Xenon decreases cell migration and secretion of a pro-angiogenesis factor in breast adenocarcinoma cells: comparison with sevoflurane

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Editor’s key points

- Volatile anaesthetics can enhance metastatic functions of tumour cells in vitro, but the effects of the anaesthetic gas xenon is not known.
- Xenon, but not sevoflurane, reduced breast cancer cell migration and release of a pro-angiogenic factor.
- Whether these potentially anti-metastatic effects are relevant during cancer surgery must be determined with in vivo models.

Background. While volatile agents have been implicated in metastasis-enhancing effects on cancer cells, the effects of xenon are unknown. We investigated xenon- and sevoflurane-mediated effects on migration and expression of angiogenesis biomarkers in human breast adenocarcinoma cells.

Methods. MDA-MB-231 and MCF-7 cells were exposed to xenon 70% with O₂ 25%, CO₂ 5%; control gas containing O₂ 25%, CO₂ 5%, N₂ 70%; or sevoflurane 2.5 vol% administered in O₂ 60%, N₂ 37%, or control gas. Cell viability was determined by the MTT assay. Migration at 24 h was determined using the Oris™ Cell Migration Assay. Secretion of angiogenesis factors was measured using a membrane-based immunosassay array.

Results. Xenon reduced MDA-MB-231 migration to 59 (13%) after 1-h exposure (P=0.02), 64 (10%) after 3 h (P=0.01), and 71 (9%) after 5 h (P=0.04) compared with control gas, without affecting viability. Similarly, MCF-7 migration was significantly reduced at all timepoints [to 58 (12%) at 1 h, 65 (12%) at 3 h, and 65% (12%) at 5 h]. Sevoflurane did not affect migration when delivered in control gas. Glycine, an N-methyl-D-aspartate receptor co-agonist, antagonized the effects of xenon on migration. Expression of the pro-angiogenesis factor regulated on activation, normal T cell expressed and secreted (RANTES) was reduced in conditioned medium from xenon-exposed MDA-MB-231 cells compared with cells exposed to either control gas or sevoflurane [mean dot density 2.0 (0.2) compared with 3.0 (0.1) and 3.1 (0.3), respectively (P=0.02)].

Conclusion. Xenon, but not sevoflurane, inhibited migration in both oestrogen receptor positive and negative breast adenocarcinoma cells. Furthermore, xenon decreased release of the pro-angiogenic factor RANTES from MDA-MB-231 cells.

Keywords: anaesthetics, sevoflurane; anaesthetics, xenon; cancer, angiogenesis; cancer, breast; cell function, migration

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because of its prohibitive production cost.\textsuperscript{14} \textsuperscript{15} Its effects on cancer cell biology are unknown. As xenon has numerous clinical advantages over currently used volatile agents, we hypothesized that it might have more favourable effects on cancer cell function. Therefore, we investigated the direct effect of xenon on migration and expression of known pro-angiogenesis factors, which are both essential to the metastatic potential of breast cancer cells, in oestrogen receptor-positive (ER+) and oestrogen receptor-negative (ER−) breast adenocarcinoma cancer cells in vitro.

Methods

Cell lines

MDA-MB-231 is an ER− human breast adenocarcinoma cell line. MCF-7 is an ER+ and progesterone-receptor-positive human breast adenocarcinoma cell line. MDA-MB-231 cells were routinely cultured in L-Liebowitz 15 medium supplemented with 15% (v/v) fetal bovine serum (FBS), 1% (v/v) penicillin–streptomycin solution, while MCF-7 cells were routinely cultured in Minimum Essential Medium Eagle with Earle’s salts and sodium bicarbonate, supplemented with 10% (v/v) FBS, 1% (v/v) non-essential amino acids, and 1% (v/v) penicillin–streptomycin solution. Both cell lines were grown in T75 flasks (Cellstar filter cap flask) at 37°C in a humidified atmosphere containing 5% CO\textsubscript{2} and were purchased from the European Collection of Cell Cultures (ECACC, Salisbury, UK).

