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SHORT COMMUNICATIONS

Reduced cerebral embolic signals in beating heart coronary surgery detected by transcranial Doppler ultrasound†

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Cerebral emboli detected by transcranial Doppler imaging were recorded in 20 patients undergoing multiple-vessel coronary artery bypass surgery, either with or without cardiopulmonary bypass, in a prospective unblinded comparative study. Emboli were recorded continuously from the time of pericardial incision until 10 min after the last aortic instrumentation. The numbers of coronary grafts and of aortic clampings were also documented. Patients undergoing revascularization with cardiopulmonary bypass had more emboli (median 79, range 38–876) per case compared with patients having off-pump surgery (median 3, range 0–18). No clinically detectable neurological deficits were seen in either group. Beating heart surgery is associated with fewer emboli than coronary surgery with cardiopulmonary bypass. Further research is necessary to determine whether a smaller number of emboli alters the incidence of neurological deficit after cardiac surgery.

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Cerebral complications cause considerable morbidity after cardiac surgery, with an incidence of stroke between 1 and 6% and of more subtle neuropsychological changes between 20 and 40%.[1] Although many factors contribute to the neurological outcome, large numbers of emboli detected by transcranial Doppler (TCD) imaging during cardiac surgery with cardiopulmonary bypass (CPB) are known to be associated with more neurological deficits.[2 3] Clarke and co-workers suggested that the number of cerebral emboli detected with TCD is a useful intermediate endpoint in evaluating new surgical techniques with respect to the neurological outcome.[2] Multiple-vessel off-pump coronary artery bypass grafting (OPCAB) on a beating heart is an increasingly common procedure. In this study we describe the frequency of right middle cerebral artery emboli detected by TCD in patients undergoing multiple vessel coronary artery bypass grafts (CABG) with or without CPB.

Methods and results

After we had obtained ethical approval and patient consent, we studied 20 patients undergoing CABG with or without CPB. Patients without a suitable acoustic bone window for TCD were not included in the study. The choice of operation was at the surgeon's discretion. None of the patients had radiographic evidence of calcification of the proximal aorta. All patients received fentanyl 15–20 mg kg^{-1} and an infusion of propofol 3 mg kg^{-1} h^{-1}. The lungs were ventilated with an oxygen–air mixture to keep blood oxygen saturation Sp_{O_2} above 94%. Arterial Pa_{CO_2} was maintained between 35 and 40 mm Hg. Metaraminol boluses 0.5 mg were given if blood pressure fell by more than 10% from baseline.

After induction of anaesthesia, a 2-mHz bidirectional transcranial Doppler probe (Sci Med, Bristol, UK) was positioned over the right temple until an adequate signal was obtained from the proximal segment of the right middle cerebral artery. The probe was kept in place by a purpose-built headband (Sci Med) maintaining the angle and depth of insonation. Flow velocity profiles were displayed continuously in real time. All patients were operated on through a median sternotomy.

In patients undergoing conventional CABG with CPB, a

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Table 1 Summary data for patient groups having CABG with CPB or without CPB (OPCAB). Data are mean (SD) unless otherwise stated

	CABG with CPB $n=10$	OPCAB $n=10$
Age (range) (yr)	61 (47–69)	60 (48–70)
Sex	10 M	8 M, 2 F
Body mass index	27.61 (3.72)	27.34 (3.25)
Lowest nasopharyngeal temperature intraoperatively	34.0 (0.56)	35.3 (0.69)*
Parsonnet score		
0–5	9	6
6–10	0	2
>10	1	2
Total no. grafts	29	27
Total no. aortic cross-clamps	10	0
Total no. partial aortic clampings	12	13
Time recorded (min)	123 (14.3)	105 (24.3)
Microembolus count (median and range)	79 (38–876)	3 (0–18)**

*$P<0.05$; **$P<0.001$.

transaortic cross-clamp was applied after establishment of CPB and intermittent warm-blood cardioplegia was administered into the aortic root. CPB was with non-pulsatile flow, a membrane oxygenator (Bard, Haverhill, MA, USA) and a 40-μm in-line arterial filter (Bard). Alpha stat pH management was used during CPB, and nasopharyngeal temperature was maintained between 34 and 37°C. The cross-clamp was removed on completion of distal anastomoses and an aortic side-biting clamp was applied in order to perform the proximal anastomoses.

For the OPCAB patients, distal anastomoses were performed on the beating heart after the heart had been positioned and stabilized with a purpose-made retractor. After completion of each distal anastomosis, the heart was returned to its native position and an aortic side biting clamp applied to perform the proximal anastomosis.

Embolic signals were identified with TCD by a well-recognized[4] combination of a sudden change in the acoustic density of the signal, visible as an instantaneous bright signal on the visual display, and a characteristic high-frequency audible response similar to a chirping or whistling sound. Counts of emboli were recorded continuously by one of the investigators (MW) during the period from pericardial incision until 10 min after the last aortic manipulation. In the OPCAB group, this was after the last removal of the aortic side-biting clamp, whereas in the CPB group this was after removal of the aortic cannula. The number of aortic clampings in each group was recorded, as was the total time during which emboli were detected.

Counts of emboli were compared using the Mann–Whitney *U*-test. Continuous data were analysed using Student's *t*-test. A P value of <0.05 was considered statistically significant.

