungen beobachteten Inzidenz eines POD von 30% sowie einer postulierten Reduktion um 50% berechnet.

Insgesamt erlitten 30 (11,7 %) der 256 Patienten ein POD innerhalb der ersten 4 postoperativen Tage, davon 12 (9,7 %) in der Xenongruppe und 18 in der Sevoflurangruppe (13,6 %, p=0,33). Weiterhin zeigte sich kein Unterschied hinsichtlich des Auftretens eines POD nach dem vierten postoperativen Tag (Xenon 4,0 versus Sevofluran 8,0 %, p=0,46). Xenon reduzierte signifikant den mittleren *Sequential Organ Failure Assessment*-Score (0,57 ±0,84 versus 1,01 ±1,77) an Tag drei. Insgesamt wurden bei 114 (91,2 %) Patienten der Xenongruppe und 125 (94,7 %) Patienten der Sevoflurangruppe unerwünschte Ereignisse festgestellt (p=0,27). Schwerwiegende unerwünschte Ereignisse waren häufiger in der Sevoflurangruppe (21 Patienten, 16 %) als in der Xenongruppe (10 Patienten, 8%, p=0,05). Es kam zu keinem Todesfall in der Xenongruppe, währen 5 Patienten aus der Sevoflurangruppe verstarben (p=0,06).

Einfluss auf postoperative Übelkeit und Erbrechen (Publikationen 7.6, 7.7 & 7.8 Seite 107 ff.)

Zunächst wurden unabhängige Prädiktoren für PONV nach Xenon-basierter Anästhesie anhand einer Sekundäranalyse prospektiv erhobener Daten im Rahmen einer multizentrischen Anwendungsbeobachtung an 488 Patienten ermittelt (Ärztekammer Berlin ETH-019/08, Ethikvotum HHU 3386 sowie BfArM AL-PMS-01/07GER). Leiter der primären Studie war Herr Priv.-Doz. Dr. Matthias Reyle-Hahn, Berlin. An unserem Studienzentrum wurden 71 Patienten eingeschlossen. Planung und Durchführung der Sekundäranalyse erfolgten durch unser Studienzentrum.

Es wurde zunächst die Rohinzidenz von PONV aller Patienten, die keine medikamentöse antiemetische Prophylaxe erhielten, mit der nach dem Apfel-Score [57] erwarteten Inzidenz verglichen. 136 (28%) Patienten des Gesamtkollektives erlitten PONV. In der Subgruppe aller Patienten, die keine antiemetische Prophylaxe erhalten haben, lag die Inzidenz bei 92 von 333 Patienten (28 %) und somit unter der nach Apfel-Score erwartete Inzidenz (42%, [95% Konfidenzintervall 42;45], $p<0.001$). Die Fläche unter der *Receiver Operating Characteristic* – Kurve des Apfel-Scores lag bei 0,60.

Anschließend wurden unabhängige Prädiktoren für PONV nach Xenonanästhesie mittels logistischer Regressionsanalyse ermittelt. Es konnten weibliches Geschlecht, jüngeres Patientenalter und eine längere Dauer Xenon-basierter Anästhesie als unabhängige Prädiktoren identifiziert werden (Tabelle 1).

Weiterhin konnten 182 Patienten (91 mit und 91 ohne antiemetische Prophylaxe) anhand eines *Propensity Score Matchings* einander zugeordnet werden. Nach suffizientem Ausgleich der Risikofaktoren für PONV kein Unterschied hinsichtlich der Inzidenz von PONV zwischen Patienten mit und Patienten ohne Prophylaxe festgestellt werden 27 versus 31 Patienten, $p=0,63$).

Prädiktor	aOR	95% KI	*p-Wert*
Patientenbezogene Faktoren			
Weibliches Geschlecht	1.76	1.08–2.89	0.025
Alter (pro 10 Jahre)	0.82	0.69–0.97	0.023
Nichtraucherstatus	1.48	0.87–2.51	0.15
Anamnese von PONV oder Reisekrankheit	1.44	0.83–2.50	0.19
Anästhesiebezogene Faktoren			
Dauer (pro Stunde)	1.36	1.17–1.59	<0.001
Postoperative Morphinäquivalente (pro mg)	1.02	0.99–1.05	0.13
Antiemetische Prophylaxe			
Dexamethason	0.72	0.32–1.60	0.41
5-HT_3-Antagonisten	1.39	0.65–2.98	0.40
Andere	1.06	0.41–2.76	0.91
Prophylaxe *per se*	0.98	0.54–1.77	0.93

Tabelle 1 Unabhängige Prädiktoren für postoperative Übelkeit und Erbrechen (PONV) bis 25 Stunden nach Xenon-basierter Anästhesie. aOR: adjustiertes Odds Ratio, KI: Konfidenzintervall, 5-HT_3: 5-Hydroxytryptamin Typ III-Rezeptor
Modifiziert und übersetzt aus: Schaefer et al. Br J Anaesth 2015; 115:61-67, Elsevier. Vorbehaltenes Recht des Autors.

Schließlich wurde die Fragestellung, ob die emetogenen Effekte inhalativer Anästhetika suffizient durch eine medikamentöse antiemetische Prophylaxe kompensiert werden können, anhand zweier systematischer Meta-Analysen (www.crd.york.ac.uk/PROSPERO, CRD42015019571) getrennt für erwachsene Patienten [99] und Kinder [100] untersucht: Nach systematischer Literaturrecherche (MEDLINE, EMBASE und CENTRAL) wurden 14 randomisierte Studien an erwachsenen Patienten [51,101–113] mit einer Gesamtanzahl von 2.051 Patienten, die eine Anästhesie mit einem inhalativen Anästhetikum und medikamentöser antiemetischer Prophylaxe mit einer TIVA verglichen, eingeschlossen. Primäre Zielvariable für diese Untersuchung war die Inzidenz von PONV innerhalb von 24 Stunden nach Operation. Es zeigte sich diesbezüglich kein Unterschied zwischen den

beiden Gruppen (Abbildung 11). Ebenfalls fand sich kein Unterschied in Hinblick auf postoperatives Erbrechen (relatives Risiko, RR 1,17 [0,78; 1,76]), dem postoperativen Bedarf einer antiemetischen Medikation (RR 1,16 [0,68; 1,99]) sowie PONV in der frühen postoperativen Phase (RR 1,06 [0,88; 1,27]). Allerdings zeigten Patienten, die eine TIVA erhielten, ein höheres Risiko für PONV in der späten postoperativen Phase (RR 1,41 [1,10; 1,79]). Schließlich fand sich ebenfalls ein erhöhtes Risiko für PONV nach TIVA, wenn ein Modell fixierter Effekte verwendet wurde (Abbildung 11). Nach Untersuchung des Funnel-Plots für die primäre Zielvariable anhand des Arcsine-Test zeigte sich eine signifikante Asymmetrie, die eine Publikationsverzerrung zugunsten einer TIVA suggerierte.

Es wurden weiterhin vier randomisierte, kontrollierte Studien mit insgesamt 558 Kindern analysiert [114–117]. Da postoperative Übelkeit bei Kindern schwer zu diagnostizieren ist, wurde als primäre Zielvariable die Inzidenz postoperativen Erbrechens (POV) gewählt. Es zeigte sich kein Unterschied hinsichtlich des Risikos für POV nach TIVA oder inhalativer Anästhesie mit medikamentöser antiemetischer Prophylaxe (Abbildung 12). Desweiteren fand sich ebenfalls kein Unterschied im Risiko für frühes (RR 1,48 [0,78; 2,83]) und spätes (RR 0,89 [0,56; 1,42]) POV sowie des Bedarfs einer postoperativen antiemetischen Medikation (RR 2,4 [0,8; 7,1]). Alle vier Studien untersuchten Kinder, die sich einer Strabismus-Operation unterzogen und drei Studien dokumentierten die Inzidenz eines intraoperativen okulokardialen Reflex, die signifikant höher unter TIVA war [RR 1,9 [1,01; 3,41]) und häufiger mit Atropin behandelt werden musste [RR 2,5 [1,2; 5,1]).

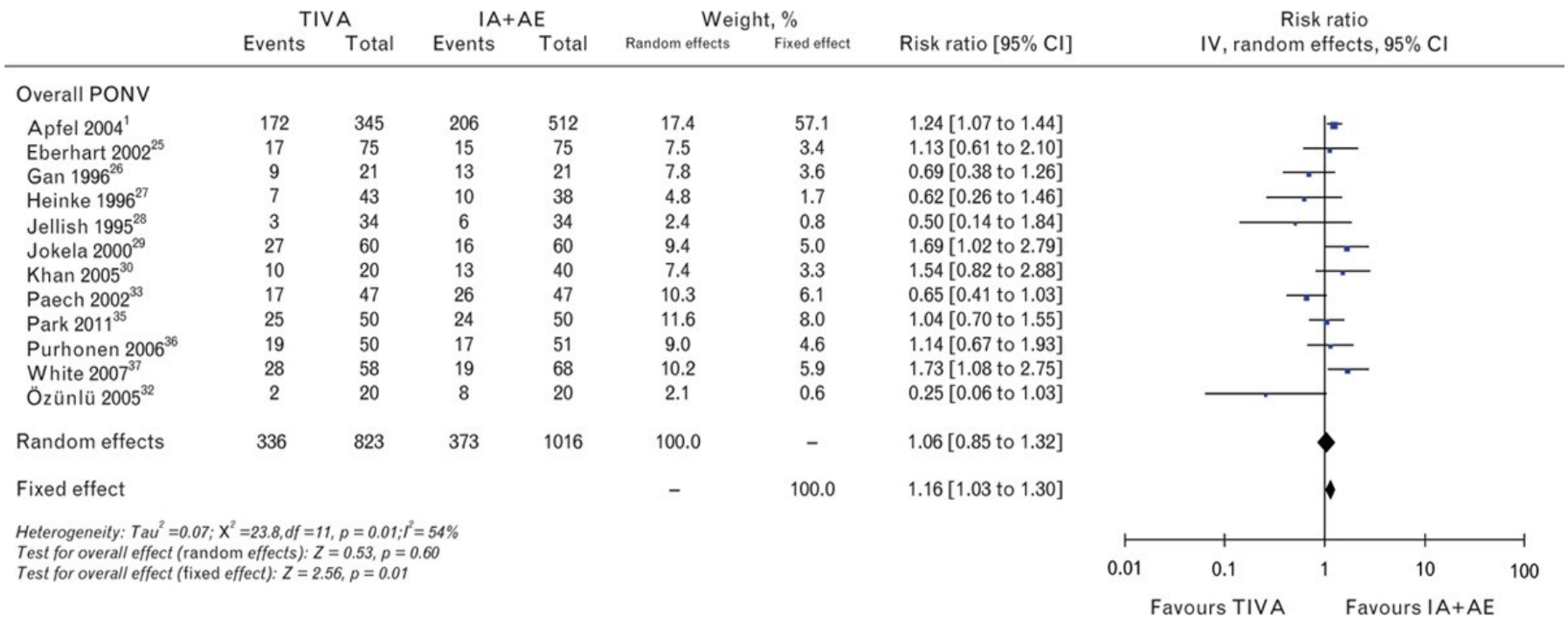

Abbildung 11 Forest-Plot für das relatives Risiko [95% Konfidenzintervall] für Postoperative Übelkeit und Erbrechen (PONV) nach totaler intravenöser Anästhesie (TIVA) *versus* inhalative Anästhesie (IA) mit einfacher medikamentöser antiemetischer Prophylaxe (AE). Zusätzlich sind die Ergebnisse unter Verwendung eines Modells fixierter Effekte gezeigt. IV: Inverse Varianz-Wichtung.

Aus: *Schaefer et al. Eur J Anaesthesiol 2016; 22:750-760, mit Genehmigung von Wolters Kluwer Health, Inc*

	TIVA		IA + AE				Risk ratio
	Events	Total	Events	Total	Weight, %	Risk ratio [95% CI]	IV, random effects, 95% CI
POV							
Klockgether-Radke 1995	20	60	12	30	18.1	0.83 [0.47; 1.47]	
Splinter 1997	41	156	39	144	37.2	0.97 [0.67; 1.41]	
Tramer 1998	19	38	13	40	19.2	1.54 [0.89; 2.66]	
Watcha 1991	25	60	15	30	25.6	0.83 [0.52; 1.33]	
Total	**105**	**314**	**79**	**244**	**100.0**	**0.99 [0.77; 1.27]**	

Heterogeneity: Tau^2 = 0.01; χ^2 = 3.4, df = 3, P = .34; I^2 = 11%
Test for overall effect: Z = 0.06, P = .95

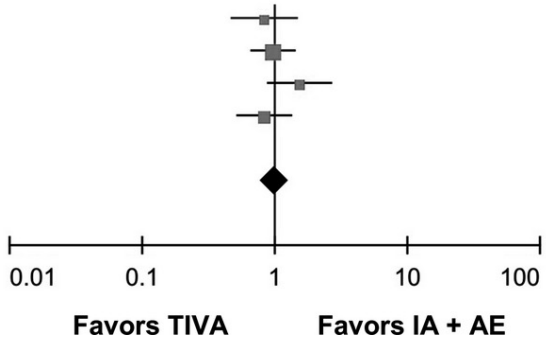

Abbildung 12 Forest-Plot für das relatives Risiko [95% Konfidenzintervall] für Postoperatives Erbrechen (POV) nach totaler intravenöser Anästhesie (TIVA) *versus* inhalative Anästhesie (IA) mit einfacher medikamentöser antiemetischer Prophylaxe (AE) bei kindlichen Patienten. IV: Inverse Varianz-Wichtung. Aus: *Schaefer et al. Ped Anesth 2017; 27:1202-1209, mit Genehmigung von John Wiley and Sons.*

Die Effekte Xenons auf das Zentralnervensystems lassen sich somit folgendermaßen zusammenfassen: Die Inzidenz eines POD nach Xenonanästhesie unterschied sich nicht statistisch signifikant im Vergleich zu Sevofluran. Weibliche Patientinnen jüngeren Alters mit längerer Anästhesiedauer zeigen ein erhöhtes Risiko für PONV nach Xenon. Patienten, die eine inhalative Anästhesie und ein Antiemetikum erhielten, wiesen ein Risiko für PONV auf, das vergleichbar war mit Patienten, die eine TIVA erhielten.

3. Diskussion

3.1 Zusammenfassung der Ergebnisse

Grundlegende Eliminationskinetik

- Xenon zeigt einen raschen Abfall innerhalb einer Stunde nach Beendigung der Exposition auf 4% der Konzentration während Exposition. Die weitere Elimination ist gekennzeichnet durch eine biphasische Kinetik mit einer terminalen Elimination erster Ordnung und einer Halbwertszeit von 2,7 Stunden. Xenon ist in geringen Konzentrationen 24 bis 48 Stunden im Blut nachweisbar

Beeinflussung des kardiovaskulären Systems

- Die vorbeschriebene Erhöhung der Noradrenalinkonzentration im Plasma vermittelt Xenon durch NMDA-Rezeptor-abhängige Wiederaufnahmehemmung von Noradrenalin.
- Xenon zeigt keinen Einfluss auf das frequenzkorrigierte QT-Intervall.

Beeinflussung des respiratorischen Systems

- Xenon steigert den maximalen Inspirationsdruck, ohne den transpulmonalen Druck zu beeinflussen. Es erhöht ebenfalls den Atemwegswiderstand sowie die dynamische, nicht aber die statische Compliance. Wenn der Einfluss auf den Atemwegswiderstand um die rheologische Eigenschaften des Edelgases adjustiert wird, wird dieser durch Xenon gesenkt. Xenon zeigt unmittelbar nach Beendigung des Einwaschvorgangs keinen Einfluss auf die Lungenbelüftung. Lediglich bei adipösen Patienten kommt es zu einer marginalen Re-Dorsalisierung der Verteilung des applizierten Tidalvolumens.

Beeinflussung des zentralen Nervensystems

- Es konnte keine Verbesserung in der Inzidenz eines postoperativen Delirs nach Xenon im Vergleich zu Sevofluran festgestellt werden. Patienten nach

Xenonanästhesie zeigen einen verbesserten SOFA-Score am 3. postoperativen Tag sowie leiden vermindert unter schwerwiegenden, unerwünschten Ereignissen.

- Von den Risikofaktoren des Apfel-Scores ist im Rahmen einer Xenonanästhesie lediglich das weibliche Geschlecht prädiktiv für postoperative Übelkeit und Erbrechen. Desweiteren sind jüngeres Patientenalter sowie längere Anästhesiedauer unabhängige Risikofaktoren. Wenn eine medikamentöse Einfachprophylaxe gegeben wird, entspricht das Gesamt-Risiko für postoperative Übelkeit und Erbrechen nach inhalativer Anästhesie bei erwachsenen Patienten und Kindern dem nach totaler intravenöser Anästhesie mit Propofol. Wird nur die späte postoperative Phase betrachtet, reduziert eine medikamentöse Prophylaxe postoperative Übelkeit und Erbrechen bei Erwachsenen, verglichen mit einer totalen intravenösen Anästhesie. Unter Berücksichtigung eines Publikationsbias ist die medikamentöse Prophylaxe einer TIVA im Hinblick auf die Vermeidung postoperativer Übelkeit und Erbrechen überlegen. Im Rahmen einer Xenonanästhesie konnte nicht bewiesen werden, dass eine medikamentöse antiemetischen Prophylaxe mit Dexamethason, einem 5-Hydroxytryptamin Typ III-Rezeptorantagonisten oder einer Kombination beider postoperativer Übelkeit und Erbrechen vorbeugen.

3.2 Die Eliminationskinetik von Xenon im Patienten

Die vorliegenden Daten bestätigen die Annahme, dass der ausgesprochen niedrige Blut/Gas-Verteilungskoeffizient Xenons [64], sowie seine vergleichsweise geringe Lipophilie [70–72] mit einer raschen Elimination der Substanz nach Beendigung der Applikation assoziiert ist. So betrug die Xenonkonzentration im Blut eine Stunde nach Exposition 4% der während der Anästhesie gemessenen Konzentration. Im Vergleich lagen in Tierversuchen die relativen residualen Konzentrationen anderer Anästhetika mit größerem Blut/Gas-Verteilungskoeffizienten wie Halothan zum selben Zeitpunkt um mindestens 50% höher. [118] Diese Beobachtungen stimmen somit gut mit der in klinischen Untersuchungen beschriebenen, sehr kurzen Zeit bis zum Erwachen nach Beendigung der Xenonapplikation [66–69,119] überein und bilden die Grundlage der guten Steuerbarkeit einer Xenonanästhesie.

Trotz initial rascher Elimination suggerierten Voruntersuchungen [74,75] sowie computergestützte, mathematische Modelle [120] eine Nachweisbarkeit von Xenon in Blut (und Urin) bis 24 Stunden nach Exposition. Die vorliegenden Ergebnisse bestätigen dies. Die nähere Betrachtung der Eliminationskinetik Xenons offenbart ein biphasisches Profil: Diese ist durch einen raschen, initialen Abfall der Xenonkonzentration im Blut, gefolgt von einer zweiten Phase mit einer längeren Halbwertszeit gekennzeichnet. Nach initialer Elimination des im Blut befindlichen Xenons über die Lunge, ist die sekundäre, verlangsamte Elimination typischerweise durch langsame Elimination aus tiefen Kompartimenten wie Muskel- und Fettgewebe bedingt. Neben einer gewissen Affinität zu Albumin [121] weist Xenon, verglichen mit anderen inhalativen Anästhetika zwar eine deutlich geringere Lipophilie auf [72], bei einem Ostwald-Koeffizienten von 1,7 bis 1,8 [122] besitzt es dennoch eine ausreichende Löslichkeit, um sich im Fettgewebe anzureichern. Welches Kompartiment letztlich entscheidend für die beschriebene zweite Eliminationsphase ist, lässt sich jedoch aufgrund der vorliegenden Untersuchungen nicht abschließend beantworten. Desweiteren zeigt sich bei inhalativen Anästhetika wie Sevofluran, dass die Sättigung tiefer Kompartimente teilweise mehrere Stunden benötigt. [118] Somit wird die Nachweisbarkeit

Xenons im Blut sehr wahrscheinlich sowohl durch die Dauer der Exposition, als auch den Körperfettgehalt und die generelle körperliche Konstitution des Patienten bestimmt. Es muss jedoch betont werden, dass die gemessenen Xenonkonzentration im Blut nach 24 Stunden weniger als 0,1% der während der Anästhesie gemessenen Konzentration betrug. Eine Detektion dieser minimalen residualen Xenonkonzentrationen war somit nur mittels hochsensitiver Methodik wie der Tandem-Gas-Chromatographie/Massenspektrometrie möglich. In wieweit subanästhetische Konzentrationen Xenons klinisch relevante Effekte aufweisen und die postoperative Erholung beeinflussen, ist bislang nicht bekannt. Eine relevante, direkte Beeinflussung zentraler Organsysteme erscheint zunächst unwahrscheinlich. Interessanterweise konnte jedoch gezeigt werden, dass die intraoperative, niedrigdosierte (<1l/min) nasale Applikation Xenons signifikant postoperative Schmerzen und Opioidbedarf reduziert. [123] Desweiteren konnte bisher lediglich für die Dauer der Exposition inhalativer Anästhetika, jedoch nicht für die gewählte Konzentration eine Dosis-Wirkungsbeziehung hinsichtlich der Inzidenz von PONV gezeigt werden. Somit muss zum jetzigen Zeitpunkt davon ausgegangen werden, dass auch subhypnotische Konzentrationen inhalativer Anästhetika PONV induzieren können. Letztendlich gilt es nun zu klären, welchen direkten Einfluss die hier gemessenen postoperativen Konzentrationen Xenons, die im Verlauf zwischen 4 und 0,1% lagen, auf den postoperativen Verlauf des Patienten haben.

3.3 Beeinflussung des kardiovaskulären Systems

Die vorliegenden Ergebnisse bestätigen zunächst die beschriebene hämodynamische Stabilität unter Xenonanästhesie [79]. In Voruntersuchungen [1] konnte gezeigt werden, dass Xenon seine anästhetischen Eigenschaften per Antagonismus an cerebralen NMDA-Rezeptoren [87,124] vermittelt, ohne die muskelsympathische Aktivität und den Baroreflex zu beeinflussen. [91] Diese Beobachtungen würden jedoch lediglich hämodynamische Stabilität unter Xenon-Monoanästhesie erklären. Die Tatsache, dass Xenon selbst bei zusätzlicher Gabe von kreislaufdepressiven Medikamenten wie Opoiden [125] oder im hämorrhagischen

Schock [126] hämodynamische Stabilität vermittelt, wird erst durch die Beobachtung erklärbar, dass Xenon die Plasmakonzentration von Noradrenalin annähernd verdoppelt [1,91] und somit durch indirekte periphere Vasokonstriktion einem Blutdruckabfall entgegenwirkt. Unklar war jedoch bisher, durch welchen Mechanismus das Edelgas die Noradrenalinkonzentration im Plasma erhöht. Unter physiologischen Umständen erreichen lediglich 10% des über sympathische Nervenendigungen sezernierten Noradrenalins das Blut, während annähernd 90% unmittelbar wieder aufgenommen werden. [127] Da eine Störung der Noradrenalin-Wiederaufnahme den Anteil an Noradrenalin, der den synaptischen Spalt verlässt und ins Blut gelangt, um das bis zu vierfache erhöht [128], lässt sich der beobachtete Anstieg gut mit der hier beobachteten Wiederaufnahmehemmung erklären, insbesondere, da dies unter klinisch üblichen Xenonkonzentrationen nachgewiesen werden konnte. Jedoch müssen zusätzliche Mechanismen wie eine vermehrte Sezernierung von Noradrenalin aus extrasympathischen Neuronen [129] oder eine Hemmung des hepatischen Katecholaminabbaus durch Xenon bedacht werden.

Angesichts des Zusammenhangs zwischen intraoperativer Hypotension mit postoperativem myokardialem Schaden [7–9], sowie postoperativer Morbidität [11] könnte Xenon somit das anästhesie-assoziierte, kardiovaskuläre Risiko vermindern, indem es im Gegensatz zu anderen Anästhetika das sympathische Nervensystems nicht beeinflusst und somit keine arterielle Hypotension verursacht. Weiterhin wirkt es durch Erhöhung der Noradrenalinkonzentration im Plasma einer durch andere Medikamente (wie beispielsweise Opioide) verursachten hämodynamischen Instabilität entgegen. Xenon erscheint somit weiterhin als attraktive Wahl, wenn ein erhöhtes Risiko für perioperative kardiovaskuläre Ereignisse vorliegt, beispielsweise bei Patienten mit koronarer Herzkrankheit und strukturellen Herzerkrankungen. [130] Diese Patienten sind weiterhin besonders vulnerabel für lebensbedrohliche ventrikuläre Herzrhythmusstörungen, die zwar selten, aber lebensbedrohlich sind. [13,131] Ein Risikofaktor hierfür sind Anästhesie-induzierte QT-Verlängerungen, die unter anderem durch andere inhalative Anästhetika begünstigt werden. [14–17] Deren Grundlage stellt wahrscheinlich eine Blockade der für die kardiale

Repolarisierung verantwortlichen, schnell-reagierenden Untereinheit des myokardialen verzögerten Gleichrichter-Kaliumkanals dar. [132] Die vorliegenden Daten zeigen nun, dass Xenon das QTc-Intervall weder bei gesunden Freiwilligen, noch bei Patienten verlängert, was zusätzlich die Sicherheit einer Anästhesie in Bezug auf das kardiovaskuläre Risiko, insbesondere bei kardial vorerkrankten Patienten, steigert. Diese Beobachtungen stimmen überein mit vorhergehenden *in vitro*-Voruntersuchungen, bei denen sich im direkten Vergleich zu Halothan und Isofluran ein um 76% geringerer Einfluss auf auswärts gerichtete Kaliumströme unter Xenon zeigte. [80] Sinnvoll wäre nun die Ermittlung der tatsächlichen Inzidenz ventrikulärer Herzrhythmusstörungen unter Xenon im Vergleich zu anderen Anästhetika. Aufgrund der Seltenheit dieser Ereignisse benötigen entsprechende Studien jedoch eine extrem hohe, prospektiv kaum zu realisierenden Patientenzahl und existieren daher in dieser Form selbst für Arzneimittel mit bekanntem Einfluss auf das QTc-Intervall nicht.

3.4 Beeinflussung des respiratorischen Systems

Es konnte gezeigt werden, dass der regelhaft unter Xenon gesteigerte P_{max} [82] nicht mit einer Erhöhung des letztendlich für pulmonale Schädigungen verantwortlichen P_{tp} einhergeht. Somit kann trotz Erhöhung des am Beatmungsgerät gemessenen inspiratorischen Spitzendrucks angenommen werden, dass Xenon die Gefahr eines pulmonalen Barotraumas im Vergleich zu anderen Anästhetika nicht zusätzlich erhöht. Ein Anästhesie-assoziiertes Risiko durch Begünstigung postoperativer pulmonaler Komplikationen über den Mechanismus eines Barotraumas erscheint durch Xenon angesichts der vorliegenden Ergebnisse somit als äußerst unwahrscheinlich.

Prinzipiell sind zur Erklärung des Anstiegs des P_{max} unter Xenon zwei Mechanismen denkbar: 1. Eine Erhöhung des intraalveolären Drucks mit zunächst Steigerung des P_{tp} und konsekutiver Erhöhung des P_{max}, beispielsweise durch Begünstigung der Entstehung von Atelektasen mit Überblähung abhängiger Lungenareale. 2. eine Steigerung des R_{AW}. In den

vorliegenden Untersuchungen konnte keine Erhöhung des P_{tp} festgestellt werden. Es zeigte sich jedoch eine signifikante Steigerung des R_{AW} um 52% nach Beendigung des Xenon-Einwaschvorgangs. Somit lässt sich der vielbeobachtete Anstieg von P_{max} unter Xenon gezielt auf den Anstieg des R_{AW} zurückführen. Dies erklärt sich durch die verhältnismäßig hohe Dichte und dynamische Viskosität Xenons, die wiederum einen hohen Reibungswiderstand des inspiratorischen Gasgemischs an den Atemwegen bedingen. Um einen zusätzlichen pharmakologischen Effekt auf den Bronchialdurchmesser durch Xenon-induzierte Bronchokonstriktion oder -dilatation zu untersuchen, wurde der relative Anstieg des R_{AW} unter Xenon um die rheologischen Eigenschaften des Edelgases adjustiert und somit der Einfluss erhöhter Reibung auf den Atemwegsfluss mathematisch eliminiert. [133] Unter Annahme eines gemischt laminar-turbulenten Flusses, wie er in den Atemwegen üblicherweise vorherrscht [134], zeigt sich, dass Xenon, verglichen mit 95% Sauerstoff, den durch die Atemwege selbst bedingten Anteil des R_{AW} tatsächlich um etwa 15% senkt. Somit bestätigen diese Ergebnisse am Patienten frühere Untersuchungen im Schweinemodell. [135] In Zusammenschau mit den zuvor präsentierten Ergebnissen lässt sich dies gut durch die Xenon-vermittelte Erhöhung der Katecholaminkonzentrationen im Plasma erklären, da Adrenalin und – in geringerem Maße auch Noradrenalin – eine Bronchodilatation mittels Agonismus am β_2-Adrenorezeptor bewirkt. [136] Zusammengenommen dominiert offensichtlich jedoch die Reibungs-vermittelte Erhöhung des R_{AW} und somit könnte Xenon die klinischen Symptome einer vorbestehenden Obstruktion der unteren Atemwege aggravieren. Xenon sollte somit mit Bedacht bei Patienten mit chronischer Erhöhung des Atemwegswiderstands wie chronisch obstruktiver Lungenerkrankung angewendet werden.

Bereits 1976 stellte L. D. Wood die These auf, dass die Inhalation von Gasen mit hoher Dichte eine Zunahme der Homogenität der Lungenbelüftung bewirken könnte. [83] Da berichtet wurde, dass Xenonanästhesie die Oxygenierung verbessert [73], wurden die vorliegenden Untersuchungen mit der Hypothese durchgeführt, dass Xenon durch Verlängerung der Exspiration einen intrinsischen positiven end-exspiratorischen Druck aufbaut, der den Kollaps dorsaler Lungenareale vermeiden und möglicherweise eine

Rekrutierung atelektatischer Lungenanteile bewirken kann. Jedoch konnte in den hier vorliegenden Untersuchungen allgemein weder ein Einfluss auf die Homogenität der Lungenbelüftung, noch auf die Verteilung des Tidalvolumens und die anästhesie-induzierte Entstehung dorsaler Atelektasen festgestellt werden. Die in der Subgruppe adipöser Patienten statistisch signifikante Re-Dorsalisierung der Lungenbelüftung unter Xenon ist mit lediglich 1% Änderung zum Wert unter Propofol wahrscheinlich nicht von klinischer Relevanz. Um zeitlich bedingte Einflüsse wie beispielsweise das Abklingen der zur Intubation induzierten neuromuskulären Blockade zu minimieren, wurden die Messungen unter Xenonanästhesie unmittelbar nach Beendigung des Einwaschvorgangs durchgeführt. Es besteht somit die Möglichkeit, dass für eine Xenon-induzierte Rekrutierung anästhesie-induzierter Atelektasen [33,34] nicht genug Zeit blieb. In der Tat beschrieben Abramo und Kollegen eine Verbesserung der Oxygenierung durch Xenon bei adipösen Patienten erst eine Stunde nach Beginn der Applikation. [73]. Somit stellt sich die Frage, welchen Effekt eine längere Dauer der Xenonexposition bei Patienten mit höherem Risiko für intraoperative Atelektasen, zum Beispiel bei stärkerer Ausprägung der Adipositas, zeigt. Desweiteren könnte Xenon aufgrund direkter lungenprotektiver Eigenschaften [81] sowie der zuvor beschriebenen, raschen Eliminationskinetik das Auftreten pulmonaler Komplikationen reduzieren, da inhalative Anästhetika mit rascher Elimination eine schnellere Wiederherstellung der Schutzreflexe der oberen Atemwege nach Extubation gewährleisten [4], was wiederum Hypoxämie und Aspiration vorbeugen kann. Die klinische Relevanz direkter und indirekter lungenprotektiver Effekte Xenons muss nun in anschließenden Untersuchungen evaluiert werden.

3.5 Beeinflussung des zentralen Nervensystems

Aufgrund einer effektiven Protektion des zentralen Nervensystems auf zellulärer Ebene [84–86], der beschriebenen, raschen Elimination mit unmittelbarer Wiederherstellung örtlicher, räumlicher und situativer Orientierung [69] sowie seiner primären Wirkung als Antagonist an NMDA-Rezeptoren [87], erschien es plausibel, dass Xenon das Auftreten anhaltender Beeinträchtigungen des zentralen Nervensystems nach Allgemeinanästhesie reduzieren könnte. In der vorliegenden internationalen, multizentrischen, randomisierten Studie mit POD als primärem Endpunkt konnte dies jedoch nicht bestätigt werden.

