

## Nitrous oxide in 2010: who will have the last laugh? (Part 2)

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### Introduction

As has been alluded to in the first part of this series, nitrous oxide ( $N_2O$ ) is not the known quantity many of us think it is. It appears to be becoming “scientific fashion” among many anaesthetists to view nitrous oxide as an “anaesthetic untouchable” or, at best, a “second rate citizen”.

I wish to re-examine this conventional wisdom and see how much of it still holds true. In part two of this three part series, the ENIGMA trial will critically appraise, as will nitrous oxide’s claimed haematological, immunological, neurological, cardiovascular, and respiratory effects. Its influence on postoperative nausea and vomiting will also be evaluated.

### Critical appraisal of the risks and benefits of nitrous oxide

#### *The ENIGMA trial*

The results of the ENIGMA trial were published in 2007.<sup>1</sup> Entitled “Avoidance of nitrous oxide for patients undergoing major surgery”, this publication was expected to toll the death knell for nitrous oxide, a view endorsed by the accompanying editorial.<sup>2</sup>

The investigators recruited 2 050 subjects, randomly assigning them to either a nitrous oxide-free (80% oxygen, 20% nitrogen) group or a nitrous oxide-based (70% nitrous oxide, 30% oxygen) group. All patients were scheduled to undergo major surgery of at least 2 hours duration. ENIGMA was presented as a pragmatic study with no attempt to control for possible confounding variables, and the anaesthetist had the option to cross over from one group to the other. The primary endpoint was duration of hospital stay. Secondary endpoints included duration of intensive care unit (ICU) stay, and incidence of severe post-operative nausea and vomiting (PONV),

pneumonia, pneumothorax, pulmonary embolism, wound infection, myocardial infarction, venous thromboembolism, stroke, awareness, and death within 30 days.

The results showed that there was no difference between the two groups with regard to the primary endpoint, duration of hospital stay. Analysis of the secondary endpoints, however, appeared to show a lower rate of major complications (wound infection, atelectasis, and pneumonia) and severe PONV. No significant differences in major cardiac adverse events or death were reported. The validity of these results, particularly with relevance to the secondary endpoints, has generated a flurry of controversy.

The opponents of nitrous oxide use have enthusiastically endorsed these results as definitive evidence to abandon its use. This view is inappropriate for a number of reasons. The chief reason is that the primary endpoint of the study showed no difference between the two groups. Presumably this endpoint was selected as a composite endpoint to reflect significant postoperative adverse events, and was adequately powered to detect significant differences. The fact that no difference could be demonstrated can thus be seen, as one correspondent put it, “as additional evidence of the remarkable safety of nitrous oxide over the past 150 years”.<sup>3</sup>

In addition, results of the secondary endpoints must be viewed with suspicion. As even the authors of ENIGMA noted, they “undertook multiple comparisons, which increases the chance of a type I error; the secondary, exploratory, and subgroup analyses should be treated cautiously.”

Other criticisms of ENIGMA include the choice of 80%  $O_2$ /20%  $N_2$  as a control group. It has frequently been asked if there is a difference between the groups due to a nitrous oxide effect, or an oxygen

effect. Although academically interesting, I don't think this issue discredits the study. It simply means that, if we believe there is a difference between the groups, it could be due to avoidance of nitrous oxide or use of a high inspired concentration of oxygen. It may be useful to know which of these it is but, as a high  $\text{FiO}_2$  would be impossible to achieve with the use of nitrous oxide, for our purposes it makes little practical difference.

A more important factor to take into account is that the depth of anaesthesia between the two groups was not equivalent. The median end-tidal agent concentration in the nitrous oxide-free group was 0.87 MAC, while in the nitrous oxide group the total was 1.31 MAC. Monk et al showed that cumulative deep hypnotic time was an independent predictor of postoperative mortality.<sup>4</sup> The difference in depth of anaesthesia between the two groups casts significant doubt on the validity of the findings of the study.

In addition, due to the pragmatic nature of the study, other confounding variables may not have been adequately accounted or controlled for. For example, the nitrous oxide-free group received significantly more propofol. It's not possible to say whether this affected the PONV results, particularly, or any other outcomes.

The authors of ENIGMA have also been accused of bias against nitrous oxide. They appear to have highlighted the adverse secondary outcomes over the neutral primary outcome. And, finally, the study was not blinded.

It should also be highlighted that ENIGMA included only patients undergoing major surgery predicted to last longer than 2 hours. This represents only a proportion of surgical procedures, and a group of patients at particular risk of adverse peri-operative outcomes at that.

As a final word on ENIGMA, clinical practice should generally not be altered on the outcomes of a single study. This is especially true when decisions are based on secondary outcomes of doubtful validity.

