Haemodynamic comparison of sevoflurane and isoflurane anaesthesia in surgical patients

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Purpose: To compare the haemodynamic responses to surgical incision during sevoflurane and isoflurane anaesthesia and to compare the haemodynamic effects of each anaesthetic alone with those obtained using an equipotent mixture of each anaesthetic plus N₂O during steady-state surgical stimulation.

Methods: Twenty-four patients undergoing gastrectomy were randomized to receive sevoflurane (n = 12) or isoflurane (n = 12). At 1.5 MAC, haemodynamic measurements were performed before and after surgical incision. During intestinal anastomosis, patients in each group were given (in random order) either 1.5 MAC of the designated anaesthetic or 0.85 MAC of the volatile plus 0.65 MAC N₂O. Haemodynamic measurements were repeated under each condition.

Results: One patient in the sevoflurane group and two in the isoflurane group were excluded from the incision study because of hypotension. In both groups, incision increased the heart rate (HR), mean arterial pressure, mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac index, and systemic vascular resistance index (SVRI). There were no intergroup differences in the effects of incision. Inclusion of N₂O resulted in an increase of MPAP (P < 0.05) in both groups, an increase of central venous pressure and PCWP in the sevoflurane group (P < 0.005), and a decrease of HR (P < 0.005) and an increase of SVRI (P < 0.05) in the isoflurane group. There were no intergroup differences in the effects of N₂O.

Conclusions: At 1.5 MAC, sevoflurane and isoflurane do not prevent the haemodynamic response to incision. The haemodynamic effects of each volatile anaesthetic with N₂O are minimal compared with those of equi-MAC volatile alone.

Objectifs : Comparer les réponses hémodynamiques à l'incision chirurgicale pendant l'anesthésie au sévoflurane et à l'isoflurane; comparer les effets hémodynamiques de chacun de ces anesthésiques seuls avec ceux d'un mélange équipotent de chacun associé au N₂O pendant une stimulation chirurgicale une fois l'état d'équilibre atteint.

Méthodes : Vingt-quatre patients subissant une gastrectomie étaient répartis aléatoirement pour recevoir du sévoflurane (n = 12) ou de l'isoflurane (n = 12). À 1,5 MAC, les mesures hémodynamiques étaient effectuées avant et après l'incision. Pendant l'anastomose intestinale, les patients de chaque groupe recevaient (de façon aléatoire) soit 1,5 MAC de l'agent désigné ou 0,85 MAC de l'agent volatil plus 0,65 MAC de N₂O. Les mesures hémodynamiques étaient alors répétées.

Résultats : Un patient du groupe sévoflurane et deux patients du groupe isoflurane ont été exclus parce qu'ils étaient hypotendus au moment de l'incision. Dans les deux groupes, l'incision a provoqué une accélération de la fréquence cardiaque (FC), une augmentation de la pression artérielle moyenne, de la pression artérielle pulmonaire moyenne (PAPM), de la pression capillaire bloquée (PCB), de l'index cardiaque et de la résistance vasculaire systémique indexée (RVSI). Il n'y avait pas de différences entre les groupes en ce qui concerne les effets de l'incision. L'ajout du N₂O a provoqué une augmentation de la PAPM, une augmentation de la tension veineuse centrale et de la PCB dans le groupe sévoflurane (P < 0,005) : une diminution de la FC (P < 0,005) et une augmentation de la RVSI (P < 0,05) dans le groupe isoflurane. Il n'y avait pas de différence entre les groupes au regard des effets du N₂O.

Conclusion : À 1,5 MAC, le sévoflurane et l'isoflurane n'influencent pas la réponse hémodynamique à l'incision. Les effets hémodynamiques de chacun des agents volatils associés au N₂O sont minimes comparativement à ceux des agents volatils seuls à concentrations équipotentes.