Obwohl nach Xenonanästhesie ein Drittel weniger Patienten ein POD erlitten als nach Sevofluran, ist dieser Unterschied nicht statistisch signifikant. Mit einer Inzidenz von 13,6% in der Kontrollgruppe war die beobachtete Häufigkeit eines POD allerdings deutlich geringer als in Voruntersuchungen beschrieben [39–41] und weniger als die Hälfte der zur Fallzahlberechnung herangezogenen, erwarteten Inzidenz von 30%. Da zur zuverlässigen Abbildung von Fluktuationen eines POD alle Patienten über fünf Tage zweimal täglich von geschultem Studienpersonal visitiert wurden, erscheint es unwahrscheinlich, dass ein signifikanter Anteil an POD übersehen wurde. Somit ist es naheliegend, dass der Grund für die unerwartet niedrige Inzidenz in der Verteilung der bekannten Prädiktoren und Modifikatoren eines POD begründet liegen: Um den Einfluss nicht-anästhesiebedingter Risikofaktoren möglichst gering zu halten und den Effekt von Xenon – gegen Sevofluran – deutlicher herausarbeiten zu können, wurden in die vorliegende Studie nur Patienten eingeschlossen, die, gemessen anhand einer Punktzahl im *Mini-Mental State Examination-Test* von ≥24, auch nach genauerer Untersuchung keine Demenz aufwiesen. Desweiteren wurden Patienten bereits mit moderater Depression ausgeschlossen, da beide Erkrankungen relevante Risikofaktoren für ein POD darstellen. [38,137] Der explizite Ausschluss dieser Patienten modifizierte somit das übliche Kollektiv von Patienten mit operativer Versorgung einer Hüftfraktur und reduzierte dadurch die in anderen Populationen gemessene hohe Inzidenz eines POD. Tatsächlich mussten über 2000 Patienten untersucht werden, um 256 Patienten einzuschließen. Desweiteren wurde die Narkosetiefe unter Verwendung des

bispektralen Index überwacht und dokumentiert. Da bereits zu Beginn der Studie bekannt war, dass eine zu tiefe Anästhesie ein Risiko für ein POD darstellt [44], stellt deren Vermeidung einen weiteren möglichen Grund für das hier beobachtete unerwartet seltene Auftreten eines POD dar. Letztendlich konnten neben der Allgemeinanästhesie eine Vielzahl weiterer Faktoren identifiziert werden, die die Entstehung eines POD begünstigen können. [137] In Zusammenschau mit den vorliegenden Ergebnisse muss somit postuliert werden, dass der potentielle Einfluss des verwendeten Anästhetikums auf ein POD möglicherweise geringer ausfällt, als zunächst angenommen. Die vorliegende Untersuchung zeigt jedoch, dass das Anästhesie-assoziierte Risiko nach Xenon höchstens dem nach einer Anästhesie mit Sevofluran entspricht.

Eine anhaltende Beeinträchtigung des zentralen Nervensystems während der postoperativen Phase nach Xenonanästhesie wird regelhaft an einer weiteren Stelle beobachtet: In vorherigen Studien zeigte sich, dass Xenonanästhesie die Inzidenz von PONV erhöht. [89] Da die Identifikation von Risikopatienten eine zentrale Rolle in der Entwicklung von Strategien zur Vermeidung von PONV darstellt [57,138], galt es zunächst, Prädiktoren für PONV nach Xenon zu identifizieren. Die vorliegende Untersuchung konnte zeigen, dass der für volatile Anästhetika sowie Propofol validierte und etablierte Apfel-Score [57] PONV nach Xenon nur mit einer eingeschränkten Genauigkeit vorhersagt (Fläche unter der *Receiver Operating Characteristic*-Kurve 0,6). Dies ist dadurch bedingt, dass drei von vier Faktoren – Nichtraucherstatus, postoperative Opioidgabe und PONV nach inhalativen Anästhetika in der Anamnese – keine Prädiktoren für PONV nach Xenonanästhesie darstellen. Lediglich weibliches Geschlecht weist ebenfalls einen prädiktiven Wert nach Xenonanästhesie auf. Die mit zunehmender Expositionsdauer erhöhte Wahrscheinlichkeit für PONV nach Xenon konnte ebenfalls für die Verwendung von Lachgas [139] und volatilen Anästhetika [140] gezeigt werden und scheint somit unabhängig vom Zielrezeptor der einzelnen Substanzen zu sein. Vor dem Hintergrund der Tatsache, dass die Konzentration von Xenon im Blut innerhalb einer Stunde nach Exposition bereits auf 4% der intraoperativen Spiegel abfällt und nach 24 Stunden bei unter 0,1% liegt, erscheint es zumindest fraglich, ob PONV an dieser

Stelle über direkte emetogene Effekte Xenons induziert wird. Es scheint somit wahrscheinlicher, dass indirekte Mechanismen eine Rolle spielen. So interagiert Xenon mit einer Reihe von Genen, die die neuronale Übertragung beeinflussen [141] und induziert Proteine wie den Hypoxie-induzierbaren Faktor 1α. [142,143] Ob dies jedoch tatsächlich zum Pathomechanismus des Xenon-induzierten PONV beiträgt, bleibt aufgrund des bislang unvollständigen Verständnisses der Pathogenese von PONV ungeklärt.

Das prinzipiell emetogene Potential Xenons erzeugt an dieser Stelle ein Dilemma: Soll die Inzidenz von PONV im Sinne eines günstigen postoperativen Verlaufs bei Patienten mit hohem Risiko reduziert werden, so empfiehlt ein internationaler Konsens [59] die Vermeidung inhalativer Anästhetika und Durchführung einer TIVA. Dies bedingt wiederum den Verzicht auf die Vorteile Xenons wie rasche Elimination und vorteilhafter Beeinflussung des kardiovaskulären Systems. Die vorliegenden Daten aus zwei Meta-Analysen zeigen an über 2000 erwachsenen Patienten sowie über 550 Kindern, dass das durch inhalative Anästhetika bedingte, erhöhte Risiko für PONV durch eine einmalige Gabe einer einfachen medikamentösen antiemetischen Prophylaxe auf das Risiko einer Propofol-basierten TIVA gesenkt werden kann. Interessanterweise zeigt sich die medikamentöse Prophylaxe sogar effektiver, wenn es um die Vermeidung von PONV in der späteren postoperativen Phase (ab 2 bis 6 Stunden nach Operation) bei Erwachsenen Patienten geht. In einer randomisierten Studie an über 1180 Patienten konnten Apfel und Kollegen die Verwendung inhalativer Anästhetika als unabhängigen Risikofaktor für frühes, aber nicht spätes PONV identifizieren. [140] Somit schützt eine medikamentöse Prophylaxe offensichtlich in der frühen postoperativen Phase vor der emetogenen Wirkung inhalativer Anästhetika. Nach Abklingen dieser Effekte in der späten postoperativen Phase ist sie dann einer TIVA mit Propofol, dem selbst antiemetische Effekte zugeschrieben werden [144], überlegen. Desweiteren konnte in der Meta-Analyse an erwachsenen Patienten anhand der objektivierten Analyse des Funnel-Plots eine signifikante Asymmetrie festgestellt werden, die eine Publikationsverzerrung zugunsten einer TIVA suggeriert. Eine Sensitivitätsanalyse, bei der ein Modell fixierter Effekte zur Reduktion des Effekts kleinerer Studien angewandt wurde, zeigt eine Reduktion

des Risikos für PONV nach antiemetischer Prophylaxe im Vergleich zu einer TIVA. Möglicherweise ist eine medikamentöse Einfachprophylaxe einer TIVA somit auch in Bezug auf die Gesamtinzidenz von PONV überlegen. Die Publikationsverzerrung lässt sich vielleicht durch die Tatsache erklären, dass bereits zu Zeiten der durch Thomas Morton eingeführten Ätheranästhesie die Verwendung inhalativer Anästhetika mit Übelkeit und Erbrechen assoziiert war. Da Propofol zusätzliche antiemetische Effekte aufweist [144], galt eine TIVA somit früh als Mittel der Wahl zur Vermeidung von PONV. Untersuchungen, die einen positiven Effekt einer TIVA im Vergleich zu einer inhalativen Anästhesie in Bezug auf PONV zeigten, hatten möglicherweise somit eine höhere Wahrscheinlichkeit, publiziert zu werden.

Es ist auffällig, dass die Inzidenz von PONV bei Erwachsenen, beziehungsweise POV bei Kindern, trotz Prophylaxe mit 39 beziehungsweise 33% der Patienten noch sehr hoch lag. Dies kann dadurch erklärt werden, dass alle Studien zur Minimierung der benötigten Fallzahl ein entsprechendes Kollektiv mit hohem Risiko für PONV bzw. POV untersuchten. Dennoch ist eine Inzidenz von mehr als einem Drittel aller Patienten im klinischen Alltag inakzeptabel hoch. Die vorliegenden Daten unterstreichen somit die Notwendigkeit einer multiplen antiemetischen Prophylaxe. Apfel und Kollegen konnten im Rahmen einer großen, internationalen Multicenterstudie zeigen, dass Antiemetika mit unterschiedlichen Angriffspunkten, wie beispielsweise 5-Hydroxytryptamin Typ III-Rezeptorantagonisten sowie dem antidopaminergen Droperidol, unabhängig voneinander die PONV-Inzidenz um jeweils circa 25% senken. [51] Aufgrund der Vielzahl an verfügbaren Antiemetika mit unterschiedlichen Wirkmechanismen, lassen sich somit genügend Substanzen kombinieren [59], um auch unter Verwendung inhalativer Anästhetika in Hochrisikokollektiven eine klinisch zufriedenstellende PONV-Inzidenz zu erreichen. Angesichts des unterschiedlichen Wirkmechanismus von Xenon sowie der Tatsache, dass Prädiktoren für PONV nach Xenon nicht an jeder Stelle mit denen nach inhalativen Anästhetika übereinstimmen, musste weiterhin geklärt werden, ob diese Substanzen auch PONV nach Xenonanästhesie effektiv vermeiden können. Hierzu wurde in der vorliegenden Studie ein *Propensity Score Matching* durchgeführt. Nach Abschluss des Matchings zeigte sich eine gute Kontrolle möglicher

Störvariablen jedoch konnte kein prophylaktischer Effekt der verwendeten Antiemetika Dexamethason (4-8mg), Granisetron (1-3mg), Tropisetron (2-4mg) oder Ondansetron (4-8mg) feststellen werden. Die Dosierungen der verwendeten Substanzen waren hierbei allseits im nach inhalativen Anästhetika als effektiv beschriebenen Bereich. [51,59,145,146] Es ist bekannt, dass Antiemetika eine ineffektive Kontrolle von PONV bieten, wenn zuvor eine Prophylaxe mit demselben Wirkmechanismus verabreicht wurde. [147,148] Da Xenon als Antagonist am 5-Hydroxytryptamin Typ III-Rezeptoren fungiert [149], erklärt dies möglicherweise die fehlende Effektivität von Antiemetika, die ebenfalls über diesen Mechanismus wirken. Weiterhin erhielt der Großteil der Patienten eine Prophylaxe mit Dexamethason oder einem 5-Hydroxytryptamin Typ III-Rezeptorantagonisten. Somit sollten auf der Basis der vorliegenden Daten zur Prophylaxe von PONV nach Xenon zunächst Substanzen mit anderen Wirkmechanismen als Dexamethason oder 5-Hydroxytryptamin Typ III-Rezeptorantagonisten verwendet werden, bis die Wirksamkeit der gängigen Antiemetika zur Vermeidung von PONV nach Xenonanästhesie in randomisierten, kontrollierten Studien untersucht wurde.

3.6 Synthese und Ausblick

In der vorliegenden Arbeit wurden die Eliminationskinetik sowie Einflüsse des als Anästhetikum verwendeten Edelgases Xenon auf das Herz-Kreislauf-System, das respiratorische System und das zentrale Nervensystem untersucht. Es konnte gezeigt werden, dass Xenon gemäß seines niedrigen Blut/Gas-Verteilungskoeffizienten sowie seiner vergleichsweise geringen Lipophilie rasch eliminiert wird. Residuale Xenonkonzentrationen, die sich im Patientenblut 24 Stunden nach Anästhesie nachweisen lassen, liegen im Bereich von unter 0,1% der Konzentration während Anästhesie. Xenon vermittelt hämodynamische Stabilität, indem es das sympathische Nervensystem nicht beeinflusst und NMDA-Rezeptorabhängig die zelluläre Wiederaufnahme von Noradrenalin hemmt. Hierdurch steigert Xenon die systemischen Katecholaminspiegel, was hämodynamische Stabilität trotz zusätzlicher Verwendung kreislaufdepressiver Substanzen oder im hämorrhagischen Schock erklärt. Xenon beeinflusst das myokardiale QTc-Intervall nicht und stellt zusammengenommen eine attraktive Wahl für Patienten mit kardiovaskulären Vorerkrankungen und hohem Risiko für perioperative kardiale Ereignisse dar. Xenon erhöht signifikant den maximalen Inspirationsdruck, indem es den Atemwegswiderstand erhöht. Es beeinflusst jedoch nicht den transpulmonalen Druck. Ein Anästhesie-assoziiertes Risiko im Hinblick auf das respiratorische System durch Begünstigung postoperativer pulmonaler Komplikationen über den Mechanismus eines Barotraumas unter Xenon erscheint somit als sehr unwahrscheinlich. Es konnte nicht bewiesen werden, dass Xenon die Inzidenz eines postoperativen Delirs zu senken vermag. Weiterhin verursacht Xenon eine anhaltende, postoperative Beeinträchtigung des zentralen Nervensystems im Sinne postoperativer Übelkeit und Erbrechen, insbesondere bei jungen Frauen, die sich einer länger dauernden Xenonanästhesie unterziehen. Prinzipiell kann jedoch das emetogene Potential inhalativer Anästhetika durch die Gabe einer einfachen antiemetischen Prophylaxe kompensiert werden. Ob dies letztendlich auch für Xenon gilt, bleibt abzuwarten, da nicht gezeigt werden konnte, dass gängige Antiemetika wie Dexamethason oder 5-HT_3-Rezeptorantagonisten PONV nach Xenon effektiv entgegenwirken können. Zusammenfassend stellt Xenon

aufgrund seiner günstigen Pharmakokinetik und der Induktion hämodynamischer Stabilität ein vielversprechendes Anästhetikum zur Vermeidung anästhesieassoziierter Risiken und der günstigen Beeinflussung des postoperativen Verlaufs dar.

Aus den vorgestellten Ergebnissen ergeben sich eine Reihe neuer Fragestellungen, deren Beantwortung das Ziel folgender Untersuchungen sein muss. So suggeriert der Nachweis von Xenon bis zu 48 Stunden im Blut von Patienten, wenn auch in sehr niedrigen Konzentrationen, eine Speicherung in „tiefen Kompartimenten“ wie Muskulatur oder Fettgewebe. Es gilt nun zu differenzieren, wie und in welchem Gewebe Xenon im Körper gespeichert wird und wie sich die körperliche Konstitution verschiedener Patienten auf die Elimination auswirkt. Weiterhin muss der Einfluss der Dauer der Exposition auf die Elimination ermittelt und die klinische Relevanz residualer Xenonkonzentrationen untersucht werden. Die Beobachtung, dass Xenon NMDA-Rezeptorabhängig die zelluläre Wiederaufnahme von Noradrenalin hemmt, wirft die Frage auf, wie der NMDA-Rezeptor mit dem humanen Noradrenalintransporter interagiert und welchen genauen Einfluss Xenon an dieser Stelle ausübt. Es bleibt weiterhin ungeklärt, wie sich Xenonanästhesie auf das QT-Intervall sowie potentielle Herzrhythmusstörungen kardial vorerkrankter Patienten und solchen mit vorbestehender QT-Verlängerung auswirkt. Außerdem gilt es nun, den Einfluss des Edelgases auf die pulmonale Mechanik von Patienten mit schweren Lungenerkrankungen wie dem Adult Respiratory Distress Syndrome zu untersuchen. Schließlich kann aus den vorliegenden Untersuchungen die Hypothese generiert werden, dass ein spezielles Patientenkollektiv ausgeprägt adipöser Patienten möglicherweise durch eine Begünstigung der Ventilationsverteilung von Xenon profitiert. Dies, sowie der Einfluss einer längeren Expositionsdauer mit Xenon auf die Lungenbelüftung sollte in einer folgenden randomisierten kontrollierten Studie untersucht werden. Folgende Untersuchungen müssen weiterhin die niedrigere Inzidenz eines postoperativen Delirs bei entsprechender Selektion von Patienten im Rahmen prospektiver Fallzahlkalkulationen berücksichtigen. Schließlich ist die Pathophysiologie der Induktion von Übelkeit durch Xenon noch nicht verstanden. Dies

sowie die Effektivität verschiedener Antiemetika unter Xenon gilt es nun, in weiteren Studien systematisch zu untersuchen.

4. Zusammenfassung

Inhalative Anästhetika können durch Interaktion mit zentralen Organsystemen signifikant den perioperativen Verlauf beeinflussen. So begünstigt eine rasche Eliminationskinetik eine gute Steuerbarkeit der Anästhesie mit potentieller Vermeidung früher respiratorischer Komplikationen. Diese können weiterhin durch direkte Interaktion des Anästhetikums mit dem respiratorischen System beeinflusst werden. Eine Depression des kardiovaskulären Systems sowie eine Beeinflussung des zentralen Nervensystems im Sinne eines postoperativen Delirs (POD), sind assoziiert mit erhöhter perioperativer Letalität. Schließlich beeinträchtigen postoperative Übelkeit und Erbrechen (PONV) die postoperative Erholung. Xenon verfügt über die günstigsten pharmakokinetischen Eigenschaften aller inhalativen Anästhetika. Es vermittelt hämodynamische Stabilität und wirkt nicht über den GABA-Rezeptor. Xenon erhöht jedoch den Inspirationsdruck und erhöht die Inzidenz von PONV. Zur Analyse des Einflusses von Xenon auf Anästhesie-assoziierte Risiken und die postoperative Erholung wurde die Eliminationskinetik Xenons sowie die Beeinflussung des kardiovaskulären, des respiratorischen und des zentralen Nervensystems im Rahmen von acht Originalarbeiten an Patienten, gesunden Freiwilligen sowie durch Meta-Analysen randomisierter, kontrollierter Studien systematisch untersucht.

Untersuchungen

Die Eliminationskinetik von Xenon wurde durch Ermittlung des Xenongehalts mittels Tandem-Gas-Chromatographie/Massenspektrometrie im Blut von Patienten quantifiziert. Die Xenonkonzentration im Blut fiel innerhalb einer Stunde nach Anästhesie von 1341 auf 54 µmol l^{-1} ab. Anschließend wurde Xenon mit einer Kinetik 1. Ordnung eliminiert und war bis zu 48 Stunden im Blut nachweisbar.

Zur Untersuchung der Vermittlung hämodynamischer Stabilität durch Xenon wurde, basierend auf Voruntersuchungen, der Einfluss Xenons auf die zelluläre Noradrenalinwiederaufnahme geprüft sowie der Einfluss auf das kardiale QTc-Intervall beschrieben. Xenon reduzierte signifikant die Noradrenalinwiederaufnahme humaner Neuroblastomzellen, die den NMDA-Rezeptor exprimieren. Das QTc-Intervall änderte sich

unter Xenonanästhesie bei gesunden Probanden (409 ±45 versus 409 ±30 ms, p=0,55, mittlere Änderung +0,11 ms [-22,4; 22,7]) und Patienten (414 ±25 versus 417 ±32 ms, p=0,3, mittlere Änderung +4,4ms [-4,6; 13,5]) nicht.

Der Einfluss von Xenon auf die Mechanik und Belüftung der Lunge wurde durch Ermittlung des transpulmonalen Drucks sowie elektrischer Impedanztomographie an Patienten untersucht. Xenon erhöhte signifikant den inspiratorischen Spitzendruck von 20,8 ±3 auf 22,6 ±3 cm H_2O (p<0,001) sowie den Atemwegswiderstand (0,94 ±0,16 versus 1,42 ±0,25 cm H_2O l^{-1} s, p<0,001) ohne Beeinflussung des transpulmonalen Drucks (1,5 ±3,6 versus 2,0 ±3,9 cmH_2O, p=0,15). Es zeigte allgemein keinen Einfluss auf die ventilierte Lungenfläche (288 ±85 versus 289 ±86 Pixel, p=0,99), die dorsoventrale Verteilung (*Center of Ventilation Index, CVI* 0,59 ±0,04 versus 0,59 ±0,04, p=0,29) sowie die Homogenität der Lungenbelüftung (Inhomogenitätsindex 0,37 ±0,03 versus 0,37 ±0,03, p=0,99). Lediglich in einer Subgruppe adipöser Patienten reduzierte es den *CVI* (0,600 versus 0,596, p=0,002).

Der Einfluss Xenons auf die Inzidenz eines POD wurde im Rahmen einer multizentrischen, randomisierten, kontrollierten klinischen Studie gegen Sevofluran geprüft. Es konnte kein Unterschied hinsichtlich der Inzidenz eines POD innerhalb der ersten vier postoperativen Tage nach Xenon (12 von 124 Patienten, 9,7%) versus Sevofluran (18 von 132 Patienten, 13,6%) festgestellt werden. Insgesamt war die Inzidenz eines POD niedriger als angenommen (30 von 256 Patienten, 11,7%).

Prädiktoren für PONV nach Xenonanästhesie wurden anhand multivariater Adjustierung der Daten einer prospektiven Kohortenstudie ermittelt. Weibliches Geschlecht (adjustiertes Quotenverhältnis, aOR 1,76 [1,08;2,89], jüngeres Patientenalter (aOR 0,82 pro 10 Jahre [0,69; 0,97]) sowie längere Anästhesiedauer (aOR 1,36 pro Stunde [1,17;1,59]) erhöhten signifikant das Risiko für PONV nach Xenon. Anschließend wurde die Attenuierung emetogener Effekte inhalativer Anästhetika durch Gabe einer medikamentösen antiemetischen Prophylaxe anhand zweier Meta-Analysen quantifiziert. Das Risiko für PONV, respektive postoperatives Erbrechen unterschied sich nicht zwischen inhalativer Anästhesie mit antiemetischer medikamentöser Prophylaxe und totaler intravenöser

Anästhesie bei 2.051 erwachsenen Patienten (RR 1,06 [0,85;1,32], p=0,60) und 558 Kindern (RR 0,99 [0,77; 1,27], p=0,95). Erwachsene litten nach totaler intravenöser Anästhesie signifikant häufiger unter PONV in der späten postoperativen Phase (RR 1,41 [1,10;1,79], p=0,006).

Schlussfolgerungen

Xenon zeigt generell einen günstigen Einfluss auf Anästhesie-assoziierte Risiken und die postoperative Erholung und stellt somit eine attraktive Wahl dar: Es zeichnet sich durch eine rasche Eliminationskinetik aus und vermittelt durch Hemmung der zellulären Wiederaufnahme von Noradrenalin hämodynamische Stabilität. Nachteilig ist die Induktion postoperativer Übelkeit und Erbrechens, insbesondere bei jüngeren weiblichen Patientinnen, die nach inhalativen Anästhetika prinzipiell durch die Gabe einer medikamentösen antiemetischen Prophylaxe kompensiert werden kann. Jedoch konnte kein protektiver Effekt der gängigen Antiemetika im Rahmen einer Xenonanästhesie nachgewiesen werden.

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7. Publikationen der zugrundeliegenden Originalarbeiten

7.1 Xenon elimination kinetics following brief exposure

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Xenon elimination kinetics following brief exposure

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Xenon is a modern inhalative anaesthetic with a very low solubility in tissues providing rapid elimination and weaning from anaesthesia. Besides its anaesthetic properties, Xenon promotes the endogenous erythropoietin biosynthesis and thus has been enlisted as prohibited substance by the World Anti-Doping Agency (WADA). For effective doping controls, knowledge about the elimination kinetics of Xenon and the duration of traceability are of particular importance. Seventy-seven full blood samples were obtained from 7 normal weight patients undergoing routine Xenon-based general anaesthesia with a targeted inspiratory concentration of 60% Xenon in oxygen. Samples were taken before and during Xenon inhalation as well as one, two, 4, 8, 16, 24, 32, 40, and 48 h after exposure. Xenon concentrations were assessed in full blood by gas chromatography and triple quadrupole tandem mass spectrometry with a detection limit of 0.25 μmol/L. The elimination of Xenon was characterized by linear regression of log-transformed Xenon blood concentrations, as well as non-linear regression. Xenon exposure yielded maximum concentrations in arterial blood of 1.3 [1.1; 1.6] mmol/L. Xenon was traceable for 24 to 48 h. The elimination profile was characterized by a biphasic pattern with a rapid alpha phase, followed by a slower beta phase showing a first order kinetics ($c[Xe] = 69.1e^{-0.26x}$, $R^2 = 0.83$, $t_{1/2} = 2.7$ h). Time in hours after exposure could be estimated by $50*\ln(1.39/c[Xe]^{0.077})$. Xenon's elimination kinetics is biphasic with a delayed beta phase following a first order kinetics. Xenon can reliably be detected for at least 24 h after brief exposure. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: doping in sports; kinetics; performance-enhancing substances; pulmonary elimination; Xenon

Introduction

Xenon was approved as a general anaesthetic in Europe more than 10 years ago. Its very low solubility in tissues and blood is considered to be a major advantage in clinical anaesthesia.[1] Accordingly, when Xenon administration is discontinued in patients under Xenon-based anaesthesia, it is rapidly eliminated via the lungs and associated with almost immediate awakening.[2,3] Besides its anaesthetic properties, Xenon inhibits the metabolism of the sympathetic vasoconstrictor norepinephrine.[4] As a consequence, arterial hypotension is rarely observed during Xenon-based anaesthesia. Xenon was further described to stimulate the release of endogenous erythropoietin,[5-7] which has potentially been recognized by some athletes who were reported to have inhaled Xenon to gain performance advantages.[8] In turn, the World Anti-Doping Agency (WADA) added Xenon to the list of prohibited substances in sports in September 2014.[9] Doping controls are facilitated when the precise elimination characteristics of the substance are available. Accordingly, the time line of Xenon exposure prior to competition can be estimated. Finally, duration of traceability from blood has only been investigated in a single individual.[10] Since ethical concerns were anticipated when planning on exposing athletes to Xenon, Xenon elimination kinetics were determined from patients scheduled for surgery under routine Xenon-based general anaesthesia.

Materials and methods

After IRB approval (Ethikkommission der medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf, Germany, study number 4635), registration at ClinicalTrials.gov (NCT02105077) and written informed consent, patients scheduled for routine Xenon-based general anaesthesia were included into this prospective observational study. Anaesthesia was induced and maintained at the discretion of the attending anaesthesiologist: Inhaled Xenon (Xenon pro Anaesthesia, Air Liquide Deutschland GmbH, Düsseldorf, Germany) was combined with the opioid analgesic remifentanil (0.1-0.5 $\mu g\,kg^{-1}\,min^{-1}$). Xenon anaesthesia was administered with a closed-circuit anaesthesia machine (Felix Dual, Air Liquide international, Paris, France) at an initial targeted inspiratory concentration of 60%, allowing continuous recording of inspiratory Xenon concentrations. From these data, the total dose of Xenon as inspiratory fraction (in %), multiplied by the duration of Xenon exposure in hours (F_I% h), as well as the median inspiratory concentration was calculated for each patient.

Study subjects

To increase comparability to athletes, we limited our collective to patients with a normal body mass index (20–25) since Xenon elimination may be influenced by body fat content due to a high affinity

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to fatty tissue.[11] Also, patients with impaired kidney function (creatinine < 1.2 mg/dL, urea < 56 mg/dL) and abnormal haematocrit values (outside the normal range of 37–45% in female and 42–50% in male patients) were excluded. Further, to reduce influence of significant blood loss during surgery, only patients undergoing minimally invasive vascular surgery were included.

Blood samples

To depict Xenon's elimination kinetics, blood samples were drawn from routinely placed central venous catheters[12] before exposure and at 1, 2, 4, 8, 16, 24, 32, 40, and 48 h after discontinuation of Xenon application. Additionally, to assess maximum blood concentrations, a blood sample was obtained from additional routinely placed arterial catheters shortly before discontinuation of Xenon. Values from this measurement were compared to expected concentrations, as calculated from the respective inhalative Xenon concentration with a blood-gas distribution coefficient of 0.115[1] and the assumption of ideal gas properties at 37 °C[13] with an alveolar pH_2O of 6.3 kPa. Samples were drawn in 3 mL EDTA tubes (Vacutainer®, BD, Heidelberg, Germany), which were immediately sealed airtight (Blenderm™, 3 M Deutschland GmbH, Neuss, Germany). To allow conditions comparable to routine doping testing, samples were stored at +4 °C and a maximum 30 h time to analysis was allowed.

Quantification of xenon concentrations by gas chromatography-mass spectrometry

Xenon concentrations in full blood were analysed using gas chromatography-triple quadrupole tandem mass spectrometry (GC-MS/MS). Sample preparation and the GC-MS/MS protocol were adapted from two earlier studies.[10,14] In brief, 1 mL of each sample was placed in an autosampler vial (Macherey-Nagel, Düren, Germany), fortified with 1.8 μmol of internal standard (d_6-cyclohexanone) and heated at 70 °C for 20 min. Subsequently, 10 μL of the headspace was injected into the GC-MS/MS system with a HP-Ultra 1 column (Agilent, Waldbronn, Germany) in split mode (1:5) with helium used as carrier gas at 1.10 bar. In contrast to the published methodology, the volume injected from the headspace was increased to 10 μL, facilitating a decrease of the detection limit from 0.5 to 0.25 μmol/L. Nitrogen was used as collision gas (collision energy 5 eV). For quantification, blank EDTA blood samples fortified with different Xenon concentrations (0.5, 5, 50, and 500 μmol/L) were prepared by serial dilution, analysed and compared to patient samples to estimate concentrations, providing an accurate measurement of Xenon with a coefficient of variation below 20%.

Sample size estimation and statistical analysis

Xenon concentrations in pig blood during exposure of 67% Xenon have been reported to be 70 ± 9 μl/mL,[12] which corresponds to 63 ± 8.1 μL/mL at 60% inspiratory Xenon concentrations, or 2.4 ± 0.3 mmol/:L at 37 °C.[13] We estimated the characteristic of Xenon elimination to be best described by an exponential decay function. Also, we knew from previous findings that Xenon was traceable for at least 24 h.[10] With these assumptions, we created a model data set by means of a hypothesized decay function, which was described by $c[Xe] = 2.4\ e^{-0.38\ h}$, where *c[Xe]* is the Xenon concentration and *h* the time in hours after discontinuation of inhalation. We found that at least 5 observations per time point were needed to detect a significant decrease of xenon concentrations at a 0.05 alpha level. To compensate for possible loss due to transport, storing or processing of the blood samples, we increased our sample size to a total of 7 patients.

Raw data are expressed as median [interquartile range]. Also, Xenon concentrations were log-transformed and, after visual inspection, linear regression analyses on log-transformed values were performed. Since log transformation of 0 is impossible, values below the limit of detection were set to 0.01 μmol/L. When visual inspection indicated an exponential decay of xenon concentrations, non-linear regression analysis with multiple curve fits was applied to raw values in order to maximize goodness-of-fit, as quantified by the R^2 value. Initially, a single exponential, two-factor function was calculated. Subsequently, multiple-factor and double-exponential functions were calculated and R^2 values were compared. Calculations were made with SigmaPlot 13.0 (Systat Software, Inc., San José, CA, USA) and SPSS 22 (IBM, Armonk, NY, USA).

Results

Seventy-seven full blood samples were obtained and analyzed from seven consecutive patients who underwent Xenon-based anaesthesia. Table 1 depicts patient characteristics as well as anaesthesia and surgery details.

Management of anaesthesia

Duration and concentration of Xenon exposure for all individual patients are expressed in Figure 1. The total dose of Xenon was 137

Table 1. Patient characteristics and anaesthesia details. Values are median [interquartile range] or absolute numbers (%)

Age (years)	74 [66;77]
Female	3 (43)
Weight (kg)	66 [65;77]
Height (cm)	173 [172; 181]
Body mass index	24 [21;24]
Preoperative haematocrit (%)	41 [39; 43]
Duration of anaesthesia (min)	185 [160; 225]
Duration of Xenon inhalation (min)	146 [121;187]
Xenon consumption (L)	22.9 [21; 23]
Type of surgery	
Endovascular aortic repair	6 (86)
Carotid endarterectomy	1 (14)
Estimated blood loss (mL)	80 [50;100]

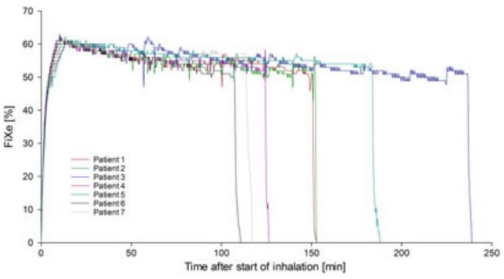

Figure 1. Time course of inspiratory Xenon concentrations (F_iXe) for all 7 patients.

[110; 154] F_i% h with a median Xenon concentration of 54 [54;54] F_i %. At the end of anaesthesia, when arterial samples were obtained, the inspiratory Xenon concentrations were 52 [51; 54] F_i%. To facilitate surgical tolerance, 0.41 [0.40;0.45] µg kg^{-1} min^{-1} intravenous remifentanil was administered additionally.

Xenon concentrations and duration of traceability

Xenon concentrations in full blood were below the detection limit in all samples before exposure. During exposure, the expected calculated concentration was 2062 [2023; 2122] µmol/L. The measured arterial Xenon blood concentration during inhalation in blood was lower, reaching 1341 [1069;1630] µmol/L. Subsequently, Xenon concentrations in central venous blood dropped to 54 [49; 64] µmol/L within the first hour after discontinuation (Figure 2). Xenon was traceable for 48 h in one, 40 h in two, 32 h in two, and 24 h in another two patients.

Elimination profile

Log-transformation of concentrations showed a biphasic pattern with a rapid decrease of concentrations within the first hour (-1.34 log(c[Xe]) per hour, R^2 0.97) and a subsequent slower decrease (-0.07 log(c[Xe])per hour, R^2 0.77, Figure 3). The second elimination phase fitted a single exponential, two-factor function ($c[Xe] = 69.1e^{-0.26h}$, $R^2 = 0.83$). Applying double-exponential and multiple factor functions did not increase goodness-of-fit ($R^2 = 0.83$ for each subsequent curve). The curve revealed a concentration-dependent elimination of first order kinetics (Figure 4). Time in hours after Xenon inhalation could be estimated as $50*\ln(1.39*c[Xe]^{-0.077})$ with a Xenon half-life in the second elimination phase of 2.67 h.