None of the OPCAB procedures were converted to CABG with CPB. No clinical neurological deficits were detected in either group. The results are summarized in Table 1.

Comment

In this study, patients undergoing multiple-vessel OPCAB had markedly fewer cerebral emboli, detected intra-operatively by TCD of the right middle cerebral artery, than patients undergoing CABG with CPB. This has not been reported previously for patients requiring multiple-vessel revascularization, who could have received CABG with CPB, although BhaskerRao and co-workers have shown similar results in a group of patients considered unsuitable for CPB, who had predominantly single-vessel grafting through a left minithoracotomy with no proximal aortic clamping.[5]

The incidence of emboli detected by TCD is known to be related to aortic instrumentation.[6] Although partial aortic clamping to perform proximal anastomoses is usually required in both on- and off-bypass coronary surgery, only with on-bypass surgery are a transaortic cross-clamp and aortic and cardioplegia cannulae required. In the patients undergoing CABG with CPB, although noticeable increases in embolic signals occurred during aortic instrumentations, embolic signals also occurred throughout the bypass period. The total number of emboli detected was similar to the numbers reported in previous studies in which a membrane oxygenator and a 40-μm in-line arterial filter were used.[7] The few emboli in the OPCAB group occurred only on removal of aortic side-biting clamps.

The study was unblinded and not randomized, and therefore the possibility of bias exists. However, all recordings were made continuously by a single observer, and emboli detected by TCD have a characteristic quality that is easy to recognize and difficult to misinterpret. Considering the magnitude of the difference in emboli counts, observer bias is unlikely to have affected the difference seen between the two groups. Secondly, although all patients could have received conventional CABG using CPB, patient selection for OPCAB is dictated by the anatomical position of the coronary lesions and surgical preference. It is possible, but unlikely, that this might have led to a difference in associated aortic atheroma between the two groups. The groups were likely to be similar, given the similar Parsonnet risk scores and the similar numbers of coronary grafts (Table 1), together with the absence of any calcification on pre-operative chest x-ray or angiography. We consider it unlikely that possible differences in atheroma could significantly affect the large difference in emboli counts seen. Also, factors affecting cerebral blood flow, such as core temperature (which was actually higher in the off-bypass group), would be unlikely to affect the embolus counts to the degree observed.

We cannot conclude from this study that OPCAB surgery is associated with better neurological outcome. It is impossible using TCD to determine the nature of the emboli recorded. Gaseous emboli, for example, may pose less risk to the patient than solid atheroemboli dislodged during aortic manipulation. However, the finding that OPCAB

surgery is associated with so few cerebral emboli warrants further investigation into whether OPCAB surgery is associated with less neurological deficit than CABG with CPB.

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Effects of isoflurane, sevoflurane and propofol anaesthesia on jugular venous oxygen saturation in patients undergoing coronary artery bypass surgery

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We investigated the effect of sevoflurane, isoflurane and propofol on jugular venous bulb oxygen saturation (Sj_{O_2}) in 21 patients undergoing coronary artery bypass graft surgery (CABG) during and after normothermic cardiopulmonary bypass (CPB). Patients received a standardized anaesthetic consisting of fentanyl, midazolam and were then randomly allocated to receive either isoflurane, sevoflurane or propofol for maintenance. Sj_{O_2} values were significantly lower than baseline 1 h after CPB in the propofol but not the isoflurane or the sevoflurane groups. Furthermore, Sj_{O_2} values were significantly higher during CPB in the isoflurane group ($P=0.0081$) and significantly lower 6 h after CPB in the sevoflurane group ($P=0.0447$) when compared to the propofol group. We conclude that jugular venous desaturation during and after normothermic CPB is more likely during propofol anaesthesia.

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Jugular venous desaturation, common during cardiopulmonary bypass (CPB),[1–3] has been correlated with postoperative neuropsychiatric dysfunction.[3] Furthermore, the incidence of delayed jugular venous desaturation which was common early after hypothermic CPB was not attenuated by the supplemental propofol.[4 5] The aim of this study was

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to investigate the temporal relationship between CPB and jugular venous desaturation during isoflurane, sevoflurane and propofol anaesthesia.

Methods and results

After Local Research Ethics Committee approval and informed written consent were obtained, 21 patients undergoing elective CABG were enrolled in the study. Patients were managed with a standardized normothermic CPB protocol and were allocated randomly to receive isoflurane, sevoflurane or propofol for maintenance of general anaesthesia (each group $n=7$). Patients with a history of neurological or cerebrovascular disease were excluded.

After premedication with morphine 15 mg and scopolamine 0.3 mg, anaesthesia was induced with midazolam 0.1 mg kg^{-1} and fentanyl 15 μg kg^{-1}, and maintained with 0.5–1.0% isoflurane, 1.5–2% sevoflurane or propofol 3 mg kg^{-1} h^{-1}. Neuromuscular blockade was achieved with pancuronium 0.1 mg kg^{-1} and the lungs were ventilated with an air/oxygen mixture, aiming for an arterial carbon dioxide tension (Pa_{CO_2}) of 35–40 mm Hg during mechanical respiratory support. Mean arterial pressure (MAP) was maintained above 50 mm Hg with volume loading and vasoactive agents (phenylephrine). In addition to the standard monitors for cardiac anaesthesia, a right jugular bulb catheter (Vygon Leader Cath 14G; Vygon, Gloucs, UK) was sited and its position confirmed radiographically. Blood sampled from the catheter was analysed for oxygen saturation using bench Co-Oximetry (Rapid lab ™ 860, Chiron Diagnostics, US) after induction of anaesthesia (T0, baseline), 30 min after starting (T1) and immediately after weaning from CPB (T2), and then at 1, 6, 12 and 18 h after CPB (T3, T4, T5 and T6 respectively).