In response to these concerns, ENIGMA II commenced enrolment in 2007.<sup>5</sup> This study aims to recruit 7 000 patients at risk of coronary artery disease, undergoing non-cardiac surgery, to test the hypothesis that omitting nitrous oxide will reduce the incidence of death and major adverse cardiac events. A key difference versus ENIGMA is that the control group will now use a 70%  $\text{N}_2$ / 30%  $\text{O}_2$  mix to avoid the possible confounding effect of the high  $\text{FiO}_2$  in ENIGMA. Thus

far, 2 367 patients have been randomised, and we eagerly await the results of this study.

The claimed risk and benefits of nitrous oxide will now be evaluated individually.

### *Haematological effects*

On any list of nitrous oxide-related adverse effects, haematological complications feature prominently. These are secondary to methionine synthase inhibition and include bone marrow depression, megaloblastic changes, megaloblastic anaemia, leukopenia, thrombocytopenia, and agranulocytosis.

It appears that prolonged exposure, of at least 12 - 24 hours, is required to cause significant megaloblastic bone marrow changes in healthy patients. Of more concern are studies pointing to the development of these changes after relatively short periods in certain vulnerable groups. One such trial described the presence of megaloblastic bone marrow changes in critically ill patients. 18 of 22 patients with megaloblastic changes had been administered a nitrous oxide-based anaesthetic for at least 2 - 6 hours. However, four patients with megaloblastic changes had not received nitrous oxide.

In another study, the results of nitrous oxide exposure in 69 elderly patients undergoing eye surgery were examined. The investigators noted that patients exposed to nitrous oxide exhibited decreased serum folate levels and increased mean red cell volume. No significant differences in red cell folate, haematocrit and haemoglobin levels were found between the nitrous oxide and nitrous oxide-free groups. Three patients exposed to nitrous oxide developed symptoms suggestive of folate deficiency, which responded to folate therapy. It appears that these megaloblastic changes may resolve as early as 12 hours after cessation of the exposure, and can be avoided by pre-operative folate or  $\text{B}_{12}$  supplementation. The clinical implications of these haematological changes, when they do occur, are not clear, but there is little evidence to suggest that these contribute directly to adverse outcomes.<sup>6, 7, 8, 9, 10</sup>

In conclusion, it appears that the haematological effects of nitrous oxide exposure have been overstated. Healthy patients should safely tolerate exposure times of 12 hours or longer. It does seem prudent, however, to exercise more caution with patients at risk of  $\text{B}_{12}$  or folate deficiency if lengthy procedures (longer than 2 hours) are planned. These risk groups include the elderly, critically ill, or malnourished. Ideally these patients should be tested to identify those truly

**Table I:** Claimed risks and benefits associated with nitrous oxide administration.

	Claimed risks	Claimed benefits
<b>Haematological</b>	Bone marrow suppression and megaloblastic anaemia	
<b>Immunological</b>	Immunosuppression Increased infectious complications	
<b>Neurological</b>	Neurotoxicity Myelinopathies Intracranial dynamics Postoperative cognitive dysfunction	Neuroprotection Improved cerebral blood flow
<b>Cardiovascular system</b>	Endothelial dysfunction Thromboembolism Myocardial ischaemia Sympathetic stimulation Myocardial depression Pulmonary vasoconstriction	Haemodynamic stability Improved vasoreactivity
<b>Respiratory</b>	Hypoxia Atelectasis	Reduced respiratory depression Improved oxygenation
<b>PONV</b>		
<b>Expansion of air-filled spaces</b>	Bowel Pneumothorax Pulmonary bullae Pneumocephalus Venous air embolism Middle ear Intraocular Cuff	
<b>Teratogenicity Foetotoxicity</b>		
<b>Occupational</b>	Reproductive Genotoxicity Neurological Haematological	
<b>Environmental</b>		
<b>Awareness</b>		
<b>Anaesthetic-sparing</b>		Volatiles Opioids Muscle relaxants
<b>Cost effective</b>		
<b>Induction</b>		Faster Smoother Fewer adverse events
<b>Emergence</b>		Rapid
<b>Miscellaneous</b>		Simple to use Extensive experience Familiarity Established safety profile

deficient in B<sub>12</sub> or folate, but if this is impractical or too costly, empirical peri-operative B<sub>12</sub> and folate supplementation is simple, safe and cost effective.

#### *Immunological effects*

Immunosuppression is another well known adverse effect of nitrous oxide.<sup>6, 7, 8, 9, 10</sup> In addition to the theoretical risk of leukopenia or granulocytopenia from bone marrow suppression, a number of in vitro studies have fuelled these immunological concerns. These have reported reduced neutrophil

chemotaxis, reduced mononuclear proliferation, impaired cell-mediated cytotoxicity, and reduced alveolar macrophage activity. In contrast, unaltered and increased neutrophil chemotaxis have also been reported. In addition, impaired methionine production may impair protein synthesis and thus wound healing.