Discussion

The Xenon elimination kinetics presented a rapid initial alpha phase, followed by a much slower beta-elimination that was characterized by a first order kinetics and a Xenon half-life of 2.7 h. Despite its very low solubility in tissues, Xenon exposure was reliably detected for at least 24 h in each patient.

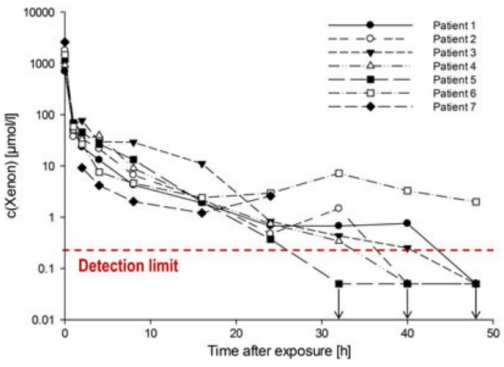

Figure 2. Intra- and postoperative Xenon blood concentrations in all 7 patients.

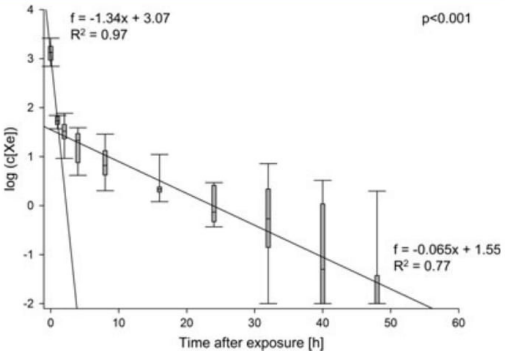

Figure 3. Log-transformation of Xenon concentrations with linear regression analysis showing a biphasic elimination pattern. Mathematical functions for regression lines are indicated next to the respective line with corresponding R^2 values.

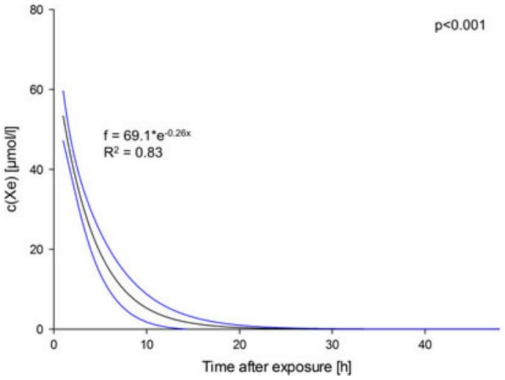

Figure 4. Non-linear regression of the second (beta-) elimination phase showing a first order kinetics. Black: regression line; Blue: 95% confidence interval.

Xenon concentrations and duration of traceability

Our results confirm previously reported data from a single patient, where Xenon could be traced in blood 24 h after exposure.[10] Also, Xenon is consistently detectable in urine from patients at least 24 h after anaesthesia, and is even traceable for more than 40 h after exposure in 40% of patients.[14] In this context, our data confirm the reliable traceability in human blood 24 h after Xenon inhalation and, taken together with previously published data, suggest equal success rates from blood and urine samples. However, testing for Xenon more than one day after exposure will return negative results in many subjects.

During inhalation, measured arterial Xenon concentrations of 1.3 mmol/L differed from calculated expected concentrations of 2.0 mmol/L. This difference can be explained since we allowed a sample storage time for up to 30 h before analysis to facilitate conditions comparable to those observed for detection of doping in athletes. In a previous study, storage times of 20–30 h decreased signal intensity of Xenon isotope 129 by about 35%.[10] With this

assumption, actual arterial concentrations during inhalation can be corrected to 1.3 mmol/L x $(1\text{-}0.35)^{-1}$ = 2.0 mmol/L, and are therefore equal to expected values. For these reasons, storage time before analysis should be reduced whenever possible. Also, superfluous open-close-cycles of doping control sample containers intended for Xenon analyses should be avoided.[10]

Elimination profile

The observed biphasic elimination profile is typical for substances that are stored in multiple compartments, such as inhalational anaesthetics.[15-17] Xenon has the lowest blood-gas-partition coefficient of all anaesthetics,[1] causing rapid elimination from blood when alveolar concentrations decrease. However, after initial alpha-elimination via the lungs, residual Xenon in blood results from its release from deep compartments as indicated by beta-elimination. In this context, tissue affinity might play a role. Xenon has a rather high solubility in oil, with an Ostwald's coefficient of 1.7 to 1.8 at 37 °C,[11] providing affinity to adipose tissue. Also, as with other lipophilic inhalative anaesthetics such as sevoflurane, saturation of deep compartments may take several hours.[17] Therefore, duration of exposure,[18] as well as body fat content may be determinants of the traceability of Xenon after inhalation. Of note, binding to blood proteins may also play a role, since Xenon exerts a high affinity to albumin[19] and is enriched in cellular compartments of the blood.[11]

From our data, the time after single Xenon exposure can be calculated from measured residual concentrations in blood. However, repetitive exposition might increase residual blood concentrations, as opposed to single exposure.[20] Consequently, one next step needs to be the investigation of the influence of repetitive exposition to Xenon, such as described in Russian athletes over several years.[8] Although no published data exist on the efficacy of different patterns of inhalation, a presentation made available to Russian athletes and sport officials recommends repetitive Xenon inhalation 'two to three times over a period of 7 to 10 days'.[8,21] In a recent study, Katz *et al.* established a computer model for the elimination of xenon from the human body after repetitive exposure.[20] Since human data had not been available, the authors validated their calculation on data derived from porcine xenon exposure.[12] It is suggested that residual Xenon may be detected for at least 24 h following a single exposure. Of note, our results are in line with this theoretical model confirming the assumptions made in a clinical situation of Xenon administration. Moreover, repetitive exposition to Xenon may increase residual xenon concentrations,[20] allowing its detection for an even longer period after termination of the last exposure. However, these results after chronic exposure to xenon in a computer model need to be verified prospectively in humans.

Limitations

Due to ethical concerns, we enrolled patients undergoing routine Xenon-based anaesthesia and did not perform Xenon inhalation in young athletes. Naturally, this needs to be considered when transferring our findings to professional sports since patients undergoing vascular surgery differ from athletes in several aspects that might influence Xenon storage in the body, elimination and traceability. Assuming that fatty tissue is a major storage compartment of Xenon, duration of traceability in athletes with minimum body fat content may be reduced. Additionally, haematocrit, age, fluid status and several other factors may diverge between patients and athletes. However, to increase comparability, we excluded patients with an abnormal body mass index (over 25 or under 20). Additionally, any possible influence of surgery was kept to a minimum by restricting to minimally invasive procedures with clinically irrelevant blood loss.

Xenon was administered to our patients with inspiratory concentrations of 54%, depending on the duration of anaesthesia and admixture of nitrogen. Since so far, data on Xenon-induced erythropoietin release are scarce and no dose-response relationship has been established, Xenon concentrations in our study might not necessarily equal concentrations used for doping purposes. Ma *et al.* administered 70% Xenon in oxygen for 2 h to mice and found an increase to 160% in erythropoietin concentrations 24 h later.[6] In patients following cardiac surgery under Xenon-based anaesthesia (median dose 118 $F_{i\%}$ h), erythropoietin plasma concentrations were 48% higher in patients with Xenon anaesthesia than in patients receiving sevoflurane.[7] As a result, and probably based on additional unpublished data, the aforementioned Russian presentation recommends inhalation of a 50:50 Xenon:Oxygen mixture for performance enhancement.[8,21] Therefore, inhaled concentrations in our study reflect recent practice and recommendations of Xenon inhalation for doping purposes.

In conclusion, we were able to show that humans can reliably be tested for Xenon inhalation within 24 h after exposure, and occasional positive test results may even be achieved more than 40 h after inhalation. This prolonged traceability is the result of a biphasic elimination kinetics including delayed beta elimination. Future investigations should focus on the influence of repetitive administration of Xenon on its traceability, and need to further differentiate the influence of body fat content to increase comparability to athletes.

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7.2 Cardiovascular stability and unchanged muscle sympathetic activity during xenon anesthesia: role of norepinephrine uptake inhibition

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BJA

CLINICAL PRACTICE

Cardiovascular stability and unchanged muscle sympathetic activity during xenon anaesthesia: role of norepinephrine uptake inhibition

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Editor's key points

- The mechanism of the effect of xenon (Xe) on cardiovascular stability was studied.
- Human volunteers anaesthetized with Xe alone had increased arterial pressure.
- In cells, Xe decreased the uptake of norepinephrine (NE) by inhibiting the NE transporter, thereby increasing local NE availability.
- This may explain cardiovascular stability during Xe anaesthesia.

Background. Intraoperative hypotension is associated with increased risk of perioperative complications. The *N*-methyl-D-aspartate (NMDA) receptor (NMDA-R) antagonist xenon (Xe) induces general anaesthesia without impairment of cardiac output and vascular resistance. Mechanisms involved in cardiovascular stability have not been identified.

Methods. Muscle sympathetic activity (MSA) (microneurography), sympathetic baroreflex gain, norepinephrine (NE) plasma concentration (high-performance liquid chromatography), anaesthetic depth (Narcotrend® EEG monitoring), and vital parameters were analysed *in vivo* during Xe mono-anaesthesia in human volunteers (n=8). *In vitro*, NE transporter (NET) expressing HEK293 cells and SH-SY5Y neuroblastoma cells were pre-treated with ketamine, MK-801, NMDA/glycine, or vehicle. Subsequently, cells were incubated with or without Xe (65%). NE uptake was measured by using a fluorescent NET substrate (n=4) or [^{3}H]NE (n=6).

Results. *In vivo*, Xe anaesthesia increased mean (standard deviation) arterial pressure from 93 (4) to 107 (6) mm Hg and NE plasma concentration from 156 (55) to 292 (106) pg ml^{-1}, P<0.01. MSA and baroreflex gain were unaltered. *In vitro*, ketamine decreased NET activity (P<0.01) in NET-expressing HEK293 cells, while Xe, MK-801, and NMDA/glycine did not. Xe reduced uptake in SH-SY5Y cells expressing NET and NMDA-Rs (P<0.01). MK-801 (P<0.01) and ketamine (P<0.01) also reduced NET activity, but NMDA/glycine blocked the effect of Xe on [^{3}H]NE uptake.

Conclusions. *In vivo*, Xe anaesthesia does not alter sympathetic activity and baroreflex gain, despite increased mean arterial pressure. *In vitro*, Xe decreases the uptake of NE in neuronal cells by the inhibition of NET. This inhibition might be related to NMDA-R antagonism and explain increased NE concentrations at the synaptic cleft and in plasma, contributing to cardiovascular stability during Xe anaesthesia.

Keywords: adrenergic regulation; autonomic nervous system; norepinephrine; sympathetic activity; xenon anaesthesia

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Intraoperative hypotension is associated with increased risk of perioperative complications.[1 2] Until now, it is unclear whether decreased arterial pressure causes increased postoperative mortality or it is an indicator of severity of the disease and therefore independently associated with adverse outcome.[3] Nevertheless, intraoperative hypotension is often unfavourable and usually requires immediate reversal with i.v. applied vasopressors, such as norepinephrine (NE). Most common anaesthetics interfere with sympathetic cardiovascular control and impair cardiac output and also vascular resistance, resulting in a decrease in mean arterial pressure.[4] In contrast, during xenon (Xe)-based anaesthesia, arterial pressure is maintained or even increased.[5 6] However, mechanisms of this important observation have not been identified. To assess the effects of Xe on the cardiovascular system, perioperatively administered drugs should be avoided, such that the effect of Xe alone can be identified.

The sympathetic nervous system is responsible for short-term arterial pressure regulation at rest and during cardiovascular challenges (e.g. hypovolaemia). Muscle sympathetic

activity (MSA) correlates well with muscle vascular resistance. When a 50% increase in MSA was induced by lower body negative pressure, blood flow measured in the forearm and calf decreased significantly.[7 8] Therefore, increased MSA may counteract arterial hypotension by increasing systemic vascular resistance.[4] Despite the idea of individual regulation of sympathetic outflow to various organs, MSA correlates well with cardiac and renal sympathetic outflow.[9 10]

Microneurography is the only technique available to directly assess MSA in humans. Its advantage is the ability to detect rapid changes in sympathetic nerve traffic. Accordingly, it can be used to study both static and dynamic situations, for example, determination of the offset and the gain in situations of sympathetic activation induced by certain challenges. Thus, direct evaluation of MSA by microneurography may elucidate mechanisms underlying the cardiovascular stability during Xe anaesthesia in humans.[4]

We therefore tested the hypothesis that in healthy volunteers, administration of Xe increases NE plasma concentration by increased MSA and maintains sympathetic baroreflexes.

When NE plasma concentration was increased during Xe without sympathetic activation, we further speculated that Xe increases NE plasma concentration by the inhibition of NE transporters, irrespective of sympathetic outflow.

Methods

In vivo study

After IRB approval of the study protocol (IRB Medical Faculty, University of Düsseldorf, study ID MO-LKP-394, October 26, 2009), this open-label, single-group assignment phase I clinical trial was approved by the German Authorities (BfArm, EudraCT-No. 2009-012449-48) and registered at www.ClinicalTrials.gov (NCT01043419). The clinical trial was performed in accordance with the Helsinki Declarations and GCP Regulations. Healthy volunteers, who had been recruited with the help of adverts in the medical school, were enrolled and gave written informed consent. Trial monitoring and data management were done by the clinical trials coordinating centre at the University Hospital Düsseldorf, Germany.

Eight non-premedicated, healthy, normotensive volunteers [ASA classification I, mean age 25 (2) yr, male/female: 6/2, mean BMI: 23.5 (1.8) kg m^{-2}] were included in this study. None of the subjects was taking any medication. After an overnight fast, all subjects were studied in the supine resting position in the morning.

Muscle sympathetic activity

Multiunit postganglionic MSA was recorded by microneurography (Supplementary methods) in the peroneal nerve at the fibular head as previously described.[11–14] The nerve signal was amplified, filtered (bandpass, 0.5–2 kHz), and fed through a discriminator for further noise reduction and audio monitoring (662C-3 Nerve Traffic Analysis System, University of Iowa, Bioengineering, USA). An integrated mean voltage signal was obtained by passing the original signal through a resistance–capacitance circuit. MSA recording sites were accepted when burst amplitude was at least twice as great as baseline noise, bursts occurred 1.2–1.4 s after an R-wave of the ECG, and reproducible increases in MSA were obtained in response to a standardized challenge (apnoea of >40 s). Subsequently, MSA bursts were counted and expressed as burst frequency (bursts min^{-1}) during 3–5 min recording periods.

Cardiovascular variables

Heart rate was determined from the surface ECG. After determination of resting arterial pressure by oscillometry at the right upper arm, a catheter (20 G) was inserted into the left radial artery under local anaesthesia and radial arterial pressure was continuously recorded by electromanometry.

NE plasma concentrations

Arterial blood drawn from the radial arterial catheter was sampled at specific intervals into chilled tubes with EDTA, cooled to $+4^{\circ}C$, and immediately centrifuged. Plasma was stored at $-80^{\circ}C$ until analysis using high-performance liquid chromatography with electrochemical detection in an authorized laboratory (Dr Limbach, Heidelberg, Germany). The lower detection limit was 10 pg ml^{-1} with a normal reference range of 165–460 pg ml^{-1}.

Blood gas analyses

Arterial oxygen and carbon dioxide partial pressures and also pH and base excess were assessed by standard blood gas measurements (ABL 700 series, Radiometer, Willich, Germany).

Data recording and processing

Analogue variables (MSA, ECG, radial arterial pressure) were fed into a personal computer and digitized (sampling frequency: 200 Hz, DT 3000, Data Translation Bietigheim-Bissingen, Germany). All analyses were performed with computer support (offline) using customized software (Professor Dr M. Elam and T. Karlsson, Göteborg, Sweden).

Sympathetic baroreflex gain during spontaneous arterial pressure fluctuations

Sympathetic baroreflex gain during spontaneous arterial pressure fluctuations were determined as previously described (Supplementary methods).[14] During a 3–5 min observation period, all diastolic pressures and corresponding MSA bursts were determined compensating for a baroreflex delay of 1.2–1.4 s.

For the calculation of baroreflex gain during spontaneous pressure fluctuations, all diastolic pressures of individual heartbeats were grouped into intervals of 2 mm Hg. For each of these pressure categories, the percentage of cardiac cycles associated with a sympathetic burst (burst incidence) was plotted against the mean of the individual's diastolic pressures followed by a linear regression analysis.

The slope of this regression line represents the individual's sympathetic baroreflex gain during spontaneous arterial pressure fluctuations. For graphical data presentation, the lowest diastolic arterial pressure during each observation period was inserted into the linear equation of the regression analysis. Accordingly, corresponding nerve activities could be calculated for the lowest diastolic arterial pressure observed in each individual.[14]

Treatment protocol

The final 5 min of a 30 min resting period was used to calculate baseline MSA and spontaneous baroreflex gain. Subsequently, oxygen ($F_{I_{O_2}}$>0.9) was administered via a closed facemask by a commercially available Xe anaesthesia machine (Tangens 2C mobile 12, EKU Elektronik, Leiningen, Germany), indicating breathing frequency, minute ventilation, gas measurement, and EEG monitoring of anaesthesia depth (Narcotrend®, Drs B. and A. Schulz, Hannover, Germany). After subjects' adaptation to the facemask and closed circuit breathing, the final 5 min of a 20 min resting period was used to calculate MSA and spontaneous baroreflex gain. Then, arterial blood samples were obtained for determination of blood gases and catecholamine plasma concentrations. Xe anaesthesia was induced with 70% Xe in oxygen (LENOXe, Air Liquide Santé, Paris, France). After achieving steady-state conditions with end-tidal Xe concentrations of at least 60%, MSA and spontaneous baroreflex gain were determined from 3 to 5 min recording periods. Again, arterial blood samples were obtained for determination of blood gases and catecholamine plasma concentrations. At the end of the study, Xe administration was discontinued and volunteers awoke from anaesthesia.

In vitro study

Cell cultures

Human epithelial kidney cells (HEK239) stably expressing human NE transporters (hNET),[15] their parental wild-type cells (HEK293 wild-type), and human neuroblastoma cells (SH-SY5Y; ATCC® number CRL-2266) have been characterized before.[16] All cell lines were cultured under equal conditions including a humidified atmosphere containing 5% carbon dioxide at 37°C and were grown in Dulbecco's Modified Eagle Medium (DMEM; Gibco, Life Technologies, Carlsbad, CA, USA) supplemented with 10% heat-inactivated fetal calf serum and 50 U ml^{-1} penicillin and 50 $\mu g\ ml^{-1}$ streptomycin. Reverse transcriptase–polymerase chain reaction (RT–PCR) and western blot analysis to confirm expression of NET and *N*-methyl-D-aspartate-receptor (NMDA-R) were performed using standard protocols as described previously (Supplementary methods).[17] For western blot analysis, mouse monoclonal anti-NET antibody (cat no. MAB5620; Millipore, Billerica, MA, USA) and rabbit monoclonal anti-NMDA-R1 (D65B7) antibody (cat. no. 5704; Cell Signaling, Danvers, MA, USA) were used as primary antibodies. For RT–PCR, total RNA from HEK293 cells (wild-type and hNET) and SHSY5Y cells was extracted using Trizol Reagent (Ambion, Life Technologies) according to the manufacturer's protocol. RNA was reverse transcribed and amplified. The primer sequences were as follows: for hNET 5′-GGATTGATGCCGCA ACTCAGA-3′, hNET-rev 5′-GGCCTCTGGATACAGGATGA-3′ (306 bp, 35 cycles), for NMDA-R subunit 1 5′-AACCTGCAGAA CCGCAAG-3′, NMDA-R subunit 1_rev 5′-GCTTGATGAGCAGGT CTATGC-3′ (333 bp, 35 cycles), and for glyceraldehyde 3-phosphate dehydrogenase (GAPDH) 5′-ACCACAGTCCATGCCA TCAC-3′ and GAPDH_rev 5′-TCCACCACCCTGTTGCTGT3′ (451 bp, 25 cycles). PCR products were electrophoresed on 1.5% agarose gels and photographed under UV light with a digital camera (Photometrics, Tucson, AZ, USA).

The i.v. anaesthetic and NMDA-R antagonist ketamine was used as a positive control as the inhibitory effect on NE uptake has been described before.[18 19] Additionally, the specific NMDA-R antagonist MK-801 was used to evaluate the role of specific NMDA-R antagonism on NE uptake and the highly potent NET inhibitor desipramine was used to determine the degree of unspecific NE uptake in the used cell culture model. Unless stated otherwise, reagents were purchased from Sigma Aldrich (St Louis, MO, USA).

Xe gas application

A pre-made gas mixture containing Xe (Xe 65%, O_2 30%, CO_2 5%) and a gas mixture without Xe (N_2 65%, O_2 30%, CO_2 5%; negative control) were provided by Air Liquide Santé. To investigate the concentration–response relationship, additional gas mixtures containing 32.5% or 50% Xe were used. All experiments were performed in a specialized gas chamber under temperature control as described before (Supplementary methods).[20] Briefly, dishes containing cells were placed on a tray in the centre of the chamber. The respective gas mixtures were administered from below the culture dishes and distributed by a fan inside the chamber. Gas concentrations were monitored at the outlet of the chamber by a gas analyzer (Capnomatic Ultima; Datex, Helsinki, Finland). The temperature within the chamber was kept at 37°C by means of a heating plate installed at the bottom of the chamber. A temperature-controlling device (Model T48; Red Lion Controls, York, PA, USA) connected to a thermometer probe exactly regulated the heating plate and thus the temperature within the chamber.

Fluorescence-based uptake assay

For measurements of neurotransmitter uptake, cells were detached from tissue culture flasks, counted, and plated on poly-D-lysine (0.1 mg ml^{-1})-coated, black 96-well plates at a density of 1×10^5 cells per well. Subsequently, cells were allowed to adhere for at least 12 h. For pre-treatment with ketamine (1 mmol $litre^{-1}$), desipramine (5 μmol $litre^{-1}$), a combination of *N*-methyl-D-aspartic acid (25 μmol $litre^{-1}$; NMDA) and glycine (10 μmol $litre^{-1}$), MK-801 (2 μmol $litre^{-1}$), or no additive (vehicle; negative control), the culture medium was replaced with substances diluted in Hank's buffered salt solution (HBSS; Gibco Invitrogen) supplemented with 0.1% bovine serum albumin. Treated cell culture

plates were placed in the gas application chamber as described above and the Xe or control gas mixture was applied for 20 min. A fluorescent substrate for neurotransmitter transporters[21] was then added following the manufacturer's recommendations (Neurotransmitter Uptake Kit; Molecular Devices, Sunnyvale, CA, USA) followed by incubation for 20 min during continued gas application. The fluorescent substrate is combined with a masking dye that prevents fluorescence unless the substrate has been transported into the cell. Therefore, the fluorescence intensity of samples at a wavelength of 520 nm was detected after excitation at 440 nm using a fluorescence plate reader (Synergy 2; BioTek Instruments, Winooski, VT, USA) as a measure for substrate uptake immediately after the end of incubation time.

[^{3}H]NE uptake assay

To determine intracellular [^{3}H]NE content, cells were detached from tissue culture flasks, counted, and plated on poly-D-lysine (0.1 mg ml^{-1})-coated, clear 6-well plates at a density of 1×10^5 cells per well. After at least 12 h incubation for cell adherence, pre-treatment with ketamine (1 mmol litre^{-1}), desipramine (5 μmol litre^{-1}), NMDA (25 μmol litre^{-1}), glycine (10 μmol litre^{-1}), MK-801 (2 μmol litre^{-1}), or vehicle (HBSS buffer; negative control) during gas application as described above was performed. After 20 min of gas application, [^{3}H]NE (200 nmol litre^{-1}) was added. After a further 5 min, [^{3}H]NE uptake was stopped by washing all samples with ice-cold phosphate-buffered saline (PBS; Gibco Invitrogen). Cells were then lysed by 5 min exposure to a solution containing 300 mmol litre^{-1} NaCl, 25 mmol litre^{-1} Tris–HCl, and 0.1% Triton-100. The cell lysates were then resuspended with 1 ml PBS and transferred to analysis tubes containing 4 ml of scintillation fluid (Ultima Gold; PerkinElmer, Waltham, MA, USA). The amount of intracellular [^{3}H]NE was measured by means of decay counts per minute using a liquid scintillation counter (Tricarb 2100 TR; Packard, Berkshire, UK).

Data analysis and statistics

Values from fluorescence-based uptake measurements and decay counts per minute from scintillation counting were normalized to samples that were pre-treated with vehicle (negative controls), while subtracting the mean background fluorescence that was detected despite maximal transporter inhibition with desipramine (5 μmol litre^{-1}).

All data are expressed as mean [standard deviation (SD)]. Differences between means were tested by Student's *t*-test or one- or two-way analysis of variance (ANOVA) followed by Bonferroni's *post hoc* test as appropriate. Graph Pad Prism Software version 5.0 (GraphPad Software Inc., La Jolla, CA, USA). A *P*-value of <0.05 was considered significant.

Results

In vivo

Xe anaesthesia was successfully performed in all subjects reaching an end-tidal Xe concentration of 63 (6)%. All volunteers lost consciousness when the end-tidal Xe concentration reached 40–50%, and did not respond to verbal or touch stimuli. The EEG-index (Narcotrend®) decreased from 98 (1) to 46 (10) indicating anaesthesia. Subjects' spontaneous movements resulted in a loss of MSA recording sites in five out of eight subjects during emergence from anaesthesia. Two subjects with a history of postoperative nausea and vomiting during previous anaesthesia experienced short-lasting nausea and vomiting immediately after awakening. Further adverse events were not observed.

MSA was similar during oxygen breathing and during breathing of room air without a mask 19 (9) and 20 (10) bursts min^{-1}, respectively. Sympathetic baroreflex gain during spontaneous arterial pressure fluctuations significantly decreased during oxygen breathing from 4.6 (1.7) to 3.7 (1.5) bursts 100 heartbeats^{-1} mm Hg^{-1} ($P=0.02$), while arterial pressure and heart rate remained unchanged.

After induction of Xe anaesthesia (70%), MSA was not altered. Representative recordings of MSA during oxygen breathing and also during Xe anaesthesia of all subjects are shown in Figure 1A. Generally, Xe anaesthesia did not alter MSA (Fig. 1B) and sympathetic baroreflex gain during spontaneous arterial pressure fluctuations (Fig. 2). However, despite unchanged sympathetic outflow, NE plasma concentrations increased significantly from 156 (55) to 295 (106) pg ml^{-1} ($P<0.01$; Fig. 3). This increase in NE plasma concentration was associated with a significant increase in mean arterial pressure from 93 (4) to 107 (6) mm Hg ($P<0.05$), while heart rate remained unchanged [awake 63 (10) beats min^{-1}; Xe 70 (10) beats min^{-1}; $P=0.12$].

Xe anaesthesia was also associated with an increase in spontaneous breathing frequency and minute ventilation (Table 1). Arterial carbon dioxide partial pressure and pH were not altered; oxygen partial pressure was decreased as after Xe anaesthesia ($F_{I_{O_2}} \approx 0.35$; Table 1).

In vitro

RT–PCR of hNET HEK293 and SH-SY5Y cells confirmed stable expression of hNET, while hNET expression was not detected in parental HEK293 wild-type cells (Supplementary Fig. S1). Additionally, stable gene expression of NMDA-R subunit 1 was detected only in SH-SY5Y cells, and was absent from HEK293 hNET and HEK293 wild-type cells (Supplementary Fig. S1). Western blot analysis of protein expression confirmed these findings (Supplementary Fig. S1).

Fluorescence-based uptake experiments ($n=4$) revealed that fluorescence intensity was decreased in HEK293 hNET cells (not expressing NMDA-R) by ketamine (1 mmol litre^{-1}; $P<0.01$; Fig. 4A). On the contrary, Xe (65%), MK-801 (2 μmol litre^{-1}), and also NMDA (25 μmol litre^{-1}) and glycine (10 μmol litre^{-1}) in combination did not exhibit any effects (Fig. 4A). As expected, there was no specific increase in fluorescence intensity and therefore NET activity in HEK 293 wild-type cells (data not shown).

In contrast, Xe reduced fluorescence intensity in SH-SY5Y neuroblastoma cells expressing NMDA-R in addition to hNET

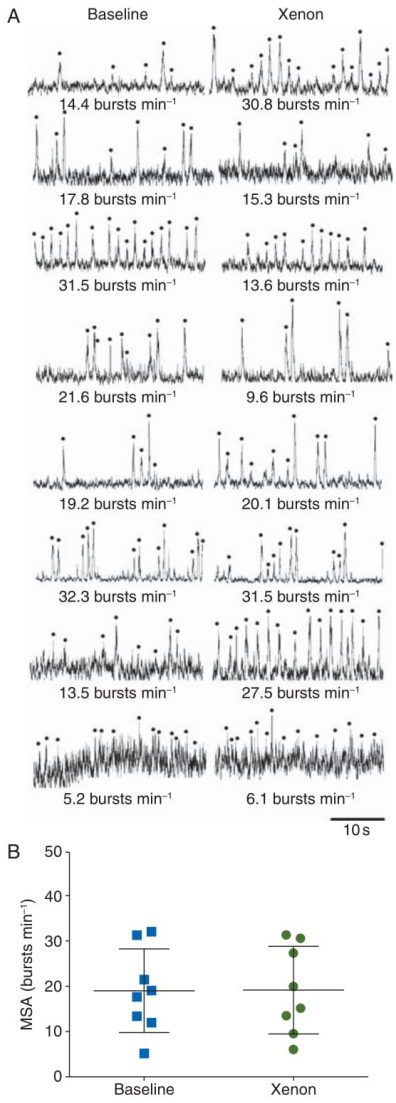

Fig 1 MSA during Xe mono-anaesthesia. (A) Original recordings of MSA of each subject (n=8) in the awake state (baseline) and during Xe anaesthesia. Bursts considered for analysis are indicated by a dot. In four individuals, there was no change in MSA, while two exhibited an increase and two a decrease. (B) Xe anaesthesia does not alter MSA compared with baseline values as determined from 3 to 5 min recording periods. Data presented as individual data points and mean (SD). Blue squares are baseline values and green circles are during Xe anaesthesia.

(P<0.01, Fig. 4B). While MK-801 and ketamine also reduced NET activity, both P<0.01, the combination of these substances with Xe had no additive effect (Fig. 4B).

Radiometric results (n=6) confirmed the inhibition of NE uptake in SH-SY5Y cells by Xe (P<0.01; Fig. 5) and MK-801, P<0.01). The combination of Xe and MK-801 did not exhibit additive effects compared with the application of MK-801 alone. The agonistic combination of NMDA and glycine reversed the inhibition of NE uptake by Xe almost completely (Fig. 5).

To investigate a possible concentration–response relationship, additional experiments were conducted comparing the effect of 0, 32.5, 50, and 65% Xe (Fig. 6). While 32.5% Xe did not lead to a significant effect, 50% Xe resulted in a reduction in NE uptake function (n=6; P<0.05). Increasing Xe concentration to above 65% had no further effect.

Discussion

Despite unchanged sympathetic outflow to muscle, NE plasma concentrations almost doubled during Xe anaesthesia in healthy volunteers. As shown *in vitro*, clinically relevant concentrations of Xe decreased the uptake of NE in human neuroblastoma cells by an NMDA-R-dependent mechanism. Thus, our findings explain increased NE concentrations at the synaptic cleft and in plasma, contributing to the observed cardiovascular stability in patients during Xe.

We have demonstrated that NE plasma concentrations are increased during Xe mono-anaesthesia in healthy volunteers, despite unchanged sympathetic outflow to muscle. Since sympathetic outflow to muscle correlates well with cardiac and renal sympathetic activity, it is rather unlikely that sympathetic activation to other organ systems accounts for the observed increase in NE plasma concentrations.[4 9 10 22] Nevertheless, how can an increase in NE plasma concentration be explained in the face of unchanged sympathetic activity? NE reuptake transport restores about 90% of NE originating predominantly from sympathetic nerves, while only about 10% of released NE reaches the blood stream.[23] We found that Xe inhibited NE uptake by approximately one-third at a concentration that is commonly used for maintaining anaesthesia. Considering that a reduction in NET reuptake function could possibly lead to an increase in NE escaping from the synaptic cleft (extra-neuronal turnover) by up to four times, this effect may lead to increased systemic spillover and therefore contribute to the doubled NE plasma concentration and the observed sympathetic effects.[24] Nevertheless, other mechanisms such as reduced hepatic catecholamine clearance[25] or increased release of NE[26] during Xe anaesthesia cannot be excluded.

Yoshida and colleagues[26] recently reported that Xe increases the release of NE in the cerebral cortex of rats as measured using a microdialysis technique. Although they clearly demonstrated that Xe at a clinically relevant concentration induced a considerable increase in dialysed NE and therefore extracellular NE concentration, their results do not allow discrimination between increased NE release and

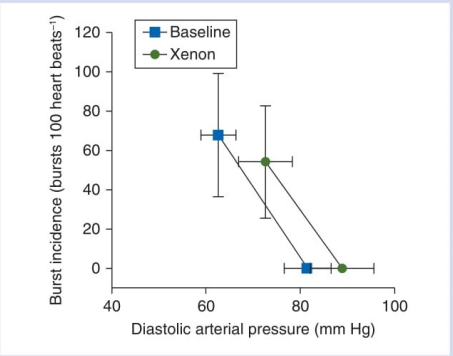

Fig 2 Sympathetic baroreflex gain during Xe mono-anaesthesia. Sympathetic baroreflex gain during spontaneous arterial pressure fluctuations in the awake state (F_{IO_2}>0.9) and during Xe anaesthesia. Although the overall range of observed diastolic arterial pressures is slightly shifted to higher pressures by Xe, the slope of the regression line indicating the sympathetic response to spontaneous arterial pressure variations is not altered (n=8). Data presented as mean (SD). Blue squares are baseline values and green circles are during Xe anaesthesia.