Standard normothermic (36–7°C) non-pulsatile bypass with membrane oxygenation was used with α-stat management of Pa_{CO_2}. Perfusion pressure was maintained between 50 and 70 mm Hg by altering the concentration of the anaesthetic agent administered during CPB. Isoflurane (0.5–1.0%) or 1.5–2% sevoflurane were administered continuously through the bypass circuit and propofol 3 mg kg^{-1} was administered continuously intravenously. Anaesthetic agents were discontinued after the patients were haemodynamically stable on the intensive care unit (after T3). Postoperative sedation consisted of propofol 2 mg kg^{-1} in the propofol group and midazolam (2–4 mg boluses, with a cumulative dose ranging between 4 and 10 over the first 6 h after the surgery) in the volatile-anaesthetic groups.

All values are expressed as mean and standard deviation. Jugular venous saturation (Sj_{O_2}) data were compared using analysis of variance (ANOVA) factorial or repeated measures as appropriate. A P value of <0.05 was considered significant. When significance was found, post-hoc tests (Bonferoni/Dunn) with correction for multiple comparisons were applied.

There were no significant differences between between the groups in age, height, weight, total CPB or aortic clamp time. Sj_{O_2} values were significantly lower than baseline 1 h after CPB in the propofol but not the isoflurane or the sevoflurane groups. Furthermore, Sj_{O_2} values were significantly higher during CPB in the isoflurane group ($P=0.0081$) and significantly lower 6 h after CPB in the sevoflurane group ($P=0.0447$) when compared to the propofol group (Fig. 1). MAP was maintained >50 mm Hg in all patients without significant differences between the three anaesthetic subgroups at any stage of the study.

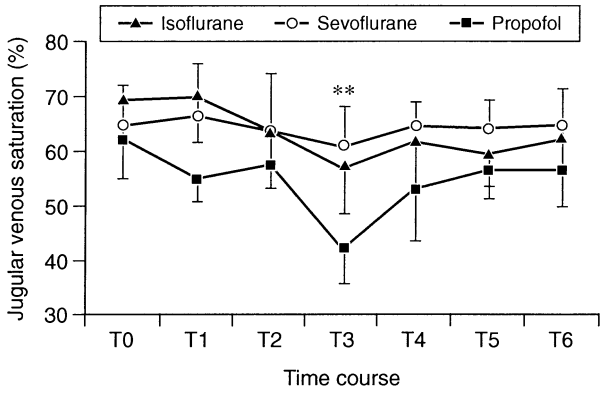

Fig 1 Time course of jugular venous saturation (Sj_{O_2}) values during the entire study period. T0=after induction of anaesthesia; T1=30 min after starting cardiopulmonary bypass (CPB); T2=immediately after CPB; T3, T4. T5, T6=1, 6, 12, 18 after CPB. $^{**}P<0.05$ compared the propofol group with the isoflurane and sevoflurane groups.

Comment

We have demonstrated a significant decrease in Sj_{O_2} values 1 h after normothermic CPB during propofol but not isoflurane or sevoflurane anaesthesia for CPB surgery. Furthermore, Sj_{O_2} values are lower during propofol than isoflurane anaesthesia during CPB, and than sevoflurane anaesthesia 6 h after CPB.

Jugular venous desaturation has been reported to occur during and after CPB.[1–3] While the most prominent reductions in Sj_{O_2} occur during rewarming, such desaturation has also been reported early during the establishment of normothermic CPB.[2] Furthermore, a recent publication documented late jugular venous desaturation following hypothermic CPB.[4] The last two studies suggest that rewarming from hypothermic CPB cannot be the only cause of jugular desaturation, and that imbalances between cerebral oxygen supply and demand can occur in other settings associated with CPB. Our data suggest the occurrence of pathophysiological events in the first hour after CPB that are of a magnitude sufficient to disrupt normal flow-metabolism relationships.

Previous attempts to attenuate the early desaturation after CPB by reducing oxygen demand have been unsuccessful. Souter and colleagues used burst suppression doses of propofol as an adjunct in patients anaesthesized with isoflurane in an attempt to decrease cerebral oxygen

requirement during weaning from CPB, but found no benefit.[5] Indeed their data show a trend for greater jugular desaturation in the group treated with propofol, which they attributed to an increased incidence of hypotension in this group. The reductions in Sj_{O_2} that we observed appear to be independent of changes in MAP, since there was no incidence of significant hypotension during the study period. Our data suggest that volatile anaesthesia can substantially attenuate jugular venous desaturation occurring during the entire study period when compared to patients receiving propofol anaesthesia. We do not have any data that provide an explanation for either the decrease in Sj_{O_2} or the difference that we have observed between the different anaesthetic/sedative regimens that were used in this study.

