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CLINICAL PRACTICE

Hypercapnia and surgical site infection: a randomized trial†

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Editor's key points

- The Bohr effect underpins why hypercapnia favours unloading of oxygen at the tissue level.
- Permissive hypercapnia-enhanced tissue oxygenation could reduce surgical site infection.
- This study found that mild hypercapnia could possibly reduce the risk of surgical site infection but such an effect appears small.
- Obesity is associated with higher rates of surgical site infection.

Background. Tissue oxygenation is a strong predictor of surgical site infection (SSI). Mild intraoperative hypercapnia increases peripheral, gastrointestinal, and splanchnic tissue oxygenation and perfusion. Hypercapnia also has anti-inflammatory effects. However, it is unknown whether hypercapnia reduces SSI risk. We tested the hypothesis that mild intraoperative hypercapnia reduces the risk of SSI in patients having colon resection surgery.

Methods. With institutional review board approval and subject consent, patients having elective colon resection (e.g. hemicolectomy and low-anterior resection) expected to last >2 h were randomly assigned to intraoperative normocapnia ($P_{E'_{CO_2}} \approx 35$ mm Hg; $n=623$) or hypercapnia ($P_{E'_{CO_2}} \approx 50$ mm Hg; $n=592$). Investigators blinded to group assignment evaluated perioperative SSI (Center for Disease Control criteria) for 30 postoperative days. SSI rates were compared.

Results. Patient and surgical characteristics were comparable among the groups. The SSI rate for normocapnia was 13.3%, and for hypercapnia, it was 11.2% ($P=0.29$). The Executive Committee stopped the trial after the first *a priori* determined statistical assessment point because of much smaller actual effect compared with the projected. However, because the actual difference found in the SSI rates (15–16%) were within the 95% confidence intervals (CIs) of the projected relative difference of 33% (95% CI −43 to +24%), our results cannot be considered as 'no difference', and cannot exclude a Type II error. Time to first bowel movement was half-a-day shorter in the hypercapnia group.

Conclusions. Mild hypercapnia appears to have little or—possibly—no ability to prevent SSI after colon resection. Other strategies for reducing SSI risk should thus take priority.

Trial registration. ClinicalTrials.gov (NCT00273377).

Keywords: carbon dioxide, hypercapnia; complications, infections; infection; surgery, abdominal; surgery, gastrointestinal

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†A part of the data shown in the manuscript was presented at the American Society of Anesthesiologists annual meeting in Chicago, IL, USA, October 2011.
‡ Participating investigators are listed in Appendix 2.

Background

Surgical site infections (SSIs) are common and serious complications of anaesthesia and surgery.[1–3] Even with the best sterile technique, surgical wounds may become infected. Oxidative killing by neutrophils—the primary defence against pathogens[4 5]—requires molecular oxygen and critically depends on local tissue oxygen partial pressure.[6 7] Consequently, SSI is inversely related to tissue oxygenation during and for a few hours after surgery.[8–10] Tissue oxygenation, reflecting local perfusion and arterial oxygen partial pressure (Pa_{O_2}), is enhanced by cardiac output,[11] pain control,[12] supplemental fluid,[13] management of carbon dioxide,[14 15] and epidural anaesthesia.[16]

Mild hypercapnia also increases subcutaneous[11 17] and splanchnic[14 18] oxygenation and perfusion, primarily by increasing cardiac output and oxygen availability.[19 20] Hypercapnia also appears to be anti-inflammatory when applied during acute lung injury models in animals.[21 22] We therefore tested the hypothesis that mild hypercapnia [end-tidal partial pressure ($P_{E'CO_2}$) of 50 *vs* 35 mm Hg] during general anaesthesia reduces the incidence of SSI (followed up for 30 days) in patients undergoing colon resection.

Methods

With institutional review board approval of participating centres and written consent, we enrolled adults 18–80 yr old who were undergoing elective colon resection expected to last between 2 and 6 h. Exclusion criteria included chemotherapy in the 6 months preceding surgery, anticipated secondary wound closure, fever ($\geq$38°C) or infection at admission, severe COPD [i.e. forced expiratory volume 1 (FEV_1)/forced vital capacity $<$70%; $FEV_1<$50% predicted, with or without chronic symptoms], unstable angina pectoris, hypertensive cardiomyopathy, congestive heart failure (according to the Modified Framingham Criteria), myocardial infarction within 6 months, known bowel obstruction (confirmed or clinical suspicion of obstruction defined by the primary surgeon), and ASA Physical Status $\geq$IV.