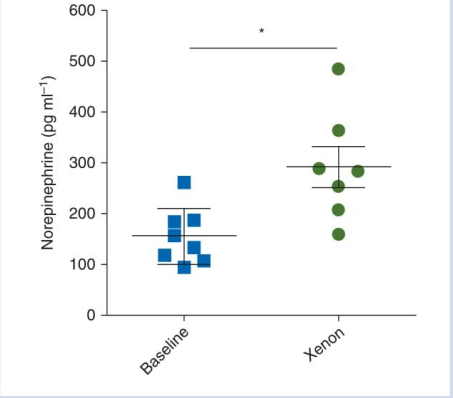

Fig 3 Effect of Xe mono-anaesthesia on NE plasma concentrations. NE plasma concentration was significantly increased during Xe anaesthesia compared with awake state (n−7). Data are presented as individual data points and mean (SD). Blue squares are baseline values and green circles are during Xe anaesthesia. *P<0.01 (n=7; baseline *vs* Xe treatment, paired Student's *t*-test).

Table 1 Results of blood gas analysis and respiratory parameters. Data are presented as means (SD). *P<0.01

	Awake (F_{IO_2}>0.9)	Xenon anaesthesia (end-tidal concentration 63%)
P_{O_2} (mm Hg)	471 (29)	173 (19)*
pH	7.41 (0.02)	7.43 (0.04)
P_{CO_2} (mm Hg)	40 (3)	45 (6)
Base excess (mmol litre^{-1})	1.0 (1.1)	1.3 (1.6)
Respiratory rate (bpm)	12.1 (2.4)	23.1 (7.6)*
Minute ventilation (litre min^{-1})	6.9 (2.0)	10.9 (2.1)*

inhibited reuptake as the responsible mechanism. Our data clearly support their findings and suggest that inhibited reuptake might play an important role for increased NE during Xe application. Increased central noradrenergic activity yields increased sympathetic outflow that in turn is immediately decreased by baroreflex inhibition. Thus, MSA was not altered, despite increased arterial pressure, indicating an altered setpoint of the baroreflex.[27]

Despite an increase in arterial pressure and unimpaired baroreflexes, heart rate surprisingly did not decrease. Regulation of heart rate is even more complex than sympathetic baroreflexes to the vasculature because it is immediately modulated by parasympathetic innervation as well. However, we did not study parasympathetic outflow to the heart in our volunteers. Nevertheless, a similar line of arguments may apply also to heart rate control during Xe compared with muscle sympathetic outflow to the vasculature. First, sympathetic baroreflex gain is not altered in our volunteers during Xe, despite increased arterial pressure. We believe that this observation is caused by the inhibition of NE uptake in the brain and therefore increasing sympathetic outflow. Thus, the setpoint of sympathetic baroreflexes may be altered to higher arterial pressures. Central sympathetic innervation of the heart may be modulated in a similar manner.

Xe is known to exert its anaesthetic and analgesic properties at least in part by the inhibition of NMDA-Rs[28–30] similar to ketamine.[31] Racemic ketamine increased arterial pressure and NE plasma concentrations, while MSA was actually decreased due to baroreflex inhibition.[13] Instead of direct effects on sympathetic outflow, ketamine causes an inhibition of NET function leading to impaired reuptake in part depending on NMDA-R expression as reported earlier and confirmed by our data.[18 32] Accordingly, a greater fraction of NE released from neurones reaches the systemic circulation, leading to an increase in NE plasma concentration. While Xe inhibits NE uptake via an NMDA-R-dependent mechanism, ketamine inhibits NET function even in the absence of NMDA-R. This phenomenon warrants further investigation.

We would like to point out that the inhibition of NET function despite unchanged MSA is a reasonable mechanism for even increased cardiac output and systemic vascular

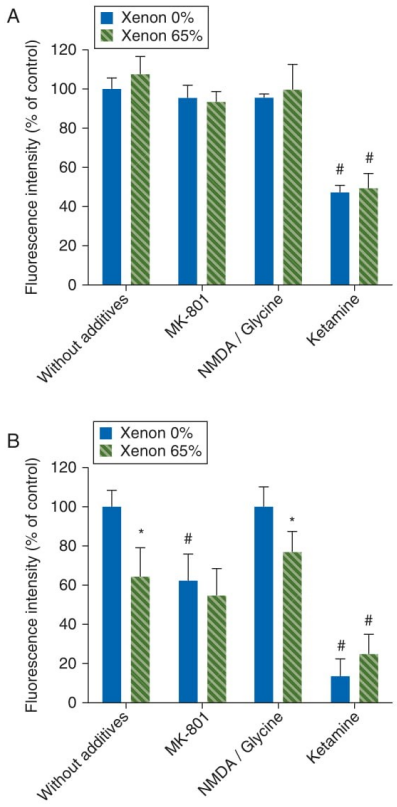

Fig 4 Effect of Xe on neurotransmitter transporter function. (A) In HEK293 cells overexpressing only hNETs in the absence of NMDA receptors, fluorescence intensity as a measure for neurotransmitter uptake was not changed by incubation with 65% Xe compared with control conditions. Ketamine (1 mmol litre^{-1}) inhibited neurotransmitter uptake. Coapplication of Xe had no additive effect. (B) In human neuroblastoma cells (SH-SY5Y) endogenously expressing NETs and NMDA receptors, Xe inhibited neurotransmitter uptake significantly. Specific NMDA inhibition by MK-801 (2 μmol litre^{-1}) mimicked this effect, while additional agonistic stimulation with NMDA (25 μmol litre^{-1}) and glycine (10 μmol litre^{-1}) restored neurotransmitter uptake in the presence of Xe to the level of controls. Data are presented as mean (SD). Blue bars are values after 0% Xe treatment, and green striped bars are values after treatment with 65% Xe. *$P<0.01$ *vs* Xe 0%; #$P<0.01$ *vs* without additives ($n=4$; two-way ANOVA and *post hoc* Bonferroni test).

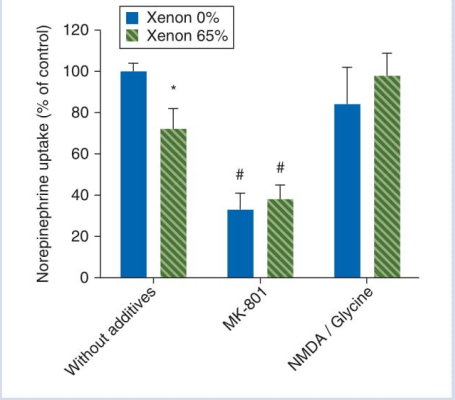

Fig 5 Effect of Xe on uptake of [^{3}H]NE. Confirming the results of fluorescence-based measurements, Xe (65%) inhibited the uptake of [^{3}H]NE. Specific NMDA inhibition by MK-801 (2 μmol litre^{-1}) mimicked this effect, while the agonistic stimulation with NMDA (25 μmol litre^{-1}) and glycine (10 μmol litre^{-1}) reversed it. Data are presented as mean (SD). Blue bars are values after 0% Xe treatment, and green striped bars are values after treatment with 65% Xe. *$P<0.01$ *vs* Xe 0%; #$P<0.01$ *vs* without additives ($n=6$; two-way ANOVA and *post hoc* Bonferroni test).

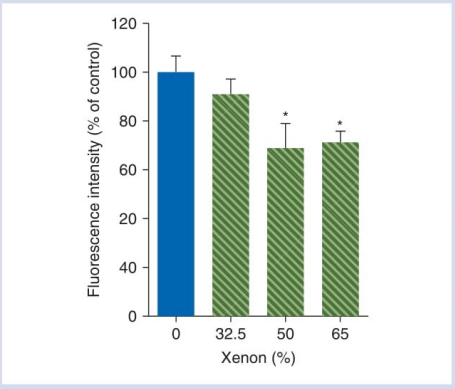

Fig 6 Concentration-dependent inhibition of neurotransmitter transporter function. The effect of 32.5% was not significantly different from control conditions, but 50% Xe inhibited neurotransmitter uptake. Increasing the concentration to 65% Xe did not enhance inhibition. Data are presented as mean (SD). Blue bars are values after 0% Xe treatment, and green striped bars are values after treatment with Xe. *$P<0.05$ ($n=6$; all values *vs* controls without Xe, one-way ANOVA and *post hoc* Bonferroni test).

resistance in patients undergoing Xe-based anaesthesia.[33] Even in patients with markedly impaired left ventricular function undergoing cardioverter defibrillator implantation,

arterial pressure and cardiac function were not depressed. Furthermore, our results explain maintained left ventricular contractility during Xe anaesthesia, either in patients without cardiovascular disease or in those awaiting coronary artery bypass surgery.[5] In contrast to most other anaesthetics, not only resting sympathetic outflow but also sympathetic baroreflexes are not impaired even at slightly increased arterial pressure.[4] Thus, the cardiovascular system is still able to respond to challenges, for example, perioperative hypovolaemia or haemorrhage, despite general anaesthesia.

In many animal and human studies, Xe has been administered in combination with opioids so that the described cardiovascular effects could not be attributed to Xe alone. Since NE plasma concentrations were reported to be decreased in patients anaesthetized with a combination of Xe and remifentanil[34] and increased in dogs,[35] the underlying mechanism for the observed haemodynamic stability had not been pinpointed to the sympathetic nervous system. Since opioids decrease MSA at rest and sympathetic baroreflex gain,[12] the combination of Xe and opioids is clinically very favourable but does not allow an evaluation of the intrinsic effect of Xe.

Whether maintained arterial pressure during Xe-based anaesthesia translates into a decrease in perioperative morbidity and mortality is currently being evaluated in larger randomized controlled multicentre trials (www.clinicaltrials.gov NCT01120405 and NCT00919126).

In addition to the potential effects of the described mechanism on haemodynamics, enhanced agonistic effects of NE on α-2-adrenoceptors may have widespread implications for clinical anaesthesia.[36] Furthermore, NMDA-R antagonism and NE are known to be key mediators in pain modulation.[37] Therefore, the findings of this study encourage further investigation of spinal inhibitory mechanisms of Xe-mediated antinociception.

Our findings suggest that the effect of Xe on NE uptake depends on the presence of NMDA-R. Furthermore, specific inhibition of NMDA-R by MK-801 mimics the effect of XE on NET activity. This finding is supported by another study demonstrating that MK-801 significantly increases NE release from rat prefrontal cortex.[38] Nevertheless, the exact mechanism by which NMDA-R inhibition by Xe induces a reduction in NET activity remains to be elucidated.

Limitations

It was the goal of our study to assess the effects of Xe anaesthesia on muscle sympathetic outflow. Accordingly, we did not administer other additional anaesthetics despite the comparatively low anaesthetic potency of Xe (MAC_{50} 50–70 vol%). Cardiovascular variables were recorded in unconscious participants while Narcotrend® EEG monitoring (values of 40–60) confirmed general anaesthesia. Participants were spontaneously breathing via a facemask so that tracheal intubation and mechanical ventilation were avoided. Nevertheless, $\sim$1 MAC_{50} of Xe was achieved without significant respiratory depression. In contrast, even a doubling of minute ventilation was observed while end-tidal P_{CO_2} remained unchanged. Since oxygenation was not impaired, we may exclude pulmonary atelectasis but rather assume increased impact of dead space ventilation cardiac output to be the major cause of increased minute ventilation during Xe anaesthesia. Furthermore, metabolism and CO_2 production are ultimately linked to cardiac output. The inhibition of NE uptake during unchanged sympathetic outflow may increase cardiac output and metabolism. As observed in a canine model, i.v. infusion of NE increases cardiac output and CO_2 production in a linear fashion.[39] Accordingly, we speculate that increased NE concentration at the level of adrenergic receptors may have caused the observed increase in P_{CO_2} and ventilation. As heart rate did not change significantly during Xe anaesthesia, increased cardiac inotropy may be speculated to be the cause. However, a slight decrease in heart rate without changes in arterial pressure under Xe anaesthesia after induction with propofol has been reported in volunteers previously.[40] These, at first glance, contradictory results to our observation can be explained: subjects in our study were not receiving any other medication while in the study by Rex and colleagues, propofol was administered for induction of anaesthesia. Accordingly, residual propofol at calculated plasma concentrations even below 1 μg ml^{-1} may have caused a reduction in efferent sympathetic activity[41 42] counteracting the sympathetic effects of Xe.

MSA may be influenced by respiration and at least in males, breathing rate correlates positively with sympathetic activity and total peripheral resistance.[43] However, while all volatile anaesthetics increase spontaneous breathing rate up to several hundred per cent, isoflurane, sevoflurane, and desflurane markedly decrease MSA.[4] Thus, it seems rather unlikely that MSA during Xe anaesthesia is maintained solely by increased breathing rate.

We would have preferred to evaluate the effect of Xe on the baroreflex setpoint more extensively reported previously.[13] Unfortunately, because of spontaneous movements during Xe anaesthesia, it was not possible to normalize arterial pressure by titrating nitroprusside before losing the MSA recording site.

One limitation of the *in vitro* observations is that the fluorescence-based assay does not only measure the uptake function of NET but also the function of dopamine and serotonin transporters.[21] Therefore, after achieving positive results by the fluorescent screening method, a specific uptake assay using radiolabelled NE was used to confirm that Xe reduces NE uptake.

In conclusion, NE plasma concentrations and arterial pressure increase during Xe anaesthesia, despite MSA and sympathetic baroreflex gain remaining unaltered. Xe inhibits NE uptake *in vitro* in an NMDA-R-dependent manner. This mechanism may be responsible for increased concentrations of NE at the synaptic cleft and in plasma and therefore contribute to the haemodynamic stability of patients during Xe anaesthesia.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

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

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/m²)	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).

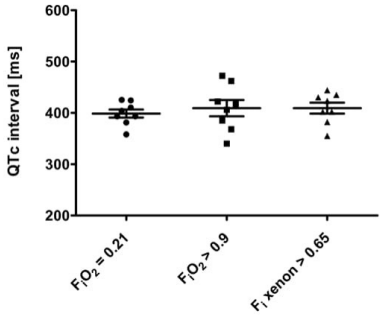

Fig. 1. Depicted are *data points* from each individual volunteer (n = 8), means and SD of heart rate–corrected cardiac QT interval awake, after denitrogenation before xenon and during xenon monoanesthesia. F_{IO_2} = inspiratory oxygen fraction; FI xenon = inspiratory xenon fraction; QTc interval =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

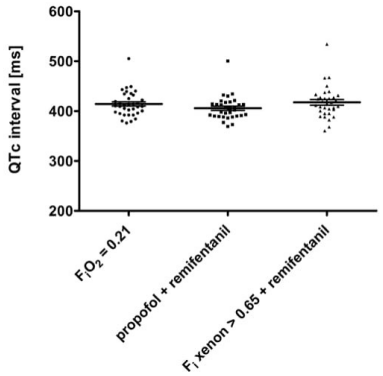

Fig. 2. Depicted are *data points* from each individual patient (n = 35), means and SD of heart rate–corrected cardiac QT interval awake, during general anesthesia with propofol/remifentanil before xenon and during xenon/remifentanil anesthesia. F_{IO_2} = inspiratory oxygen fraction; FI xenon = inspiratory 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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7.4 Influence of xenon on pulmonary mechanics and lung aeration in patients with healthy lungs

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Respiration and Airway

Influence of xenon on pulmonary mechanics and lung aeration in patients with healthy lungs

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A preliminary account of the results of this study has been presented at the European Society of Anaesthesiology annual meeting, Geneva, Switzerland, June 3–5, 2017.

Abstract

Background: The anaesthetic xenon shows potent organ-protective properties. Due to high density and dynamic viscosity, peak inspiratory pressure (P_{max}) increases during xenon application. Thus, barotrauma may counteract organ protection. Accordingly, we investigated the influence of xenon on lung mechanics and lung aeration in patients with normal and reduced thoracic wall compliance.

Methods: After registration and ethical approval, 20 patients free of pulmonary disease undergoing routine xenon-based anaesthesia were mechanically ventilated. The primary outcome variable transpulmonary pressure (P_{tp}) was determined from plateau pressure and intraoesophageal pressure before and after xenon wash-in. We recorded P_{max}, and calculated airway resistance (R_{AW}), and static (C_{stat}) and dynamic (C_{dyn}) respiratory compliances. Finally, lung aeration was quantified by electrical impedance tomography-derived centre of ventilation index (CVI) and global inhomogeneity index (GI) in the awake state, before and during xenon.

Results: Xenon increased P_{max} [20.8 (SD 3) *vs* 22.6 (3) cm H_2O, $P<0.001$] and R_{AW} [0.9 (0.2) *vs* 1.4 (0.3) cm H_2O litre^{-1} s, $P<0.001$], without affecting P_{tp} [1.5 (4) *vs* 2.0 (4) cm H_2O, $P=0.15$]. While C_{stat} remained unchanged, C_{dyn} was reduced [33.9 (7) *vs* 31.2 (6) ml (cm H_2O)$^{-1}$, $P<0.001$]. A ventral tidal volume shift after anaesthesia induction [CVI 0.53 (0.03) *vs* 0.59 (0.04), $P<0.001$] was unaltered during xenon [CVI 0.59 (0.04), $P=0.29$]. Homogeneity of lung aeration was also unchanged during xenon [GI 0.37 (0.03) *vs* 0.37 (0.03), $P=0.99$]. There were no clinically meaningful differential BMI-related effects.

Conclusions: Xenon increases calculated airway resistance and peak inspiratory pressure without affecting transpulmonary pressure, independent of BMI.

Clinical trial registration: NCT02682758.

Keywords: anaesthetics, inhalation; mechanical ventilation; respiratory mechanics; tidal volume; xenon

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Editor's key points

- Xenon is much denser than air, but the effects on pulmonary mechanics during mechanical ventilation are unknown.
- Inhaled xenon 60% increased peak airway pressure and airway resistance, but transpulmonary pressure was unchanged.
- Altered distribution of ventilation after induction of anaesthesia was unaffected by xenon.
- These effects were similar in obese patients.
- These data do not support the concept of xenon-related barotrauma in healthy patients.

Mechanical ventilation at high volume and high inspiratory pressure is deleterious to the lungs in various animal models.[1,2] In patients with injured lungs, mortality is decreased when peak inspiratory pressure (P_{max}) and tidal volume are restricted to 30 cm H_2O and 6 ml kg^{-1}, respectively.[3] Also, in patients with healthy lungs, low tidal volumes in combination with PEEP have been beneficial.[4,5] The success of these strategies is attributed to the reduction of transpulmonary pressure (P_{tp}), decreasing pulmonary mechanical stress, and barotrauma.[6] Secondly, the addition of PEEP and the use of recruitment manoeuvres counterbalance anaesthesia-related formation of atelectasis[7,8] and reduces atelectasis-induced postoperative pulmonary complications.

The noble gas xenon is an inhalation anaesthetic with cardioprotective,[9,10] neuroprotective,[11–13] and nephroprotective[14,15] properties. Moreover, xenon attenuates inflammatory stress in lung epithelial cells by activation of the hypoxia-inducible factor-1-alpha pathway and inhibition of apoptosis.[16] However, compared with air, xenon is characterised by peculiar physicodynamic properties: it has a 380% higher density and a 25% higher dynamic viscosity. In this context, an increase in P_{max} is regularly observed when xenon is applied in mechanically ventilated patients.[17] However, it is unclear whether this is exclusively caused by viscosity-dependent prolongation of gas flow with a consecutive increase of airway resistance (R_{AW}) during inspiration,[18] or whether xenon actually increases P_{tp}. In addition, inhalation of high-density gases may cause homogenisation of tidal volume distribution[19] and therefore counterbalance anaesthesia-induced atelectasis.

Thus, we investigated the influence of xenon in mechanically ventilated patients during general anaesthesia on pulmonary mechanics and lung aeration. Since obesity-induced reduction of thoracic wall compliance both influences pulmonary mechanics[20,21] and formation of atelectasis,[22] we differentiated these effects in obese and normal weight patients.

Methods

After registration at clinicaltrials.gov (NCT02682758) and ethical approval (Ethikkommission der Heinrich-Heine-Universität Düsseldorf, Germany, #5161R), 20 consecutive adult patients free of pulmonary disease undergoing routine xenon-based anaesthesia for elective surgery were included into this prospective study after written informed consent had been obtained. To study patients with normal and reduced thoracic wall compliance, patient inclusion was stratified by BMI, facilitating the inclusion of 10 patients with a BMI of ≤25 and 10 patients with a BMI of ≥30 kg m^{-2}. Patients were excluded when at least one of the following criteria was fulfilled: pregnancy, ASA status >III, cardiac pacemaker or internal cardioverter/defibrillator, obstructive or restrictive pulmonary disease, cardiothoracic or abdominal surgery, history of oesophageal, gastric or nasopharyngeal surgery, liver cirrhosis Child-Pugh B or C with or without the presence of oesophageal varices, or ongoing effective anticoagulation.

Anaesthesia and ventilator management

Xenon-based anaesthesia was performed as to institutional standards: Anaesthesia was induced with propofol (1–2 mg kg^{-1}) and remifentanil (0.3–0.5 μg kg^{-1} min^{-1}) and tracheal intubation was facilitated with rocuronium (0.6 mg kg^{-1}). Effective neuromuscular relaxation was monitored by peripheral stimulation of the ulnar nerve with 50 mA train-of-four stimulation, and double burst stimulation with a 50 Hz tetanus (TOF-watch®; Organon Ltd., Dublin, Ireland). All patients were ventilated with a closed-circuit anaesthesia machine (Felix Dual®; Air Liquide Medical Systems, Antony, France) in volume-controlled mode (tidal volume 8 ml kg^{-1} predicted body weight) with a PEEP of 5 cm H_2O, a ventilatory frequency of 10 and an inspiratory:expiratory ratio of 1:2. Anaesthesia was initially maintained with propofol (8 mg kg^{-1} h^{-1}) and remifentanil (0.15–0.25 μg kg^{-1} min^{-1}), while the lungs were ventilated with 100% oxygen to wash-out residual nitrogen. When denitrogenation was complete (expiratory oxygen fraction >0.9), xenon (Xenon Pro Anaesthesia®; Air Liquide Deutschland GmbH, Düsseldorf, Germany) wash-in was initiated. Because the minimum alveolar concentration (MAC) of xenon has finally been estimated as 51–69% inspiratory concentration[23] and the synergistic effect of remifentanil with xenon on the MAC has to date been poorly investigated, a targeted inspiratory xenon concentration of 60% was chosen as the standard anaesthesia regimen for all patients, reflecting the practice in previous trials.[24] After xenon wash-in, when all measurements were completed, propofol infusion was discontinued and anaesthesia was maintained with xenon and remifentanil (0.15–0.3 μg kg^{-1} min^{-1}, titrated to clinical needs) until the end of surgery.

Measurement of pulmonary mechanics

The primary outcome variable P_{tp}, was derived from plateau pressure (P_{plat}) and intrapleural pressure, which was estimated from intraoesophageal pressure (P_{es}): after induction of anaesthesia, an intraoesophageal balloon catheter (adult oesophageal balloon catheter kit 5 French; CooperSurgical, Trumbull, CT, USA) was connected to a standard pressure transducer (MX960; Smiths Medical, Hythe, UK). The catheter was placed in the stomach and the balloon was inflated. This position was confirmed by gentle compression of the patient's abdomen with the observation of a corresponding pressure response. Next, the catheter was retracted to the lower third of the patient's oesophagus. Correct placement was confirmed by visualisation of cardiac artefacts in the catheter pressure curve and by artefacts caused by compression of the patient's thorax. P_{plat} at end-inspiratory hold with corresponding P_{es} was recorded (1) during initial propofol anaesthesia and (2) after completion of xenon wash-in. P_{tp} was calculated as the difference of $P_{plat}-P_{es}$. P_{max} was recorded continuously. Subsequently, static (C_{stat}) and dynamic (C_{dyn}) compliance of the respiratory system, and R_{AW} were calculated. To differentiate

between the direct effects of xenon on airway diameter and friction because of its high density (η) and viscosity (ρ), we adjusted R_{AW} by the method used by Pedley and colleagues,[25] as suggested before.[18] To this end, a laminar flow model with a relative η of 1.09, and a mixed flow model with a relative $(\eta^*\rho)^{1/2}$ of 1.78 (60% Xe/40% O_2 as compared with 90% O_2) were applied.

Measurement of lung aeration

Distribution of the applied tidal volume was assessed by electrical impedance tomography (EIT, PulmoVista® 500; Drägerwerk AG & Co., Lübeck, Germany).[7,26–28] Upon arrival at the operation theatre, the patient was equipped with a 16 electrode silicone EIT belt, placed between the 4th and 5th intercostal space. A maximum impedance of 300 Ω for each electrode was tolerated. Image frequency was set to 20 Hz with automatic operating frequency of the EIT system. Then, the patient was prompted to breathe calmly and evenly, and a baseline recording was conducted for 1 min. After intubation, a second 1-min recording was conducted during initial anaesthesia maintenance with propofol and remifentanil and a third recording after completion of xenon wash-in. The 32×32 pixels raw EIT recordings were imported to the EIT data analysis tool 6.1 (Drägerwerk AG & Co, Lübeck, Germany). First, a 50 min^{-1} low pass filter was applied to separate impedance changes caused by heart activity. Then, end-expiratory to end-inspiratory impedance changes were calculated for every breathing cycle. The resulting tidal images within the 1-min recording period were then averaged to generate a functional EIT (*f*EIT) minute image, which was exported as ASCII to Excel 2016 (Microsoft Corporation, Redmond, WA, USA).

To quantify the distribution of ventilation in the dorso-ventral direction for every single of the three abovementioned time points, the centre of ventilation index (CVI) was calculated from *f*EIT minute images as described before.[7,26,27] First, the ventilated lung area was identified with application of a 20% threshold from maximum impedance change.[7,29,30] Then, the relative impedance changes per row of the *f*EIT image were added and the weighted average of the resulting dorsoventral histogram was calculated, representing the CVI with a minimum value of 0 and a maximum value of 1. By definition, values of more than 0.5 represent a more ventral distribution of tidal volume, while values less than 0.5 represent a dorsal distribution.

Homogeneity of lung aeration was quantified with the global inhomogeneity index (GI) as described before.[28] In brief, this index quantifies the variance of impedance changes throughout the *f*EIT minute image as the normalised sum of the differences from the images' median impedance change for every single pixel.

Statistical analysis and sample size estimation

We conducted an *a priori* sample size estimation, based on the primary outcome P_{tp}, resulting in a required sample size of seven patients to detect a 20% increase in P_{tp} with a power of 80%. To compensate for failed measurements (e.g. because of failure of placement of oesophageal catheters), we increased the sample size to 10 patients per group.

Means and standard deviations were calculated for all variables. Since measurements of lung mechanics were conducted at two time points (during propofol and during xenon), a paired *t*-test was applied for these outcomes. For measurements of lung aeration, which were conducted at three time points (before induction, during propofol, and during xenon), a repeated measures analysis of variance (ANOVA) with *post hoc* Dunn–Sidak test was applied. Additionally, a mixed ANOVA was conducted for analysis of the subgroups of patients with BMI<25 and BMI>30 kg m^{-2}. To reduce the number of statistical tests, subgroup analyses were only conducted for P_{tp}, P_{max}, CVI, and GI. A two-tailed *P*-value of 0.05 was considered to be statically significant. All analyses were performed with STATA IC 10.1 (Statacorp, College Station, TX, USA) and SPSS statistics version 23 (IBM Corporation, Armonk, NY, USA). Sample size estimation was made with G*Power 3.1.9 (A. Buchner and team, Heinrich-Heine University Düsseldorf, Germany).[31]

Results

Ten patients with a BMI<25 and 10 patients with a BMI >30 kg m^{-2} completed the study. Patient characteristics are depicted in Table 1. In one patient of the BMI<25 stratum, placement of the oesophageal balloon catheter was impossible but all EIT measurements were completed. Thus, full datasets are available for 19 patients for pulmonary mechanics and 20 patients for lung aeration variables. Measurements were completed in all patients before skin incision. Baseline measurements during anaesthesia were performed at 6 (3) min after intubation, while measurements during xenon were at 15 (3) min after intubation. The average time gap between the two measurements was 8 (1) min. End-tidal CO_2 concentrations remained stable between the two time points [4.67 (0.39) *vs* 4.67 (0.43) kPa, P=0.99] and peripheral nerve stimulation indicated full neuromuscular relaxation in all 20 patients at both time points (no response to either train-of-four or double burst stimulation).

Influences on pulmonary mechanics

Inspiratory gas flow rate remained stable [0.33 (0.04) *vs* 0.34 (0.04) litre s^{-1}, P=0.42] between both measurements. Patients of normal weight (BMI<25) had a significantly higher respiratory compliance than patients with a BMI>30 (C_{stat} 49 (8) *vs* 39 (11) ml (cm H_2O)$^{-1}$, P=0.04). In all patients, and in the BMI subgroups, xenon wash-in to 60% inspiratory concentrations had no significant effect on P_{tp} (Fig 1). P_{max} increased by 9 (6)% from 20.8 (3) to 22.6 (3) cm H_2O, P<0.001 in all patients, from 19.1 (0.4) to 20.6 (0.4) cm H_2O, P=0.003 in patients with normal weight, and from 22.2 (1) to 24.4 (1) cm H_2O, P=0.001 in obese

Table 1 Patient characteristics and types of surgery. All values are mean [range], mean (standard deviation), or absolute numbers (%).

	All patients	BMI<25 kg m^{-2}	BMI>30 kg m^{-2}
Age (yr)	52.8 [21–80]	50.7 [21–80]	54.9 [31–74]
Female	10 (50)	5 (50)	5 (50)
Height (cm)	171 (6)	171 (6)	171 (7)
Weight (kg)	84.6 (19)	70.7 (11)	98.5 (13)
ASA status (I/II/III)	5/8/7 (25/40/35)	4/6/0 (40/60/0)	1/2/7 (10/20/70)
Surgery			
ENT	15 (75)	7 (70)	8 (80)
Orthopaedic	4 (20)	3 (30)	1 (10)
Vascular	1 (5)	0 (0)	1 (10)

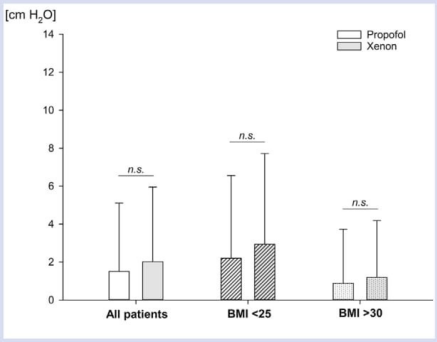

Fig. 1. Transpulmonary pressure during propofol and subsequent xenon-based anaesthesia in all patients, and separate for subgroups of patients with normal weight (BMI <25 kg m^{-2}) and obese patients (BMI>30 kg m^{-2}). n.s.: not significant.

patients. The increase in P_{max} was accompanied by a significant 54 (25)% increase in R_{AW} after xenon wash-in, which was further reflected by an 8 (8)% decrease in C_{dyn} with no alteration of C_{stat} (Fig 2). Adjustment of R_{AW} by density and viscosity of the gas mixture resulted in a decrease of R_{AW} after xenon inhalation, when a mixed flow model was applied (Table 2).

Influences on lung aeration

Induction of anaesthesia significantly decreased ventilation in the dorsal half of the *f*EIT minute image [ventilated lung area 153 (41) *vs* 95 (63) pixels, $P<0.001$], while total ventilated lung area remained unchanged [324 (66) *vs* 288 (85) pixels, $P=0.08$). This was reflected by a significant shift of CVI towards ventral lung regions (Fig 3). This effect was more pronounced in patients with a BMI>30 than patients with a BMI<25 [CVI +15 (0.5) *vs* +10 (0.5)%, mixed ANOVA interaction $P=0.043$). After xenon wash-in, there was no change in CVI in the overall patient collective and in patients with a BMI<25 kg m^{-2} (Fig 3). In patients with a BMI>30 kg m^{-2}, CVI was decreased by 1 (0.6)% after xenon wash-in. Xenon wash-in had no effect on total ventilated lung area in the whole *f*EIT minute image [288 (85) *vs* 289 (86) pixels, $P=0.99$], nor in the dorsal half of the image [95 (63) *vs* 97 (62) pixels, $P=0.41$]. Induction of anaesthesia significantly increased ventilation inhomogeneity, which remained unchanged after xenon wash-in (Fig 4).

Table 2 Adjustment of airway resistance (R_{AW}) by the physical properties of the inhaled gas mixtures according to Pedley and colleagues.[25] Values for gas mixtures are cm H_2O litre^{-1} s, while ratios (in bold) are relative values.

	Unadjusted R_{AW}	Adjusted R_{AW}: laminar flow	Adjusted R_{AW}: mixed flow
N_2/O_2 10/90%	0.94	0.94	0.94
Xe/O_2 60/40%	1.42	1.31	0.80
Ratio ($Xe/O_2/N_2/O_2$)	**1.52**	**1.39**	**0.85**

Discussion

In this study, we demonstrate that wash-in of 60% xenon increases peak inspiratory pressure and airway resistance but does not affect transpulmonary pressure. Induction of anaesthesia results in a ventral shift of tidal volume distribution that is accompanied by increased inhomogeneity of lung aeration. Xenon administration does not alter these effects.