Gases

Four gas mixtures were evaluated: premixed xenon containing O\textsubscript{2} 25%, CO\textsubscript{2} 5%, and xenon 70% (L’Air Liquide, Paris, France); control gas containing O\textsubscript{2} 25%, CO\textsubscript{2} 5%, and N\textsubscript{2} 70% (L’Air Liquide); and sevoflurane, delivered as 2.5 vol% via a Tec 7 Vaporizer either in a carrier gas mixture of O\textsubscript{2} and air containing approximately O\textsubscript{2} 60% and N\textsubscript{2} 37%, or in the control gas.

Gas exposure

All gas exposures were conducted in a hermetic chamber (Enzyscreen BV), of which there were two to allow concurrent gas exposure with experimental or control gas if required. Before introducing the cell cultures to the chamber, cell line-appropriate FBS-free medium was enriched with the experimental gases (xenon, control gas, sevoflurane in O\textsubscript{2}, or sevoflurane in control gas) using a glass gas wash bottle (Dreschel pattern, DuranR) at a flow rate of 0.4–0.6 litre min\textsuperscript{−1} for 20 min, adjusted to the lowest flow that maintained bubbling through the filter disc. The removal of FBS during this procedure was to prevent frothing. Separate gas wash bottles were used for each cell line and were similarly cleaned before the next gas enrichment. FBS in cell line-appropriate concentrations was subsequently added to the enriched media for the migration studies outlined below.

Non-treated media was decanted from the cell cultures, the cells were washed with phosphate buffered sodium (PBS) and enriched media was introduced (appropriate to the cell lines). The plates were introduced to the chamber and the atmosphere of the chamber was replaced by the desired experimental gas mixture at 20 litre min\textsuperscript{−1} for 3 min. The concentration of xenon in the chamber was stabilized at 65–70% as determined using a portable gas analyser (Hitech K6050), and the concentration of sevoflurane in the chamber was similarly stabilized at 2.3–2.5 vol% as determined using an anaesthetic gas analyser (HP M1026A). Where indicated, a paired control gas plate and chamber were similarly prepared. The chambers were sealed before closure of gas supplies. The hermetic chambers were then introduced into an incubator for 1, 3, or 5 h at 37°C in 5% CO\textsubscript{2}, as determined by viability, migration, or angiogenesis protocol. The gas-exposed cultures (experimental or control) were removed from the chambers after the appropriate time and returned to an incubator at 37°C in 5% CO\textsubscript{2} for 24–48 h before analysis.

Evaluation of cell viability

The methylthiazolyldiphenyl-tetrazolium-bromide (MTT) assay was used to determine the effect of xenon gas on cell viability. This assay detects living, but not dead, cells and measures the reduction of the cell permeable yellow salt MTT to impermeable purple formazan crystals by active mitochondrial dehydrogenases in viable cells.\textsuperscript{16} Cells were seeded into 96-well plates at a density of 2 × 10\textsuperscript{4} cells cm\textsuperscript{−2} and allowed to adhere overnight. Viability was initially compared in cells incubated in either FBS-free medium or FBS-containing medium for 24 h at 37°C in 5% CO\textsubscript{2}, as it was necessary to use FBS-free medium for the gas exposure protocol. Gas exposure was conducted as described above and cell cultures were incubated for 48 h at 37°C in 5% CO\textsubscript{2}.

MTT solution was prepared by adding 0.5 mg ml\textsuperscript{−1} MTT to cell line-appropriate FBS-containing media. Experimentally enriched medium was removed from the 96-well plate and a 100-μl aliquot of MTT solution was added to each of the wells and allowed to incubate for 3 h at 37°C in 5% CO\textsubscript{2}. The solution was removed from the wells and the formazan crystals were solubilized by the addition of 100 μl of dimethyl sulphoxide (DMSO), after which the plate was left for 20 min on a rocker. The absorbance of each well was read at 570 nm using a microplate reader. Viability was expressed as a percentage compared with wells exposed to control gas.