Mild hypercapnia increases subcutaneous tissue P_{O_2} by 26–32 mm Hg in patients undergoing major abdominal surgery compared with normocapnia at an $F_{I_{O_2}}$ of 0.40.[14 15] Previous work suggests that using the more conservative 26 mm Hg increase in tissue oxygen partial pressure would reduce infection risk by a third, from 8.2% in normocapnic patients to 5.4% in those assigned to hypercapnia.[8] A total of 1994 patients would therefore provide 80% power to identify a statistically significant difference between the groups at a one-tailed alpha level of 0.05; we therefore planned to study 2000 patients with an interim analysis at 1000 patients.

Protocol

Patients were given electrolyte bowel preparation without antibiotics the night before surgery. According to surgical routine, cefuroxime (1.5 g i.v.) and metronidazole (0.5 g i.v.), cefotetan (2 g i.v.), or ertapenem (1 g i.v.) were given during anaesthetic induction. Propofol (2–4 mg kg^{-1}) were used for induction of anaesthesia and muscle relaxation provided by rocuronium (0.6 mg kg^{-1}) or vecuronium (0.1 mg kg^{-1}); anaesthesia subsequently was maintained with desflurane or sevoflurane, fentanyl, and neuromuscular blocking drugs as clinically required. Postoperative epidural analgesia was permitted.

After induction of anaesthesia, patients were assigned to normocapnia or hypercapnia, stratified by centre. Assignments were based on computer-generated randomizations that were kept in sealed, sequentially numbered envelopes until used. Envelopes were opened in the operating theatre just before the start of surgery. Subjects assigned to normocapnia were maintained at a target intraoperative $P_{E'CO_2}$ of 35 mm Hg; the target in patients assigned to hypercapnia was 50 mm Hg. In hypercapnia patients, CO_2 absorbent was removed from the partial-rebreathing circle system. Tidal volume was set at 8–10 ml kg^{-1} with a respiratory rate of 8–10 bpm , and fresh gas flow was adjusted to maintain $P_{E'CO_2}$ at 50 mm Hg. Patients assigned to normocapnia were similarly ventilated, but with CO_2 absorbent in the partial-rebreathing circle system as usual. Inspired oxygen concentration was controlled at 80% in the initial 620 patients because of the reported beneficial effects of supplemental oxygen.[1] The final 585 patients were assigned to 30 or 80% intraoperative oxygen and to receive 4 mg i.v. dexamethasone or placebo in a factorial approach. During the study enrolment period, new evidence from another randomized controlled trial reported negative results challenging the potential benefits of supplemental oxygen.[23] Therefore, we decided to randomize inspired oxygen concentrations to 30 or 80%. Corticosteroids impair innate immune responses and, as a result, may impair healing. As might be expected, chronic preoperative corticosteroid use increases wound infection risk,[24 25] but there are only very limited data looking into the effect of single-dose corticosteroids on SSI and wound healing.[26] Therefore, we decided to include a single-dose dexamethasone (or placebo) as another treatment factor, which was also assigned under factorial randomization. The current report is restricted to the hypercapnia *vs* normocapnia randomization.

Volatile anaesthetic administration was adjusted to maintain mean arterial pressure (MAP) at ~90% of pre-induction value. Small boluses of phenylephrine (i.e. 50–100 μg) and fluid administration were also used as necessary. Intraoperative crystalloids were generally given at a rate of 6–10 ml kg^{-1} h^{-1}, which is considered as a relatively restrictive approach;[27] however, variations based on clinical judgement were permitted. Target minimum haematocrit (HCT) was determined before randomization based on the patient's age and cardiovascular status. The target HCT was 26% in patients aged $<$65 yr having no significant cardiovascular disease and 28% in patients aged $\geq$65 yr or having cardiovascular disease. Significant cardiovascular disease was defined as history of myocardial infarction or peripheral vascular disease. HCT was maintained $\geq$30% in patients having both significant cardiovascular disease and age $\geq$65 yr. Intraoperative core temperature was maintained near 36°C. Core temperature was maintained to the extent possible with upper body, forced-air covers. Fluids were warmed if necessary. Patients who were

hypothermic (<36°C) upon arrival in the post-anaesthesia care unit were warmed with a full body, forced-air cover.