Influences on pulmonary mechanics

In principle, the increase in P_{max} during administration of xenon in mechanically ventilated patients may be attributable

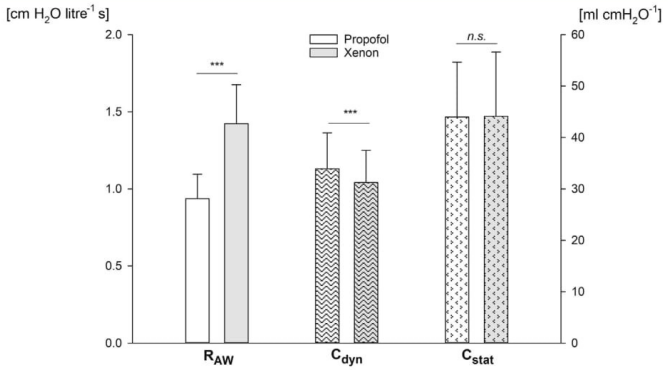

Fig. 2. Airway resistance (R_{AW}), dynamic (C_{dyn}), and static (C_{stat}) compliance of the respiratory system during propofol and subsequent xenon-based anaesthesia. *** $P<0.001$; n.s.: not significant.

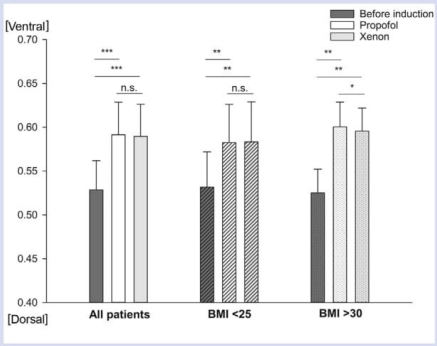

Fig. 3. Distribution of tidal volume in the anterior-posterior direction, as quantified by the centre of ventilation index before induction of anaesthesia, during initial propofol, and subsequent xenon-based anaesthesia. BMI (kg m^{-2}). ***P<0.001; ** P<0.01; *P<0.05; n.s.: not significant.

to the following general mechanisms: (1) an increase in alveolar pressure that in turn increases P_{max} and P_{tp} (e.g. because of air trapping with overdistension of dependent lung areas or formation of atelectasis); and (2) an increase in R_{AW}. In our study, we neither observed an increase in P_{tp}, nor in alveolar pressure (which was assessed by P_{plat}) after xenon wash-in. Also, lung aeration was practically identical during propofol and xenon. However, our results indicate a 52% increase of R_{AW} after xenon wash-in. Thus, we did not find any evidence for xenon-induced increase in alveolar pressure or P_{tp}, and we conclude that the increase in P_{max} during xenon application is attributable to an increase in R_{AW}. Since the noble gas is characterised by a high density and viscosity, this effect is further attributable to an increased friction at the airway

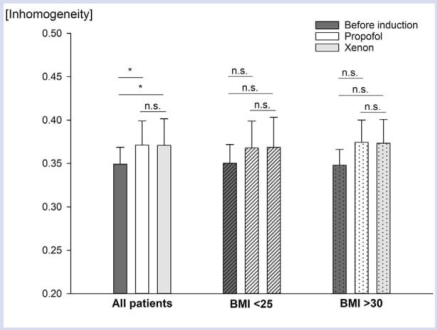

Fig. 4. Homogeneity of lung aeration, as determined by global inhomogeneity index before induction of anaesthesia, during initial propofol, and subsequent xenon-based anaesthesia. BMI (kg m^{-2}). *P<0.05; n.s.: not significant.

walls. However, additional effects such as xenon-induced alterations in bronchial diameter must be considered as well.[18] To this end, we adjusted the measured R_{AW} for xenon's physical properties.[25] We found that, after mathematically eliminating the effect on airway friction, R_{AW} was decreased by 15%, confirming the findings of Baumert and colleagues[18] in a pig model. This suggests that xenon might even cause slight bronchodilation, which can be explained by the fact that xenon increases systemic catecholamine concentrations,[32] facilitating bronchodilation via activation of β_2 receptors. However, apparently friction-induced increase in R_{AW} outweighs xenon's bronchodilatatory effects, resulting in a net increase of R_{AW}. Therefore, xenon application may aggravate clinical signs of airway obstruction (e.g. in patients with chronic obstructive pulmonary disease or status asthmaticus).

We did not find any influence of xenon on transpulmonary pressure. Thus, in clinical routine, an increase in P_{max} after xenon wash-in can be tolerated without fearing xenon-induced barotrauma. Notably, the 9% increase of P_{max} in our study seems rather moderate compared with other studies reporting a 35% increase of P_{max} during xenon.[17] This difference may be explained by the fact that, in the study of Rueckoldt and colleagues,[17] 14 out of 37 patients reported a history of pulmonary disease and baseline inspiratory pressures were already very high (37 cm H_2O). Also, the authors applied a higher inspiratory flow as compared with our study (0.56 *vs* 0.34 litre s^{-1}), that may have aggravated airway friction and further increased P_{max}.

We are aware that our reported absolute P_{tp} values are comparably low. This finding can be explained by the fact that intraoesophageal pressure, which is subtracted from P_{plat} to calculate P_{tp}, is influenced by the weight of the heart.[33] Therefore, a correction is applied to subtract cardiac weight from measured P_{es}, whereas this correction always results in higher P_{tp} values. To this end, two methods have been proposed: (1) measurement of a resting P_{es} at maximum expiration and subsequent subtraction of resting P_{es} from P_{es} at end-inspiration[34,35] or (2) general subtraction of 5 cm H_2O.[33,36] The first method leads to very high estimation of the absolute P_{tp}, while the second method is used when realistic estimation of the absolute P_{tp} is aimed for. However, the general subtraction of 5 cm H_2O would have been made at both time points evenly. Since we were interested in the change in P_{tp} rather than absolute values, we decided not to adjust measured P_{es} by cardiac weight, which would have had no influence on our results.

Influences on lung aeration

We were unable to detect any effect of xenon inhalation on homogeneity of lung aeration. Also, there was no general effect on tidal volume distribution, as measured by CVI. Only in obese patients, we observed a marginal re-dorsalisation of tidal volume, but the effect was less than 1%. In 1976, Wood and colleagues[19] hypothesised that inhalation of high-density gases homogenises tidal volume distribution. Furthermore, increased oxygenation has been reported during xenon anaesthesia.[37] Therefore, we hypothesised that by prolonging expiration, xenon produces intrinsic PEEP in dependent lung areas, leading to recruitment of atelectatic lung and prevention of collapse in lung areas at risk. The fact that we did not observe any influence on lung aeration may be explained by the fact that assessments were made shortly after xenon wash-in was completed, leaving not enough time for xenon to

counterbalance anaesthesia-induced formation of atelectasis.[7,27] Indeed, improvement of oxygenation in obese patients undergoing xenon anaesthesia only becomes evident 1 h after induction of anaesthesia.[37] Taken together, we show that xenon does not exert any immediate effects on lung aeration, but our data encourage further investigations after longer duration of xenon application.

In summary, we do not have any indications for xenon-related barotrauma despite increased inspiratory pressures during mechanical ventilation with xenon.

Limitations

We compared lung mechanics during propofol anaesthesia before and after xenon wash-in at two different, consecutive time points. We chose this design because 1. It reflects the clinical procedure of routine xenon-based anaesthesia and 2. Selecting an inhalation anaesthetic as control compromises the isolation of xenon-induced effects as all inhalation anaesthetics alter either airway resistance or lung aeration.[38–41] Hence, when compared with volatile anaesthetics (e.g. isoflurane, sevoflurane), the xenon-induced increase of airway resistance may be overestimated because of bronchodilation associated with these substances. Moreover, while nitrous oxide does not alter bronchial diameter, it may cause pulmonary atelectasis associated with its uptake.[42] Accordingly, we wanted to exclude another variable on pulmonary aeration making evaluation of xenon-induced effects more difficult.

Still, our study design is subject to time-dependent influences such as fading neuromuscular relaxation, changes in arterial and alveolar CO_2 concentration, alterations in bronchial mucosa thickness, and others. To control these influences, we kept the interval between the two measurements as short as possible, controlled neuromuscular relaxation and expiratory CO_2 values, and completed all measurements before surgery.

We investigated the effects of xenon on pulmonary mechanics and pulmonary aeration in patients free of pulmonary disease before surgery was initiated. Also, our patients were on average 53 yr old. Therefore, nothing can be said on the influence of xenon application in patients with pulmonary disease such as chronic bronchial obstruction or the acute respiratory distress syndrome, and elderly patients. Of interest, Abramo and colleagues[37] have shown that xenon enhances oxygenation in morbidly obese patients, possibly because of prevention of atelectasis, encouraging further investigations in patients undergoing surgery with high risk for atelectasis and postoperative pulmonary complications, such as upper abdominal surgery.

Authors' contributions

Study design: M.S.S., T.A.T., P.K.
Patient recruitment: M.S.S.
Data acquisition: M.S.S., J.G.
Data analysis: M.S.S., J.G., P.K.
Data interpretation: M.S.S., M.N., P.K.
Drafting of the manuscript: all authors.

Declaration of interest

P.K. has been consulting for Baxter GmbH Germany, Air Liquide Medical GmbH Germany, and TEVA Ratiopharm Germany and received lecture fees and travelling expenses from these companies. He is an Associate Editor of *BMC Anesthesiology*.

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7.5 The hip fracture surgery in elderly patients (HIPELD) study to evaluate xenon anaesthesia for the prevention of postoperative delirium: a multicentre, randomized clinical trial

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The hip fracture surgery in elderly patients (HIPELD) study to evaluate xenon anaesthesia for the prevention of postoperative delirium: a multicentre, randomized clinical trial

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Abstract

Background: Postoperative delirium occurs frequently in elderly hip fracture surgery patients and is associated with poorer overall outcomes. Because xenon anaesthesia has neuroprotective properties, we evaluated its effect on the incidence of delirium and other outcomes after hip fracture surgery.

Methods: This was a phase II, multicentre, randomized, double-blind, parallel-group, controlled clinical trial conducted in hospitals in six European countries (September 2010 to October 2014). Elderly (≥75yr-old) and mentally functional hip fracture patients were randomly assigned 1:1 to receive either xenon- or sevoflurane-based general anaesthesia during surgery. The primary outcome was postoperative delirium diagnosed through postoperative day 4. Secondary outcomes were delirium diagnosed anytime after surgery, postoperative sequential organ failure assessment (SOFA) scores, and adverse events (AEs).

Results: Of 256 enrolled patients, 124 were treated with xenon and 132 with sevoflurane. The incidence of delirium with xenon (9.7% [95% CI: 4.5 -14.9]) or with sevoflurane (13.6% [95% CI: 7.8 -19.5]) were not significantly different (P=0.33). Overall SOFA scores were significantly lower with xenon (least-squares mean difference: −0.33 [95% CI: −0.60 to −0.06]; P=0.017). For xenon and sevoflurane, the incidence of serious AEs and fatal AEs was 8.0% *vs* 15.9% (P=0.05) and 0% *vs* 3.8% (P=0.06), respectively.

Conclusions: Xenon anaesthesia did not significantly reduce the incidence of postoperative delirium after hip fracture surgery. Nevertheless, exploratory observations concerning postoperative SOFA-scores, serious AEs, and deaths warrant further study of the potential benefits of xenon anaesthesia in elderly hip fracture surgery patients.

Clinical trial registration: EudraCT 2009-017153-35; ClinicalTrials.gov NCT01199276.

Key words: anaesthesia, general; aged; delirium; hip fractures; xenon

Editor's key points

- Postoperative delirium is common in the elderly and is associated with poor outcome.
- Xenon has been shown to have neuroprotective properties in animal studies.
- This study found no evidence that xenon-based anaesthesia reduced the incidence of delirium after hip fracture surgery in the elderly.
- This study is likely to be underpowered, so beneficial effects of xenon may have gone undetected.

With an ever-aging population, hip fracture is a major medical problem that imposes huge medical, financial, and societal burdens, and impairs the quality of life for patients, care-providers, and care-givers.[1,2] In the UK alone, there were over 67 000 hip fractures reported in 2014.[3] Hip fracture is also associated with high 30-day mortality rates (8 – 10% in the UK) and high one-yr mortality rates, which were reported to be 19 – 40% across several European countries.[3,4]

Postoperative delirium (POD) is also strongly associated with hip fracture surgery in older patients, with reported incidence rates of 13 – 50%.[5–10] POD is an acute state of confusion associated with changes in the levels of consciousness, arousal, and cognition after surgery.[11] While usually short-lived, POD is associated with increased hospital stays and costs, higher morbidity and mortality, higher risks of institutionalisation, cognitive decline, dementia, and poorer overall outcomes.[5,12–14]

The aetiology of POD is complex, poorly understood, and multifactorial.[15,16] The risk of POD increases with age, preexisting cognitive impairment, dementia, depression, comorbidity and vascular disease.[11,16,17] Recent data support the proposal that POD is a *cognitive disintegration* with a breakdown in neural network connectivity, possibly mediated through an increase in inhibitory γ-amino-butyric acid (GABA)-ergic tone, resulting in impaired integration of information in fronto-parietal networks.[15,18] Indeed, many of the modifiable risk factors for POD interact with GABAergic signaling.[11,15,17,19,20]

The noble gas xenon is an anaesthetic that blocks N-methyl- D-aspartate receptors and activates two-pore-domain potassium channels but has no activity on GABA receptors.[21–23] Xenon has been demonstrated to exert organoprotective effects including neuro- and cardio-protection, and to maintain haemodynamic stability better than other anaesthetics.[21–30] In two small studies in cardiac surgery patients, xenon has exhibited potentially promising, though inconsistent, effects in preventing POD.[29,31] However, neither study was designed or powered to specifically address the prevention of POD by xenon.

As a result of the potentially beneficial qualities of xenon, we hypothesized that the incidence of POD in hip fracture surgery patients would be lower with xenon-based anaesthesia than with sevoflurane-based anaesthesia. We therefore conducted a clinical trial to specifically compare the incidence of POD and other outcomes in hip fracture surgery patients anaesthetized with either xenon or sevoflurane.

Methods

Study design

The design and protocol of the study have been published previously[32] and are summarized in the Supplementary material. Briefly, this was a phase II, observer-blinded, parallel-arm, multicentre, randomized controlled trial conducted at 13 university or tertiary hospitals in six European countries (France, Belgium, Germany, Spain, UK, and Italy) between September 2010 and October 2014. The study protocol and subsequent substantial amendments were approved by local independent ethics committees and the competent regulatory authority in each country for each investigational site. The study was

registered with EudraCT (2009-017153-35) and ClinicalTrials.gov (NCT01199276), and conducted according to Good Clinical Practice guidelines, any local guidelines, the Declaration of Helsinki (2008), and European Directive 2001/20/CE. Written informed consent was obtained from all subjects.

During the course of the study, there were several protocol amendments. As a result of enrolment that was slower than anticipated with five centres, the recruitment period was extended on four successive occasions, and eight study sites were added to achieve the target enrolment (one in Belgium, five in France, and two in Germany). The collection of survival information at 28-days post-surgery was also added because it was identified as a key outcome parameter in the UK's National Hip Fracture Database.[3]

Participants

Hip fracture patients≥75 yr old with planned surgery within 48 h of fracture were eligible for study participation. Notable exclusion criteria included a history of severe dementia, Alzheimer's disease, schizophrenia, or moderate to severe depression; a recent brain trauma or history of stroke; delirium, as determined by a shortened version of the Confusion Assessment Method (CAM),[33] which is a worksheet version adapted from the original CAM by SK Inouye[34]; or a score of <24 in the Mini-Mental State Examination (MMSE). Complete exclusion criteria are listed in the Supplementary material and in Coburn, et al. 2012.[32]

Procedures

Patients were randomly assigned to the xenon or sevoflurane treatment groups using a blocked randomization scheme stratified by centre, with a block size of six, and assigned to groups from a computer-generated list. Block size was not specified in the protocol nor communicated to the investigators to avoid predictability of the next treatment. Patient selection and follow-up visits and assessments were performed by a study physician who was blinded to the allocated anaesthetic (Physician 1). The identity of the randomization-allocated anaesthetic was contained in an envelope bearing the sequential randomisation number of the patient and was revealed to the attending anaesthetist (Physician 2) who opened the envelope only immediately before surgery. Study Physicians 1 and 2 had no access to the case report forms of their physician counterparts. Study eligibility, vital signs, baseline scores for (i) delirium as determined by the CAM,[33] for (ii) Sequential Organ Failure Assessment (SOFA),[35] and for (iii) pain (by the visual assessment score [VAS]) and concomitant medications and diseases, were assessed at the selection visit.

Benzodiazepine premedication was avoided. General anaesthesia was induced with propofol (1 - 2 mg/kg), which was continued at 0.05 - 0.15 mg/kg per min for approximately 10min until maintenance anaesthesia with the randomization-allocated anaesthetic (either sevoflurane or xenon gas delivered using a Felix Dual™ Workstation [Air Liquide Medical Systems, France]) could be initiated. Patients in the xenon group received 60 (5%) xenon (approximately 1 minimum alveolar concentration [MAC]) in oxygen (FiO_2=0.35 to 0.45); patients in the sevoflurane group received 1.1 -1.4% sevoflurane (1 MAC adjusted to age) in oxygen and medical air (FiO_2=0.35 to 0.45).[36] Depth of anaesthesia was monitored continuously using the Bispectral Index (BIS VISTA™, Aspect Medical Systems, Norwood, MA) and was kept between 40 and 60.

After weaning from anaesthesia, vital signs, recovery parameters, and the Aldrete score were monitored every 15 min until recovery was complete with a score of ≥ 9. Beginning at 3 h after surgery and at twice-daily visits [10 am (30min) and 6 pm (30 min)] through discharge (or for a maximum of 28 days), patients were assessed for POD, severity of pain (VAS), vital signs, concomitant medications, adverse events (AEs), and serious adverse events (SAEs). SOFA scores and laboratory analysis results were recorded at each visit through day four and were optional thereafter.

Outcomes

The primary endpoint was the occurrence of at least one episode of POD as assessed by the shortened worksheet version of the CAM within four days post-surgery. This worksheet includes the first four criteria of the full CAM, all of which are necessary and sufficient for detecting delirium.[33] The CAM assessment was performed by investigators (Physician 1 or a research nurse), who were blinded to the group assignment and who received extensive and specific training before the study according to the CAM training manual and coding guide.[34] Training was conducted by an external study-sponsored physician via a remote presentation during study site initiation. Secondary exploratory endpoints were POD from postoperative day five through discharge; SOFA on postoperative days one to four; recovery parameters; and mortality. Safety was assessed from the AEs and SAEs recorded throughout the study and from laboratory parameters. Diagnostic criteria for specific AEs were those used in standard practice at each study site and were not harmonised across the study sites.

Statistical analysis

The sample size was calculated based on an expected POD event rate of 30% within four days after surgery with sevoflurane anaesthesia.[32] It was estimated that this POD event rate would be 50% lower with xenon yielding an event rate of 15%. We estimated a large effect size (odds ratio of 0.50) for this older population, which is larger than what would be considered as a clinically significant improvement. Type I error was set to $\alpha = 0.05$ (two-sided conditions), and power was 80% to detect the 50% reduction. Power calculations were performed using nQuery Advisor® Version 6.01 (Statistical Solutions, Saugus, MA) and yielded 121 patients per group. With an expected dropout rate of 5%, the target enrolment was set to 256 randomized patients (128 per group).

In the primary analysis of the primary outcome, the POD incidence within four days post-surgery in each group in the intention-to-treat population was compared using a χ^2 test that included observed cases only. The Pearson's analysis was also repeated for the per-protocol population (patients with no major protocol deviations) in sensitivity analyses and to handle missing data. Sensitivity, secondary, exploratory, and post-hoc analyses are described in the Supplementary material. Statistical analyses were performed using SAS® software (SAS Institute, Cary, NC, USA) Version 9.2. Statistical significance for all tests was fixed at $\alpha = 0.05$. However, a value of $\alpha = 0.10$ was applied during the initial two-factor regression analysis to identify potentially confounding factors to be used in the subsequent multivariate regression analysis, and during the stepwise backward selection of these factors in the multivariate regression model.

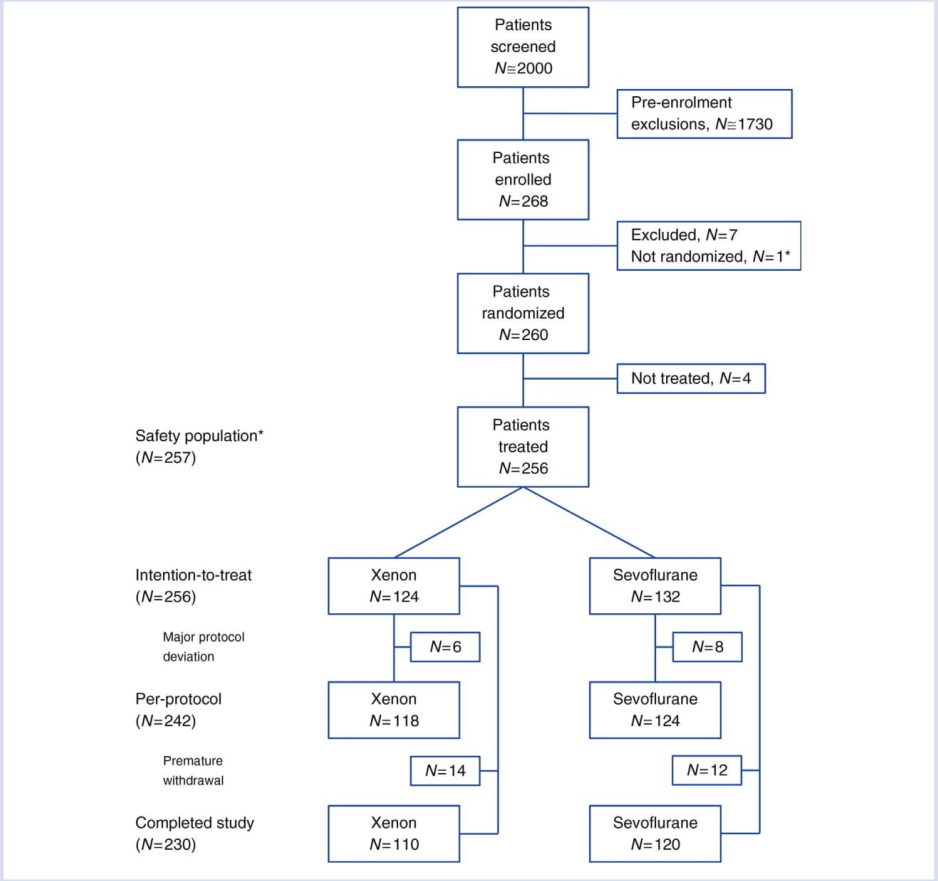

Fig 1. **Patient disposition.** Among the over 2000 patients who were screened for enrolment in the HIPELD study, 268 were enrolled. Records were not kept for patients not enrolled, but most of these patients failed to meet the MMSE score criterion. Of the enrolled patients, 260 patients were eventually randomly assigned and 257 were treated and followed for safety. One non-randomized patient was treated with xenon anaesthesia and included in the safety population but was not included in any other analyses and did not complete the study (*). Most patients excluded from the per-protocol analyses had multiple missing CAM evaluations (nine patients).

Results

From over 2000 hip fracture patients screened for the study, only 268 were enrolled and 260 were randomly assigned to the treatment groups between September 2010 and October 2014 (Fig. 1). Most pre-enrolment exclusions were because of low MMSE scores. Among these, 256 randomized patients were treated and eligible for analysis. Fourteen patients who had major protocol deviations were included in the intention-to-treat population but were excluded from per-protocol analyses. Most were excluded for multiple (≥five) missing CAM evaluations (nine patients) after surgery or for missing CAM evaluations at selection (three patients). A total of 110 patients in the xenon group and 120 in sevoflurane group completed the study.

Patient population

Baseline characteristics were similar for both groups (Table 1). Most patients in each group were women and the mean age was 84 yr. Most patients had an ASA physical status of II or III and a moderate level of pain. Pre-operative SOFA scores were

Table 1 Baseline patient characteristics. CAM, Confusion Assessment Method; MMSE, mini mental state examination; n, number of patients with the characteristic or for which results are available; N, number of patients in the group; SD, standard deviation; SOFA, sequential organ failure assessment; VAS, visual analogue scale. *Percentages are calculated for patients without missing data, which included >95% of the patients in each group, except where noted otherwise. †Mean total scores calculated for 85 patients in the xenon group and 72 patients in the sevoflurane group without missing values

Patient characteristics	Xenon (N=124)	Sevoflurane (N=132)
Men, n (%)*	34 (27.4)	29 (22.0)
Women, *n* (%)	90 (72.6)	103 (78.0)
Age, yr		
Mean (SD)	83.8 (5.1)	84.4 (4.6)
Range	75.1 – 98.5	75.5 – 95.4
BMI, mean kg/m^2 (SD)	23.7 (3.8)	24.2 (4.3)
Type of hip fracture, *n* (%)		
Displaced femoral neck	50 (40.3)	52 (39.4)
Non-displaced or impacted femoral neck	31 (25.0)	26 (19.7)
Stable intertrochanteric fracture	15 (12.1)	20 (15.2)
Unstable intertrochanteric fracture	13 (10.5)	17 (12.9)
Other hip fracture	15 (12.1)	17 (12.9)
Smoking history, *n* (%)		
Never smoked	92 (75.4)	109 (83.2)
Ex-smoker	19 (15.6)	14 (10.7)
Current smoker	11 (9.0)	8 (6.1)
Alcohol consumption, *n* (%)		
Never	86 (70.5%)	92 (70.8%)
Occasionally	29 (23.8%)	36 (27.7%)
Regularly	7 (5.7%)	2 (1.5%)
ASA physical status, *n* (%)		
ASA I	5 (4.2)	7 (5.5)
ASA II	74 (61.7)	75 (58.6)
ASA III	41 (34.2)	46 (35.9)
ASA IV	0 (0.0)	0 (0.0)
Pain/VAS, mean mm (SD)	38 (25)	36 (23)
Total MMSE score, mean (SD)	27.1 (1.8)	27.1 (1.7)
Delirium diagnosis by CAM, *n* (%)		
Yes	0 (0)	0 (0)
No	122 (100)	131 (100)
Missing	2	1
Total SOFA score, mean (SD)†	0.61 (0.95)	0.69 (1.03)
Concomitant diseases, *n* (%)		
At least one concomitant disease	120 (96.8)	125 (94.7)
Hypertension	89 (71.8)	92 (69.7)
Dyslipidaemia	19 (15.3)	14 (10.6)
Diabetes mellitus	10 (8.1)	18 (13.6)
Hypercholesterolemia	12 (9.7)	14 (10.6)
Type 2 diabetes mellitus	11 (8.9)	15 (11.4)
Cardiac disorders	42 (33.9)	46 (34.8)
Musculoskeletal/connective tissue disorders	32 (25.8)	26 (19.7)
Renal/urinary disorders	23 (18.5)	29 (22.0)
Gastrointestinal disorders	26 (21.0)	25 (18.9)
Nervous system disorders	19 (15.3)	20 (15.2)
Psychiatric disorders	20 (16.1)	15 (11.4)
Respiratory/thoracic/mediastinal disorders	19 (15.3)	16 (12.1)
Eye disorders	14 (11.3)	13 (9.8)

low; however, concomitant diseases such as hypertension, cardiac disorders, and musculoskeletal disorders were frequent (95%).

Hip fracture surgeries and anaesthesia

Surgery-related data and duration of the procedures were similar for the two groups (Table 2). During recovery from anaesthesia, the times to open eyes, to react to verbal commands, and to extubation were all significantly shorter for xenon than for sevoflurane (P<0.001). The time to reach an Aldrete score of nine was similar for both groups. Total length of hospital stay was similar for both groups, and >95% of the patients in each group were discharged from the hospital within 30 days after surgery. Depth of anaesthesia during surgery (BIS values; Supplementary Fig. S1) and haemodynamic variables during surgery (Supplementary Fig. S2) were similar across groups.

Postoperative delirium incidence

In the primary analysis, a total of 12 out of 124 (9.7% [95% CI: 4.5 14.9%]) patients in the xenon group *vs* 18 out of 132 (13.6% [95% CI: 7.8 –19.5%]) patients in the sevoflurane group had at least one POD episode during the first four days after surgery (Table 3). These incidence rates were not significantly different

Table 2 Intraoperative and postoperative characteristics of hip fracture surgeries. *Treatment groups compared using the log-rank test. †One patient in the xenon group had an extraordinarily long recovery time of 363 min. No other patient in either group had a recovery time longer than 33 min. ‡Treatment groups compared using the Wilcoxon rank sum test for quantitative variables

Characteristic	Xenon (*N*=124)	Sevoflurane (*N*=132)	*P*-value
Type of hip fracture surgery performed, *n* (%)			
Hemi-arthroplasty of the hip	31 (25.0)	23 (17.4)	
Total hip replacement: cemented	21 (16.9)	19 (14.4)	
Dynamic hip screw	12 (9.7)	12 (9.1)	
Total hip replacement: non-cemented	4 (3.2)	3 (2.3)	
Other	56 (45.2)	75 (56.8)	
Mean time interval between hip fracture and surgery, h (SD)	47.9 (40.1)	37.4 (27.4)	
Duration of anaesthesia, min (SD)			
Mean duration of induction	21.6 (14.1)	20.5 (12.8)	
Mean duration of maintenance	105.2 (47.9)	89.9 (37.7)	
Mean total duration	125.8 (50.9)	109.3 (38.7)	
Mean duration of surgery, min (SD)	72.4 (39.1)	62.0 (31.1)	
Anaesthesia recovery parameters			
Mean time to Aldrete score of ≥ 9, h (SD)	0.70 (1.20)	0.72 (0.72)	0.22*
Median time to open eyes, min (range)	4.0 (0–363)†	8.0 (0–33)	<0.001‡
Median time to react on verbal command, min (range)	5.0 (0–363)†	8.5 (1–33)	<0.001‡
Median time to extubation, min (range)	5.4 (0–373)†	9.1 (1–35)	<0.001‡
Hospitalization			
Mean time to discharge, days (SD)	10.8 (5.2)	11.4 (6.2)	0.53†
Patients discharged within 30 days, *n*	120	125	
Patients not discharged within 30 days, *n*	4	2	
Patients who died, *n*	0	5	

(*P*=0.33). Similar results were obtained for the per-protocol population (*P*=0.40) and in sensitivity analyses performed for only those patients who had undergone all planned CAM assessments up to the afternoon of day 4 and if all patients who were withdrawn because of an AE or who died were included in the analysis and considered to have had a POD episode (Supplementary Table S1).

Incidence rates for POD at five or more days after surgery or at any time after surgery were not significantly different (*P*=0.46 for each; Table 3). Six (4.8%) patients in the xenon group and 11 (8.3%) patients in the sevoflurane group had multiple POD episodes during the study. The mean time to a first POD episode during the first four days after surgery (also the Kaplan-Meier diagram in Supplementary Fig. S3) and the mean duration of POD episodes were similar in both groups, with most episodes lasting 0.5 days.

In multivariate-factor logistic regression analyses of patient factors possibly associated with POD within the first four

Table 3 Incidence and characteristics of postoperative delirium (POD) episodes in hip-fracture surgery patients. Results shown for all randomized, treated patients (intention-to-treat population). All POD episodes diagnosed by CAM. CAM, Confusion Assessment Method; CI, confidence interval for percentage of patients with a POD episode of the type described; POD, postoperative delirium. *Treatment groups compared by χ^2 test. †Per-protocol population: xenon (N=118); sevoflurane (*N*=124)

Metric	Xenon (*N*=124)	Sevoflurane (*N*=132)	*P*-value*
At least one POD episode by post-surgery day 4, *n* (%) [95% CI] - intention-to-treat [%]	12 (9.7) [4.5 – 14.9]	18 (13.6) [7.8 – 19.5]	0.33
At least one POD episode by post-surgery day 4, *n* (%) [95% CI] - per-protocol† [%]	12 (10.2) [4.7 -15.6]	17 (13.7) [7.7 - 19.8]	0.40
At least one POD episode on post-surgery day 5 or later, *n* (%) [95% CI] [%]	5 (4.0) [0.6 – 7.5]	8 (6.1) [2.0 – 10.1]	0.46
At least one POD episode during the study, *n* (%) [95% CI] [%]	14 (11.3) [5.7 -16.9]	19 (14.4) [8.4-20.4]	0.46
Number of POD episodes, *n* (%)			
0	110 (88.7)	113 (85.6)	
1	8 (6.5)	8 (6.1)	
2	3 (2.4)	5 (3.8)	
≥3	3 (2.4)	6 (4.5)	
Mean time to first POD episode within post-surgery day 4, h (SD)	28.9 (34.3)	24.4 (25.8)	
Duration of first POD episode within post-surgery day 4			
Episodes, *n*	12	18	
Mean duration, days (SD)	0.87 (0.96)	0.91 (0.80)	
0.5 day, *n* (%)	9 (75.0)	10 (55.6)	
1 - 2 days, *n* (%)	2 (16.7)	7 (38.9)	
3 - 4 days, *n* (%)	1 (8.3)	1 (5.6)	

days after surgery, four were identified as potentially important after backward selection: male gender, ASA physical status III, being a current smoker, and the presence of a previously diagnosed mild neurologic disorder at selection (Supplementary Table S2). Of these potential confounders, only being a current smoker (adjusted odds-ratio [AOR] 5.35 [1.65 – 17.32]; P=0.005) and the presence of a previously diagnosed mild neurologic disorder (AOR 3.27 [1.12 – 9.57]; P=0.030) were significantly associated with POD (P<0.05). The adjusted odds-ratio (AOR) for POD with xenon treatment was not statistically significant (0.50 [95% CI 0.20 – 1.20]; P=0.12; Supplementary Table S2 and Fig. S4).

Excessively deep anaesthesia and long delays before surgery have been reported to be risk factors for POD.[19,37] However, in post-hoc analyses, we found no significant associations between POD and cumulative time at low BIS values (<40; P=0.86) during surgery or between POD and time-to-surgery (P=0.34) (Supplementary Table S3).