Migration assay

The effect of experimental gases on breast cancer cell migration on a collagen substrate was determined using the Oris\textsuperscript{TM} Cell Migration Assay (Platypus Technologies, Madison, WI, USA), according to the manufacturer’s protocol. This assay involved measuring the migration of cells into an exclusion zone and is superior to the scratch assay, as it does not involve injury to the cells or the extracellular matrix.\textsuperscript{17} Cells grown to 90–99% confluence in T75 flasks were removed by trypsinization, re-suspended in appropriate medium, and seeded into an Oris\textsuperscript{TM} Pro Collagen (collagen-coated) 96-well plate. Each separate and independent experiment used two 96-well plates for each cell line. These two plates were seeded at the same time with the same passage of
cells. Each well had an Oris™ cell seeding stopper in situ to restrict cell seeding to the outer regions of the well. The plate was seeded with a concentration of 100,000 cells in 100 µl of appropriate medium per well. A total of 16–24 wells were used for each gas exposure, for each cell line: 8–12 experimental wells and 8–12 control wells for analysis of background fluorescence. The seeded plates were incubated for 24 h at 37°C in 5% CO₂ to allow cell attachment.

For each cell line, stoppers for the experimental wells were removed to create a detection zone of 2 mm diameter into which cells could migrate. This was done immediately before the gas exposure protocol. Xenon and paired control gas plates were exposed for 1, 3, or 5 h. Sevoflurane in O₂, sevoflurane in control gas plates, and their respective control gas counterparts were exposed for 3 h. After each gas exposure, the 96-well plates were incubated for 24 h at 37°C in 5% CO₂ to allow time for migration. After this incubation period, the stoppers were removed from the background fluorescence wells immediately before cell staining, such that no migration could have occurred in these wells. Staining was with calcein AM (Sigma-Aldrich, St Louis, MO, USA) as per the manufacturer’s instructions.

Cells migrating into the detection zone were quantified using a bottom-reading fluorescence plate reader (SpectraMax M3, Molecular Devices, Sunnydale, CA, USA) with excitation and emission wavelengths of 485 and 525 nm, respectively. A template mask (Oris™) was used to shield all regions of the wells, other than the 2-mm detection zone. Values were obtained as relative fluorescent units (RFUs) for each well. Experimental RFU values were averaged across the 8–12 experimental wells for each cell line to obtain a single experimental RFU. Background RFU values were also averaged across 8–12 wells per cell line and this value was subtracted from the mean experimental RFU to obtain a single result RFU value, indicative of cell migration, for each cell line. This procedure was repeated for both experimental gas and control gas plates.

The results of each migration study are presented as a percentage of control gas migration on parallel plates. Three or four separate and independent experiments were conducted for each experimental gas.

### Influence of glycine on cell migration

The mechanism of action of the effect of xenon on migration was investigated using the Oris™ Cell Migration Assay with modification to the migration protocol outlined above. For each cell line, experimental wells received 100 µl of enriched medium treated with 1 µl of 100 µM solution of glycine dissolved in PBS (final concentration 1 µM glycine) or 100 µl of enriched medium with 1 µl of 100 nM solution of glipizide dissolved in DMSO (final concentration 1 nM glipizide), while control wells received either 100 µl of enriched medium with 1 µl of DMSO (final concentration 1%, v/v, DMSO) or received enriched medium alone. The results of each mechanism of action subgroup (glycine, glipizide, DMSO) were presented as a percentage of vehicle-treated cells.

### Angiogenesis

The presence of and potential alteration of angiogenesis markers in the conditioned medium was assessed using Human Angiogenesis Array C1 (RayBiotech, Norcross, GA, USA). One millilitre of MDA-MB-231 cells (5.4 × 10⁶ cells ml⁻¹) suspended in appropriate medium was added to 2 ml of appropriate medium in T25 flasks (Greiner, Bio-One GmbH, Frickenhausen, Germany), such that each flask contained a volume of 3 ml. The T25 flasks were incubated for 24 h at 37°C in 5% CO₂ to allow cell attachment and confluence to 90–99%. Media were removed and the cells washed with PBS. Two millilitres of gas-enriched medium, prepared as per the gas exposure protocol, was added to each flask. Xenon, sevoflurane in control gas, and control gas were used. The flasks (with loosened caps) were then exposed to the corresponding gases in hermetic chambers, as per the gas exposure protocol, for 3 h. The flasks were then removed, caps tightened, and they were incubated for a further 24 h at 37°C in 5% CO₂. After each exposure period the conditioned medium was removed and frozen at − 80°C in a 2 ml cryotube vial (Sigma).