Anaesthesiologists were not blinded to group assignments, but gas monitors were shielded to prevent surgeons from determining randomized group assignment. After giving the report to the post-anaesthesia care nurse, the anaesthesia record was sealed in an envelope as a part of the blinding process until patient's discharge (except at the University of Vienna and the Cleveland Clinic, which both used electronic records). Postoperative pain relief was maintained by patient-controlled i.v. morphine or hydromorphone analgesia, or by epidural analgesia in patients who received epidural analgesia. Epidural catheters were most often inserted in the lumbar rather than thoracic region; local anaesthetic, epidural opioids, or both were only given after operation.

Attending surgeons, who were blinded to the randomized assignments, made hospital discharge decisions. Discharge timing was based on routine surgical considerations, including return of bowel function, control of infections (if any), adequate healing of the incision, and overall recovery during the post-operative period. Major complications including readmission, anastomotic leak, ileus, wound dehiscence, pneumonia, sepsis, and acute renal failure were monitored up to 30 days after operation (see Appendix 1).

The SSI outcome was monitored for up to 30 days. Patients were called on the 15th and 30th postoperative days for follow-up if they were not at the hospital or surgeon's clinic on those days. Patients were asked to return to their physician or to the hospital if their answers suggested they had an infection.

Measurements

Factors potentially influencing infection risk were recorded, including patient comorbidity, laboratory values, and anaesthetic and surgical management. End-tidal carbon dioxide ($P_{E'_{CO_2}}$) pressures were measured from the side-stream end-tidal gas measurement unit of Datex-Ohmeda systems. Intraoperative haemodynamic values and $P_{E'_{CO_2}}$ were collected every 15 min, and these values were averaged for each patient. Patients were asked to rate their pain on a 10 cm visual analogue scale (VAS) during the first hour of recovery, and on the first postoperative morning. In the recovery period, pain VAS scores were recorded at 30 min intervals. On the first postoperative morning, patients were asked to provide a single VAS value that summarized their pain experience as leaving the recovery unit.

Infection risk was evaluated with the system from the Efficacy of Nosocomial Infection Control (SENIC) of the Centers for Disease Control and Prevention (CDC), which assigns one point for each of the following factors: three or more underlying diagnoses at discharge, surgery that lasts ≥2 h, an abdominal site of surgery, and the presence of a contaminated or infected wound.[28] As in previous studies, we modified the system by using the number of diagnoses at admission rather than at discharge. Although the SENIC score was established well before laparoscopic surgery became common, we designated patients having laparoscopic-assisted colectomies as having an abdominal surgical site. Infection risk was also evaluated with the National Nosocomial Infection Surveillance System, which predicts risk on the basis of the type of surgery, the rating of physical status on a scale developed by the ASA, and the duration of surgery.[29]

SSI was defined by CDC criteria[30] and characterized as superficial incisional, deep incisional, or peritoneal. Wound healing was numerically scored using the ASEPSIS system.[31] This is an established and validated system for quantifying surgical wound infections and evaluating wound healing. The score is derived from the weighted sum of points assigned for the following factors: (i) duration of antibiotic administration; (ii) drainage of pus under local anaethesia; (iii) debridement of the wound under general anaethesia; (iv) serous discharge; (v) erythema; (vi) purulent exudate; (vii) separation of deep tissues; (viii) isolation of bacteria from discharge; and (ix) hospitalization exceeding 14 days.

Wounds were evaluated daily throughout hospitalization by an investigator blinded to treatment. Subsequently, patients were phoned on the 15th and 30th days and a scripted interview was used to inquire about SSI. When answers suggested that infection was likely, efforts were made to obtain relevant records. An investigator blinded to treatment adjudicated infections and complications using all available data.

Data analysis

Our primary outcome was the incidence of SSI within 30 days of surgery. Secondary outcomes included wound-healing scores, return of bowel function, and the duration of hospitalization. Values obtained at intervals throughout surgery were averaged in each patient, and then averaged among the patients in each group. Results were compared using t or χ^2 tests, and non-parametric t-tests as appropriate. Gaussian distributions were used in deciding between parametric and non-parametric test selection with the exception of 'pain-VAS scores' and 'ASEPSIS', which were both planned as non-parametric tests *a priori*. Other outcome parameters analysed with non-parametric tests were first flatus, first food, first bowel movement, and duration of hospitalization.

Results are presented as means (SDS) and medians [interquartile ranges]; $P<0.05$ was considered statistically significant.