A disadvantage of this study protocol is the absence of continuous jugular saturation monitoring. The use of fibreoptic catheters might have allowed us to provide a more complete picture of cerebral blood flow adequacy during the study period. However, we had technical difficulties with continuous fibreoptic Sj_{O_2} monitoring during CPB, and our decision not to use this form of monitoring is supported by a recent paper that demonstrates problems with its use in the setting of CPB.[6]

While our continuing studies address both this issue and the mechanisms involved, our present results clearly show that the choice of anaesthetic agent may have important influences on cerebral oxygenation in some periods following CPB and provide a basis for further studies.

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Effect of anaesthesia on the cardiac response to intravenous adenosine†

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The cardiac response to intravenous adenosine 112 μg kg^{-1} was studied in 16 patients scheduled for coronary artery bypass surgery before and during anaesthesia with 1% end-tidal isoflurane and fentanyl 10 μg kg^{-1}. Mean time from injection to onset of adenosine-induced PR prolongation was significantly greater during anaesthesia (12.8 (SD 5) *vs* 9.9 (3) s, $P=0.032$). Atrioventricular block (assessed by the total number of non-conducted P waves) was significantly less during anaesthesia (12 *vs* 27, $P=0.016$). We conclude that anaesthesia including 1% isoflurane and fentanyl 10 μg kg^{-1} delays the onset and reduces the magnitude of adenosine-induced atrioventricular block.

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The therapeutic indication for intravenous adenosine is the conversion of paroxysmal supraventricular tachycardia. An intravenous dose of adenosine to awake subjects during sinus rhythm prolongs the PR interval, and can lead to complete atrioventricular block starting 10–20 s after injection and lasting less than 10 s.[1] Sinus bradycardia is also seen and occurs with onset and duration similar to the

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PR effect. These changes are followed by reflex sinus tachycardia.

Adenosine is a recommended first-line treatment for paroxysmal tachycardia occurring during anaesthesia.[2] No controlled studies have been carried out to assess if current dosage recommendations are appropriate in anaesthetized patients. The aim of this study was to assess the effect of anaesthesia on the cardiac response to adenosine.

Methods and results

After Local Ethics Committee approval and informed written consent had been obtained, 19 patients scheduled for elective coronary bypass surgery were recruited. Exclusion criteria comprised digoxin, theophylline or dipyridamole treatment, ECG conduction abnormalities, cardiac arrhythmia, left ventricular ejection fraction less than 50%, left main stem coronary disease and valvular heart disease requiring surgery. Anti-anginal medication was continued and patients were premedicated with intramuscular morphine 10 mg and metoclopramide 10 mg. Under local anaesthesia, cannulae were placed in an internal jugular vein (using a triple lumen catheter), a peripheral vein and a radial artery. Central venous, arterial pressure and ECG leads II and V5, including ST segment changes, were monitored continuously (Datex AS3, Engstrom, Helsinki, Finland). A three-lead ECG running at a paper speed of 100 mm s^{-1} (Mingocard 4, Siemens-Elma, Sweden) was used to record and later measure the PR and PP intervals. The study plan was based on one used previously to evaluate the clinical efficacy of adenosine in cardiac transplant patients.[3] Before anaesthesia, adenosine 112 μg kg^{-1} was injected rapidly via the distal lumen of the jugular venous catheter and flushed with 10 ml saline. A continuous ECG was recorded from 30 s before to 2 min after injection. Anaesthesia was induced using etomidate 10 mg and fentanyl 10 μg kg^{-1}. Pancuronium 0.1 mg kg^{-1} was used to facilitate tracheal intubation and ventilation of the lungs with oxygen in air to an end-tidal carbon dioxide concentration of 4–4.5%. Anaesthesia was maintained using isoflurane. Metaraminol 0.25–0.5 mg was used if needed to maintain the systolic blood pressure at or above 90 mm Hg. When a stable end-tidal isoflurane concentration of 1% had been established, the sequence of ECG recording and adenosine administration was repeated.

PR and PP intervals before and during anaesthesia were measured to within 5 ms and plotted. Baseline intervals were measured from the mean of five beats before adenosine injection and noted together with baseline mean arterial pressure.

Time to onset of the PR effect was defined as the time from completion of adenosine injection to the start of PR prolongation, as estimated from the plot of PR intervals. The number of non-conducted P waves after adenosine injection was used as a measure of the magnitude of the effect on atrioventricular conduction. Duration of the PR effect was taken as the time during which the PR interval was increased by 10 ms or more compared with baseline.

Sinus bradycardia after adenosine injection was an inconsistent finding. Therefore, no attempt was made to evaluate bradycardia from the magnitude or duration of PP prolongation. In addition, some patients had atrial ectopic beats or transient sinus bradycardia early after adenosine injection. This may have been a topical effect of adenosine on the sinus node from within the right atrium.

The reflex sinus tachycardia that followed the direct cardiac effect of adenosine was quantified from each recording as the minimum PP interval observed after drug administration, and was expressed as a percentage of the baseline PP interval.

Data analysis was performed using Microsoft Excel version 5c. Paired *t* tests were used to analyse continuous variables before and during anaesthesia. The total number of non-conducted P waves before and during anaesthesia was compared using the chi-squared test. Statistical significance was defined as $P<0.05$.