Again, the clinical impact of the laboratory data is not clear. The results of ENIGMA have been discussed in some detail already. Although the apparent increased incidence of wound sepsis and pneumonia in the nitrous oxide group is of concern, these results

must be viewed with circumspection. In contrast to ENIGMA, Fleischmann et al reported on the effect of nitrous oxide on wound infection in colonic surgery patients<sup>11</sup>. 418 patients were randomised to receive either 65% N<sub>2</sub>O or 65% N<sub>2</sub>. The rate of wound infection in the N<sub>2</sub>O group (15%) did not differ significantly from that in the N<sub>2</sub> group (20%). Other studies have pointed to a possible reduction in wound infection with the use of high inspired oxygen concentrations. The validity of these results and required inspired concentration is still a topic of debate.

In summary, surgery and anaesthesia impair immune function, irrespective of the anaesthetic agents used, with no real evidence to support one agent over the other. It is likely that attention to temperature control, prophylactic antibiotics, glycaemic control, and respiratory hygiene is more likely to influence the risk of peri-operative infectious complications than the choice of anaesthetic agent.

#### *Neurological effects*

The effects of nitrous oxide on the nervous system have generated more controversy and comment than probably any other characteristic of this agent. Many of the debates are still ongoing, but some clarity appears to be emerging from the confusion.

#### *Myelinopathies*

Nitrous oxide has been well documented as a cause of myelinopathies.<sup>6, 13, 14, 15</sup> The presentation may range from the classic subacute combined degeneration of the cord, to any combination of mental state abnormalities, seizures, paraesthesias/dysaesthesias, weakness, or spasticity. This form of toxicity appears to be directly related to inhibition of methionine synthase.

These effects are classically described in nitrous oxide abusers or patients who received long-term nitrous oxide sedation in the ICU.<sup>6, 14</sup> Case reports do exist of neuropathies following routine nitrous oxide exposure in patients with vitamin B<sub>12</sub> or folate deficiency.<sup>6, 13, 14, 15</sup> These cases appear to respond to well appropriate supplementation.<sup>15</sup> Therefore, a high index of suspicion for B<sub>12</sub> or folate deficiency, and a low threshold for B<sub>12</sub> and folate pre-treatment or therapy, should essentially abolish this small risk. Folate supplementation should never be given in isolation, as it may worsen neurological injury in patients with an unrecognised B<sub>12</sub> deficiency.<sup>6</sup>

There are case reports of severe adverse neurological outcomes in patients with rare congenital abnormalities

of B<sub>12</sub> or folate metabolism, for example methylene tetrahydrofolate reductase (MTHFR) deficiency.<sup>6,12,15</sup> These disorders are extremely rare and unlikely to be more common than an idiosyncratic reaction to any other drug, or an adverse effect such as malignant hyperthermia associated with the volatiles. This should not affect the use of nitrous oxide in the paediatric population. Again, though, common sense, a high index of suspicion in any child with unexplained neurological symptoms, and a low threshold for investigation and treatment of any unexplained postoperative neurological symptoms should allow for appropriate management of these rare cases.

#### *Neurotoxicity and neuroprotection*

An area of great controversy is whether nitrous oxide is neurotoxic or, in fact, neuroprotective.

Focusing first on hypoxic-ischaemic or excitotoxic injury, selective NMDA-receptor antagonists have been shown experimentally to exacerbate neuronal injury. Nitrous oxide itself has been shown to impair electrophysiological recovery from hypoxic injury in the rat brain.<sup>8</sup> In addition, it has been found that cerebral injury in a model of near-complete ischaemia was worse in nitrous oxide/fentanyl-exposed rats and ketamine-exposed rats versus those anaesthetised with isoflurane. No difference was found with incomplete ischaemia, however.<sup>16</sup> Other studies have shown morphological changes consistent with neurotoxicity in rat cortices after nitrous oxide exposure. However, these changes only occurred with hyperbaric exposure to nitrous oxide and resolved within 3 hours.<sup>6</sup> In addition, further studies have shown that coadministration of a GABAergic agent, for example a volatile or propofol, as occurs in clinical practice, can prevent these changes.<sup>6,8</sup>

To further complicate matters, it is well known that excessive stimulation of the NMDA receptors by glutamate leads to an excessive neuronal calcium load. This may lead to neuronal injury or death, especially if cellular energy stores are depleted, as with ischaemia. Thus, NMDA-receptor inhibition may actually be neuroprotective. It has been shown that nitrous oxide reduced the injury associated with intracerebral NMDA injection and reduced infarct volume after middle cerebral artery occlusion in rats.<sup>17</sup>

The effect of nitrous oxide on dopamine release may also play a role in its neurotoxic/neuroprotective effect. Some studies show nitrous oxide increases dopamine release, with haloperidol, a dopamine antagonist, protecting against the subsequent neurotoxicity.<sup>6</sup> In contrast, others showed that nitrous oxide resulted

in less dopamine release after oxygen-glucose deprivation in a rat-brain model.