Results

For administrative reasons related to data entry and validation, the initial interim analysis, which was to be at 1000 patients, was delayed until 1139 patients were enrolled. Based on a futility analysis, the study was stopped by the Executive Committee. An additional 76 patients were enrolled while the committee evaluated the initial results; consequently, 1215 patients were enrolled when the study was stopped and 1206 included in final analysis. Nine patients were removed from the study by the attending anaethesiologist after randomization, because they did not find the patients suitable to the study. Therefore, no additional data were collected from these patients. Six study centres enrolled patients: University of Vienna (n=369), Cleveland Clinic (n=295), Washington

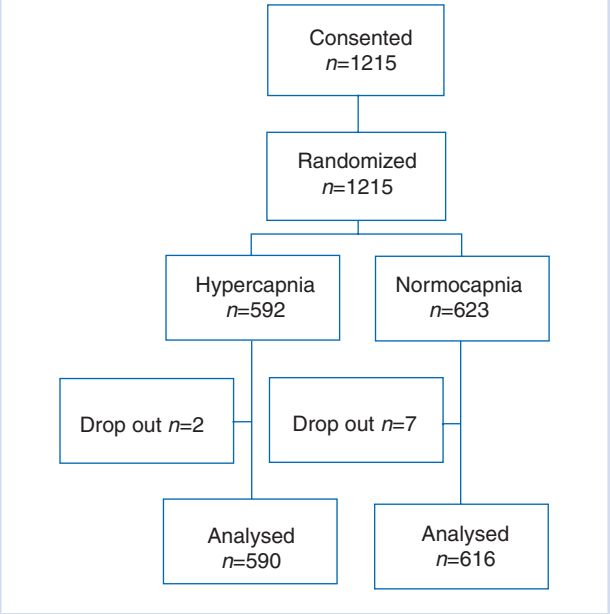

Fig 1 Trial diagram: patient flow.

University ($n=201$), University of Louisville ($n=195$), Mater Misericordiae University Hospital Dublin ($n=96$), and University of Bern ($n=59$). Figure 1 shows the trial profile diagram.

Clinical characteristics, diagnoses, surgical procedures, duration of surgery, haemodynamic values, and anaesthetic management were generally similar in patients randomized to each intervention (Table 1). Prophylactic antibiotics were given 36 (40) min [mean (SD)] before the surgery started. Patients in the initial randomization ($n=629$) and the factorial randomization ($n=586$) were similar based on their patient characteristic, morphometrics, primary illnesses, type of surgery, and medical history.

Pa_{CO_2} was 5.2 (1.3) kPa in patients assigned to normocapnia and 7.1 (0.9) kPa in those assigned to hypercapnia. $P_{E'CO_2}$ values, which were recorded every 15 min throughout surgery, were 4.7 (0.7) kPa and 6.3 (0.8) kPa, respectively. $P_{E'CO_2}$ values corresponding to the randomized carbon dioxide levels are presented in Figure 2 to show compliance to randomization. The major reason clinicians obtained arterial blood analysis was to determine haemoglobin concentrations; Pa_{CO_2} values were thus available only in a subset of the study population (518 patients). In 72 of these patients (~14%), at least one pH measurement was <7.25. There were a total of 14 values of pH<7.20 of 518 (2.7%). All but 1 of the 14 values were in the hypercapnia group (5%).

Overall, SSI rates in the centres ranged from 8 to 20% ($P=0.098$), but the rates were similar in each centre as a function of randomized treatments. There were also no significant differences among the treatment groups in ASEPSIS score, duration of hospitalization, major complications, or mortality. A total of 160 patients received epidural analgesia; their incidence of SSI was 10%. After accounting for randomized carbon dioxide management, there were no differences in SSI rates in patients who did and did not receive epidural analgesia ($P=0.48$).

Major complications included readmission in 49 patients, electrolyte imbalance in 17, anastomotic leak in 12, ileus in 6, wound dehiscence in 6, pneumonia in 6, sepsis in 5, and acute renal failure in 5. The first postoperative bowel movement was about half a day earlier in the hypercapnia compared with the normocapnia group ($P=0.007$, Table 2).

SSI developed in 11.2% of the 590 subjects who received hypercapnia and in 13.3% of the 616 who received normocapnia (two-tailed Fisher's exact test, $P=0.29$). The relative risk [interim-adjusted 95% confidence interval (CI)] was 0.84 (0.57, 1.24), $P=0.24$. The observed Z-statistic of -1.2 crossed neither the efficacy boundary ($Z<-2.5$) nor the futility boundary ($Z>-0.238$). However, the conditional power for finding a statistically significant difference if the study were to continue to completion with a similar trend was only 50%. If the study had continued with the hypercapnia and normocapnia groups having the same rate of SSI, 4168 patients would have been needed to reach an α (P) of 0.05 under 90% power. The Executive Committee thus stopped the trial.