Three of the 19 patients recruited to the study developed a nodal rhythm after induction of anaesthesia and were excluded from the analysis. Sixteen patients (12 male) with a mean age of 57 (SD 10) years and mean weight of 84 (16) kg completed the study. The results are given in Table 1.

Comment

Our study population was selected for its routine invasive monitoring. This choice can be criticized. Many anti-anginal drugs have cardiac electrophysiological effects, but these drugs were continued as withdrawal could have increased the risk of perioperative myocardial ischaemia. Similarly, we thought it unethical to omit premedication and the 'awake' studies were performed in premedicated patients. In addition these patients had coronary disease, which could reduce drug delivery to the cardiac conduction system. We believe these criticisms are partly offset by the paired nature of the study; each patient was acting as their own control. A criticism of the study design is that effects of adenosine observed during sinus rhythm are surrogate end-points for the drug's clinical effect, which is to end an attack of tachycardia. However, similar surrogate end-points have been used previously.[3]

We showed that anaesthesia with 1% end-tidal concentration isoflurane/fentanyl increases the time to onset and reduces the magnitude of adenosine-induced atrioventricular nodal block. A longer transit time from the point of injection to the coronary circulation during anaesthesia could explain the delay in onset of the effect of adenosine, and the reduced effect of adenosine because of the drug's very short plasma half-life (less than 2 s).[4] A longer transit time would allow greater adenosine metabolism and reduce the drug concentration reaching the effector site.

Anaesthesia attenuated the reflex tachycardia and, by inference, the reflex sympathetic activation[5] that follows

Table 1 Baseline ECG measurements, baseline mean arterial pressure and cardiac response to intravenous adenosine 112 μg kg^{-1} before and during 1% isoflurane anaesthesia. Values are mean (SD). *Two patients did not develop adenosine-induced PR prolongation while awake, and these two patients, together with a third, did not develop it during anaesthesia. Paired *t* tests were therefore performed only on data from the 13 patients with PR prolongation both before and during anaesthesia

	Before anaesthesia	During anaesthesia	*P* value
Baseline PR interval (ms)	177 (25)	166 (24)	0.007
Baseline PP interval (ms)	1067 (168)	1099 (253)	0.546
Baseline mean arterial pressure (mm Hg)	88 (11)	76 (9)	0.003
Time to onset of PR prolongation in 13 patients (s)*	9.9 (3)	12.8 (5)	0.032
Duration of PR prolongation in 13 patients (s)*	10.1 (3)	10.1 (4)	0.595
Total number of non-conducted P waves	27	12	0.016
Minimum PP interval after adenosine (% of baseline)	75 (8)	87 (6)	0.001

the direct cardiac effects of an intravenous bolus of adenosine. This could reflect anaesthesia-induced sympatholysis.

The attenuation of the atrioventricular blocking effect of adenosine shown in this study is a consideration when an anaesthetized patient develops supraventricular tachycardia. A standard intravenous adenosine 3, 6, 12 mg regimen without additional higher doses is currently recommended. We suggest that, for the anaesthetized patient, the current maximum dose presented above needs to be reviewed.

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Carbon dioxide elimination during high-frequency jet ventilation for rigid bronchoscopy

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Oxygen saturation and carbon dioxide values should be monitored during high-frequency jet ventilation (HFJV). Modern transcutaneous P_{CO_2} (Ptc_{CO_2}) measurement allows the estimation of ventilation efficiency. We studied how tests of lung function could predict carbon dioxide elimination during HFJV. Lung function tests from 180 adult patients undergoing rigid bronchoscopy were analysed as factors affecting carbon dioxide elimination. The lung function test results showed a significant relationship with the efficiency of carbon dioxide elimination; the greatest impairment of carbon dioxide elimination was found in patients with combined abnormalities of lung function. Further factors associated with difficult carbon dioxide elimination were male gender and elevated body weight. Of the patients investigated, 72% had normal carbon dioxide elimination, whereas in 23% hypercapnia could be avoided only by increasing the driving pressure. The prevalence of abnormal preoperative lung function test results predicts (sensitivity 76%, positive predictive value 27%) impaired carbon dioxide elimination during jet ventilation and rigid bronchoscopy.

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High-frequency jet ventilation (HFJV) is a convenient method of ventilation during rigid bronchoscopy, since it offers optimal visibility and easy access for diagnostic and surgical instruments into the airway. However, monitoring of gas exchange is more difficult than during conventional ventilation and requires special equipment. We have recently described a new transcutaneous blood gas sensor prototype, the Sp_{O_2}-Ptc_{CO_2} ear probe (Linde Medical Instruments, Basel, Switzerland). This device provides reliable carbon dioxide partial pressure values compared with simultaneously determined Pa_{CO_2}, and has an *in vivo* latency period of 57±20 s.[1] Because of the speed and ease of use of this device, we now routinely use transcutaneous carbon dioxide measurement during HFJV as an approximation for Pa_{CO_2}. Since the jet driving pressure (DP) and the resulting transcutaneous PCO_2 (Ptc_{CO_2}) values are inversely related, we calculate a carbon dioxide elimination coefficient (Ec_{CO_2}) which helps to quantify the individual carbon dioxide elimination capacity under HFJV and under standardized conditions.[2]

A value of 1.0 results if Ptc_{CO_2} is normal (37.5 mm Hg) during jet ventilation with a moderate DP of 2.0 atm and represents a normal carbon dioxide elimination capacity. Reduced values indicate impaired carbon dioxide elimination. As an empirical cut-off value, we use an Ec_{CO_2} of 0.75 to differentiate between normal and compromised carbon dioxide elimination. We set out to assess the relation between preoperative lung function test results and carbon dioxide elimination during jet ventilation for rigid bronchoscopy.