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THE haemodynamic effects of sevoflurane have been extensively studied in volunteers,¹ in patients without surgical stimulation,² and in the laboratory.^{3,4} However, clinicians are more interested in modification of the haemodynamic response to surgical stimulation by anaesthesia. Therefore, we investigated the capacity of sevoflurane to attenuate or abolish changes in haemodynamic variables induced by surgical incision. Similarly, a comparison of the cardiac haemodynamic effects of sevoflurane/nitrous oxide (N_2O) with those of sevoflurane alone has been performed in volunteers.¹ However, in surgical patients, the cardiovascular responses to sevoflurane (with or without N_2O) may be affected by ongoing surgical stimulation. Therefore, we also compared the haemodynamic effects of sevoflurane without N_2O to an equipotent mixture of sevoflurane plus N_2O during steady-state surgical stimulation. All data obtained with sevoflurane were compared to those obtained with isoflurane, which is currently the most widely used volatile anaesthetic.

Methods

With approval from the Hospital Ethics Committee and written informed consent from each subject, we studied 24 ASA Physical Status 1–2 patients undergoing elective total or subtotal gastrectomy. Exclusion criteria were cardiopulmonary disease (including hypertension) and diabetes mellitus. Patients were randomly assigned to receive either sevoflurane ($n = 12$) or isoflurane ($n = 12$).

Premedication comprised 20 mg famotidine and 0.125 mg triazolam *po* at bedtime before surgery, and 20 mg famotidine and 5 mg diazepam *po* 90 min before induction of anaesthesia. With all routine monitors in place (ECG, pulse oximeter, radial arterial catheter) and after a 10-min stabilization period, the baseline heart rate (HR) and mean arterial pressure (MAP) were recorded. Anaesthesia was induced with 3–4 mg·kg⁻¹ thiamylal, tracheal intubation was facilitated with 0.15 mg·kg⁻¹ vecuronium, and ventilation was controlled so as to maintain the $P_{ET}CO_2$ between 35 and 40 mmHg (BP 508, Nippon Colin, Japan). Anaesthesia was maintained with an end-tidal concentration of 1.5 minimum alveolar concentration (MAC) sevoflurane or isoflurane (Anaesthetic Gas Monitor AM-1, Acoma, Japan) in air/oxygen (32%). The MAC of sevoflurane was taken as 1.71%⁵ and that of isoflurane as 1.15%.⁶ An infusion of 10–15 ml·kg⁻¹·hr⁻¹ of warmed (about 37°C) lactated Ringer's solution was given until surgical incision was completed. After induction of anaesthesia, the right internal jugular vein was cannulated with a pulmonary artery

catheter (CCOM catheter, CO-CH1307 7F, TERUMO, Japan) and the positioning of its tip in the pulmonary artery was confirmed by the pressure waveform. Pressures were monitored using pressure transducers (Physiological pressure transducer, P 10 EZ, Ohmeda, USA) and a pressure monitor (BP 508, Nippon Colin, Japan). Subsequent muscle relaxation was obtained with vecuronium *iv* as necessary. The rectal temperature (RT) was also monitored.

Haemodynamic effects of surgical incision during sevoflurane or isoflurane anaesthesia

After at least 15 min stabilization with 1.5 MAC anaesthesia (end-tidal sevoflurane 2.6% or end-tidal isoflurane 1.7%, in air/oxygen (32%)), surgical incision was performed. If the MAP decreased to < 45 mmHg before incision, the anaesthetic concentration was decreased and the subject was excluded from the incision study. We chose this pressure level because it is the lower limit of MAP during deliberate hypotension.⁷ Just before and after incision, the HR, MAP, RT, central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) were measured. All haemodynamic measurements were performed at end-expiration. Thermodilution cardiac output was measured using a cardiac output computer (COMOCARDIO CO-203, TERUMO, Japan) at end-expiration with 10 ml of ice-cold dextrose 5% in water. Measurement was in triplicate before incision and only once (because of the rapid changes) after incision. Surgical incision was defined as dissection of the skin, subcutaneous tissue, and peritoneum. Neither abdominal retractor insertion nor intraperitoneal manipulation were performed until the measurements were completed. The cardiac index (CI), stroke volume index (SVI), pulmonary vascular resistance index (PVRI), and systemic vascular resistance index (SVRI) were calculated using standard formulae.