The neurobiological and animal data are thus inconsistent and often contradictory. The best available clinical data in humans come from a study by Pasternak et al.<sup>18</sup> This study was a post hoc analysis of a subset of data from the Intra-operative Hypothermia for Aneurysm Surgery Trial (IHAST). A previous report had shown no adverse effects of nitrous oxide on outcomes in the full cohort of IHAST patients. In fact, there was a trend to improved three month neurological outcome, and more patients were discharged home (vs. a long-term care centre) in the nitrous oxide group.<sup>18, 19, 20</sup> As a result of vocal opposition to the use of nitrous oxide in patients with, or at risk of, ischaemic brain injury, the authors decided to perform a further analysis on the IHAST patients at greatest risk of ischaemic cerebral injury: those who underwent temporary cerebral artery clipping. It was felt that, if nitrous oxide did adversely influence outcome, it would be apparent in this group. In fact, the study showed that nitrous oxide had no detrimental effect on long-term gross neurologic or neuropsychological function. Although there was an initial increase in delayed ischaemic neurological deficits in the nitrous oxide group, there was a significantly decreased risk of impairment in one or more neuropsychological tests at 3 months.

Although this study has the flaws inherent in any post hoc analysis, the large sample size and the quality of the IHAST database makes this the best available evidence on the use of nitrous oxide in neurosurgery, and in particular in patients at risk of cerebral ischaemia. It is unlikely that a larger study will be undertaken in this population any time soon. Thus, the conclusion from the original analysis that “nitrous oxide is unlikely to lead to adverse neurological... outcomes in neurosurgical patients at risk of cerebral ischaemia” remains the final word for the foreseeable future.

#### *Neurodevelopment*

Concerns about the possible adverse neurodevelopmental effects of nitrous oxide have also been raised, and this has created much alarm amongst paediatric anaesthetists. NMDA-receptor antagonists were initially thought to cause widespread neuronal apoptosis in neonatal rats.

Subsequently it was shown that nitrous oxide, on its own and up to a concentration of 75%, does not have this effect. It does, however, appear to worsen isoflurane-induced neurodegenerative changes, with

the combination of nitrous oxide, midazolam and isoflurane resulting in widespread apoptosis and learning impairment after 6 hours of exposure in 7-day-old rats.<sup>6,21</sup> In contrast, Slikker et al showed that 3 hours of exposure to ketamine (an NMDA-This study mimics clinical paediatric anaesthesia more closely than the other studies mentioned above.

These findings must be put into perspective. Practically every anaesthetic agent has been shown to cause neurodegenerative changes in some animal model. The extrapolation of animal studies to humans is fraught with difficulty. As an example, synaptogenesis lasts from two days before to two weeks after birth in rats. In humans, however, the equivalent period spans from the last trimester of pregnancy to the first few years of life. A six-hour anaesthetic in a seven-day-old rat equates roughly with a few days of anaesthesia in a human infant. Other sources suggest that the vulnerable period for rats and monkeys, actually, more closely correlates with the 22<sup>nd</sup> to 26<sup>th</sup> weeks of human gestation.<sup>22</sup> In addition, it is not known if the apoptosis shown in these studies is pathological, or is merely an acceleration of the apoptosis that is essential for normal brain development. Furthermore, there is no clinical evidence linking nitrous oxide specifically to any adverse neurodevelopmental outcomes in humans. There is a potential link to anaesthesia in general, but these studies are heavily flawed. If anything, they suggest that only a very small number of individuals who have an anaesthetic exposure early in life may be susceptible to anaesthesia-induced neurodevelopmental problems.<sup>22</sup> It must be emphasised that these studies focus on anaesthesia in general, and not nitrous oxide specifically.

In summary, there is no current evidence to suggest any adverse neurodevelopmental effects in routine clinical practice.

#### *Postoperative cognitive dysfunction*

Nitrous oxide has also been linked to postoperative cognitive dysfunction (POCD) in rat models.<sup>23</sup> Clinical trials could not prove this. The available evidence suggests that POCD results from a neuro-inflammatory response to surgery, and that the choice of anaesthetic plays little role in its development.<sup>6</sup>

#### *Intracranial dynamics*

With regard to intracranial dynamics, nitrous oxide is widely believed to increase cerebral metabolic rate (CMRO<sub>2</sub>); cerebral blood flow (CBF) and thus cerebral blood volume (CBV) and intracranial pressure (ICP); and impair autoregulation. The increase in CBF

appears to be a result of an indirect vasodilatory effect secondary to the increased  $CMRO_2$ . Some sources, however, state that the increased CBF is independent of cerebral metabolic rate.<sup>8</sup> The specifics and clinical implications are, however, more complex.