Methods and results

After informed consent had been obtained, 180 adult patients of ASA physical status 1–4 who were scheduled for elective interventional rigid bronchoscopy under general anaesthesia and HFJV were included in this study. Vital capacity (VC) and forced expiratory volume in 1 s (FEV_1) were measured and compared with values predicted from standard equations.[3] A restrictive pattern was assumed if the measured VC was below 70% of the predicted value, and an obstructive abnormality if the measured FEV_1 was below 70% of the predicted value.

Total intravenous anaesthesia (TIVA) was conducted with propofol and remifentanil for induction and maintenance and succinylcholine for muscle relaxation. In addition to usual monitoring, continuous transcutaneous blood gas measurement with a calibrated Sp_{O_2}-Ptc_{CO_2} ear-clip sensor prototype (Linde Medical Instruments, Basel, Switzerland) was used.[1] Jet ventilation was performed with an AMS 1000 Universal Jet Ventilator- (Acutronic Medical Systems, Hirzel, Switzerland) via the rigid bronchoscope. A respiratory frequency of 150 cycles min^{-1} and an inspiration duration of 40% were set during the study. Therefore, the DP was the only variable in the HFJV setting.

The DP was set at 1.5, 2.0 and 2.5 atm for 5 min each, and the resulting Ptc_{CO_2} was documented 3 min after each change of DP setting. If oxygenation was poor (Sp_{O_2} <89%), HFJV was supplemented by manually assisted ventilation. Ec_{CO_2} values calculated at various DP settings were averaged. The physical and clinical characteristics of patients with normal carbon dioxide elimination were compared with those of patients with impaired elimination by the use of the Mann–Whitney test. The influence of lung function on Ec_{CO_2} was tested for dissimilarity by one-way analysis of variance (ANOVA). *Post hoc* comparisons of categories were performed using the Bonferroni–Dunn test. Frequencies were examined for variability by the chi-squared test; $P < 0.05$ was considered significant. In eight patients the Sp_{O_2} could not be maintained continuously above 89%, which prevented further analysis of carbon dioxide elimination under standardized study conditions. Thus, the data come from 172 patients. Ptc_{CO_2} values had a range of 24.8–66.8 mm Hg. One hundred and thirty-five patients had normal carbon dioxide elimination ($Ec_{CO_2} > 0.75$), and in 37 patients carbon dioxide elimination was compromised ($Ec_{CO_2} < 0.75$). Patients with compromised carbon dioxide elimination had a significantly greater body weight and a smaller VC and FEV_1, and the percentage of males was higher in this group of patients (Table 1).

Allocation of patients to the four prospectively defined patients the Sp_{O_2} could not be maintained continuously with normal lung function, (ii) 57 patients (33%) with obstructive abnormality, (iii) 22 patients (13%) with restrictive abnormality and (iv) 24 patients (14%) with combined (obstructive plus restrictive) abnormality. Elimination of carbon dioxide, as assessed by Ec_{CO_2}, was best in patients with normal lung function ($P = 0.0007$ in the overall ANOVA) and deteriorated progressively in patients with obstructive, restrictive and combined abnormality.

Normal values of lung function variables (VC and/or FEV_1) had a negative predictive value of 87% for normal carbon dioxide elimination ($Ec_{CO_2} > 0.75$), whereas the prevalence of at least one pathological lung function variable resulted in a positive predictive value of only 27% for compromised carbon dioxide elimination ($Ec_{CO_2} < 0.75$). Of patients with impaired carbon dioxide elimination ($Ec_{CO_2} < 0.75$), 76% had abnormal lung function tests (sensitivity) and normal results were present in only 44% of patients with normal carbon dioxide elimination ($Ec_{CO_2} > 0.75$) (specificity).

Table 1 Biometrical and clinical data during jet ventilation for rigid bronchoscopy in patients with normal and compromised carbon dioxide elimination. Frequencies were compared with the chi-squared test, the other variables with the Mann–Whitney test). Values are mean (SD). n.s. = not significant.