Haemodynamic effects of sevoflurane/ N_2O vs sevoflurane alone during steady-state surgical stimulation: comparison with isoflurane

After the incision study, patients in each group were further randomly allocated to a N_2O -first group or a N_2O -last group. In the N_2O -first group, subsequent anaesthesia was maintained with 0.65 MAC N_2O (BP 508, Nippon Colin, Japan) and sevoflurane or isoflurane, whereas the N_2O -last group received anaesthesia with sevoflurane or isoflurane in 32% air/oxygen. To obtain a steady state of surgical stimulation, we adopted the period of intestinal anastomosis, because the main surgical manipulation at this time is suturing. In addition, we confined measurements to the period of

manual suturing and did not obtain data until at least 10 min had elapsed. At least 10 min after the commencement of manually performed intestinal anastomosis and at least 15 min after the steady-state anaesthetic conditions of 1.5 MAC were achieved (0.85 end-tidal MAC of sevoflurane or isoflurane plus 0.65 end-tidal MAC N₂O for the N₂O-first group and 1.5 end-tidal MAC sevoflurane or isoflurane in 32% air/oxygen for the N₂O-last group), the HR, MAP, RT, CVP, MPAP, PCWP, and triplicate CO were measured. Then the anaesthesia was changed to 1.5 MAC sevoflurane or isoflurane in 32% air/oxygen in the N₂O-first group and to 0.85 MAC sevoflurane or isoflurane plus 0.65 MAC N₂O in the N₂O-last group. At least 15 min after a steady state of the respective anaesthetic conditions was achieved (manual intestinal anastomosis was ongoing for at least 10 min), the above measurements were repeated. The MAC of N₂O was taken as 104%⁸ and the MAC of sevoflurane or isoflurane was assumed to be additive to that of N₂O. Before intestinal anastomosis, normovolaemia was maintained with lactated Ringer's solution by observing the haemodynamic variables, and colloids and blood products were infused as required. During anastomosis, lactated Ringer's solution was administered at a rate of 8–10 ml·kg⁻¹·hr⁻¹ and no other fluids, including blood products, were given.

Data are expressed as the mean ± SD. The patient characteristics, baseline HR, baseline MAP, the induction dose of thiamylal, the time from induction of anaesthesia to incision, and the time from induction of anaesthesia to intestinal anastomosis were compared by Student's *t*-test. To determine the effects of the order of anaesthesia with N₂O, data obtained at comparable anaesthetic levels but at different times were compared using the Mann-Whitney *U* test. Other haemodynamic data were analyzed by two-way repeated-measures analysis of variance (ANOVA). *P* < 0.05 was taken to indicate statistical significance.

Results

The age, weight, height, sex, body surface area, baseline HR, baseline MAP, induction dose of thiamylal, time from induction to incision, and time from induction to intestinal anastomosis were comparable between the groups (Table).

One patient in the sevoflurane group and two patients in the isoflurane group did not tolerate the anaesthetic because of excessive hypotension (MAP < 45 mmHg). All other patients in both groups tolerated 1.5 MAC. For patients included in the analysis, the pre-incisional values of HR, MAP, MPAP, PCWP, CI, SVI, PVRI, and SVRI were not different between the

TABLE Patient characteristics, baseline heart rate (HR), baseline mean arterial pressure (MAP), the induction dose of thiamylal, the time from induction of anaesthesia to incision, and the time from induction of anaesthesia to intestinal anastomosis.

	Sevoflurane group (<i>n</i> = 12)[<i>n</i> = 11]	Isoflurane group (<i>n</i> = 12)[<i>n</i> = 10]
Age (yr)	60 ± 11 [59 ± 11]	59 ± 10 [58 ± 10]
Weight (kg)	52 ± 11 [52 ± 11]	57 ± 10 [58 ± 10]
Height (cm)	158 ± 11 [158 ± 11]	157 ± 7 [157 ± 9]
Sex (M:F)	8 : 4 [7 : 4]	7 : 5 [6 : 4]
Body surface area (m ²)	1.51 ± 0.20 [1.51 ± 0.21]	1.56 ± 0.14 [1.57 ± 0.14]
Baseline HR (beats·min ⁻¹)	74 ± 16 [76 ± 16]	74 ± 9 [72 ± 9]
Baseline MAP (mmHg)	100 ± 13 [102 ± 11]	100 ± 12 [101 ± 13]
Induction dose of thiamylal (mg·kg ⁻¹)	3.7 ± 0.4 [3.7 ± 0.4]	3.7 ± 0.4 [3.7 ± 0.4]
Time from induction to incision (min)	[31 ± 8]	[29 ± 8]
Time from induction to intestinal anastomosis (min)	71 ± 22	56 ± 20