SOFA scores

Mean total SOFA scores (SD) increased after surgery and were highest at day 1, with scores of 0.87 (0.94) in the xenon group and 1.19 (1.49) in the sevoflurane group (Supplementary Fig. S5). Mean total score in the xenon group [0.57 (0.84)] was significantly lower than in the sevoflurane group [1.01 (1.77)] on day three only (P=0.04). Comparison of the overall difference in SOFA scores over time by repeated ANCOVA analysis yielded a statistically significant least-squares mean difference of −0.33 [95% CI: −0.60 to −0.06] (P=0.02) in favour of xenon.

Safety

AEs were reported for 114 of 125 patients (91.2%) in the xenon group (495 AEs) and for 125 of 132 patients (94.7%) in the sevoflurane group (573 AEs; Table 4). Most AEs were treatment-emergent and of mild-to-moderate severity, and about 50% in each group were considered by the investigators to be related to study treatment. SAEs were nearly twice as common in the sevoflurane group (45 for 21 patients) than in the xenon group (22 for 10 patients; P=0.05). The proportion of patients with SAEs that were graded severe was significantly greater in the sevoflurane group than in the xenon group (P=0.008).

Mortality

Vital status at 28 days after surgery was available for 103 (83%) patients in the xenon group and 110 (83%) patients in the sevoflurane group; no additional deaths were reported. By the end of the study, only one patient in the xenon group and three patients in the sevoflurane group had ongoing SAEs (Table 4). No patients in the xenon group died but five patients in the sevoflurane group (3.8%) succumbed to fatal SAEs (P=0.06). Causes of death were septic shock and multi-organ failure; pneumonia and respiratory failure; pneumonia, septic shock and acute renal failure; right ventricular failure; and cardiac failure. Three of the patients who died had at least one POD episode within four days of surgery.

Discussion

In this international randomized clinical trial, xenon-based anaesthesia did not significantly reduce the incidence of POD

Table 4 Safety summary. Results shown for all treated patients (Safety set). AE, adverse event; CRP, C-reactive protein; n, number of patients with the specified category or type of AE; ND, not determined; SAE, serious adverse event. *χ^2 test for patients with at least one specified AE. †Fisher's exact test for patients with at least one specified AE

	Xenon (N=125)		Sevoflurane (N=132)		P-value
	Patients with at least one, n (%)	Total AEs, n	Patients with at least one, n (%)	Total AEs, n	
AEs	114 (91.2)	495	125 (94.7)	573	0.27[a]
Severe	13 (10.4)	19	22 (16.7)	50	0.14[a]
Treatment-emergent	114 (91.2)	457	123 (93.2)	540	0.55[a]
Severe	12 (9.6)	18	21 (15.9)	49	0.13[a]
Considered to be related to study treatment	65 (52.0)	150	62 (47.0)	157	0.42[a]
Most common AEs (>20% of patients)					
Anaemia	45 (36.0)	-	60 (45.5)	-	ND
Hypotension	44 (35.2)	-	53 (40.2)	-	ND
Elevated CRP	29 (23.2)	-	25 (18.9)	-	ND
Gastrointestinal disorders	36 (28.8)	-	34 (25.8)	-	ND
SAEs	10 (8.0)	22	21 (15.9)	45	0.05[a]
Treatment-emergent	10 (8.0)	22	21 (15.9)	45	0.05[a]
Severe	4 (3.2)	6	16 (12.1)	30	0.008[a]
Considered to be related to study treatment	1 (0.8)	1	5 (3.8)	8	0.21[c]
Most common SAEs (>2% of patients)					
Pneumonia	0 (0)	-	4 (3.0)	-	ND
Acute myocardial infarction	1 (0.8)	-	3 (2.3)	-	ND
Respiratory failure	0 (0)	-	3 (2.3)	-	ND
SAE outcomes					
Ongoing	1 (0.8)	1	3 (2.3)	3	0.62[b]
Recovered	9 (7.2)	19	13 (9.8)	26	0.45[a]
Recovering	1 (0.8)	2	3 (2.3)	4	0.62[b]
Recovered with sequelae	0 (0.0)	0	2 (1.5)	2	0.50[b]
Death	0 (0.0)	0	5 (3.8)	9	0.06[b]
Unknown	0 (0.0)	0	1 (0.8)	1	1.00[b]

in elderly hip fracture surgery patients. Differences in secondary outcomes were either statistically significant and not clinically meaningful in this study (SOFA scores) or potentially clinically pertinent but not statistically significant (SAEs, mortality).

The incidence of POD after hip fracture surgery in the elderly is typically high.[5–9,11] In the studies we used to calculate the sample size needed to evaluate the primary efficacy criterion of at least one POD episode within four days after surgery, the incidence varied between 28% and 50%;[6–10,32,38,39] however, the actual incidence of POD in the sevoflurane control group (13.6%) was much lower than the expected rate (30%). The lower-than- expected incidence of POD in the sevoflurane group likely reflects our use of strict inclusion criteria; patients were excluded for any preoperative signs of delirium, moderate to severe depression, or a poor functional mental state (MMSE score<24). As a consequence, the patient population in the study may have differed from the general elderly population that routinely undergoes hip fracture surgery, in whom the incidence of POD is higher.[13,16] Indeed, it proved difficult to recruit patients into the study because many patients who fulfilled the other inclusion criteria failed to satisfy the mental state criteria. We estimate that less than 15% of those screened were eligible for enrolment. Another contributing factor to the low incidence of POD may have been the use of BIS technology to monitor the depth of anaesthesia; in a recent meta-analysis, the incidence of POD was found to be lower with BIS-guided anaesthesia than with BIS-blinded anaesthesia or clinical judgment.[40]

The POD incidence in the xenon group was not 50% lower than in the sevoflurane group as required by the power analysis, but only 33% lower. Despite this, an overall reduction of 33% in POD, if statistically significant, would still represent a clinically meaningful benefit, which future studies should consider. Nonetheless, the overestimations of both the POD-incidence rate and the effect size rendered the power of the study insufficient to detect significant differences between the two groups for the primary efficacy endpoint. Despite the low incidence of POD in the study, we were able to identify two patient factors that were significantly associated with POD: being a current smoker and having a previously diagnosed mild neurologic disorder.[13,16,41,42]

The association of POD with the type of anaesthesia or anaesthetic agent used for surgery is unclear. There is some evidence that the incidence of POD may increase with the depth of anaesthesia, but regional anaesthesia was not found to be preventative, perhaps as a result of sedation in the regional anaesthesia group.[19,43] In a small pilot study in 42 patients who received either xenon or sevoflurane-based anaesthesia during cardiac surgery, the incidence of POD was significantly lower in the group that received xenon[29]; although these latter results were not confirmed in our hip fracture surgery patients, the potential benefits of xenon in cardiac surgery patients await confirmation in a larger clinical trial.[44]

While xenon anaesthesia has previously demonstrated orga- noprotective properties and a superior haemodynamic profile compared with other anaesthetic agents,[22,24–26,29,45,46] we could not confirm these effects in hip fracture surgery patients. Though patients in the xenon-group had a slightly lower overall SOFA score (which could be interpreted as a sign for a certain degree of organoprotection), this difference was of marginal clinical relevance. Likewise, there were no significant differences between the groups in patients with SAEs (P=0.05) or in patients with fatal SAEs (P=0.06), though the proportion of patients with SAEs graded as severe was significantly smaller in the xenon group (P=0.008).

The study has several strengths and limitations. Specific inclusion and exclusion criteria resulted in a well-defined study population that was similar for the prospective risk of developing POD across the treatment groups. The high temporal resolution consequent to the twice-daily CAM evaluations ensured that a high proportion of the POD episodes could be detected. The secondary efficacy endpoints and safety data facilitated assessment of the potential benefits of xenon anaesthesia on organoprotection and mortality. One limitation regarding mortality may be that 28-day follow-up results were available for only ~80% of the patients in each group. We did not interrogate death registries to accommodate for missing data. We used BIS technology to avoid variations in and excessively deep anaesthesia during surgery and to prevent depth of anaesthesia from becoming a confounding factor between treatment groups. BIS values were carefully monitored and mean values were consistently maintained and similar during surgery for both groups suggesting that similar levels of consciousness and exposure were obtained for these two different anaesthetics. A major limitation was the low overall incidence of POD, likely because of the restrictive exclusion criteria that eliminated many patients at high risk for developing POD, and may have been additionally reduced through our use of BIS to monitor the depth of anaesthesia.[40] It is also possible that some POD episodes were missed as a result of some inconsistencies in administration of the CAM across different staff and centres and by our use of the shortened, worksheet version of the CAM. Although the full nine-item CAM is recommended for maximum sensitivity, we considered the shorter CAM to be far more practical and reasonable for an international clinical trial using twice-daily postoperative assessments. In addition, the four essential and validated criteria for determining delirium are included in the shortened CAM worksheet.[33,47] Finally, while some training is recommended for optimal use,[47] and our study personnel received extensive and specific training according the CAM training manual before the study, we cannot be certain that the CAM was administered consistently across all study centres. Indeed, training can be a factor in delirium recognition by the CAM.[48] One aspect of delirium not considered in the current study was severity. The CAM-S tool provides a revised delirium scoring system that allows assessment of delirium severity.[49] Investigators should bear these aspects in mind when designing clinical trials to investigate preventative measures for POD.

Conclusions

The incidence of POD in this study was not significantly lower with xenon anaesthesia than with sevoflurane anaesthesia. Our observations concerning postoperative SOFA-scores, SAEs, and mortality should be considered hypothesis-generating and warrant further study to assess the potential benefits of xenon anaesthesia in elderly hip-fracture surgery patients.

Authors' contributions

Study design/planning: M.C., R.D.S., M.M., R.R., M.L.N.P.
Study conduct: all authors except R.D.S., M.M.

Data analysis: M.S.
Writing paper: M.C., R.D.S., M.M., S.R., R.R., M.L.N.P.
Revising paper: all authors

Declaration of interest

The institutions of M.C., S.R., B.G., J.A.C., M.L.G.P., A.S., P.K., M.N., M.S.S., B.B., H.v.O., A.T., L.A., L.E., O.L., X.C., G.M.A., and R.R. received grant funds and/or patient inclusion fees from Air Liquide Santé International to conduct the study. M.C., R.D.S., M.M., A.S., and R.R. received consulting fees and/or travel funds from Air Liquide Santé International. M.C. received grants, consulting fees, and travel funds from Baxter Healthcare and grants from German Research Foundation outside the submitted work. S.R. received unrestricted grants from Air Liquide Santé International and Air Liquide Belgium and speaking fees from Orion Pharma. M.M. is a co-founder of NeuroproteXeon that seeks to develop xenon for protection against acute ongoing neurological injury and could receive royalties from sales of xenon as a neuroprotective agent. M.L.N.P. was a full-time employee of Air Liquide Santé International during the study. M.S. is currently a full-time employee of Air Liquide Santé International.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2017.11.015

Appendix

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7.6 Predictors for postoperative nausea and vomiting after xenon-based anaesthesia

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Predictors for postoperative nausea and vomiting after xenon-based anaesthesia

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Abstract

Background: In contrast to volatile anaesthetics, xenon acts by antagonism at *N*-methyl-D-aspartate receptors and antagonizes 5-hydroxytryptamine type 3 receptors that mediate nausea and vomiting. Therefore, it is unknown whether the same risk factors for postoperative nausea and vomiting (PONV) after volatile anaesthetics apply to xenon-based anaesthesia.
Methods: With ethics committee approval and written informed consent, 502 consecutive patients undergoing xenon-based anaesthesia were included in a multicentre prospective observational study. Antiemetic prophylaxis was administered at the discretion of the attending anaesthetists. Postoperative nausea and vomiting and need for antiemetic rescue medication were assessed for 24 h after anaesthesia. Multivariate logistic regression analysis was performed to quantify risk factors for PONV and need for rescue medication.
Results: Four hundred and eighty-eight subjects were available for the final analysis. The incidence of PONV in subjects without prophylaxis was lower than expected according to the Apfel Score (28% observed; 42% expected, $P<0.001$). Independent predictors for PONV were (adjusted odds ratio; 95% confidence interval) female sex (1.76; 1.08–2.89), younger patient age (0.82 per 10 yr; 0.69–0.97), and longer duration of anaesthesia (1.36 per hour; 1.17–1.59).
Conclusions: The incidence of PONV was significantly lower than predicted by the Apfel Score. Female sex, younger age, and longer duration of anaesthesia are risk factors for PONV after xenon-based anaesthesia.
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Key words: anaesthetics; antiemetics; risk factors

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Editor's key points

- Risk factors for postoperative nausea and vomiting (PONV) after xenon anaesthesia are unknown.
- Multivariate analysis was used to quantify risk factors for PONV and need for rescue antiemetics in a multicentre prospective trial of xenon anaesthesia.
- Incidence of PONV was lower than predicted for propofol or inhaled anaesthesia.
- Female gender, younger age, and longer duration of anaesthesia were risk factors for PONV.

Postoperative nausea and vomiting (PONV) severely impair patient satisfaction and rank together with pain among the most undesirable outcomes following general anaesthesia.[1] The identification of risk factors for PONV forms the basis for adequate prophylaxis and treatment of patients with a high probability of experiencing PONV. In addition to patient-related risk factors, inhaled anaesthetics induce PONV depending on the duration of exposure.[2 3]

As a noble gas, xenon is chemically inert in physiological conditions and therefore free of metabolites. As a result of its low solubility in blood, it is rapidly eliminated from the body during weaning from anaesthesia.[4 5] Furthermore, xenon antagonizes serotonin type 3 ($5\text{-}HT_3$) receptors that mediate nausea and vomiting during chemotherapy and after general anaesthesia.[2] Taken together, one might assume that the incidence of PONV after xenon-based anaesthesia is rather low, yet Coburn and colleagues[6] described an incidence of PONV of more than 60%. Thus, identification of risk factors could facilitate titration of prophylactic antiemetics during xenon-based anaesthesia. However, with respect to pharmacokinetic and pharmacodynamic differences compared with other inhaled anaesthetics, it is not known whether risk factors for PONV are valid in the course of xenon-based anaesthesia or if prevalent pharmacological prophylaxis is sufficiently effective in this setting. Therefore, our aim was to determine (i) the risk factors for PONV and (ii) the efficacy of routinely administered antiemetic prophylaxis after xenon-based anaesthesia.

Methods

Here we present data from a previously unpublished prospective multicentre study performed to evaluate the safety and efficacy of xenon-based anaesthesia with subjects recruited between April 2009 and February 2011. After institutional review board approval (Ethik-Kommission der Ärztekammer Berlin, study number ETH-019/08, and Heinrich-Heine Universität Düsseldorf, study number 3386) and registration at the German Federal Institute for Drugs and Medical Devices (BfArM, study number AL-PMS-01/07GER), all patients classified as ASA status I–II (age 18 yr or older) undergoing surgery during xenon-based general anaesthesia were eligible for this study after written informed consent was obtained. Patients with elevated intracranial pressure, pulmonary disease, coronary artery disease, and impaired left ventricular function were excluded. Induction and maintenance of xenon-based anaesthesia was conducted at the discretion of the attending anaesthetists.

Assessment of postoperative nausea and vomiting

Subjects were followed for 24 h after extubation by study physicians. The incidence of nausea, vomiting, or both within the 24 h period was assessed by medical chart inspection followed by a personal patient interview and recorded as a binary variable. The requirement for postoperative antiemetic medication ('rescue medication') was assessed from medical charts.

Incidence of postoperative nausea and vomiting and quantification of independent predictors

The observed incidence of PONV was compared with the expected incidence predicted by Apfel Score.[7] The initial Apfel Score was corrected for the administered postoperative opioids. This comparison was performed only in subjects who did not receive antiemetic prophylaxis to determine the unimpeded emetic activity of xenon-based anaesthesia.

We assessed predictors for PONV or rescue medication after xenon-based anaesthesia by logistic regression analysis. A recent, large meta-regression identified female sex, history of PONV or motion sickness, non-smoking status, younger age, duration of anaesthesia, use of postoperative opioids, and certain types of surgery as independent predictors for PONV after propofol or inhaled anaesthetic-based anaesthesia.[8] Therefore, we decided *a priori* to include these variables in the model. The comparison of postoperative opioid consumption was facilitated by calculation of morphine equivalents. In addition, different classes of medical antiemetic prophylaxis and study centres were also included as single binary variables in the model *a priori*. The aim of the next step was to identify further potential predictors by testing remaining variables (height, weight, body mass index, amount of intraoperative fluids, type of intraoperative opioid, and use of regional anaesthesia) for association with PONV or rescue medication by univariate analysis. As no statistically significant associations were found, we did not include these variables in our logistic regression analysis. Variables within the model were tested for collinearity using the *collin* extension of Stata (P. Ender, University of California, Los Angeles, CA, USA). Goodness of fit was assessed using the Hosmer–Lemeshow test with 10 groups.

Effectiveness of medical antiemetic prophylaxis

The effect of prophylactic antiemetics was part of the logistic regression analysis. However, we additionally performed a propensity score-matched analysis so that subjects who did or did not receive prophylactic antiemetics were comparable. To this end, a binary variable was generated indicating whether a subject received medical antiemetic prophylaxis or not. Then, a logistic regression model including sex, age, smoking status, history of PONV or motion sickness, regional anaesthesia, duration of anaesthesia, anticipated postoperative opioid use, and study centre was used to calculate the propensity for receiving medical antiemetic prophylaxis. Finally, subjects with prophylaxis were matched on a one-to-one basis with patients without prophylaxis on the logit of the propensity score using callipers of 0.2 SD of the logit.[9] Univariate analyses were performed to verify that groups were balanced on the variables used for calculation of the propensity score (i.e. that matching was successful). Additionally, standardized differences were calculated to quantify balancing of groups.[10]

The sample size estimation of the underlying study was carried out based on the primary end points depth of anaesthesia and incidences of hypertension and anaesthesia. However, when comparing an overall PONV incidence associated with general anaesthesia of 38%[11] and a previously reported PONV incidence of 27.5% after xenon-based anaesthesia,[12] a minimal sample size of 364 patients would be required. On this basis, we

considered the available number of 500 patients included in this study to be sufficient. In addition, *post hoc* power analyses of the logistic regression analysis and the propensity score-matched analysis were performed. Results are presented as adjusted odds ratios with the 95% confidence interval (CI), means (SD), median [interquartile range] or absolute numbers (percentage). A two-tailed *P*-value <0.05 was considered statistically significant. Univariate analyses were performed using Fisher's exact test, Mann–Whitney *U*-test, and in the case of normally distributed variables, Student's *t*-test. Calculations were made with Stata IC version 10.0 (StataCorp LP, College Station, TX, USA) and *post hoc* power analysis with G*Power 3.1.5.[13]

Results

A total of 502 patients undergoing xenon-based general anaesthesia were enrolled in this study. Of those, 488 were included in the final analysis (Fig. 1).

Management of anaesthesia

Attending physicians chose propofol [cumulative dose 6.4 (3.4) mg kg^{-1} until start of xenon] for anaesthesia induction and initial maintenance until the end of denitrogenation in all but three subjects, for whom etomidate [0.29 (0.04) mg kg^{-1}] was used as induction agent. Rocuronium [463 subjects, 0.6 (0.2) mg kg^{-1}] was the primarily administered Neuromuscular blocking agent. Systemic analgesia was achieved with remifentanil [292 subjects, 10.8 (3.6) μg kg^{-1} h^{-1}], fentanyl [118 subjects, 2.1 (1.4) μg kg^{-1} h^{-1}], or sufentanil [78 subjects, 0.24 (0.17) μg kg^{-1} h^{-1}]. Finally, 111 subjects received additional regional anaesthesia (Table 1). Xenon wash-in started 26 (12) min after induction of anaesthesia. In three subjects, xenon administration was discontinued before the end of surgery. One of these subjects was a 23-yr-old morbidly obese (body mass index 48 kg m^{-2}) female patient undergoing resection of a vulvar dysplasia, who experienced a decrease of oxygen saturation to <90% during xenon wash-in. The second was a 66-yr-old female patient with a body mass index of 32 kg m^{-2} undergoing laparoscopic nephrectomy with insufficient elimination of CO_2 as a result of elevated airway pressure at 1 h after xenon wash-in. In the third subject, xenon was discontinued at 45 min after wash-in because of technical problems with the anaesthetic machine. After discontinuation of xenon, anaesthesia was maintained with propofol in the first two subjects and isoflurane in the last subject. These subjects were not excluded after an intention-to-treat analysis.

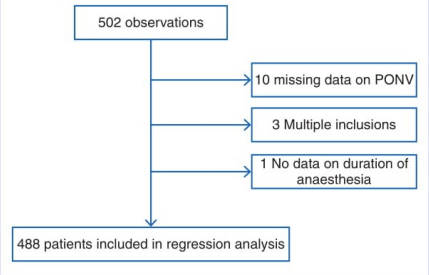

Fig 1 Study flow chart with reasons for exclusion of 14 patients. PONV, postoperative nausea and vomiting.

Incidence of postoperative nausea and vomiting and independent predictors

A total of 136 (28%) subjects suffered from PONV after xenon-based anaesthesia. In subjects without medical antiemetic prophylaxis, PONV occurred in 92 (28%) of subjects. The expected incidence in this subpopulation was 42% (95% CI 42.0–45.0) considering a median Apfel Score of 2 [1;3] (*P*<0.001 *vs* observed), and the area under the receiver operating characteristic curve

Table 1 Subject characteristics, anaesthetic characteristics, and type of surgery. Data are presented as the mean (SD) or absolute value (%). PONV, postoperative nausea and vomiting

Age [yr (range)]	53 (18–90)
Height (cm)	172 (10)
Weight (kg)	79 (17)
Apfel Score (0/1/2/3/4)	6/103/213/132/34 (1/21/44/27/7)
Female	227 (47)
Non-smoking status	364 (75)
History of PONV or motion sickness, or both	94 (19)
Postoperative opioid use	376 (77)
Duration of anaesthesia (min)	168 (94)
Duration of xenon inhalation (min)	142 (88)
Average inspiratory xenon concentration (%)	58 (8)
Additional regional anaesthesia	
Epidural	10 (9)
Spinal	72 (15)
Peripheral nerve/local instillation	29 (6)
Prophylactic antiemetic medication	155 (32)
Dexamethasone (4–8 mg)	136 (28)
5-HT_3 antagonist	116 (24)
Granisetron (1–3 mg)	51 (11)
Tropisetron (2–4 mg)	38 (8)
Ondansetron (4–8 mg)	25 (5)
Dolasetron (6.25–12.5 mg)	2 (1)
Metoclopramide (10 mg)	13 (3)
Dimenhydrinate (31–100 mg)	11 (2)
Droperidol (0.625–1.25 mg)	6 (1)
Number of prophylactic antiemetics (0/1/2/3)	333/43/96/16 (68/9/20/3)
Postoperative opioid administration	376 (77)
Piritramide	235 (48)
Oxycodone	139 (29)
Pethidine (mepiridine)	31 (6)
Cumulative morphine equivalent consumption (mg)	13 (9)
Surgery	
Gynaecological	57 (12)
Orthopaedic	178 (37)
Trauma	101 (21)
Tumour surgery	74 (15)
Other	78 (16)

for the Apfel Score was 0.60. The 24 h PONV after xenon-based anaesthesia was predicted by female gender, younger age, and longer duration of anaesthesia (Table 2). Female sex and duration of anaesthesia were additional risk factors for postoperative need for rescue medication (2.09; 1.28–3.43, P=0.003; and 1.24 per hour; 1.06–1.44, P=0.006, respectively). Non-smoking status, history of PONV or motion sickness, and amount of postoperative morphine equivalents were not significant predictors.

Efficacy of medical antiemetic prophylaxis

About one-third of all subjects received antiemetic prophylaxis, with 72% of those subjects receiving two or more classes of antiemetics (Table 1). Subjects receiving prophylaxis were more often female, younger, more likely to be a non-smoker, with a significantly higher Apfel Score, and required less postoperative opioids (left part of Table 3).

In the logistic regression model, none of the antiemetics (neither dexamethasone nor 5-HT_3 antagonists) was associated with a significant reduction in PONV. Furthermore, after propensity score matching of 182 subjects, no statistically significant difference in incidence of PONV or need for rescue medication was detected between the two groups (right part of Table 3).

Discussion

Young age, female gender, and longer duration of anaesthesia were risk factors for PONV after xenon-based anaesthesia.

Incidence of postoperative nausea and vomiting

The incidence of PONV was 28% and thus comparable with previous studies,[12 14] but it was less frequent than predicted by the Apfel Score.[7] Xenon is a potent antagonist at the 5-HT_3 receptor[15] that mediates nausea and vomiting.[16] Therefore, it has been hypothesized that xenon exerts intrinsic antiemetic properties. In contrast, Coburn and colleagues[6] demonstrated a higher incidence of PONV after xenon and remifentanil anaesthesia than after propofol and remifentanil (66 *vs* 27%). However, patients who experienced PONV in the xenon and remifentanil group less often required antiemetic rescue medication than patients suffering from PONV after propofol and remifentanil (55 *vs* 84%). This observation indicates that although PONV occurred more frequently after xenon and remifentanil, it may have been less severe than after propofol and remifentanil.

Table 2 Independent predictors for 24 h PONV after xenon-based anaesthesia. Results from logistic regression analysis. Model P-value<0.001, McFadden pseudo-r^2=0.083, Hosmer–Lemeshow χ^2=7.54, P=0.48. Study centres were included in the model as single variables (data not shown). [a]Result from a model where variables for antiemetic medication were substituted by a binary variable indicating administration of antiemetic prophylaxis

Predictor	Adjusted odds ratio	95% Confidence interval	P-value
Subject-related factors			
Female sex	1.76	1.08–2.89	0.025
Age (per 10 yr)	0.82	0.69–0.97	0.023
Non-smoking status	1.48	0.87–2.51	0.15
History of PONV or motion sickness, or both	1.44	0.83–2.50	0.19
Anaesthesia-related factors			
Duration (per hour)	1.36	1.17–1.59	<0.001
Postoperative morphine equivalent (per mg)	1.02	0.99–1.05	0.13
Prophylaxis			
Dexamethasone	0.72	0.32–1.60	0.41
5-HT_3 antagonist	1.39	0.65–2.98	0.40
Other	1.06	0.41–2.76	0.91
Prophylaxis *per se*[a]	0.98	0.54–1.77	0.93

Independent predictors

Duration of anaesthesia was a strong predictor for PONV and need for rescue medication; the incidence of PONV was roughly doubled with every additional 2 h of exposure. This relationship has also been known for other inhaled anaesthetics[17] and nitrous oxide,[3] and appears to be independent of the targeted receptors. Given that xenon has a very low blood–gas partition coefficient of 0.115[18] and does not accumulate,[4 5] it is questionable whether it can directly trigger PONV several hours after anaesthesia. However, xenon has been traced in human blood and urine up to 24 h after anaesthesia,[19 20] probably because of storage in fatty tissue.[21] Rather than triggering PONV by direct mechanisms, alterations in gene expression and protein function may contribute to PONV after xenon inhalation. For example, xenon facilitates preconditioning by inducing hypoxia-inducible factor-1α.[22 23] It also upregulates a variety of genes involved in neuronal signalling,[24] alters excitability of brain cells by increasing neuronal Ca^{2+} concentration,[25 26] and interferes with neuronal norepinephrine re-uptake.[27] However, given that the molecular mechanisms of PONV have yet to be elucidated, it remains highly speculative whether these xenon-induced cellular alterations contribute to PONV.

Not all items of the Apfel Score were predictive in our patient population. The confidence intervals for non-smoking status and history of PONV, motion sickness, or both were too wide to reach statistical significance, and effect sizes for those two factors were smaller than after 'traditional' anaesthesia.[8] It seems reasonable that PONV after anaesthesia with 'classic' inhaled anaesthetics or propofol does not necessarily predict PONV after xenon-based anaesthesia because of different mechanisms of action. However, we cannot completely rule out the possibility that in a larger sample, non-smoking status and history of PONV/motion sickness may be detected as significant predictors.

Postoperative nausea and vomiting have been widely attributed to postoperative opioid use.[7 28] In our model, the dose of postoperative opioids was not predictive for PONV. It is known that administration of postoperative opioids is correlated with the duration of anaesthesia.[7 29] When testing for collinearity, we found a positive correlation between postoperative morphine equivalent use and duration of anaesthesia (Pearson's r=0.21, P<0.001). Given that the correlation was weak, we decided *a priori* to include both variables in the model. However, this may explain why, in our multivariate logistic regression analysis, postoperative opioid use was not predictive for PONV, because the duration of anaesthesia was the stronger predictor. Indeed, when the duration of anaesthesia was excluded, postoperative opioid use was a significant predictor for 24 h PONV (1.03 per milligram morphine equivalent, 1.00–1.06, P=0.024).

Efficacy of antiemetic prophylaxis

We were unable to demonstrate a prophylactic effect of dexamethasone or 5-HT_3 antagonists for preventing PONV after xenon-based anaesthesia. Dexamethasone was administered in

Table 3 Risk factors and incidence of nausea, vomiting, and need for rescue medication before and after propensity score matching. Data are presented as the mean (SD) or absolute value (%)

	Total cohort (*n*=488)			Propensity-matched cohort (*n*=182)			
	Prophylaxis (*n*=155)	No prophylaxis (*n*=333)	*P*-value	Prophylaxis (*n*=91)	No prophylaxis (*n*=91)	*P*-value	Standardized difference
Age (yr)	47 (16)	56 (16)	<0.001	50 (17)	50 (15)	0.89	0.02
Female	111 (72)	116 (35)	<0.001	49 (54)	42 (46)	0.37	0.14
Non-smoking status	123 (79)	241 (72)	0.12	74 (81)	71 (78)	0.71	0.07
History of PONV or motion sickness, or both	36 (23)	58 (17)	0.14	20 (22)	16 (18)	0.58	0.10
Postoperative opioid use	100 (65)	276 (83)	<0.001	59 (65)	65 (71)	0.43	0.12
Duration of anaesthesia (min)	160 (96)	171 (93)	0.22	165 (96)	173 (95)	0.56	0.09
Additional regional anaesthesia	19 (12)	92 (28)	<0.001	13 (14)	12 (13)	0.99	0.03
Percentage expected risk according to Apfel Score	48 (16)	42 (17)	0.002	44.3 (16)	43.0 (20)	0.93	0.08
24 h PONV	44 (28)	92 (28)	0.91	27 (30)	31 (34)	0.63	0.09
24 h nausea only	22 (14)	56 (17)	0.51	11 (12)	14 (15)	0.67	0.09
24 h vomiting only	11 (7)	15 (5)	0.28	8 (9)	9 (10)	0.99	0.03
24 h nausea and vomiting	11 (7)	21 (6)	0.84	8 (9)	8 (9)	1.0	0
24 h need for rescue medication	43 (28)	81 (24)	0.44	25 (28)	27 (30)	0.87	0.04

doses of 4–8 mg, and 5-HT_3 antagonists were predominantly granisetron (1–3 mg), tropisetron (2–4 mg), or ondansetron (4–8 mg). Therefore, drug doses were adequate and have been shown to prevent PONV after anaesthesia with traditional inhaled anaesthetics.[30–32] The 5-HT_3 antagonists are ineffective as rescue medication in PONV occurring after previous prophylactic treatment with a substance of the same class.[33 34] Given that xenon also exerts antagonism at 5-HT_3 receptors,[15] it seems reasonable that administering a 5-HT_3 antagonist for prophylaxis after xenon might not provide additional benefit. Unfortunately, we did not record data on the efficacy of rescue medication. Droperidol, dimenhydrinate, or metoclopramide were given in a limited number of subjects that was too low to draw conclusions on their prophylactic effects. Based on our findings, we suggest administration of antiemetics targeting receptors other than serotonin antagonists in high-risk patients (i.e. young female patients with longer lasting procedures) undergoing xenon-based anaesthesia. Of note, a prospective randomized controlled trial failed to show a significant beneficial effect of dexamethasone as antiemetic prophylaxis and ondansetron as rescue medication for PONV after xenon and remifentanil anaesthesia (NCT00793663).[35]

Limitations

The data reported were obtained in a prospective cohort study investigating adverse events during xenon-based anaesthesia so that prophylaxis was not protocolized, but administered at the discretion of the attending anaesthetist. Thus, it would not have been appropriate to compare the raw incidences of PONV in patients who did or did not receive prophylactic antiemetics. This issue was addressed by controlling for other factors in the logistic regression analysis. Furthermore, we conducted a thorough propensity score matching with the objective of creating two groups of patients, with or without antiemetics, which were similar in all relevant factors. After matching was completed, univariate analyses verified that the two groups were similar in all variables except for antiemetics. To confirm these results, we also assessed the quality of the propensity score matching by calculating standardized differences. No generally agreed threshold exists to indicate relevant imbalance between groups, but standardized differences of <0.1 have been considered to represent a negligible difference.[10 36] Although the matched groups were considered to be well balanced, a marginal difference in the distribution of female patients (standardized difference 0.14) and postoperative opioid admission (standardized difference 0.12) between groups cannot be excluded. Accordingly, a minor but most likely clinically irrelevant effect of antiemetic prophylaxis might have been missed.

Postoperative nausea and vomiting were measured as a robust yes–no binary variable by physicians who visited subjects at least once, 24 h after the end of anaesthesia. Thus, underreporting of PONV is possible because subjects might not remember or might have deemed it not severe enough to report.[37] However, considering additional documentation of rescue medication, we are sure to have assessed 'clinically relevant' PONV that required targeted prophylaxis.

As we were unable to detect a protective effect of routine antiemetic prophylaxis, a possible β error because of lack of power must be considered. Dexamethasone or ondansetron reduces the incidence of PONV by 26% after general anaesthesia with propofol or inhaled anaesthetics.[32] Given that a majority of our subjects received two or three antiemetics, we conducted a *post hoc* power analysis, calculating a 91% power to detect the effect of a combination of two antiemetic medications in our matched cohort of 182 subjects (two-tailed α=0.05). Even when antiemetic prophylaxis was substituted by a binary 'dummy' variable, logistic regression analysis did not indicate an effect of any prophylactic medication, although power was high (38 subjects per factor, 83% power, two-tailed α=0.05).[38 39]

Conclusions

This is the first study to investigate risk factors for PONV after xenon-based anaesthesia. While incidence of PONV was significantly lower than predicted by Apfel Score, female sex, young age, and long duration of anaesthesia predicted PONV after xenon-based anaesthesia. A history of PONV or non-smoking status failed to reach statistical significance, probably because of lower power associated with a smaller effect size. The lack of efficacy of 5-HT_3 receptor antagonists is reasonable, because xenon antagonizes these receptors itself, yet needs to be interpreted carefully and warrants confirmation by a sufficiently powered randomized controlled study.