Once samples of all three conditioned media had been collected, it was defrosted and the release of 12 key angiogenesis factors (Table 1) into the medium was determined using a membrane-based sandwich immunoassay array as per the manufacturer’s protocol. Scanning densitometry was used to provide a semi-quantitative indication of dot intensity using the GelEval software program v1.22 (Frogdance Software, Dundee, UK).

<table>
<thead>
<tr>
<th>Angiogenesis factor</th>
<th>Mean dot intensity</th>
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<tbody>
<tr>
<td></td>
<td>Xenon</td>
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<tr>
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<td>Epidermal growth factor (EGF)</td>
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*P = 0.02
Statistical analysis
Results from migration experiments are summarized as percentage migration relative to control gas as mean (SEM) (3 ≤ n ≤ 6). Data were analysed and graphs drawn using SigmaPlot v10 (Systat Software, London, UK) and Prism v6 (Graphpad Software, La Jolla, CA, USA). Parametric and non-parametric tests were used to compare data sets, including t-test, analysis of variance, and Mann–Whitney U-test as appropriate. P-values ≤ 0.05 were considered significant.

Results
Replacing complete FBS-containing medium with appropriate FBS-free medium for 1, 3, or 5 h, as required for the viability gas exposure protocol, did not affect cell viability in either MDA-MB-231 or MCF-7 cell lines, as determined by the MTT assay (Fig. 1A). Moreover, acute exposure to either xenon or control gas mixtures for 1, 3, or 5 h had no significant effect on cell viability in either cell line (Fig. 1A).

The migration of both MDA-MB-231 and MCF-7 cells was reduced by xenon compared with the control gas mixture (Fig. 2A and B). Xenon reduced MDA-MB-231 migration to 59% (13%) after a 1-h exposure (n=4, P=0.02), to 64% (10%) after a 3-h exposure (n=4; P=0.01), and to 71% (9%) after a 5-h exposure (n=3, P=0.04). Similarly, MCF-7 migration was reduced to 58% (12%) after a 1 h exposure (n=4; P<0.01), to 65% (12%) after a 3 h exposure (n=4; P=0.01), and to 65% (12%) after a 5 h exposure (n=3; P=0.02).

In contrast, a 3 h exposure to sevoflurane in O₂ increased MDA-MB-231 migration to 245% (33%) (n=4; P=0.01) and MCF-7 to 188% (5%) (n=3; P=0.01). However, when the carrier gas was changed to the same control gas used for the

![Fig 1](image1.png) Influence of xenon on cell viability of MDA-MB-231 and MCF-7 breast adenocarcinoma cell lines. Removal of serum during the gas exposure protocol for up to 5 h had no effect on cell viability (A). Similarly, exposure to xenon for 1, 3, or 5 h did not significantly affect viability of either MDA-MB-231 or MCF-7 cells (a).

![Fig 2](image2.png) Influence of xenon and sevoflurane on cell migration of MDA-MB-231 and MCF-7 breast adenocarcinoma cell lines. Exposure of MDA-MB-231 or MCF-7 cells to xenon for 1, 3, or 5 h inhibited subsequent migration into the exclusion zone, measured at 24 h (A). Values shown are mean (SEM) compared with values for matched cells exposed to control gas at the same time. Values differing significantly from those of control gas are indicated by an asterisk (P≤0.05). Although a 3 h exposure to sevoflurane significantly increased migration of both cell lines when sevoflurane was delivered in a high oxygen content (a), when delivered in the same control gas as xenon, no significant effect on cell migration was observed after a 3 h exposure to sevoflurane.
xenon experiments, sevoflurane exhibited no effect on migration in either cell line.

Treatment with 1 μM glycine antagonized the inhibitory effects of xenon on migration (Fig. 3). When represented as a percentage of xenon-exposed control cells, glycine treatment increased MDA-MB-231 migration to 190% (44%) (n=3; P=0.02) and MCF-7 migration to 173% (17%) (n=4; P=0.02). When cells were exposed to control gas, 1 μM glycine did not alter migration in either cell line, indicating that the effects of glycine on migration are specific to xenon exposure (Fig. 3). There were no significant changes in migration with either glipizide or the DMSO vehicle (data not shown).