Values are the mean ± SD or number. [] indicates data for excluded patients who became excessively hypotensive before surgical incision. There were no differences between the groups.

groups, but the CVP before incision was higher in the isoflurane group (*P* < 0.05) (Figure 1). In both groups, surgical incision increased the HR, MAP, MPAP, PCWP, CI, and SVRI, but not SVI or PVRI. The CVP was also increased in the sevoflurane group (*P* < 0.001). The RT was decreased during incision (from 35.7 ± 0.4°C to 35.6 ± 0.4°C in the sevoflurane group (*P* < 0.001) and from 35.8 ± 0.5°C to 35.7 ± 0.5°C in the isoflurane group (*P* < 0.01)) without any between groups difference. There were no intergroup differences in the incision-induced haemodynamic effects.

The effects of sevoflurane or isoflurane plus N₂O anaesthesia were unaltered by the order of anaesthetic administration (volatile anaesthetic plus N₂O first or volatile anaesthetic alone first) and therefore the N₂O data were combined. The RT was not changed by the presence of N₂O (35.3 ± 0.5°C without N₂O and 35.4 ± 0.6°C with N₂O in the sevoflurane group; 35.5 ± 0.5°C without N₂O and 35.6 ± 0.5°C with N₂O in the isoflurane group) without any between groups difference. Isoflurane alone tended to be associated with a higher CVP than sevoflurane alone (*P* = 0.050).

FIGURE 1 Haemodynamic variables (mean $\pm$ SD) before and after surgical incision during 1.5 minimum alveolar concentration (MAC) sevoflurane/oxygen ($n = 11$) and 1.5 MAC isoflurane/oxygen ($n = 10$). * $P < 0.05$, ** $P < 0.01$, † $P < 0.005$, †† $P < 0.001$, ‡ $P < 0.0005$ vs before surgical incision. # $P < 0.05$ between groups.

Substituting 0.65 MAC of the respective volatile anaesthetic with equi-MAC N_2O resulted in an increase of MPAP ($P < 0.05$) in both groups, as well as an increase of CVP ($P < 0.005$) and PCWP ($P < 0.005$) in the sevoflurane group, while there was a decrease of HR ($P < 0.005$) and an increase of SVRI ($P < 0.05$) in the isoflurane group (Figure 2). The HR decreased in the sevoflurane group ($P = 0.053$), SVI increased in the isoflurane group ($P = 0.050$), and MAP increased in both the sevoflurane group ($P = 0.050$) and the isoflurane group ($P = 0.056$), but these changes failed to reach statistical significance. There were no intergroup differences in the N_2O -induced effects on sevoflurane and isoflurane anaesthesia.

Discussion

In the present study, neither 1.5 MAC sevoflurane/oxygen nor equi-MAC isoflurane/oxygen could prevent the cardiac haemodynamic responses to surgical incision, and these responses were similar with both anaesthetics. Our isoflurane data are compatible with the finding of Zbinden *et al.*⁹ that isoflurane as a sole agent was unable to suppress haemodynamic reactions to painful stimuli including skin incision. Roizen *et al.*¹⁰ reported that 1.6 MAC anaesthesia with enflurane

FIGURE 2 Haemodynamic variables (mean $\pm$ SD) during intestinal anastomosis under 1.5 minimum alveolar concentration (MAC) sevoflurane or isoflurane without nitrous oxide (N_2O) ($n = 12$) and under an equipotent mixture of sevoflurane or isoflurane plus 0.65 MAC N_2O ($n = 12$). * $P < 0.05$, † $P < 0.005$ vs anaesthesia without N_2O .

plus 60% N_2O also did not decrease the cardiovascular response to incision, whereas halothane plus 60% N_2O at the equi-MAC level did attenuate the response. Therefore, sevoflurane may be more like isoflurane or enflurane than halothane with respect to the haemodynamic response to incision. We chose 1.5 MAC because we assumed that the ED_{50} of sevoflurane and isoflurane for blocking the adrenergic response to incision (MAC BAR) may lie near this level and because we considered that the use of MAC BAR might abolish or attenuate the stress response to surgical incision.¹⁰ Since MAC BAR values for sevoflurane or isoflurane have not been reported, we extrapolated them from those for enflurane (1.60 MAC)¹⁰ or halothane (1.45 MAC).¹⁰