Authors' contributions

M.S.S.: data collection, data analysis, and manuscript preparation. C.C.A.: data analysis and manuscript preparation. H.-J.S., R.S., B.B., P.H.T., M.H., and M.R.-H.: study design, patient recruitment, data collection, and manuscript revision. M.N.: patient recruitment, data collection, and manuscript revision. P.K.: patient recruitment, data collection, data analysis, and manuscript preparation.

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Declaration of interest

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7.7 Total intravenous anaesthesia versus single-drug pharmacological antiemetic prophylaxis in adults – A systematic review and meta-analysis

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ORIGINAL ARTICLE

Total intravenous anaesthesia versus single-drug pharmacological antiemetic prophylaxis in adults

A systematic review and meta-analysis

Maximilian S. Schaefer*, Peter Kranke*, Stephanie Weibel, Robert Kreysing and Peter Kienbaum

BACKGROUND Postoperative nausea and vomiting (PONV) are among the most unfavourable anaesthetic outcomes attributed to the administration of inhaled anaesthetics. Accordingly, inhaled anaesthetics are frequently substituted by propofol when patients are at risk of PONV. As, on some occasions, inhalational anaesthesia may be favourable, the relative impact of propofol anaesthesia needs to be established based on robust data.

OBJECTIVE To compare the effectiveness of a single-drug pharmacological prophylaxis with total intravenous anaesthesia (TIVA) for prevention of PONV.

DESIGN Systematic review of randomised controlled trials with meta-analyses.

DATA SOURCES All available studies until 29 April 2015 were retrieved from *MEDLINE*, *CENTRAL* and *EMBASE*.

ELIGIBILITY CRITERIA Randomised controlled trials on adult patients undergoing general anaesthesia with at least one group receiving propofol-based intravenous anaesthesia without further antiemetic prophylaxis, and one group receiving inhalational anaesthesia with single-drug antiemetic prophylaxis.

RESULTS Fourteen studies involving 2051 patients were included. Compared with TIVA, after inhalational anaesthesia and single-drug antiemetic prophylaxis, there was no difference in the overall risk of PONV [relative risk (RR) 1.06, 95% confidence interval (CI) 0.85; 1.32, GRADE rating moderate], nor was there any difference in the risk of postoperative vomiting (RR 1.17, 95% CI 0.78; 1.76), need for rescue medication (RR 1.16, 95% CI 0.68; 1.99) or early PONV (RR 1.06, 95% CI 0.88; 1.27). However, TIVA was associated with an increased risk of late PONV (RR 1.41, 95% CI 1.10; 1.79, $P = 0.006$). Six studies investigated other side-effects associated with anaesthesia and found no differences between the two groups. Finally, there was evidence of a publication bias that included smaller studies favouring TIVA.

CONCLUSION This meta-analysis confirms the results from indirect comparisons in individual studies: instead of substituting inhalational anaesthesia with propofol-based TIVA, a similar antiemetic effect can be achieved by adding single-drug pharmacological prophylaxis to the inhalational anaesthetic.

STUDY REGISTRATION This systematic review with meta-analysis was registered at PROSPERO (www.crd.york.ac.uk/PROSPERO), study number CRD42015019571.

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Introduction

Postoperative nausea and vomiting (PONV) are frequent after general anaesthesia.[1] Without antiemetic prophylaxis, several million patients undergoing general anaesthesia every year will develop PONV.[2–4] Together with pain, PONV is ranked as the most undesirable event after surgery[5] and significantly increases healthcare costs.[6] Therefore, international consensus guidelines were recently published[7] recommending the identification of patients at high risk of PONV[8] and administration of a risk-adapted prophylaxis including, when general anaesthesia cannot be avoided, the patient's risk for PONV should be reduced by substitution of inhalational anaesthetics with

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propofol-based total intravenous anaesthesia (TIVA).[7] However, in several situations, modern inhalational anaesthetics may be preferable to propofol. With inhalational anaesthetics, end-tidal anaesthetic concentrations can be used to guide anaesthetic depth[9] and decrease the incidence of intraoperative awareness,[10] as well as allowing the precise control of weaning (irrespective of a patient's weight)[11] and they have favourable effects on the cardiovascular system. Thus, if inhalational anaesthetics are not to be substituted by TIVA, the question is raised as to whether the reduction in the patient's risk of PONV associated with TIVA can be compensated sufficiently with pharmacological prophylaxis. Interestingly, a large international multicentre trial (IMPACT) even suggested an inferior prophylactic effect of TIVA as compared with using one single antiemetic drug as prophylaxis; however, the published analyses did not include a direct comparison of these two strategies.[1] Furthermore, TIVA and pharmacological prophylaxis might show differential effects on PONV in the early and late postoperative phase. Therefore, the relative potency of TIVA, as compared with pharmacological prophylaxis, needs to be established based on a direct comparison. Because recent guidelines recommend TIVA as an equivalent intervention to one single antiemetic drug for prevention of PONV,[7] we restricted our analysis to studies comparing TIVA with single-drug pharmacological prophylaxis.

Thus, to compare the effectiveness of antiemetic prophylaxis with propofol-based TIVA with that of single-drug prophylaxis in association with inhalational anaesthetics, we conducted a systematic literature search and subsequent meta-analysis of all the available randomised controlled trials.

Materials and methods

Search strategy and selection criteria

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[12] The study protocol, including the full written search strategy, was registered and published online at the publicly available internet database PROSPERO (www.crd.york.ac.uk/PROSPERO, registration number CRD42015019571) before the search was conducted. All deviations from that protocol are specified in the Supplemental Digital Content, http://links.lww.com/EJA/A101 'Deviations from the PROSPERO protocol'. Our search combined a three-part strategy, including updated syntax for identification of studies including prophylactic drugs for PONV,[13] with identification of studies investigating TIVA and the modified Robinson's highly sensitive search for controlled clinical trials.[14] Searched databases included *MEDLINE* (via *Pubmed*), *EMBASE* (via *Ovid*) and the Cochrane Central Register of Controlled Trials (*CENTRAL*, via *Wiley*) without any restrictions on language or publication year.

We included all randomised, controlled trials with at least one study group receiving propofol-based anaesthesia (TIVA group) without further antiemetic prophylaxis, and at least one study group receiving inhalational anaesthesia with additional single-drug antiemetic prophylaxis. Our definition of TIVA implied the use of propofol as the primary hypnotic but no preconditions were applied regarding the use of nitrous oxide (N_2O). Studies were required to report the incidences of PONV, postoperative nausea (PON) or postoperative vomiting (POV). Studies and study groups which included multiple antiemetic prophylactics [i.e. TIVA with pharmacological antiemetic prophylaxis or inhalational anaesthesia with pharmacological antiemetic prophylaxis (IA + AE) with more than one prophylactic drug] were excluded, as well as studies involving patients less than 18 years of age. Studies were independently screened for inclusion and exclusion criteria by two investigators (M.S.S., R.K.).

Data extraction and preparation

Our primary outcome variable was the incidence of PONV within 24 h after surgery ('overall PONV'). Additionally, the following data were independently extracted by two investigators (M.S.S., R.K.): type of inhalational anaesthetics and type of intraoperative opioid; use and dose of N_2O; timing, dose and type of pharmacological antiemetic prophylaxis; type of surgery and duration of anaesthesia; PON, POV and the need for rescue medication; incidences of early and late PONV, as defined by the authors; incidences of any reported adverse events with focus on but not limited to dizziness, drowsiness, shivering, headache, gastrointestinal symptoms, extrapyramidal symptoms, awareness, prolongation of the cardiac QT interval perioperative arrhythmia and quality of recovery. If available, supplemental material and appendices were also screened for the aforementioned data. Because POV without PON is extremely rare in adults, PON was taken as a surrogate for PONV, when only PON was reported.

Risk of bias assessment

Studies were scored for risk of bias using The Cochrane Collaboration 'Risk Of Bias' Assessment Tool, which judges risk of bias in six domains: random sequence generation and allocation concealment (selection bias), blinding of participants and study personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). Additionally, we estimated the overall risk of bias for each study. Assessments were made by two investigators (M.S.S. and S.W.) who were blind to each other's assessments. Upon disagreement, judgement by a third investigator (R.K.) was used as a referee's decision. A sensitivity analysis was performed for overall PONV, excluding studies with a high risk of overall bias. For outcomes that were reported by 10 or more included studies, publication bias was assessed

using funnel plots. After visual inspection, funnel plot asymmetry was tested with the Arcsine test and a conventionally used alpha of of 0.1.[15,16]

Statistical analysis

All references were imported into Endnote X7.1 (Thomson Reuters, New York, USA). Extracted data were entered into Review Manager 5.3.5 (The Cochrane Collaboration, Copenhagen, Denmark), which was used for all analyses except for funnel plots. The latter were created and tested for asymmetry using the R software (version 3.2.2, The R Project) with the meta-package. Heterogeneity was assessed using the I^2 statistic with χ^2 test for significance.[17,18] Subsequently, pooled estimates were calculated using inverse variance weighting with random-effects modelling and alpha set to 0.05. Because the funnel plot for the primary outcome overall PONV showed significant asymmetry with different results between smaller and larger studies, we conducted an additional explorative analysis; to reduce the influence of smaller studies in the model, fixed-effect modelling instead of random-effects modelling for calculation of risk ratios for the risk for overall PONV was used.

To explore heterogeneity, a subgroup analysis was performed on the main outcome (overall PONV) with stratification according to total sample size (number of included patients $\leq$50, $\leq$100, $\leq$200, >200). To avoid a type 1 error because of repetitive testing, we adjusted alpha for subgroup analyses using the Bonferroni approach: as we created a total of four strata, alpha was corrected to 0.013 (0.05 ÷ 4).[16] Furthermore, because no preconditions had been specified regarding the use of N_2O, we conducted an additional sensitivity analysis which excluded all studies with an uneven distribution of N_2O administration between the two groups (i.e. where N_2O was used with inhalational anaesthetics but not with TIVA, or vice versa). All results are reported as relative risks (RRs) with corresponding 95% confidence interval, with a RR less than 1 favouring TIVA and a RR greater than 1 favouring IA + AE. Overall, quality of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[19] and incorporated in a Summary of Findings Table,[20] which was created for the primary outcome.

Results

Our database search was carried out on 29 April 2015 and yielded 3106 articles, 690 from *MEDLINE*, 511 from *CENTRAL* and 1905 from *EMBASE*. After elimination of duplicates, 2206 articles were screened for inclusion and exclusion criteria. Our search results included 21publications from two authors who have been discredited,[21–24] and even though not all of these articles have been retracted, we decided to exclude all 21 before further screening. Figure 1 summarises reasons for the exclusion of the remaining 2171 articles. At the end of the screening process, 14 randomised controlled trials with a total of 2051 patients were included for final analysis.[1,25–37] Study characteristics and anaesthesia details including specifics of antiemetic prophylaxis are summarised in Table 1.

Primary analysis

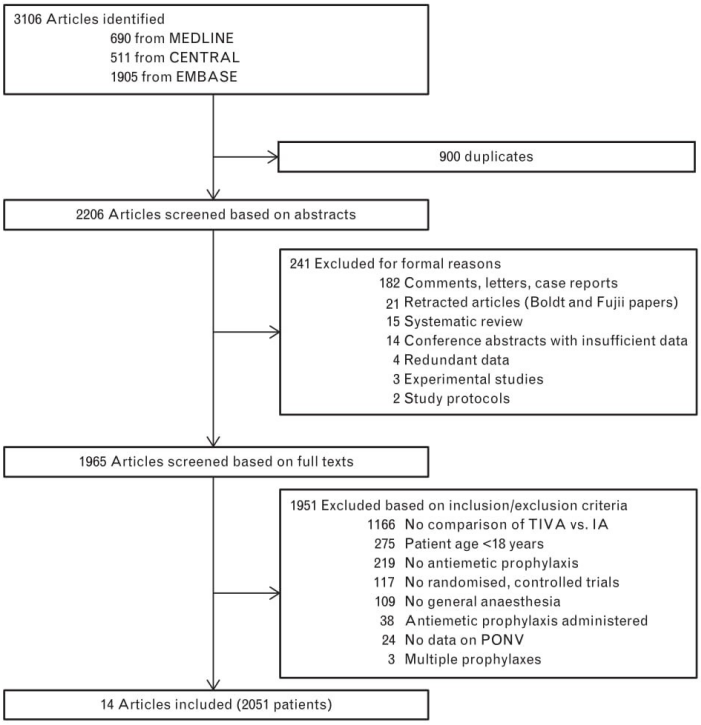
Overall PONV was reported by 12 out of 14 studies. The remaining two studies[31,34] only reported PONV separately for early and late periods. Despite an effort to contact the corresponding authors, data on overall PONV were not available. Thus, data from these two studies were only included in analyses of early and late PONV. In most studies, the distinction between early and late PONV was made at 2 h after awakening from anaesthesia (Table 2).

There was no difference in the risk of PONV between the groups that received TIVA or IA + AE when analysed using a random-effects model (Fig. 2). Similarly, there was no difference between the groups for the risk of POV, the need for rescue medication, or early PONV (Fig. 3). However, patients receiving TIVA had a significantly higher risk of experiencing PONV in the late postoperative phase [1.41 (1.10 to 1.79), $P = 0.006$, Fig. 3]. There was significant heterogeneity among studies in the analyses of overall PONV ($I^2 = 54\%$), need for rescue medication ($I^2 = 58\%$) and POV ($I^2 = 60\%$) (Figs. 2 and 3). When a fixed effect model was applied, TIVA was inferior to IA + AE in preventing overall PONV [1.16 (1.04 to 1.30), $P = 0.01$, Fig. 2]. GRADE rating for quality of evidence was 'moderate' for the main outcome of overall PONV (Table 1, http://links.lww.com/EJA/A102 Supplemental Digital Content shows the GRADE Table, http://links.lww.com/EJA/A101).

Adverse events and quality of recovery

Postoperative adverse events were investigated by six studies but only four of these studies reported analysable data.[25,30,31,35] Frequencies of postoperative shivering, dizziness and headache were investigated by two studies, whereas postoperative myalgia and drowsiness were each reported by only one study. No differences were observed between the two groups except for a tendency towards a decreased risk of postoperative shivering after TIVA [0.46 (0.19 to 1.11), $P = 0.08$, Supplemental Digital Content Figure 1, http://links.lww.com/EJA/A101]. Two other studies provided only descriptive information with no incidence data: 'the side-effect profile did not differ' between the anaesthetic techniques[29] and 'there were no differences between the groups' in drowsiness and adverse events.[36] None of these six studies assessed intraoperative awareness, prolongation of the cardiac QT interval postoperative arrhythmias or gastrointestinal symptoms. Only one study reported on the quality of recovery,[31] and it found no difference in the 'Quality of

Fig. 1



IA, inhalational anaesthetics; PONV, postoperative nausea and vomiting; TIVA, total intravenous anaesthesia

Flow chart indicating screening process with details of study exclusion.

Recovery Score 40', median 155, interquartile range (149 to 159) versus 152 (150 to 156) for TIVA and IA + AE, respectively ($P = 0.114$).

Sensitivity and subgroup analyses

In three studies, the use of nitrous oxide was not evenly distributed between the two groups.[33,35,36] After excluding these studies from the different analyses, the overall risks were basically unchanged: PONV, 1.13 (0.86 to 1.47), $P = 0.39$, $I^2 = 52\%$; POV, 1.26 (0.73 to 2.20), $P = 0.41$, $I^2 = 61\%$; early PONV, 1.07 (0.88 to 1.30), $P = 0.48$, $I^2 = 0\%$; the need for rescue medication, 1.17 (0.52 to 2.65), $P = 0.71$, $I^2 = 73\%$. However, the risk of late PONV was even more pronounced in patients who received TIVA [1.51 (1.17 to 1.94), $P = 0.002$, $I^2 = 31\%$].

Subgroup analyses by sample size revealed a significantly higher risk of PONV with TIVA in studies involving 101 to 200, and greater than 200 patients: 1.44 (1.11 to 1.87), $P = 0.006$ and 1.24 (1.07 to 1.44), $P = 0.005$, respectively, (a Forest plot is provided in Supplemental Digital Content Figure 2, http://links.lww.com/EJA/A101). There was no statistically significant difference between groups in smaller studies involving 100 patients or less.

Risk of bias

An overview of the risk of bias assessment is presented in Table 3. Low risk of bias was present in four, moderate risk in seven and high risk in three studies. Excluding high risk of bias studies did not change the result for the main analysis on overall PONV [1.11 (0.89 to 1.37), $P = 0.35$], but it reduced heterogeneity (I^2 40%, $P = 0.10$). Data from at least 10 studies were only available for overall PONV and early PONV. Therefore, funnel plot analysis was only performed for these two outcomes. Visual inspection of the funnel plot for overall PONV suggested asymmetry favouring TIVA, which was confirmed by Arcsine analysis for funnel plot asymmetry

Table 1 Overview and characteristics of included studies

Study	Language	Design	Patients TIVA/IA + AE (*n*)	Type of surgery	Maintenance TIVA	Maintenance IA	Duration of anaesthesia (TIVA/IA, min)[a]	Type of antiemetic	Timing of antiemetic
Apfel 2004[1]	English	Factorial RCT	345/512	Variety of operative procedures	Propofol with fentanyl or remifentanil and N_2O in 173 (50%) patients	Isoflurane, desflurane or sevoflurane with fentanyl or remifentanil and N_2O in 254 (50%) patients	115/105 (no SD mentioned)	Ondansetron (4 mg), dexamethasone (4 mg) or droperidol (1.25 mg) i.v.	20 min after start of anaesthesia (droperidol/ dexamethas)/ during last 20 min (ondansetron)
Eberhart 2002[25]	German	RCT	75/75	Gynaecologic surgery	Propofol with alfentanil	Desflurane with alfentanil	'Estimated duration 60 to 120 min'	Tropisetron 2 mg i.v.	10 min before end of operation
Gan 1996[26]	English	RCT	21/21	Major breast surgery	Propofol with 66% N_2O	Isoflurane with 66% N_2O	144 ± 78/156 ± 70	Ondansetron 4 mg i.v.	Before induction
Heinke 1996[27]	German	RCT	43/38	Pars plana vitrectomy	Propofol with alfentanil	Isoflurane with alfentanil	131 ± 37/130 ± 38	Droperidol 2.5 mg i.v.	At start of surgery
Jellish 1995[28]	English	RCT	34/34	Middle ear surgery	Propofol with fentanyl	Isoflurane with fentanyl	161 ± 10/163 ± 8	Droperidol 25 μg kg^{-1} i.v.	After induction
Jokela 2000[29]	English	RCT	60/60	Breast surgery	Propofol with fentanyl	Sevoflurane with fentanyl	109 ± 59/117 ± 78	Ondansetron 8 mg i.v.	At end of surgery
Khan 2005[30]	English	RCT	20/40	Diagnostic gynaecologic laparoscopy	Propofol with 60% N_2O	Isoflurane with 60% N_2O	35 ± 3/35 ± 7	Granisetron 40 μg kg^{-1} or ondansetron 40 to 60 μg kg^{-1} i.v.	3 min before induction
Mei 2014[31]	English	Factorial RCT	74/74	Gynaecologic laparoscopy	Propofol with remifentanil, titrated BIS 45 to 55	Sevoflurane with remifentanil titrated BIS 45 to 55	n.a.; duration of surgery 73 (55 to102)/78 (57 to 99)	Tropisetron 2 mg i.v.	After induction
Özünlü 2005[32]	Turkish	RCT	20/20	Gynaecologic laparoscopy	Propofol with remifentanil and 60% N_2O	Desflurane with remifentanil and 60% N_2O	58 ± 27/56 ± 25	Ondansetron 4 mg i.v.	1 min before induction
Paech 2002[33]	English	RCT	47/47	Day-case gynaecologic laparoscopy	Propofol with alfentanil or morphine	Sevoflurane with N_2O and alfentanil or morphine	n.a.; duration of surgery 30 [20 to 45]/30 [20 to 45]	Dolasetron 12.5 mg i.v.	At induction
Park 2014[34]	English	RCT	32/32	Total thyroidectomy	Propofol with remifentanil	Sevoflurane with remifentanil	105 ± 23/99 ± 21	Ramosetron 0.3 mg i.v.	Before end of surgery
Park 2011[35]	English	RCT	50/50	Gynaecologic laparoscopy	Propofol with remifentanil	Sevoflurane with 50% N_2O	131 ± 36/140 ± 37	Palonosetron 0,075 mg i.v.	Before induction
Purhonen 2006[36]	English	RCT	50/51	Gynaecologic laparoscopy	Propofol with fentanyl	Isoflurane with fentanyl and 67% N_2O	65 ± 39/65 ± 40	Ondansetron 8 mg p.o.	1 h before operation
White 2007[37]	English	RCT	58/68	Day-case gynaecologic surgery	Propofol with fentanyl	Sevoflurane with fentanyl	39 (26 to 59)/32 (24 to 50)	Dolasetron 12.5 mg i.v.	Before end of surgery

AE, antiemetic; BIS, Bispectral Index; i.v., intravenously; IA, inhaled anaesthetic; p.o., orally; RCT, randomised controlled trial; TIVA, total intravenous anaesthesia.
[a]Values are either mean ± SD or median (interquartile range).

Table 2 Definitions of early and late postoperative nausea and vomiting, as defined by the respective authors

Study	Early PONV	Late PONV
Apfel 2004[1]	0 to 2 h	2 to 24 h
Eberhart 2002[25]	ND	ND
Gan 1996[26]	0 to 6 h	ND
Heinke 1996[27]	0 to 2 h	2 to 24 h
Jellish 1995[28]	In recovery room[a]	ND
Jokela 2000[29]	0 to 2 h	2 to 24 h
Khan 2005[30]	0 to 2 h	ND
Mei 2014[31]	0 to 2 h	2 to 24 h
Özünlü 2005[32]	ND	ND
Paech 2002[33]	ND	ND
Park 2014[34]	0 to 1 h	6 to 24 h
Park 2011[35]	0 to 2 h	6 to 24 h
Purhonen 2006[36]	0 to 2 h	2 to 24 h
White 2007[37]	Before discharge[b]	After discharge[b]

IA + AE, inhalational anaesthesia with pharmacological antiemetic prophylaxis; ND, no data; PONV, postoperative nausea and vomiting; TIVA, total intravenous anaesthesia. [a] Duration of stay in the recovery room in this study was not reported. [b] Patients were ready to be discharged at median 242 (TIVA) and 216 (IA + AE) min.

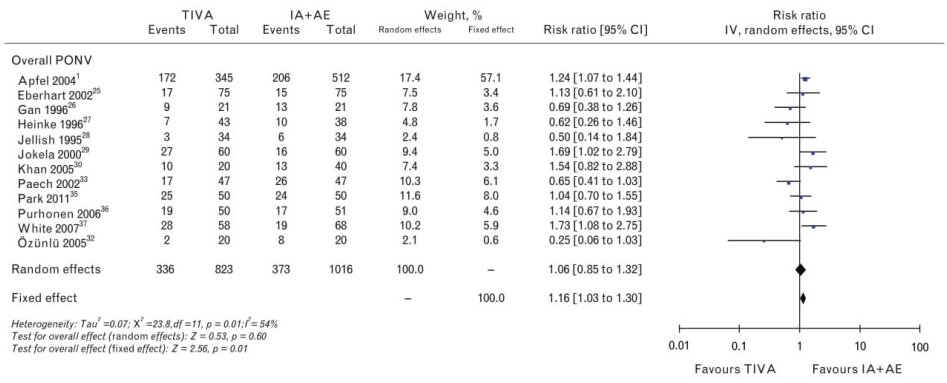
($P = 0.073$, Fig. 4). No funnel plot asymmetry was detected for early PONV ($P = 0.27$, Supplemental Digital Content Figure 3, http://links.lww.com/EJA/A101).

Discussion

The meta-analysis summarises data from 14 prospective randomised trials and a total of more than 2000 patients. In our primary analysis, there was no difference in the overall risk of PONV, POV, need for rescue medication and early PONV in patients receiving TIVA compared with patients receiving IA + AE. However, patients receiving TIVA were more likely to suffer from PONV in the late postoperative phase than patients receiving IA + AE. Also, we found evidence of a publication bias with smaller trials favouring TIVA.

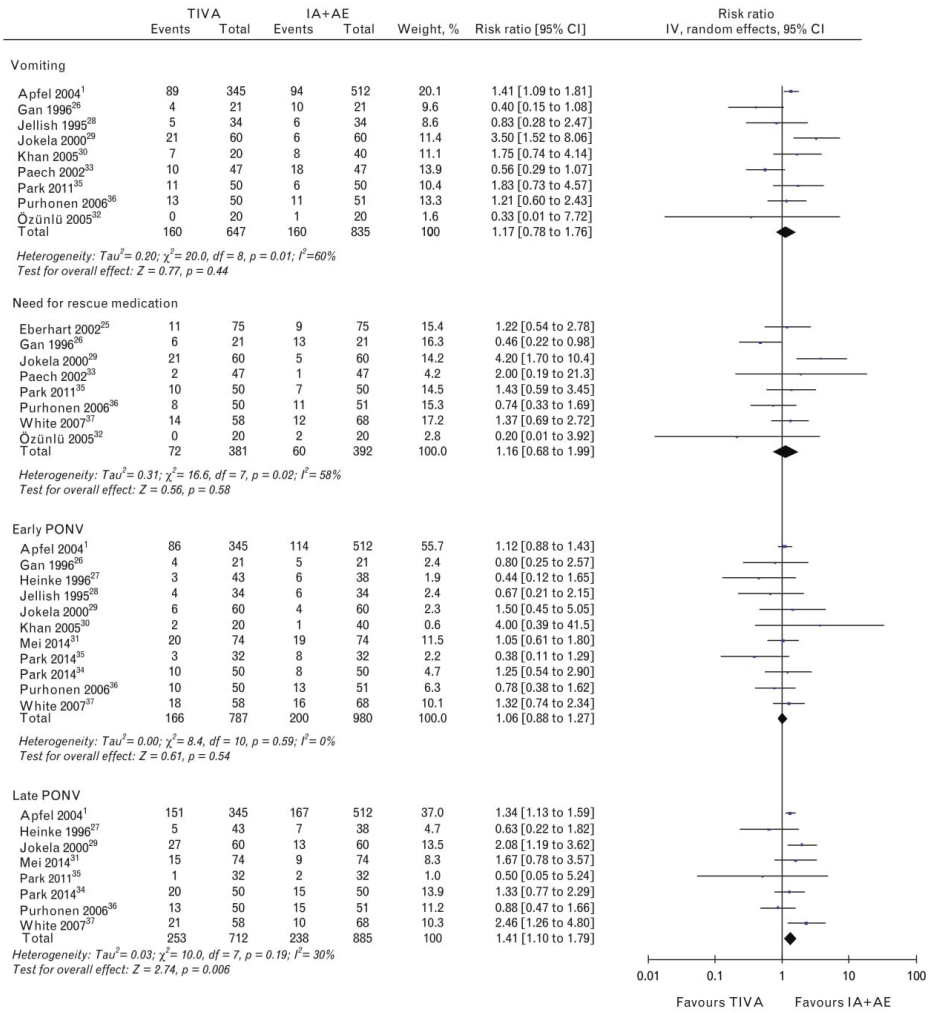
As PONV has generally been attributed to inhalational anaesthetics,[1] recommendations to reduce the patient's risk include substituting TIVA for the inhalational anaesthetics. This strategy is supported by the notion that propofol itself provides antiemetic properties.[38] As, in different clinical settings, some advantages (or disadvantages) of a type of anaesthetic are judged to be less (or more) relevant than others, factors apart from the risk of PONV may guide a physician's choice of anaesthetic.[9] In obese patients, time to awakening from anaesthesia is more precise after desflurane compared with propofol.[10] Furthermore, propofol depresses sympathetic outflow and causes arterial hypotension particularly in patients at risk of experiencing adverse cardiovascular events.[39] In contrast, sympathetic reflexes and arterial pressure are better maintained with inhalational anaesthetics.[39] Moreover, in animal models and highly selected clinical situations, potent organ protective effects have been demonstrated for all inhalational anaesthetics.[40,41] On the other hand, as well as decreasing PONV,[1] propofol significantly reduces the incidence of postoperative shivering[42] and is associated with a decreased incidence of emergence agitation.[43] In this context, our analysis shows that, if a physician chooses not to substitute TIVA for an inhalational anaesthetic, then the administration of single-drug antiemetic prophylaxis is sufficient to compensate for the missing reduction in a patient's risk of PONV. Because inhalational anaesthetics increase the incidence of PONV, particularly in the early postoperative phase,[44] to investigate differential effects on early and late PONV, we also evaluated PONV by the time of

Fig. 2



Forest plot of the primary outcome overall PONV. Additional results using a fixed effect model are reported because of significant funnel plot asymmetry with smaller studies favouring TIVA. IA + AE, inhalational anaesthesia with pharmacological antiemetic prophylaxis; IV, inverse variance; PONV, postoperative nausea and vomiting; TIVA, total intravenous anaesthesia.

Fig. 3



Forest plots for POV, postoperative need for antiemetic rescue medication, PONV in the early and PONV in the late phase. IA + AE, inhalational anaesthesia with pharmacological antiemetic prophylaxis; IV, inverse variance; PONV, postoperative nausea and vomiting; POV, postoperative vomiting; TIVA, total intravenous anaesthesia.

its occurrence. We did not find any difference between the two groups with respect to early PONV. In contrast, our analysis shows that patients receiving TIVA had a higher risk of experiencing PONV in the late postoperative phase, starting 2 to 6 h after surgery. As propofol has antiemetic properties,[38] it may be assumed that early protection is caused by residual propofol at the effect sites after cessation of its administration. However, when propofol has been eliminated from the body, patients will be unprotected if additional pharmacological prophylaxis has not been initiated. These findings are of particular relevance for ambulatory surgery when antiemetic rescue medication to treat PONV beginning 2 to 6 h after surgery may not be available.[45] The clinical relevance of late PONV following TIVA is supported by the observation that insufficient control of PONV is the leading cause of

Table 3 Risk of bias assessment for each trial

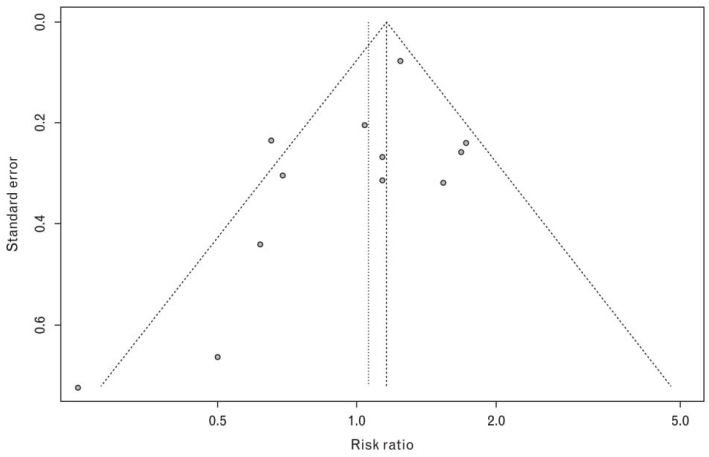
	Random sequence generation	Allocation concealment	Blinding of participants/personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall bias estimation
Apfel 2004[1]	+	+	+	+	+	?	+	Low
Eberhart 2002[25]	?	?	?	?	?	?	+	Moderate
Gan 1996[26]	+	+	?	+	?	?	+	Low
Heinke 1996[27]	?	?	?	+	?	?	+	Moderate
Jellish 1995[28]	?	?	–	+	?	?	+	High
Jokela 2000[29]	?	?	?	+	?	?	+	Moderate
Khan 2005[30]	?	?	?	?	?	?	+	Moderate
Mei 2014[31]	?	?	+	+	+	?	+	Low
Özünlü 2005[32]	+	?	+	+	?	?	+	Low
Paech 2002[33]	+	?	?	–	+	?	+	High
Park 2014[34]	+	?	?	+	?	?	+	Moderate
Park 2011[35]	+	?	?	?	+	?	+	Moderate
Purhonen 2006[36]	?	+	+	?	?	?	+	Moderate
White 2007[37]	+	+	+	–	?	?	+	High

+, low risk of bias; ?, unclear risk of bias; –, high risk of bias.

unexpected hospital admission after ambulatory surgery.[46] Thus, the risk of late PONV and postdischarge nausea and vomiting[45] needs to be recognised and administration of sufficient prophylaxis initiated.