As shown in Figure 3, the SSI rate was associated with body mass index (BMI, $P<0.01$ multivariate). Surgical approach (laparoscopic-assisted *vs* open), ASA, and SENIC scores did not significantly influence the incidence of SSI. Overall mortality was too low to be considered within any comparison, and, more importantly, the study was not powered for this outcome.

Discussion

In this large multicentre randomized-controlled trial, we could not prove our hypothesis that mild hypercapnia reduces the incidence of SSI in colorectal resection surgery patients. The study was stopped by the Executive Committee at the interim analysis—without passing the futility boundary—because the chances of a positive outcome were low even if the trial continued to the planned sample size of 2000. We considered an effect of 33% relative decrease in the SSI rate in our sample size estimate. Such relative difference represented a 2.8% absolute difference between the projected SSI rates, because our estimated SSI rates, which were used as base levels in our sample-size estimate, were relatively low (8.2 *vs* 5.4%) compared with the current rates of 11–13% or even higher previously published rates of 13–28%.[32] Our low SSI estimate represented the data from a large study we performed in colorectal surgery patients more than a decade ago.[1]

In spite of the relatively large difference between the projected SSI rates and the current actual SSI frequency, our results showed an absolute difference of 2.1% between the study groups. Obviously, the observed 2.1% difference is not much different than the projected absolute difference of 2.8%. However, the relative difference is the parameter that drives the statistically significant difference and is, therefore, the essential component of sample-size estimates. The current difference of 2.1%, which converts to a relative difference of 15–16%, is less than half of the projected 33% relative difference (efficacy). On the other hand, our projected relative

Table 1 Patient characteristic, morphometric, and potential confounding factors*. *Results presented as means (SDS) or percentage. †Numbers in parentheses beside the values in the first column represent either the missing data (i.e. missing '*n*'/total '*n*') or the '*n*' of the data source. ‡Blood loss data presented as median and inter-quartile range. MAC, minimum alveolar concentration; MAP, mean arterial pressure; VAS, visual analoge scale.

	35 mm Hg (*n*=616)	50 mm Hg (*n*=590)
Baseline		
Sex (M/F) (35/1206)†	310/288	303/270
Weight (kg) (30/1206)	78 (19)	77 (20)
Height (cm) (77/1206)	171 (13)	171 (11)
BMI (kg) m^{-2} (99/1206)	26.7 (6.2)	26.6 (6.5)
Age (yr) (114/1206)	53 (16)	51 (16)
ASA Physical Status 1/2/3 (%) (90/1206)	23/56/21	23/59/18
History of smoking [*n* (%)] (109/1206)	166 (30%)	176 (33%)
Current smoker [*n* (%)]	137 (25%)	155 (29%)
Diabetes [*n* (%)]	55 (9%)	37 (6%)
Diagnosis (%) (92/1206)		
Cancer	280 (50%)	247 (45%)
Inflammatory bowel disease	162 (29%)	181 (33%)
Other	118 (21%)	126 (23%)
Approach (%) (112/1206)		
Open	410 (73%)	367 (69%)
Laparoscopic-assisted	153 (27%)	164 (31%)
Intraoperative		
Fentanyl (mg) (163/1206)	0.69 (0.93)	0.67 (0.85)
MAC (155/1206)	0.82(0.36)	0.82 (0.33)
MAP (mm Hg) (70/1206)	82 (10)	80 (10)
Heart rate (beats min^{-1}) (69/1206)	76 (12)	78 (12)
Crystalloid (ml kg^{-1}) (140/1206)	45 (23)	46 (23)
Crystalloid (ml kg^{-1} h^{-1})	12(4)	12(5)
Colloid (ml kg^{-1}) (*n*=614)	10 (6)	11 (9)
Blood lost (ml)‡ (44/1206)‡	250 [150–500]	250 [100–500]
Red-cell transfusions (*n*=970)		
Patients (%)	67/503 (13%)	64/467 (14%)
Units of red cells	2.0 (1.2)	2.1 (1.1)
First oesophageal temperature (°C) (61/1206)	36.2 (0.5)	36.2 (0.4)
Final oesophageal temperature (°C) (72/1206)	36.1 (0.5)	36.1 (0.5)
Glucose (mg dl^{-1}) (*n*=487)	122(50)	124(39)
Arterial oxygen saturation (%) (*n*=439)	99 (2)	99 (2)
$P_{E'CO_2}$ (kPa) (32/1206)	4.7 (0.7)	6.3 (0.8)
pH (*n*=518)	7.37 (0.06)	7.29 (0.06)
Pa_{CO_2} (kPa) (*n*=518)	5.2 (1.3)	7.1 (0.9)
Pa_{O_2} (kPa) (*n*=518)	28.1 (16.8)	30.9 (15.3)
$F_{I_{O_2}}$ (36/1206)	68 (19)	69 (18)
Postoperative care unit		
Pain VAS (cm) (335/1206)	4.8 (2.7)	4.8 (3.1)
Nausea (%) (*n*=525)	125 (43%)	111 (44%)
Emesis (%) (*n*=556)	5 (2%)	4 (2%)
SENIC score 1/2/3 (%) (45/1206)	21/70/10	22/68/10
First postoperative day		
Pain VAS (cm) (370/1206)	4.6 (3.0)	4.7 (3.1)
Nausea (%) (*n*=525)	125 (43%)	103 (43%)
Emesis (%) (*n*=542)	34 (12%)	19 (8%)