Nitrous oxide has been shown to increase CBF or its surrogate, cerebral blood flow velocity (CBFV), when added to isoflurane and propofol; to decrease CBF when added to 1 MAC sevoflurane; and to have no effect with 1 MAC desflurane.<sup>16, 24</sup>

It impairs autoregulation when used on its own and when added to 1 MAC sevoflurane, but not when added to propofol or 1.5 MAC sevoflurane.<sup>25</sup>

Carbon dioxide reactivity appears to be preserved when used with both volatiles and propofol.<sup>25</sup>

These studies have raised a number of issues. Is there a dose-response relationship for the effects of nitrous oxide on cerebral dynamics? A variety of inhaled concentrations of nitrous oxide were used in these studies but none have addressed this question. Are some combinations (e.g. nitrous oxide and propofol) superior to others? It appears that the effects of nitrous oxide differ according to the agents with which it is co-administered. However, we simply do not know for certain.

In addition, the effects on CBF, CBV, and ICP are mild and, as  $CO_2$  reactivity is preserved, any increase in these parameters can be readily offset with mild hypocapnia.<sup>16, 25</sup> It should be noted, though, that the effect of hypocapnia is abolished if nitrous oxide is added after the induction of hypocapnia.<sup>25</sup>

It is also worth considering that nitrous oxide was added to 1 MAC (and above) of a volatile. I don't believe that this reflects best clinical practice, and probably defeats the purpose of using nitrous oxide. In any case, when one administers greater than 1 MAC of a volatile, the adverse effects of the volatiles on intracranial dynamics begin to predominate. It has been reported that, if a patient is lightly anaesthetised, the addition of nitrous oxide may actually depress cerebral metabolism and reduce CBF. Again this suggests that, if used appropriately, nitrous oxide does not cause the adverse effects commonly stated.<sup>25</sup>

It has been reported in a clinical trial setting that two nitrous oxide-based anaesthetic techniques resulted in good surgical conditions in patients undergoing supratentorial brain tumour surgery. This was despite many of the patients having significant midline shift.<sup>16</sup>

To further complicate matters, Hancock et al reported on the effects of nitrous oxide on zero flow pressure (ZFP) and cerebral perfusion pressure (CPP).<sup>26</sup> CPP, the driving pressure in the cerebral circulation, is essentially the difference between upstream and downstream pressure. Traditionally, CPP is thought of as being equal to mean arterial pressure (MAP) minus ICP or central venous pressure (CVP), whichever is higher. Vascular tone is, however, a potentially significant, previously ignored, determinant of the downstream pressure. The ZFP is the arterial pressure at which cerebral blood flow would cease, and reflects the interaction between ICP, CVP, and vascular tone, with vascular tone actually being the primary determinant. It thus represents a more accurate means of describing the downstream pressure. Hancock found that 50%  $N_2O$  reduced ZFP and increased CPP during normocapnia. The implication is that, although nitrous oxide-induced cerebral vasodilation increased CBV, the effect on ZFP dominated and resulted in a net increase in CPP. This study is limited by the fact that it only included subjects with normal intracranial compliance. Although the results, as they stand, cannot be extrapolated to routine clinical practice and patients with reduced intracranial compliance, it is an interesting alternative perspective to the traditional views on intracranial dynamics.

Thus, although complex and incompletely elucidated, it appears that the effects of nitrous oxide on intracranial dynamics are, at most, mild and are easily managed with mild hypocapnia. To err on the side of caution, it is probably best to avoid nitrous oxide in patients with severe, acute elevations of ICP, for example severe traumatic brain injury. This decision is based purely in the absence of definitive proof of safety in this population, and with misgivings about the volatiles and IV agents as well. Paying attention to systemic haemodynamics, and avoiding secondary insults, is probably more important than the choice of anaesthetic agent.

The haemodynamic stability of nitrous oxide deserves a mention in this context. Episodes of hypotension have been shown to correlate with adverse neurological outcomes in patients with head injury.<sup>27</sup> Nitrous oxide is less likely to cause hypotension than other anaesthetic agents, for example propofol, isoflurane and remifentanyl, and allows dose reduction of these agents. It is unlikely to be tested, but this may theoretically contribute to improved neurological outcomes in vulnerable neurosurgical patients.

The easy titratability and rapid offset of nitrous oxide are also valued during neurosurgical procedures. It must be emphasised that, used appropriately, nitrous

oxide is unlikely to cause any adverse effects in the neurosurgical population.

### Cardiovascular effects

The cardiovascular effects of nitrous oxide are an exciting area of debate and research, with much controversy and conflicting results regarding the actual balance between the purported risks and benefits.