When considering PONV prophylaxis with antiemetics, potential side-effects warrant discussion: high dosages of most available antiemetics prolong cardiac QT interval.[47] For these reasons, the antiemetic droperidol was labelled with a black box warning by the American Food and Drug Administration in 2001. This was followed by an intense debate, with the result that now the dose administered for prophylaxis and treatment of PONV is considered to be well tolerated as it is some 10-fold lower than the doses given historically for neurolept anaesthesia.[48–50] Other side-effects are characteristic of specific drugs,[7] e.g. headache after 5-hydroxytryptamine (5-HT_3) antagonists or sedation after droperidol or dimenhydrinate.[51] Although slight increases in blood glucose concentration may be observed after dexamethasone administration in

Fig. 4



Funnel plot for the primary outcome, overall postoperative nausea and vomiting with weighted regression. The filled circles represent estimated treatment effects (RR) and its precision (standard error) for each individual study. Also, the random-effects estimate (vertical dotted line) as well as the fixed-effect estimate (vertical dashed line) with 95% confidence interval limits (diagonal dashed lines) are shown in the figure. In the absence of small-study effects, the treatment effects (filled circles) would scatter symmetrically around a common average treatment effect resulting in a symmetrical triangle. However, the figure depicts three studies with high standard errors clustering asymmetrically to the left (favouring TIVA) with no corresponding studies on the right side of the figure (favouring IA + AE). IA + AE, inhalational anaesthesia with pharmacological antiemetic prophylaxis; RR, relative risk; TIVA, total intravenous anaesthesia.

nondiabetic patients,[52] low doses of dexamethasone are proven not to increase the risk of surgical site infection.[53,54] To add to this discussion, we identified six studies which investigated perioperative adverse events, including dizziness, headache, myalgia, drowsiness and shivering. Except for a trend towards increased postoperative shivering following IA + AE, which has been known for decades to be associated with inhalational anaesthetics,[42] we did not find any difference between the two groups. We acknowledge that for the individual side-effects, the data came from only one or two studies and we could not include two of the six studies in the analysis as no data on adverse events were given. Nevertheless, despite the small number of studies, we feel that our findings do not contradict the general notion that the use of low-dose antiemetics for PONV prophylaxis is well tolerated.

Our funnel plot analysis showed significant asymmetry, suggesting a publication bias favouring TIVA. This observation is supported by our subgroup analysis stratifying studies by study size: studies involving more than 100 patients favoured IA + AE, whereas smaller studies tended to favour TIVA. Although other reasons for funnel plot asymmetry exist,[16] we decided to extended our analysis to assess the implications for our findings: when heterogeneity is high and random-effects modelling is applied then smaller studies are weighted disproportionately higher than larger studies, so we re-examined our primary analysis using a fixed effect model.[16] With fixed effect modelling, TIVA was actually inferior to IA + AE in preventing overall PONV (Fig. 2). We would like to emphasise that this analysis was conducted *a posteriori*, and its results are merely explorative. To exclude any further bias because of poor study quality, individual risk of bias for each study was assessed, revealing an overall moderate risk. Excluding studies with high risk of bias did not change the results of our primary analysis. Finally, in the face of significant heterogeneity in our primary analysis, we estimated the overall quality of evidence[19] to be 'moderate'.

Limitations

Even with antiemetic prophylaxis, PONV still occurred in a high proportion (39%) of patients across all studies. Thus, irrespective of their relative effectiveness, neither strategy in isolation reduced patients' risk of PONV sufficiently. Accordingly, we would emphasise that only a multimodal approach, including administration of multiple prophylaxes, reduces the incidence of PONV satisfactorily in high-risk patients undergoing general anaesthesia. Thus, adding one or more additional antiemetic- to both strategies will further decrease the incidence of PONV. However, the aim of our analysis was to establish the relative effect of single pharmacological prophylaxis compared with TIVA, which is why we excluded studies investigating multiple prophylaxes.

Secondly, it has been shown that titration of inhalational anaesthesia to higher levels of bispectral index (BIS) with avoidance of unnecessary deep anaesthesia reduces the incidence of postoperative vomiting.[55] Unfortunately, only one study controlled for anaesthesia depth,[31] making a sensitivity analysis impossible. In the IMPACT trial, the BIS level was one of the randomised factors,[56] but these data were not published.[1] Therefore, it is possible that the relative effectiveness of pharmacological prophylaxis might be even more pronounced when anaesthetic depth is controlled; however, our data do not allow us to make any assumption about this effect.

Third, we pooled groups with different antiemetic classes and subclasses in our main analysis. Therefore, our primary findings are limited to the comparison of TIVA versus 'uncontrolled' pharmacological antiemetic prophylaxis and the results might differ between antiemetic classes. As most of the included studies investigated 5-HT_3 antagonists, it might be concluded that our findings are more or less restricted to that class. However, as has been shown in the IMPACT trial,[1] as well as many others, the prophylactic effect of antiemetics from different classes is comparable when adequate doses are used.[7]

Finally, although N_2O is known to trigger PONV,[57] we did not make any preconditions regarding its use. Consequently, administration of N_2O varies among studies and has also been administered to 'TIVA' groups in four trials. In each of these, the corresponding IA + AE groups received the same dose of N_2O. Because there is no specific interaction between N_2O and propofol or pharmacological antiemetic prophylaxis,[1] we tend to assume that N_2O independently increased the risk for PONV in both groups to the same amount. In contrast, N_2O was administered only in the IA + AE groups in three studies. Accordingly, we performed a sensitivity analysis excluding these studies which did not change any of our main findings. However, without these studies, patients receiving TIVA were even more likely to suffer from late PONV (risk ratio 1.51, as compared with 1.41).

In summary, our meta-analysis shows that when substitution of TIVA for inhalational anaesthetics to reduce a patient's risk of PONV is not an option, then the PONV risk can be compensated to an equivalent degree by the use of a single-drug pharmacological prophylaxis. Finally, as neither strategy alone decreases PONV sufficiently in high-risk patients, the use of multiple prophylactic methods should be instituted to minimise the incidence of PONV and improve surgical outcome.

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Conflicts of interest: PeKr has conducted funded Research by Acacia Ltd. and has received fees for lectures by Fresenius Kabi, Baxter GmbH, Germany and ProStrakan and is co-author of the cited consensus guideline on the management of PONV (SAMBA-Guideline), published by TJ Gan *et al*. PeKi has been consulting for Baxter GmbH Germany and Air Liquide Medical GmbH Germany, has received lecture fees and travelling expenses from both companies and is an associated editor of BMC Anesthesiology.

Presentation: preliminary data for this study have been presented at the European Society of Anaesthesiology meeting, 28 to 30 May 2016, London.

Comment from the editor: PeKr is an associate editor of the *European Journal of Anaesthesiology*.

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7.8 Total intravenous anesthesia vs single pharmacological prophylaxis to prevent postoperative vomiting in children: A systematic review and meta-analysis

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SYSTEMATIC REVIEW

WILEY Pediatric Anesthesia

Total intravenous anesthesia vs single pharmacological prophylaxis to prevent postoperative vomiting in children: A systematic review and meta-analysis

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Summary

Background: Postoperative nausea and postoperative vomiting are frequent but often missed complications after general anesthesia in pediatric patients. Because inhaled anesthetics are known to trigger postoperative vomiting, total intravenous anesthesia is often administered in high-risk children to avoid the use of inhalational anesthesia. Since inhalational anesthesia might be advantageous in some situations, the question is raised whether administration of pharmacological prophylaxis offers equal protection from postoperative vomiting compared with total intravenous anesthesia alone.

Aim: The aim of this systematic review was to compare total intravenous anesthesia with single-drug pharmacological prophylaxis for the protection of postoperative vomiting in pediatric patients.

Methods: We conducted a systematic review (*EMBASE*, *MEDLINE*, and *CENTRAL*) with meta-analysis on randomized controlled trials including patients <18 years of age undergoing general anesthesia, with one group receiving propofol-based total intravenous anesthesia and another group receiving inhalational anesthesia with single pharmacological prophylaxis. Primary outcome was the overall incidence for postoperative vomiting. Secondary outcomes included early and late postoperative vomiting, the need for postoperative antiemetic medication, time to first oral intake, duration of stay in the postanesthesia care unit, and any adverse events defined as such by the respective authors. Risk ratios (RR) or mean differences (MD) with 95% confidence intervals (95% CI) were calculated using a random effects model with inverse variance weighting.

Results: Four randomized controlled trials including 558 children were included in the final analysis. All patients underwent strabismus surgery. Total intravenous anesthesia and single pharmacological prophylaxis were equally effective in preventing overall postoperative vomiting (RR 0.99 [95% CI 0.77; 1.27]; 4 trials), as well as vomiting in the early (1.48 [0.78; 2.83]; 4 trials) and late (0.89 [0.56;1.42]; 2 trials) postoperative period. There was no difference in the need for postoperative antiemetic medication. Although patients resumed drinking and eating significantly earlier following total intravenous anesthesia (MD −1.40 hours [−2.01; −0.80], $P < .001$),

Maximilian S. Schaefer and Peter Kranke are equally contributing authors.

the duration of PACU stay did not differ between groups. The incidence of intraoperative oculocardiac reflex was the only reported adverse event, which was more likely to occur after total intravenous anesthesia (1.86 [1.01; 3.41]).

Conclusion: Single pharmacological prophylaxis appears equally effective compared with total intravenous anesthesia in preventing postoperative vomiting in pediatric patients. However, during strabismus surgery, total intravenous anesthesia increases the risk for bradycardia due to oculocardiac reflex. Thus, when anesthesia is maintained with inhalational anesthetics, its emetogenic effects can sufficiently be compensated by the addition of a single prophylactic antiemetic medication.

KEYWORDS

anesthesia, droperidol, inhalational, ondansetron, postoperative vomiting, propofol, recovery

1 | INTRODUCTION

Postoperative nausea and vomiting are frequent complications not only in adults but also in children after emergence from general anesthesia.[1] While on average 30% of children over 3 years suffer from postoperative nausea and vomiting, incidences can be as high as 70% in high-risk patients after specific procedures such as strabismus surgery when no prophylaxis is administered.[2,3] In contrast to these high incidences, postoperative nausea and vomiting is usually underrecognized in pediatric patients because young children may not adequately name nausea as the cause for their discomfort.[4] Accordingly, postoperative vomiting (POV) is usually the only detectable symptom identifying this complication in younger children suggesting this phenomenon to be even more relevant. While POV causes one fourth of all unplanned hospital readmissions in pediatric outpatient surgery,[5] it also substantially prolongs the patient's stay in the postanesthesia care unit.[6] To prevent POV, international consensus guidelines have been established, recommending a risk-adapted prophylaxis in adults and also children.[7] In general, prophylaxis is based on a poly-pragmatic approach. Eventually, many anesthesiologists tend to avoid the administration of inhaled anesthetics and substitute propofol-based total intravenous anesthesia (TIVA). However, this strategy may turn out to be difficult, eg, when the placement of an intravenous access is challenging in the awake child. In this situation, face mask induction with inhaled anesthetics is frequently preferred. In this context, the question arises whether pharmacological prophylaxis might compensate for the increased risk for POV when inhaled anesthetics cannot be avoided or should be applied for other indications. Results from a large controlled multicenter trial,[8] as well as a recent meta-analysis from our group,[9] suggest rather comparable effects of single pharmacological antiemetic prophylaxis and the sole administration of TIVA in adults at risk for postoperative nausea and vomiting. However, we do not know whether these results also apply to pediatric patients. Thus, we conducted a systematic review and meta-analysis to compare TIVA to single-drug pharmacological prophylaxis for prevention of POV in pediatric patients scheduled for general anesthesia and surgery.

What is already known?

- Total intravenous anesthesia and pharmacological antiemetic prophylaxis are both effective in preventing postoperative vomiting in children.

What this article adds?

- This meta-analysis compares both measures directly and supports the general notion that they can be equally used to prevent POV in children.

2 | MATERIALS AND METHODS

2.1 | Systematic literature search

This systematic review with meta-analysis was performed as a secondary analysis on search results from an earlier systematic review comparing TIVA to single-drug pharmaceutical antiemetic prophylaxis for postoperative nausea and vomiting in adult patients.[9] This search was conducted in April 2015. The full text of the search strategy can be assessed at the openly available online database PROSPERO (www.crd.york.ac.uk/PROSPERO, registration number CRD42015019571). In the previous review, all studies including patients <18 years of age were excluded. For this study, the initially retrieved search results were re-searched for randomized trials in children (<18 years of age) comparing propofol-based TIVA to inhalational anesthesia with single pharmaceutical antiemetic prophylaxis. The study protocol is provided as Data S1. This search was conducted by 2 investigators (MSS and JO). The searched databases were EMBASE (via Ovid), MEDLINE (via PubMed), and the Cochrane Central Register of Controlled Trials (CENTRAL, via Wiley). No

restrictions were made on publication year or manuscript language. As in the initial analysis, randomized, controlled trials reporting incidences of postoperative nausea and vomiting, POV, or postoperative nausea and including at least one study group that received inhalational anesthesia with single-drug pharmacological prophylaxis and at least one study group that received propofol-based TIVA were included. Study groups with multiple antiemetic prophylaxes (ie, TIVA with pharmacological prophylaxis, inhalational anesthesia with multidrug pharmacological prophylaxes) were excluded.

2.2 | Data extraction

All publications were stored using Endnote ×7.1 (Thomson Reuters, New York, USA). The screening of studies as well as data extraction was independently performed by 2 investigators (M.S.S. and J.O.). Because the assessment of nausea is hampered in small children due to reporting problems, POV after surgery (0-24 hours) was chosen as the primary outcome. Secondary outcomes included the overall (0-24 hours) incidence of postoperative nausea and vomiting, early and late POV, the need for antiemetic rescue medication, time to first oral intake, duration of stay in the postanesthesia care unit and/or the hospital, as well as any adverse events defined as such and reported by the authors of the respective study. Further extracted information included duration of anesthesia, dose, type and timing of the pharmacological antiemetic prophylaxis, patient age, type of surgery, as well as dose and type of any anesthetic used for maintenance of anesthesia.

2.3 | Risk of bias assessment and statistical analysis

Extracted data were entered into Review Manager 5.3.5 (The Cochrane Collaboration, Copenhagen, Denmark), which was used for further analysis. A random effects model with inverse variance weighting was applied for calculation of pooled risk ratios (RR) or mean differences (MD) with corresponding 95% confidence intervals and alpha set to 0.05. RRs were defined to favor TIVA at <1 and to favor inhalational anesthesia with single pharmacological prophylaxis at >1. In addition, inter-study heterogeneity was assessed with the I^2 statistic and chi-square test for significance.[10] Finally, a subanalysis was performed for the primary outcome overall POV, stratifying studies by class of pharmacological prophylaxis.

All studies were assessed for possible risk of bias with the use of The Cochrane Collaboration "Risk of Bias" Assessment Tool with the addition of an estimation of the overall risk of bias for each study. These assessments were made independently by 2 blinded investigators (MSS, SW), with judgment of a third investigator (PKRA) upon disagreement. A funnel plot analysis was planned for outcomes involving 10 or more studies.

3 | RESULTS

Our systematic literature search identified 3106 articles, of which 2000 articles were screened based on the retrieved full texts as potentially eligible to the purpose of the study. Of these, 275 studies included patients <18 years of age. One study had to be excluded because it included both children and adults, and the data presented could not be separated between these 2 cohorts.[11] Finally, 4 randomized controlled trials[12–15] with a total of 558 patients were included into the final analysis. The screening process is depicted in Figure 1.

All studies investigated children undergoing strabismus surgery. Table 1 summarizes patient and study characteristics of the included studies. In 3 investigations, additional nitrous oxide was administered for maintenance of anesthesia. Of note, atropine (0.01-0.02 mg/kg) was administered at induction of anesthesia on a routine basis in all 4 studies.

3.1 | Primary analysis

POV was reported by all 4 included studies and occurred in 33% of all patients. None of the studies assessed postoperative nausea. Two studies reported data on the use of postoperative antiemetic medication; however, only one of these provided data for the whole postoperative period.[14] All studies reported POV in the early postoperative period. Furthermore, late PONV was reported by 2 publications[12,15] and the time to first oral intake by another 2 trials.[14,15]

In our main analysis, there was no difference in the overall risk for POV between the 2 groups (Figure 2). Also, the risk for early and late POV did not differ between groups (Figure 3). In the one study that investigated postoperative antiemetic medication, no difference in doses of administered antiemetics was found between the 2 groups (RR 2.4 [0.8;7.1], $P = .12$). The time to first oral intake was significantly reduced in patients receiving TIVA (Figure 4). Three of the 4 studies evaluated the incidence of intraoperative oculocardiac reflex, which was more likely to occur during TIVA than during inhalational anesthesia with pharmacological prophylaxis (RR 1.9 [1.01;3.41], $P = .05$, Fig. S1). In line with the previous findings, patients receiving TIVA received more frequently intraoperative atropine (RR 2.5 [1.2; 5.1], $P = .02$, Fig. S1). Finally, there was no statistically significant difference in the duration of postanesthesia care unit stay between the 2 groups (Figure 4). Of note, no other adverse events (eg, postoperative shivering or emergence agitation) were reported in any of these trials.

3.2 | Subgroup analysis

Stratification of the analysis by class of prophylactic medication did not alter the results from the overall analysis: There was no difference in the risk for overall POV after 5-HT-3 antagonists (ondansetron)[13,14] or droperidol[12,15] vs TIVA (RR 1.17 [0.75;1.82], $P = .49$ and .83 [0.58; 1.19], $P = .32$).

3.3 | Risk of bias assessment

The overall risk of bias was moderate in 3 studies, while one study was classified with an overall high risk of bias,[13] which was caused

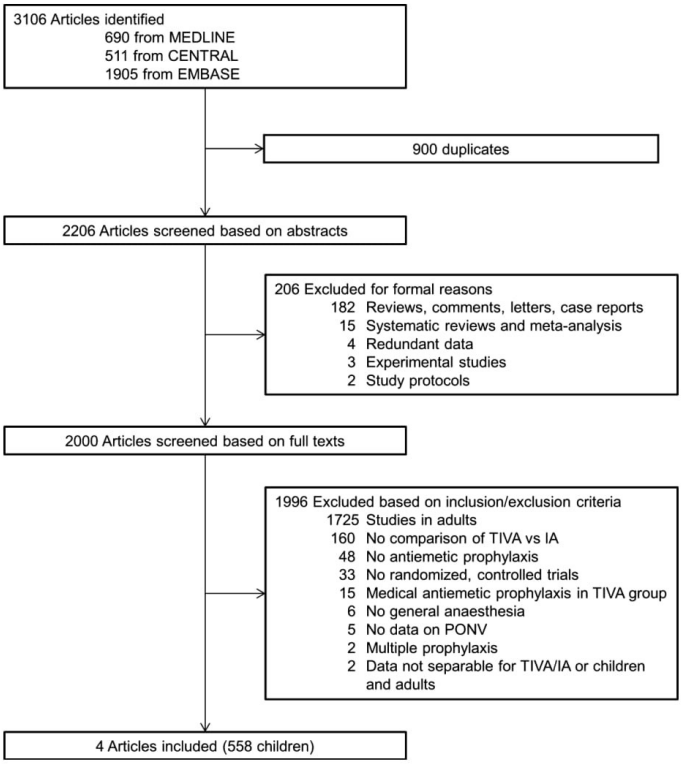

FIGURE 1 Flow chart of study screening process. TIVA, total intravenous anesthesia; IA, inhalational anesthesia

by the fact that assessment of POV after hospital discharge of ambulatory patients was performed by the patient's parents instead of trained study personnel (Table 2). However, excluding this study did not change the results of any analysis. Finally, a funnel plot analysis was not conducted due to the small number of included studies.

4 | DISCUSSION

In this systematic review and meta-analysis including a total of 558 pediatric patients, single-drug antiemetic prophylaxis was equally effective as TIVA in preventing POV after strabismus surgery in children. Patients receiving TIVA resumed drinking and eating significantly earlier. However, they were more likely to suffer from oculocardiac reflex and had a higher risk to require intraoperative treatment with atropine compared with children under inhalational anesthesia.

Postoperative nausea and vomiting, as well as POV, are clinical relevant adverse events after general anesthesia. This is not only true for adult patients, but particularly in children since incidences are even twice as high than in adults.[4] Moreover, postoperative nausea is likely to be missed, since younger children are usually unable to express nausea as the reason for discomfort. Of note, the average age of all children throughout the 4 studies was 6.6 years. Therefore, robust data investigating prophylactic strategies to prevent this phenomenon in pediatric patients are warranted. Our meta-analysis mirrors the results of an earlier systematic review with meta-analysis including studies on adult patients.[9] The latter analysis revealed that propofol and single pharmacological antiemetic prophylaxis are equally effective in preventing POV after general anesthesia. Thus, a prophylactic strategy does not necessarily need to involve substitution of inhaled anesthetics with propofol, when other advantages of inhaled anesthetics such as good control of effect-site concentrations by measuring expiratory concentrations shall not be given up. Notably, in the present analysis including patients at high risk for POV, every third child still suffered from POV after administration of a single prophylaxis (TIVA or one antiemetic), which is still unacceptably high. Of note, the aim of this analysis was not to find the overall most effective prophylactic strategy for prevention of POV, but to establish which prophylactic component (TIVA or pharmacological prophylaxis) is more effective. We would like to emphasize that, in patients at high risk for POV, a multimodal approach is recommended, based on the prophylactic administration of a combination of antiemetics.[16] Furthermore, other strategies have been proven to reduce POV in children such as the addition of regional anesthetic blocks[17,18], high doses of intravenous fluids,[19] the additive administration of nonsteroidal anti-inflammatory drugs,[20] or

TABLE 1 Overview and characteristics of included studies

Study	Patients TIVA/IA	Age (years)	Female	Type of surgery	Maintenance TIVA	Maintenance IA	Duration of anesthesia (TIVA/IA, min)	Type of AE	Timing of AE	Atropine prophylaxis
Klockgether-Radke 1995[12]	60/30	9.8 ± 3	44 (49)	Strabismus surgery	Propofol with alfentanil, 30 children additional 67% N_2O	Halothane with 67% N_2O	129 ± 36/123 ± 34	Droperidol 75 μg/kg i.v.	Before end of surgery	0.01 mg/kg at induction
Splinter 1997[13]	156/144	6.0 ± 3	n.a.	Strabismus surgery	Propofol with 70% N_2O	Halothane with 70% N_2O	57 ± 23/54 ± 22	Ondansetron 150 μg/kg i.v.	Before start of surgery	0.02 mg/kg after induction
Tramèr 1998[14]	38/40	7.3 ± 3	39 (50)	Strabismus surgery	Propofol with alfentanil	Isoflurane with alfentanil	n.a.; (duration of surgery 65 ± 27/63 ± 21)	Ondansetron 5 mg/m^2 i.v.	10 min before surgery	0.02 mg/kg at induction
Watcha 1991[15]	60/30	4.6 ± 4	41 (46)	Strabismus surgery	Propofol, 30 children additional 66% N_2O	Halothane with 66% N_2O	70 ± 18/62 ± 16	Droperidol 75 μg/kg i.v.	After intubation	0.01 mg/kg at induction

TIVA, total intravenous anesthesia; IA, inhaled anesthetic; AE, antiemetic; i.v., intravenously
Values are either mean ± SD or absolute numbers (%).

even the co-administration of subhypnotic doses of propofol as an adjunct to inhaled anesthetic-based anesthesia.[21]

Today, droperidol is seldom used as primary antiemetic prophylaxis in children, mainly due to fear of side effects such as extrapyramidal symptoms. Since droperidol has been used as antiemetic prophylaxis in 2 of 4 studies in our meta-analysis, we would like to emphasize that in adults, the overwhelming majority of data,[22] including the cited 2014 consensus guidelines authored by Gan et al,[7] indicate that the effectiveness of almost all clinically used pharmacological antiemetic prophylaxis, especially droperidol, ondansetron and dexamethasone, is equal. Thus, it is a generally accepted concept that one antiemetic medication can be exchanged by another without loss of potency. However, although POV in adults and children are likely to be based on a similar pathophysiology, we cannot presume that prophylaxis administered in adults is equally effective in children. Two of the 4 included studies administered droperidol for antiemetic prophylaxis,[12,15] and there have been very few studies investigating the effectiveness of droperidol as a prophylactic agent for POV in children. In a recent study including 315 children, Bourdaud and colleagues[23] found that droperidol was ineffective in preventing postoperative nausea and vomiting when given in combination with dexamethasone and ondansetron. However, the findings from this study are compromised by a limited power associated with a much lower observed POV incidence than expected. Furthermore, an earlier meta-analysis[24] was unable to make any assumption about the effectiveness of droperidol for prevention of POV in pediatric patients, since only one study investigating the effect of droperidol in this setting was identified. Taken together, so far there is not enough evidence to make any assumption about the effectiveness of droperidol for prevention of POV in pediatric patients. In this context, it is interesting that our general analysis and subanalysis including only studies with droperidol prophylaxis showed equal effectiveness of TIVA and droperidol, suggesting an antiemetic effect equal to TIVA.

In contrast to droperidol, other antiemetics routinely used in adult patients have been proven effective also in pediatric patients: Compared with placebo, dexamethasone reduces the risk for POV by 50% after pediatric tonsillectomy,[24,25] although an optimum dose has yet to be identified. In addition, the 5-HT_3 antagonists ondansetron, granisetron, tropisetron, and dolasetron have been proven to be effective in preventing POV in children.[24] Similar effects can be achieved by rectal or intravenous application of the antihistamine dimenhydrinate,[26] although due to its sedative effects, it is usually not used as a first-line prophylaxis.

4.1 | Limitations

All studies included were published more than 20 years ago in the 1990s. Of note, this was also an issue in another meta-analysis from 2014 comparing the effectiveness of dexamethasone and ondansetron for prevention of POV in pediatric anesthesia.[22] At that time, many standards such as detailed reporting of the randomization process, the concealment of the randomization process, and a proper blinding of outcome assessors, study personnel, and patients had not

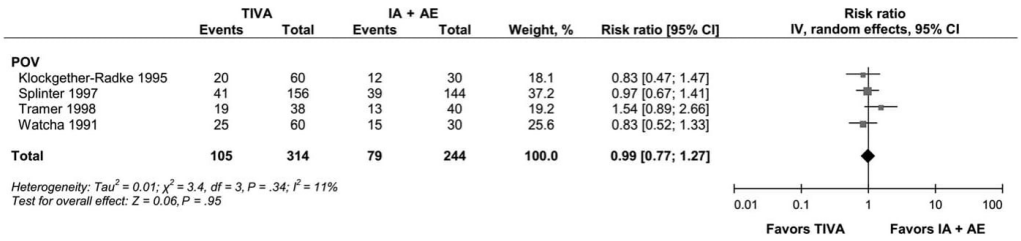

FIGURE 2 Forest plot of the primary outcome overall postoperative vomiting (POV). TIVA, total intravenous anesthesia; IA + AE, inhalational anesthesia with single antiemetic prophylaxis; IV, inverse variance

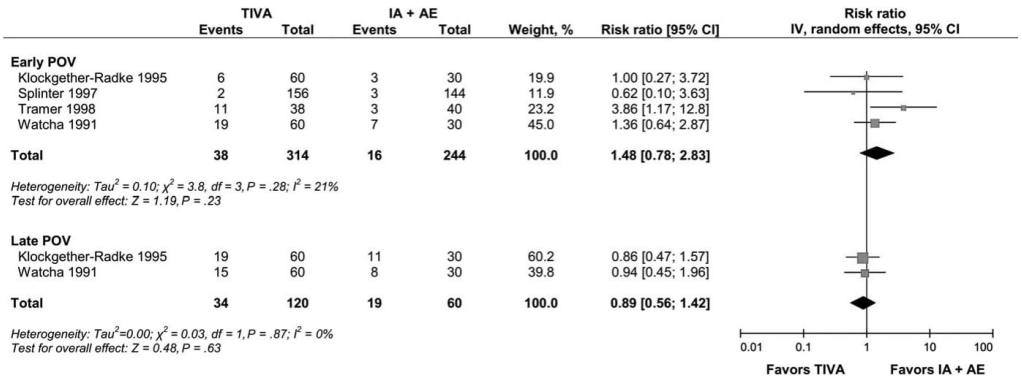

FIGURE 3 Forest plot for early and late postoperative vomiting (POV), as defined by the authors of the respective study. TIVA, total intravenous anesthesia; IA, inhalational anesthesia; IV, inverse variance

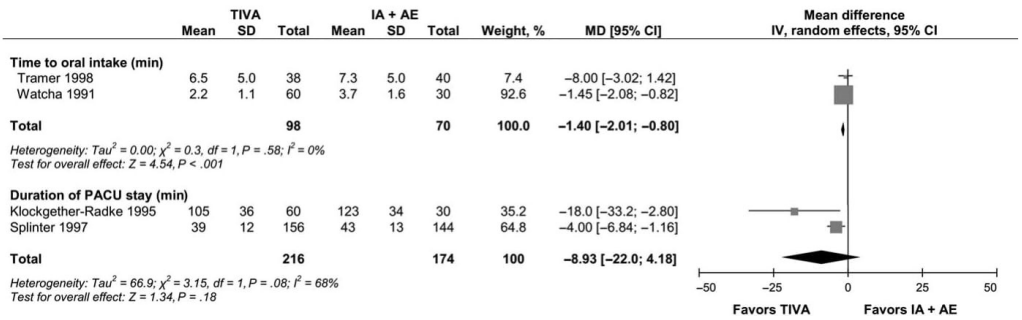

FIGURE 4 Forest plot for time to oral intake and duration of stay in the postanesthesia care unit (PACU). TIVA, total intravenous anesthesia; IA, inhalational anesthesia; SD, standard deviation; MD, mean difference; IV, inverse variance

been established. In this context, we would like to emphasize that the quality of all included trials is rather high with respect to the year of its publication. Furthermore, 3 of the 4 studies administered halothane. Due to a very high blood-gas-partition coefficient of 2.5,[27,28] the elimination of Halothane is prolonged yielding slow emergence from anesthesia and prolonged sedation.[29] It has been withdrawn from the market in many countries because of its unfavorable pharmacokinetics compared with modern inhaled anesthetics. In addition, in 2 studies, droperidol was administered in rather high doses (75 μg/kg). It has been shown that droperidol is associated with several side effects (eg, postoperative drowsiness) that are dose-dependent.[30] Accordingly, the unfavorable pharmacokinetic of halothane and much higher doses of droperidol than given today may explain the significantly longer time to first oral intake in patients receiving inhalational anesthesia with pharmacological prophylaxis compared with TIVA. We speculate that with

TABLE 2 Risk of bias assessment for each trial

	Random sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall bias estimation
Klockgether-Radke 1995[12]	?	?	?	+	?	?	+	Moderate
Splinter 1997[13]	+	?	?	?	+	?	–	High
Tramer 1998[14]	?	+	?	+	?	?	+	Moderate
Watcha 1991[15]	?	?	?	+	?	?	+	Moderate

+, low risk of bias; ?, unclear risk of bias; –, high risk of bias.

modern inhaled anesthetics and lower doses of droperidol, or other antiemetics such as 5-HT_3 inhibitors, this difference will vanish.

In addition, the question has to be raised whether results from studies that applied anesthetics like halothane, that are no longer used in modern anesthesia, can still be applied to current clinical practice: It has been shown that the type of inhaled anesthetic used does not influence the incidence of POV,[31] even when halothane is directly compared to modern anesthetics in pediatric anesthesia.[32] Furthermore, although alfentanil is still widely applied worldwide, today the opioid used for TIVA is usually remifentanil. In their landmark study, Apfel and colleagues compared the effect of remifentanil on patient's risk for postoperative nausea and vomiting to the long-lasting fentanyl and found no difference,[8] surprisingly indicating that the type of opioid does not influence postoperative nausea and vomiting. With regard to alfentanil, this notion is supported by a more recent study comparing TIVA with propofol and sufentanil to propofol and alfentanil,[33] which found no difference in incidences and severity of POV. Finally, 3 of 4 studies combined both strategies with nitrous oxide, which by itself increases the risk for POV. This was also a limitation in an earlier meta-analysis conducted by our group,[9] where we have discussed this extensively: Since nitrous oxide is an independent predictor for POV[8] and does not interact either with TIVA or inhalational anesthesia, we are confident that use of nitrous oxide did not influence the generalizability of our data.

Since randomized controlled trials in children are scarce and difficult to conduct due to ethical considerations as well as parents' reluctance to have their child included in a study, it is not surprising that no more than 4 studies with 558 pediatric patients were included in this analysis. However, considering the limited evidence and limited chance for subsequent data in this field, especially looking at the direct comparison of one antiemetic as opposed to one single antiemetic strategy (TIVA), it is of great value to have the presented data available for rational decision-making.

Interestingly, the included studies show a certain degree of homogeneity: Although we did not limit our analysis to any kind of surgical procedure, all studies investigated children undergoing strabismus surgery. This can be explained by the fact that strabismus surgery represents an independent risk factor for POV in children,[2,23] and therefore increases event rates in studies, which consecutively decreases the required sample size. As strabismus surgery independently increases the risk for POV and does not interact with either TIVA or pharmacological prophylaxis, we are confident that despite our analysis being limited to this procedure, the generalizability of our results to the general pediatric surgical population is given.

Finally, our analysis suggests that the prophylactic antiemetic effect of TIVA can equally be achieved with a single antiemetic. Nonetheless, in a high-risk population, a multimodal approach is warranted. Since in the pediatric population, dopamine antagonists such as droperidol have so far not been proven effective, or are reluctantly recommended due to an unfavorable side effect profile (eg, metoclopramide), antiemetic alternatives with proven prophylactic effects are fewer than in adults. In this context, especially when pharmacological prophylactic alternatives are scarce, TIVA constitutes an important part of a multimodal approach, although in children undergoing strabismus surgery, this needs to be weighed against the risk for perioperative bradycardia due to oculocardiac reflex.

CONFLICT OF INTEREST

M.S.S. has declared no conflicts of interest. P.Kr has conducted funded Research by Acacia Ltd. and has received fees for lectures by Fresenius Kabi, Baxter GmbH, Germany, and ProStrakan and is co-author of the cited consensus guideline on the management of postoperative nausea and vomiting (SAMBA Guideline), published by TJ Gan et al. S.W. has declared no conflicts of interest. R.K. has declared no conflicts of interest. J.O. has declared no conflicts of interest. P.Ki has been consulting for Baxter GmbH Germany, Air Liquide Medical GmbH Germany, and TEVA ratiopharm Germany and received lecture fees and traveling expenses from these companies. He is an associated editor of BMC Anesthesiology.

ETHICAL APPROVAL

No ethical approval was necessary for this systematic review with meta-analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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