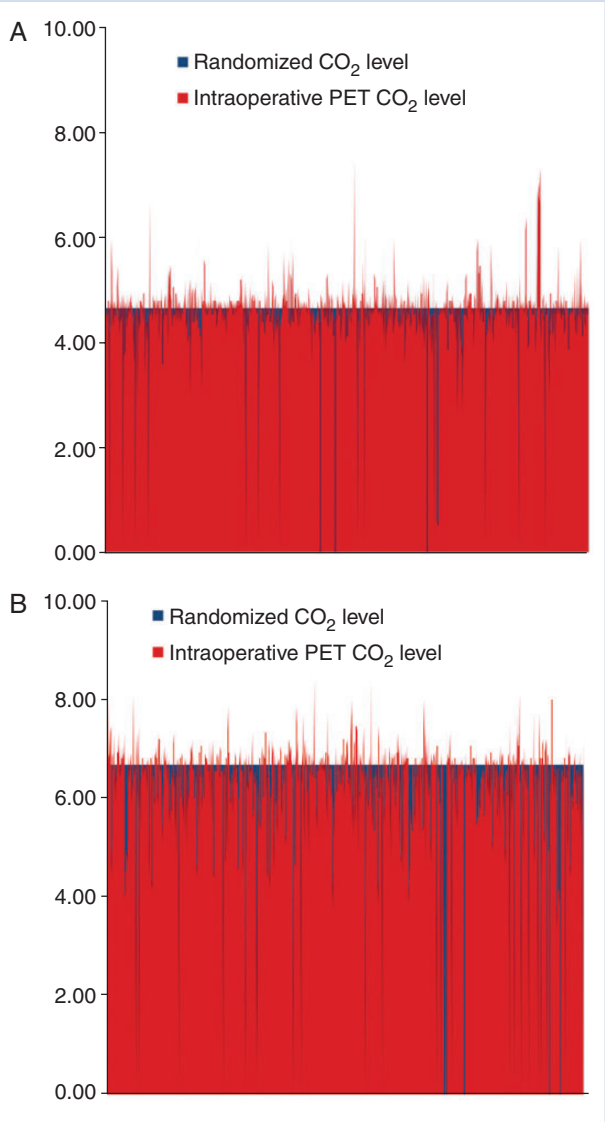

Fig 2 Randomized CO_2 level *vs* $P_{E'CO_2}$ presented for both normocapnia (35 mm Hg; A) and hypercapnia (50 mm Hg; B) groups. Exact values recorded from the E'_{CO_2} monitor were presented red and randomized CO_2 area appears in blue. The *y*-axis represents CO_2 pressures (mm Hg), and the *x*-axis represents the record numbers for $P_{E'CO_2}$ values collected.

Table 2 Postoperative Outcomes by Randomization Group (univariable)*. *Results presented as number of patients (percentage) or means (SDS). †Any CDC infection numbers are not simple totals of all the above infections. Some patients experienced superficial and deep infections simultaneously. ‡ASEPSIS score data are presented in median [inter-quartile]. *P*-values represent results of two-tailed analyses