	Normal CO_2 elimination ($EC_{CO_2} > 0.75$)	Compromised CO_2 elimination ($EC_{CO_2} < 0.75$)	Statistical significance
Patients (*n*)	135	37	
Males (*n*)	82 (63%)	29 (76%)	$P<0.05$
Age (years)	58 (17–31)	59 (83–78)	n.s.
Height (cm)	171 (9)	171 (7)	n.s.
Weight (kg)	72 (13)	79 (15)	$P<0.05$
Predicted VC (l)	3.81 (0.87)	3.79 (0.65)	n.s.
Actual VC (l)	3.16 (0.96)	2.57 (0.93)	$P<0.05$
Predicted FEV_1 (l)	3.26 (0.77)	3.27 (0.55)	n.s.
Actual FEV_1 (l)	2.22 (0.78)	1.73 (0.73)	$P<0.05$
$FEV_1 \times 100/VC$ (%)	70.4 (12.9)	67.8 (15.3)	n.s.
Ventilation duration (min)	14 (11)	14 (7)	n.s.
Mean Ptc_{CO_2} (mm Hg)	40.8 (6.9)	52.4 (6.1)	$P<0.01$
Mean DP (atm)	1.9 (0.3)	2.3 (0.3)	$P<0.01$
Mean EC_{CO_2}	1.02 (0.18)	0.66 (0.08)	$P<0.01$
Lung function categories (*n*)			
Normal	60	9	$P=0.007$
Obstructive	48	8	
Restrictive	13	10	
Combined	14	10	

Comments

During HFJV the assessment of carbon dioxide status is a challenge. An arterial catheter may be not always indicated or feasible and capnography values may be invalid unless ventilation is interrupted regularly or special equipment is used. Recently introduced transcutaneous PCO_2 monitoring allows non-invasive and continuous carbon dioxide surveillance with a fair degree of precision and an acceptable response time.

The definition of a tolerable upper limit for Ptc_{CO_2} may be arbitrary; however, in the vast majority of patients, 50 mm Hg can be tolerated safely for the duration of a bronchoscopic intervention. Although in some cases even higher carbon dioxide values may be acceptable,[4] Ptc_{CO_2} values between 30 and 50 mm Hg are a reasonable routine target. If a Ptc_{CO_2} value of 50 mm Hg is an acceptable maximum while ventilating with a moderate DP of 2.0 atm, the resulting EC_{CO_2} must be above 0.75. Therefore, we used this as a cut-off value to divide the patients into two categories: 'normal' and 'compromised' carbon dioxide elimination.

The physical and clinical data show relevant differences between the two defined carbon dioxide elimination groups (Table 1). Male gender and high body weight are known to be associated with difficulty in achieving adequate gas exchange during HFJV, particularly with carbon dioxide elimination.[2 5 6] The same is true for abnormal lung function, but this depends on the type and degree of the abnormality. Surprisingly, obstructive lung disease, which is usually considered an important hindrance to carbon dioxide elimination during jet ventilation,[7 8] was less relevant than restrictive lung function. However, the preoperative abnormal lung function predicts difficult carbon dioxide elimination (sensitivity 76%) but normal results are not good predictors of normal carbon dioxide elimination during jet ventilation (specificity 44%).

In summary, most patients with abnormal pulmonary function tests undergoing rigid bronchoscopy (96%) can be ventilated adequately with HFJV. Measurement of lung function variables such as VC and FEV_1 and the prevalence of other cofactors, such as male gender and elevated body weight, can help to estimate the expected carbon dioxide elimination. Patients with normal carbon dioxide elimination will require a lower DP. This has the benefits of lowering airway pressure to the necessary minimum and reducing the adverse effects of HFJV, such as cooling and drying of the tracheobronchial epithelium.

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Cp50 of propofol with and without nitrous oxide 67%

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The target concentration of propofol required to prevent response to surgical incision was determined in 60 unpremedicated ASA I or II patients, who breathed either oxygen-enriched air or nitrous oxide 67% in oxygen. Propofol was infused using a target-controlled infusion system incorporating the standard 'Diprifusor' pharmacokinetic model, with the target concentration for each patient decided by up/down sequential allocation. Presence or absence of movement in response to a groin incision was determined by the surgeon. The calculated blood concentration at which 50% of patients responded ($Cp50_{calc}$), determined by probit analysis, was 6.8 μg ml^{-1} for patients who breathed oxygen-enriched air and 4.9 μg ml^{-1} for those who breathed nitrous oxide 67% in oxygen.

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Target-controlled infusion systems for propofol allow anaesthetists to titrate target blood propofol concentration according to requirement, in the same way that inspired concentrations of inhalational anaesthetic agents are adjusted according to response. Eger, Saidman and Brandstater[1] determined the minimum alveolar concentration (MAC), that is, the alveolar concentration of an inhalational agent at which 50% of subjects fail to respond to a standard surgical stimulus, for a series of inhalational agents, initially in anaesthetized dogs. This has become the standard experimental technique for defining the potency of inhalational anaesthetic agents and provides important guidelines for drug administration.

Davidson and colleagues[2] determined the $Cp50_{calc}$ for propofol in patients premedicated with temazepam. $Cp50_{calc}$ is defined as the calculated plasma concentration at which 50% of patients anaesthetized with an intravenous agent do not respond to a standard surgical stimulus, the calculated plasma concentration having been maintained for long enough to permit equilibration with the effect site.[3] Anaesthesia was induced and maintained with propofol by target-controlled infusion; after an equilibration period of ⩾12 min a standard surgical incision was made. Cp50 for the calculated propofol concentration was 6.0 μg ml^{-1} in patients breathing oxygen-enriched air and 4.5 μg ml^{-1} in those breathing nitrous oxide 67% in oxygen. Since pharmacological premedication is not always appropriate, we considered it essential to determine the Cp50 for propofol in unpremedicated patients. This is particularly relevant to modern daycase anaesthetic practice.