Nitrous oxide is often thought to have little overall effect on cardiovascular physiology. This applies to both healthy adults and children.<sup>10</sup> Constant et al reported that 50% N<sub>2</sub>O in children had no effect on mean arterial pressure, systolic pressure variation, and baroreceptor sensitivity. It did decrease heart rate variability, with a shift to parasympathetic dominance, but there was a rapid return to baseline after stopping the agent<sup>13</sup>.

Although the direct effect on the heart is mild negative inotropy, this is generally offset by increased sympathetic activity.<sup>8</sup> Kawamura et al reported that 60% N<sub>2</sub>O increases cardiac output during the first hour of administration, with the cardiac output returning towards baseline during the second hour.<sup>28</sup> This suggests that the cardiovascular stimulation may be transient.

Sympathetic activation also results in vasoconstriction, most likely via  $\alpha$ -adrenergic stimulation. This has a greater effect on the pulmonary vasculature, resulting in elevated pulmonary vascular resistance and an increase in pulmonary artery pressure.<sup>10</sup> Pre-existing pulmonary hypertension is thus a relative contraindication to nitrous oxide, as it may aggravate the pulmonary hypertension and cause right ventricular afterload. This effect is at least partially counteracted by the increased right ventricular function secondary to sympathetic activation.<sup>7</sup>

The stimulatory effects of nitrous oxide may be obtunded by high-dose opioids, unmasking the direct depressant effects.<sup>7, 8</sup> This may also occur in patients with severe left ventricular dysfunction or pre-existing marked sympathetic activation.<sup>10</sup> This has led some authors to recommend the use of great caution when using nitrous oxide in patients with cardiovascular risk factors, or severe underlying cardiovascular disease with increased peripheral vascular resistance or impaired cardiac function.<sup>10</sup>

It has also been reported that the sympathetic activation may sensitise the myocardium to the arrhythmogenic effects of catecholamines.

These haemodynamic criticisms are probably exaggerated and represent a narrow view of the effects of nitrous oxide in isolation because, in comparison to other anaesthetic agents, nitrous oxide appears to actually promote haemodynamic stability.

Cardiovascular depression is particularly noticeable with > 1 MAC of the volatiles, and throughout the concentration range with propofol infusions.<sup>51</sup> However, it was reported that 65% N<sub>2</sub>O, combined with either isoflurane or sevoflurane, produced less hypotension than equi-MAC concentrations of the volatiles alone.<sup>9</sup> McKinney et al also reported that, in elderly patients, a 50% N<sub>2</sub>O/isoflurane mix produced less cardiovascular depression than 1 MAC isoflurane alone.<sup>8, 29</sup> Separately, it was shown that adding 70% N<sub>2</sub>O to increasing target concentrations of propofol did not cause any effect on the blood pressure until the target concentration was over 5  $\mu$ g/ml.<sup>9</sup> Others are of the opinion that these haemodynamic benefits are especially important if cardiovascular reserve is reduced, whether from age, pathology or medication.<sup>9</sup> As an example, the hypotensive effects of the volatiles and propofol are potentiated by calcium channel blockers, as they all inhibit myocardial and smooth muscle calcium channels. Nitrous oxide does not affect these channels, and therefore causes no additional cardiovascular depression in patients on calcium channel blockers.

The significance of the improved intra-operative haemodynamic stability is not known. It has been found that high risk patients with sustained ( $\geq$  10 minutes) intra-operative hypotension (MAP < 50 mmHg or a decrease in MAP by  $\geq$  40%) were significantly more likely to experience adverse cardiac events.<sup>30</sup> As nitrous oxide may allow improved intra-operative stability, while still allowing adequate depth of anaesthesia, its use could theoretically improve postoperative outcomes. This is purely conjecture as there is uncertainty whether this will actually improve outcome. It is, however, an exciting potential benefit that must be investigated further, particularly in high risk patients.<sup>31</sup>

Interestingly, Samarska et al found that nitrous oxide use attenuated shock-induced changes in vascular reactivity.<sup>32</sup> They examined mice anaesthetised with either 1.4% isoflurane alone, or 1.4% isoflurane and 66% nitrous oxide. Haemorrhagic shock was induced by venesectioning the mice, with subsequent fluid resuscitation. It was found that administration of nitrous oxide during the shock phase prevented vasomotor dysfunction during the post-shock period. It is thought that post-shock vascular hyporeactivity may lead to organ hypoperfusion and multiple organ

dysfunction syndrome. The volatiles also interfere with vasoresponsiveness and, thus, may lead to, or aggravate, organ hypoperfusion. The authors suggested that nitrous oxide offsets the haemodynamic effects of the volatiles, and prevents shock-induced vascular hyporeactivity, by preventing shock-induced decreases in vascular COX-1 expression. COX-1 appears to be important in endothelial production of contractile prostaglandins.