	4.7 kPa ($n=616$)	6.6 kPa ($n=590$)	*P*-value
SSI diagnosed by CDC criteria			
Superficial	63 (10.2)	49 (8.3)	0.269
Deep	27 (4.4)	30 (5.1)	0.546
Peritoneal	7 (1.1)	5 (0.8)	0.188
Any SSI infection (CDC criteria)†	82 (13.3)	66 (11.2)	0.292
ASEPSIS score‡	1 [0–4]	1 [0–3]	0.087
Epidural analgesia	80 (13)	78 (13)	0.932
First flatus, days after surgery	3.3 (2.3)	3.1 (1.7)	0.201
First solid food, days after surgery	4.7 (3.9)	4.3 (2.6)	0.131
First bowel movement, days after surgery	4.5 (3.3)	4.0 (2.6)	0.007
Duration of hospitalization after surgery, days	8.5 (4.9)	8.4 (5.2)	0.594
Patients with 30 day major complications	43 (7.0)	34 (5.8)	0.411
Patients with 30 day mortality	4 (0.6)	1 (0.2)	0.375

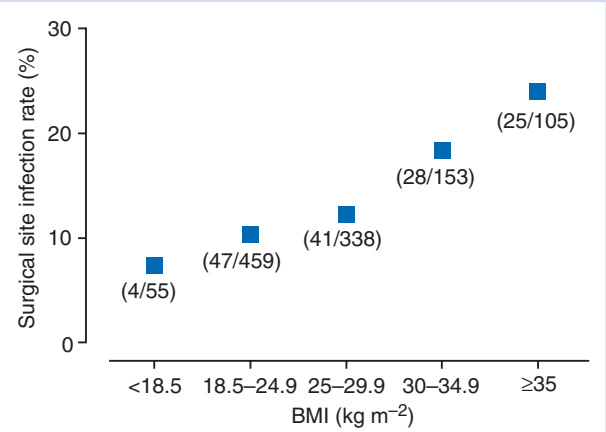

Fig 3 SSI risk as a function of BMI, ($P=0.025$, χ^2). Data are presented as means. The actual number of infections per number of subjects in each BMI range is given in parentheses.

difference of 33% (i.e. 33% reduction) is still within the 95% CI of the actual difference found (44% reduction to 24% increase). This means the observed treatment effect's CI ranged from a relative risk of 0.57 to 1.24, is consistent with a true treatment effect ranging from a 43% reduction to a 24% increase in infection rates. Therefore, this study cannot totally be considered as a study with no difference, and so there is the possibility of a Type II error. Although our results did neither cross the futility border nor report a strongly negative trial, we could not justify more than doubling our study patients compared with the projected sample-size because of limited funding. As a result, the Executive Committee decided to stop the trial prematurely at the time of initial interim analysis.

Cardiac index increases 10–15% for each 10 mm Hg increment in Pa_{CO_2}.[11 33 34] Increasing Pa_{CO_2} also shifts the oxyhaemoglobin dissociation curve rightward and decreases systemic vascular resistance, thereby improving tissue oxygen availability.[18 33–35] That mild hypercapnia improves cardiac output, increases systemic oxygen delivery, and increases both peripheral subcutaneous tissue and splanchnic oxygenation are well established facts in animals, human volunteers, and patients.[14 18 33–35] Improved oxygenation enhances surgical outcomes.[36] There was thus considerable reason to believe that mild-to-moderate hypercapnia would reduce the risk of SSI. Nonetheless, hypercapnia's effect was found much smaller than expected, and we therefore could not show a reduction in the incidence of SSI in our patients.

It is possible that a yet-to-be-detailed effect of hypercapnia in immune responses negated the putative benefits of improved tissue oxygenation. Hypercapnia may impair innate immunity or alter wound healing, especially during the perioperative period.[37–39] However, the most likely explanations for our surprising finding are that either hypercapnia could not increase tissue oxygenation by 25–30 mm Hg as expected,[14 15] which was possibly attributable to a perfusion compromise that blunted the tissue oxygen delivery, or hypercapnia caused increased tissue oxygenation increase, but possibly the rate of oxygenation increase was insufficient to produce a clinically important reduction in infection risk in the specific setting tested. Because tissue oxygen tensions were not measured in this study, these explanations are only hypothetical.

In this study, we did not measure tissue oxygenation, because the relationship between Pa_{CO_2} and tissue oxygen partial pressure is well established.[11 33 34] However, there is still a chance that our intervention of application of mild hypercapnia did not alter tissue oxygenation at the same ratio we have shown before.