Methods and results

Sixty unpremedicated patients (ASA I and II, aged 16–70 yr) scheduled for inguinal hernia repair or sapheno-femoral ligation were studied, with written informed consent and Institutional Ethics Committee approval. Exclusion criteria were concurrent medication with analgesics, and obesity (body mass index ⩾35 kg m^{-2}). Anaesthesia was induced and maintained with propofol, using a target-controlled infusion system which incorporated the standard 'Diprifusor' pharmacokinetic model proposed by Gepts and colleagues,[4] and later modified by Marsh and colleagues.[5] Patients were randomized to breathe either oxygen-enriched air or nitrous oxide 67% in oxygen from a tightly fitting facemask. The target concentration for the first patient in each group was 0.5 μg ml^{-1} higher than the Cp50 values determined by Davidson and colleagues.[2] After they had lost consciousness, patients were prepared for surgery but were otherwise left as unstimulated as possible.

A minimum of 12 min after induction (to allow equilibration between blood and brain propofol concentrations, and inspired/expired nitrous oxide partial pressures), a groin incision was made. The surgeon, who was blinded to the target propofol concentration in use and to whether the patient was breathing oxygen-enriched air or nitrous oxide

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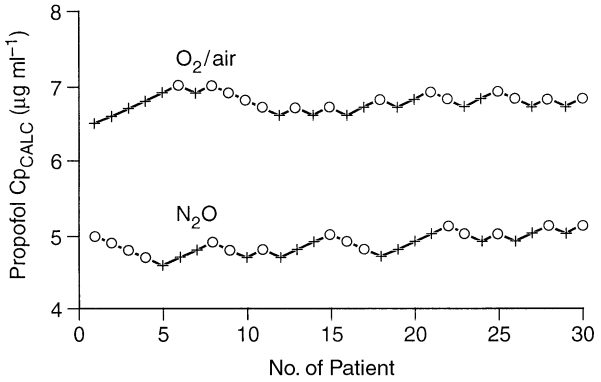

Fig 1 Dose–response data for each of the patients breathing either oxygen-enriched air or nitrous oxide 67% in oxygen; movement (+) and lack of movement (○) in response to incision.

in oxygen, decided if there was any 'gross purposeful movement'. This definition of movement was the same as that used by Eger, Saidman and Brandstater in their MAC studies.[1] Subsequent patients in each group had anaesthesia induced to a target concentration 0.1 μg ml^{-1} higher or lower than before, using up/down sequential allocation; if the patient moved on incision, the target propofol concentration for the next patient in that group was set to 0.1 μg ml^{-1} higher than before. If no movement was detected, the target for the next patient was 0.1 μg ml^{-1} lower than the previous patient in that group. The collection of study data was complete when the response to surgical incision was noted, and thereafter an appropriate dose of opioid (fentanyl or alfentanil) was administered to deepen anaesthesia. Probit analysis[6] was used to assess the dose–response data, with Minitab version 12 for Windows 95.

Mean (range) age and mean (SD) weight were 49.6 (18–70) yr and 71.1 (11.4) kg, respectively, in the nitrous oxide group and 41.2 (18–68) yr and 73.7 (15.6) kg, respectively, in those breathing oxygen-enriched air. The gender ratio (male:female) was 16:14 in the nitrous oxide group, and 19:11 in those breathing oxygen-enriched air. Arterial pressure was measured non-invasively every 3 min. Patients remained haemodynamically stable (within 20% of preoperative mean arterial pressure). No patients required assistance with ventilation (Sp_{O_2} remained >94% and $F_E'_{CO_2}$ was <7.5 kPa) and on direct questioning at the postoperative visit no patient had recall of any event during anaesthesia or surgery. The target blood propofol concentration for each patient and the response to incision are shown in Fig. 1.

The Cp50 for the target propofol concentration, corrected to one decimal place (95% confidence intervals), was 4.9 (4.8–5.0) μg ml^{-1} in patients breathing nitrous oxide 67% and 6.8 (6.7–6.9) μg ml^{-1} in those breathing oxygen-enriched air.

Comment

The Cp50 values that we have determined are slightly higher than those described by Davidson and colleagues in their premedicated patients.[2] We found that the administration of nitrous oxide 67% in oxygen reduces propofol Cp50 by 28%, which is similar to the 25% reduction demonstrated previously.[2]

Cp95 (the concentration at which only 5% of patients respond to incision) might be considered more clinically relevant than Cp50. Up/down sequential allocation and probit analysis are designed to determine Cp50 and, while it is possible to estimate Cp95 by extrapolation of the 'best-fit' line on probit graphs, the confidence intervals are so large that it is impossible to draw any firm conclusions from the result. In our study, propofol $Cp95_{calc}$ (95% confidence intervals) was 5.3 (5.1–18.9) μg ml^{-1} for patients who breathed nitrous oxide 67%, and 7.1 (6.9–9.5) μg ml^{-1} for those who breathed oxygen-enriched air.

We conclude that, in unpremedicated patients, if anaesthesia is induced to a target propofol concentration of 6.8 μg ml^{-1}, or 4.9 μg ml^{-1} when nitrous oxide 67% is used, there is a 50% chance that patients will move in response to a skin incision made a $\geqslant$12 min later.

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