The array-based system used to investigate angiogenesis was sufficiently sensitive to detect 12 angiogenesis factors secreted into conditioned medium. None of these was detectable in unconditioned medium, where only control dots were visible on the array (Fig. 4A). Of the 12 angiogenesis factors studied, a decrease in regulated on activation, normal T cell (RANTES) expression was observed in conditioned medium from xenon-exposed MDA-MB-231 cells (Fig. 4C) compared with conditioned medium from cells exposed to either sevoflurane in control gas (Fig. 4D) or control gas alone (Fig. 4B). Dot intensity for RANTES was significantly lower in the xenon-exposed conditioned medium compared with control gas-exposed conditioned medium, while none of the other angiogenesis factors studied exhibited significant differences in expression between the three groups (Table 1).

**Discussion**

Our data demonstrate that acute exposure to xenon at a clinically relevant concentration did not affect viability, but decreased migration of both an ER+ and ER− human breast cancer cells in vitro. This effect was antagonized by glycine, suggesting an N-methyl-D-aspartate (NMDA)-receptor-mediated mechanism. Importantly, decreased migration was evident after an acute 1 h exposure to xenon, a very relevant time-frame for clinical anaesthetic practice.

Although xenon has been known to have desirable anaesthetic properties for almost 75 yr, its prohibitive production costs have delayed renewed interest in its use. Xenon exhibits many qualities of an ideal inhalation anaesthetic: rapid onset and offset of action, minimal cardiovascular depression, neuroprotection, absence of impairment of hepatic or renal function, or on coagulation or immune function. It does not trigger malignant hyperthermia, and confers satisfactory analgesia.16–22 Currently used clinically only in Russia and Germany, xenon’s effects on cancer cell biology have not been reported previously.

The volatile agents currently in widespread clinical use, including sevoflurane, have been associated with potentially enhanced metastasis in experimental animal and in vitro models.10–13 The mechanisms behind these effects are attributable to direct effects on tumour cell signalling. Direct effects on tumour cells might be mediated by altered gene expression, which has been demonstrated in vitro, including upregulation of pro-angiogenesis factors (e.g. hypoxia-inducible factor 1α).12 Volatile agents have also been shown to affect innate immune cell function in experimental models, which could adversely affect immune responses to cancer.23 24

**Fig 4** Representative image showing the influence of xenon and sevoflurane on secretion of angiogenesis factors from MDA-MB-231 breast adenocarcinoma cells. Cells were exposed to control, xenon, or sevoflurane gas for 3 h, after which they were returned to the incubator for 24 h. Conditioned medium was collected and applied to a commercially available membrane-based angiogenesis array. None of the angiogenesis factors was present in non-conditioned medium that had not been in contact with cells (a), with dots visible only for positive controls. In comparison with control gas (a), xenon significantly decreased expression of RANTES (c), and this effect was not observed in sevoflurane-exposed cells (o). The dots corresponding to RANTES are circled in (a)–(o). Semi-quantitative scanning densitometry confirmed this observation (Table 1).
On the other hand, there are also data suggesting that desflurane and sevoflurane have beneficial effects by decreasing the migration of colon cancer cells, secondary to decreased matrix-metalloproteinase secretion from neutrophils. These conflicting results might be attributable to different effects of anaesthetic agents on different tumour cell types, which is consistent with the clinically observed differences in tumour behaviour according to the type of cancer.

Previous experimental work suggested that sevoflurane can lead to increased cancer cell migration. However, that protocol involved carrier gas with a high oxygen content and without CO₂, which might have been stimulatory in its own right. When the migration studies were repeated in the present studies with sevoflurane in control gas, matching the O₂ and CO₂ content, migration was not different to control, although it was stimulated when sevoflurane was delivered in a high oxygen content. This indication that a high O₂ concentration might stimulate cancer cell migration in its own right certainly warrants further study, preferably in vivo, because of its implication that high, fractional inspired O₂ concentration, often used clinically, might potentially facilitate cancer spread.