Another major factor influencing tissue oxygenation is arterial oxygen level itself. Similar ranges of inspired oxygen were applied in both study patient groups, and the resulting Pa_{O_2} values obtained were similar in patients in whom blood-gas analyses were done. Arterial blood gas measurements were not required by protocol, but the results were recorded

when obtained for clinical reasons. In the light of our previous trials, the effects of F_{IO_2} on arterial oxygenation in the colorectal surgery setting were considered to be predictable. However, our current data proved this wrong, because Pa_{O_2} levels for the F_{IO_2} 0.80 group were comparably lower than published previous trials.[1 40] One explanation for this is a possible selection bias. Because arterial blood-gas analysis was not enforced in the current trial, it is likely that the analysis was done in sicker patients with expected oxygenation problems.

After discharge, patients were followed up with standardized phone interviews. Patients were asked to return to their physician or to the hospital if their answers suggested they had an infection. Although post-discharge SSI was uncommon, partial reliance on phone interviews for a major study outcome was a limitation of our trial.

Prevalence of obesity has gradually increased in the population since the first study of supplemental oxygen and infection was published a decade ago. Obesity reduces tissue oxygenation.[17 41 42] It is also well established that obese patients experience more perioperative complications and increased SSI rates.[43] Our results extend previous findings by presenting a clear 'dose–response' type relationship between BMI and SSI. The infection rate was more than doubled in patients with a BMI >35 kg m^{-2} compared with patients with BMI 18–25 kg m^{-2}. Prevention measures, such as timely application of appropriate prophylactic antibiotics[44] and maintaining perioperative normothermia,[2] may thus be especially important in obese patients.

Laparoscopic colorectal surgery was shown to decrease SSI rate,[45] but this effect was not always consistent.[46] Laparoscopic colonic surgery significantly decreases tissue oxygenation early in the course of surgery.[47] As tissue oxygenation is one of the most important predictors of SSI,[8 48] inconsistency in results is unsurprising. Laparoscopic surgery was not an independent risk factor of SSI in our study.

The Executive Committee stopped the trial because the treatment effect appeared to be too small and unlikely to reach statistical significance even if the study was carried to completion. However, there was a slight apparent treatment effect, with infection rates of 11.2 and 13.3% in the hypercapnia and normocapnia groups, respectively. It thus remains possible that hypercapnia reduces the risk of SSI; but if it does, the effect appears to be small and could only be demonstrated by a very large trial.

In conclusion, it is well established that mild-to-moderate hypercapnia increases tissue P_{O_2} by roughly 25–30 mm Hg. However, the risk of SSI was not significantly reduced in 1206 patients randomized to mild hypercapnia ($P_{E'_{CO_2}}=50$ mm Hg, $n=590$, 11.2% SSI) compared with normocapnia ($P_{E'_{CO_2}}=35$ mm Hg, $n=616$, 13.3% SSI). Mild hypercapnia appears to have little or possibly no ability to prevent surgical wound infections in the colorectal surgery setting tested.

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Declaration of interest

None declared.

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Table A1 Major complications. These complications are chosen to be serious and plausibly related to infection or wound healing. †RIFLE-F criteria is defined as either an increase in serum creatinine $>3\times$ of baseline or creatinine $>4.0\,mg\,dl^{-1}$ or urine output $<0.3\,ml\,kg^{-1}\,h^{-1}$ for 24 h or anuria for 12 h.[49]

Complication	Requirements for acceptance
Wound complications	
Necrosis of stoma	Intraperitoneal necrosis needing surgery
Surgical wound infection	CDC criteria
Intra-abdominal abscess	Ultrasound or CT scan or surgical confirmation
Ileus	Surgical, X-ray, and CT scan confirmation
Peritonitis without leak	Surgery, excepting anastomotic leak
Anastomotic leak	Leak confirmed during secondary surgery
Wound dehiscence	Requiring secondary suture of fascia for treatment
Respiratory complications	
Pneumonia	According to the modified CPIS or CDC criteria*
Respiratory insufficiency-*Moderate-Severe*	Requiring reintubation and mechanical ventilation
Cardiovascular complications	
Acute MI	Increased levels of cardiac enzymes or new Q waves
Congestive heart failure	Proved with CXR—pulmonary congestion
General—major complications	
Sepsis	Positive blood culture and at least two of the following: Hypo- or hyperthermia, tachycardia, tachypnoea, leucopenia/leucocytosis (DIC), or multi-organ dysfunction
Bleeding	Requiring transfusion and surgery
Gastrointestinal bleeding	Requiring transfusion, surgery, or both
Electrolyte imbalance	Electrolyte levels beyond normal laboratory levels
Acute renal failure	Requiring dialysis or RIFLE-F criteria†
Death	All-cause mortality

Appendix 1

Major Complications are given in Table A1.

Appendix 2

Hypercapnia Trial Investigators

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