The CVP was higher in patients given isoflurane before surgical incision. This could be due to differences in volume status, differences in right ventricular afterload, or other unknown factors, including differences in right ventricular function. However, the volume status was not rigorously controlled. The PVRI and CI before incision were not statistically different between the groups. Therefore, the cause of difference of CVP was not readily appreciated by our study design.

Surgical incision increased all measured haemodynamic variables, except for CVP in the isoflurane group. This may be due to increased sympathetic and sympathoadrenal activity, and/or to other neuroendocrine stress responses.¹⁰ The increase of CI was ascribed to an increase in HR, because SVI did not change during incision in both groups. The reason for the lack of increase of CVP with isoflurane upon incision is not known.

Our second aim was to compare the cardiac haemodynamic effects of sevoflurane or isoflurane and N₂O mixture with an equipotent dose of sevoflurane or isoflurane during controlled surgical stimulation. Because noxious surgical stimuli increase adrenergic activity, it may be expected that surgery would modify the haemodynamic effects of a volatile anaesthetic with and without N₂O at an equi-MAC level. Changing from sevoflurane to sevoflurane/N₂O at 1.5 MAC resulted in an increase of CVP, MPAP, and PCWP. The increase of MPAP with sevoflurane is consistent with a previous report.¹ Since N₂O is known to have venoconstrictor effects,¹¹ the increased CVP, as well as an increase of MPAP and PCWP may be due to an increase in venous return. In the case of isoflurane anaesthesia, the N₂O effects may be an increase in venous return,¹¹ followed by an increase of SVI and MPAP, while filling pressures unchanged. The cause of the difference in filling pressures between both anaesthetics is not known, but it is possible that changes in ventricular compliance with N₂O is different. Further study is needed using more sophisticated methodology, such as echocardiography, or by assessing more load-independent indices of contractility.⁴

In summary, sevoflurane plus N₂O increased cardiac filling pressures, a finding which was not consistent with the volunteer study,¹ whereas isoflurane plus N₂O did not. Whether these effects of N₂O were ascribable to surgical stimulation is uncertain. Sevoflurane/N₂O was associated with a somewhat higher MAP, similar SVRI, and lower HR than sevoflurane alone. These results were similar to those of a previous study,¹ except that HR was lower with N₂O in our study. Comparison of the cardiac haemodynamics during isoflurane with 70% N₂O and those of other studies on volunteers receiving isoflurane-oxygen anaesthesia indicates that, at approximately comparable MAC levels (1.60 MAC isoflurane/N₂O vs 1.45 MAC isoflurane), MAP and SVR are higher and HR is similar during isoflurane/N₂O.¹² Again, these results were similar to ours, except that HR was lower with N₂O in the present study. The decline of HR with N₂O in our study may have been due to surgical stimulation. In a study comparing cardiovascular

responses to tetanic electrical stimulation during desflurane alone and approximately the same MAC multiples of desflurane plus 60% N₂O, addition of N₂O attenuated the peak HR response but not the peak MAP response.¹³ If this is also true for sevoflurane or isoflurane, ongoing surgical stimulation may have increased HR more during anaesthesia without N₂O than with N₂O, whereas MAP increased equally irrespective of the presence of N₂O. The resultant net effect of N₂O and surgical stimulation would be a decrease of HR with both sevoflurane and isoflurane.

In conclusion, neither sevoflurane nor isoflurane prevented the haemodynamic response to surgical incision at 1.5 MAC. Since an excessive cardiovascular response to surgical stimulation may be deleterious to patients with ischaemic heart disease, opioids, α_2 -agonists,¹⁴ and/or judicious use of β -blockers may be added to anaesthetic regimens including sevoflurane or isoflurane when managing such patients. Sevoflurane/N₂O at 1.5 MAC was associated with higher CVP and PCWP than equi-MAC sevoflurane alone, while no such effect was observed with isoflurane at 1.5 MAC.

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