This study raises the interesting prospect that the choice of anaesthetic, in particular the use of nitrous oxide, may improve postoperative outcomes, especially in trauma surgery and other major procedures, by influencing post-surgical vascular reactivity.

This was, of course, only an animal study and it did not look at clinical outcomes, but it is an exciting finding that should be explored in human clinical trials.

Against these largely positive cardiovascular effects must be balanced nitrous oxide effect on homocysteine, and a possible increased incidence of peri-operative myocardial ischaemia.

A number of investigators have reported postoperative increases in plasma homocysteine in patients exposed to nitrous oxide.<sup>7, 30, 33</sup> These elevated levels appear to persist for at least a week.<sup>7</sup> As mentioned previously, acute elevations in homocysteine may lead to endothelial dysfunction and hypercoagulability (via activation of factor V, inhibition of protein C and increased platelet aggregation).<sup>33</sup> The extent of the endothelial dysfunction seems to correlate with the duration of nitrous oxide exposure.<sup>33</sup> Chronic hyperhomocysteinaemia appears to be a risk factor for coronary artery and cerebrovascular disease, but the acute effects in this regard are not known.

Concerns have consequently been raised that nitrous oxide use may be a risk factor for peri-operative myocardial ischaemia.

Badner et al reported on 90 patients undergoing carotid endarterectomy, randomly assigned to receive either isoflurane alone or isoflurane and > 50% N<sub>2</sub>O.<sup>30</sup> The patients in the nitrous oxide group were found to have a significantly higher incidence of postoperative myocardial ischaemia, more ischaemic events, and also more ischaemic events of ≥ 30 minutes duration. There was no difference in patients with ≥ 2 hours cumulative postoperative ischaemia, and no difference in intra-operative ischaemia. Intra-operative haemodynamics did not differ between the groups, but the isoflurane-only group were administered significantly more phenylephrine. The end-tidal

isoflurane concentrations differed by only 0.19% between the groups, suggesting that the depth of anaesthesia was not equivalent between the groups. Another interesting finding is that, although N<sub>2</sub>O has a relative risk for postoperative myocardial ischaemia of 2.0, the relative risk for isoflurane concentrations of > 0.7% is 1.4. This suggests that the difference in outcomes may be related to depth of anaesthesia and not necessarily anaesthetic agent. Even if the results are taken at face value, there are a number of questions regarding their actual significance.

While it has been found that episodes of ischaemia ≥ 30 minutes correlated with adverse outcomes, other investigators found a correlation with cumulative ischaemia of 2 hours or more. Where does this study leave us, with more episodes of ischaemia of ≥ 30 minutes but no significant difference in those ≥ 2 hours? We simply do not know. Another factor to consider is that myocardial ischaemia is only a surrogate marker and we have no idea, from this study, of the effect of nitrous oxide on any clinical cardiac outcomes.

It is often quoted that, in ENIGMA, the incidence of myocardial infarction was 0.7% in the N<sub>2</sub>O-free group versus 1.3% in the nitrous oxide group. This was not, however statistically significant.

Other investigators found that, although nitrous oxide increased the risk of intra-operative ischaemia, there was no difference in postoperative ischaemia.<sup>30</sup>

In contrast to the above results, it has separately been shown that nitrous oxide does not induce myocardial ischaemia in patients with ischaemic heart disease, with or without left ventricular dysfunction.<sup>30</sup>

In one trial, the investigators randomised 70 patients undergoing carotid artery surgery to receive either isoflurane alone or isoflurane and 60% N<sub>2</sub>O. Although they found no significant difference in intra-operative and postoperative myocardial ischaemia/infarction, there was a trend towards a lower incidence of intra-operative ischaemia and postoperative infarction in the nitrous oxide group.<sup>30</sup>

Another factor to consider is that postoperative increases in homocysteine can be prevented by vitamin B<sub>12</sub> supplementation prior to surgery. This implies that, if nitrous oxide does increase the risk of peri-operative myocardial ischaemia as a result of elevated homocysteine, this can easily be prevented by peri-operative B<sub>12</sub> supplementation.<sup>9</sup>

We are thus left with a rather interesting dilemma when administering nitrous oxide. On the one hand, there is



improved haemodynamic stability and preservation of vascular reactivity. Against this must be balanced the possible increased risk of peri-operative myocardial ischaemia. Identifying which side of the risk-benefit ratio the scales are tipped is of particular importance in those at high cardiac risk. Based on available evidence, I am of the opinion that nitrous oxide use is of cardiovascular benefit if used optimally and with a low threshold for B-vitamin supplementation. This applies particularly to the patient with cardiovascular risk factors undergoing major non-cardiac surgery. In future, our decision making may be refined by the use of biomarkers and genetic profiling. As with any intervention, we are most likely to see positive results if we tailor care to the individual patient.