Nitrous oxide (N₂O) has been associated with accelerated lung and liver metastasis in a murine model of breast cancer. However, in a follow-up analysis of a previous unrelated randomized controlled trial, N₂O demonstrated no difference in recurrence rates in patients undergoing colectomy for colorectal cancer.

Regarding the mechanism of action by which xenon exerts its effect on migration, we focused on two of xenon’s known targets: the glycine binding site of the NMDA receptor (a ligand-gated ion channel) and the adenosine triphosphate-dependent potassium (K⁺ATP) channel. Importantly, functional NMDA receptors are expressed in breast cancer cells, and in several recent studies, NMDA receptor expression and activation has been linked to tumour cell proliferation, invasion, and migration, both in vivo and in vitro, in various cancer types of non-neural origin.

There is accumulating evidence that xenon mediates neuroprotection by binding to the glycine site and thereby preventing NMDA receptor channel opening. We postulated that competition between xenon and glycine, at the NMDA receptor glycine site would reverse xenon’s effect on cell migration. Using a low concentration of glycine, which is commonly used to mediate competition at the glycine site but is unlikely to have pleotropic effects, concomitant exposure of both cell lines to glycine and xenon restored cell migration. As glycine had no effect on migration in the absence of xenon, it suggests that decreased breast cancer cell migration is specifically mediated by the action of xenon at the glycine site. Further studies using more selective NMDA antagonists should help confirm how perturbation of NMDA receptor signalling by xenon influences migration. However, Ca²⁺ influx is known to be critical to cytoskeletal changes within cancer cells, which would be important for cell movement.

The K⁺ATP channel has similarly been postulated to be involved in the neuroprotective effect of xenon against hypoxia and ischaemia. Xenon is thought to act at the Kir6.2 subunit, resulting in channel opening. Glipizide is a potent blocker of K⁺ATP channels, and it was thought that blocking xenon’s effect on this channel could have effects on cytoskeletal changes involved in tumorigenesis and potentially migration. However, glipizide had no effect on breast cancer migration in our model.

Angiogenesis plays a key role in the proliferation and invasion of tumours, ultimately resulting in metastasis. Any direct effects of anaesthetic agents on secreted angiogenesis factors could potentially be clinically significant. RANTES, otherwise known as CCL5 and acting on receptor CCR5, is a cytokine consistently increased in breast cancer subtypes, and has been associated with promotion of metastasis and progression of breast cancer. Xenon decreased the amount of RANTES secreted into the conditioned medium of MDA-MB-231 cells compared with both control gas and sevoflurane. We have previously shown in randomized trials that clinical anaesthetic technique affects serum expression of angiogenesis factors in breast cancer. Xenon has previously been shown to protect against ischaemic damage by inducing expression of hypoxia-inducible factor 1α and its pro-angiogenic downstream effector vascular endothelial growth factor (vEGF). However, those observations were made in models of acute renal ischaemia, and it is possible that different mechanisms underlie tumour-driven angiogenesis.

In conclusion, acute exposure of breast adenocarcinoma cells to xenon but not sevoflurane inhibited migration without affecting viability. Xenon also decreased secretion of the angiogenesis cytokine RANTES/CCL5 from MDA-MB-231 breast adenocarcinoma cells.

In vivo studies should evaluate whether the apparent beneficial effects of xenon on in vitro cancer cells translate into measurable benefits in orthoptic models of breast cancer metastasis.

Authors’ contributions

S.A.A. and G.I.V.: design of experimental protocol and conduct of laboratory experiments, analysis and interpretation of data, drafting of manuscript for intellectual content. M.L.: design of experimental protocol and conduct of laboratory experiments, analysis and interpretation of data. P.D.C.: conduct of laboratory experiments, drafting of manuscript for intellectual content. A.N.M.: conduct of laboratory experiments. H.C.G.: sourcing funding, conceptualization and design of laboratory experiments, analysis and interpretation of data, drafting of manuscript for intellectual content. D.J.B.: conception of idea, sourcing funding, design of laboratory experiments, analysis and interpretation of data, overall responsibility for manuscript.

Declaration of interest

D.J.B. is a member of the Editorial Board of BJA.

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