### *Respiratory effects*

The respiratory effects of nitrous oxide are complex, which include diffusion hypoxia. As mentioned earlier, this is overemphasised as an adverse effect of nitrous oxide, and is easily preventable. In patients without significant cardiorespiratory disease, routine use of supplemental oxygen is not required in the recovery room, even if N<sub>2</sub>O has been used.<sup>24</sup> Also on the negative side, nitrous oxide has been reported to blunt the hypoxic respiratory drive, even at low concentrations. All anaesthetic agents exhibit this effect to some degree though. Due to its rapid removal following cessation of delivery, this is unlikely to be clinically significant with nitrous oxide postoperatively. Nitrous oxide may lead to absorption atelectasis as readily as high inspired oxygen concentrations.<sup>14</sup> The evidence that this leads to significant postoperative atelectasis/ postoperative pulmonary complication is not convincing.

In favour of nitrous oxide is the improvement in arterial oxygenation due to its persisting concentrating and second gas effects. Peyton et al showed that this effect improves oxygenation despite the competing effect of absorption atelectasis.<sup>34</sup> This may not be too important clinically, but does show that absorption atelectasis is probably not a significant concern with nitrous oxide.

Also on the positive side, nitrous oxide causes less respiratory depression than the volatile agents.<sup>13, 14</sup> Nitrous oxide/volatile mixtures have been shown to reduce the ventilatory depression associated with the administration of equipotent concentrations of a volatile alone. This occurs with halothane, isoflurane and sevoflurane. Einarsson et al demonstrated the practical advantages of this effect.<sup>14</sup> They randomised patients undergoing abdominal hysterectomy to receive either 1.3 MAC sevoflurane or an equi-MAC

sevoflurane/65% N<sub>2</sub>O mix. The sevoflurane/N<sub>2</sub>O group resumed spontaneous breathing 8 minutes earlier than the sevoflurane-only group and was extubated 13 minutes earlier; both statistically significant differences. These findings were obtained in the context of a rigid trial protocol, and more rapid times to spontaneous breathing and extubation can be obtained in the "real-world" setting. The study does, however, demonstrate quite elegantly one of the benefits of nitrous oxide that can be exploited clinically.

In summary, the respiratory benefits of nitrous oxide outweigh the disadvantages.

### *Post-operative nausea and vomiting*

Nitrous oxide is a risk factor for PONV. However, the full story is far more complex. Firstly, there is a dose-dependent, and not all-or-nothing, effect on PONV.<sup>35</sup> Secondly, the effect of nitrous oxide on PONV has probably been overemphasised.

Apfel et al showed that the antiemetics ondansetron, dexamethasone and droperidol each reduced the risk of PONV by 26%, and administering propofol versus a volatile reduced the risk by 19%. Omitting nitrous oxide only reduced the risk by 12%.<sup>36</sup> While nitrous oxide, the volatiles and opioids are all risk factors for PONV, the only anaesthesia-related risk factors included in current scoring systems are the volatiles (isoflurane) and postoperative opioids.<sup>37</sup> In another study, it was reported that the omission of nitrous oxide had no significant effect on the complete control of PONV, with only a reduction in postoperative vomiting in high-risk patients thought to be significant. It was noted that, because of the increased risk of awareness, the potential risk for harm from omitting nitrous oxide negated any possible benefit on PONV.<sup>29</sup>

In an elegant review, Apfel et al put the role of N<sub>2</sub>O in PONV in perspective.<sup>38</sup> Since propofol TIVA (avoiding nitrous oxide and volatiles) only reduces the incidence of PONV by 20 - 25%, inhaled agents are clearly not the most important risk factors for PONV. In addition, while volatiles increase the risk two- to three-fold in the first 24 hours, nitrous oxide has a relative risk of only 1.3. Peri-operative opioids are probably of greater importance. Since omitting both volatiles and nitrous oxide is only as effective as using a single prophylactic antiemetic, omitting nitrous oxide (or volatiles) is unlikely to have any additional effect when appropriate prophylactic antiemetics are used.<sup>38, 39</sup> It appears that, in this case, another adverse effect has been overstated.

## Conclusion

It is becoming clear that many of the adverse effects of nitrous oxide have been overstated. ENIGMA, far from sounding the death knell for nitrous oxide, actually provides further evidence in support of its relative safety. Nitrous oxide appears to be largely free from haematological, immunological, neurological, respiratory and cardiovascular adverse effects, and the effect on PONV is relatively minor. In addition, there are a number of attractive benefits that are often ignored or have not been fully elucidated. In the third part of this series, the remaining claimed risks and benefits of nitrous oxide (see Table I) will be discussed, alternatives to nitrous oxide will be explored, and the evidence presented in the series will be summarised.

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