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Chapter 3

Influence of variations in arterial pCO$_2$ on evaluation of surgical conditions during laparoscopic surgery

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ABSTRACT

Background

Although deep neuromuscular block (post-tetanic-count 1-2 twitches) improves surgical conditions during laparoscopic retroperitoneal surgery compared to a standard block (train-of-four 1-2 twitches), the quality of surgical conditions varies widely, possibly related to diaphragmatic contractions. Hypocapnia may improve surgical conditions by silencing the diaphragm. In this study we assessed the effect of changes in arterial carbon dioxide concentrations on surgical conditions in patients undergoing laparoscopic surgery under general anaesthesia and deep neuromuscular block.

Methods

Forty patients undergoing elective laparoscopic surgery for prostatectomy or nephrectomy received propofol/ remifentanil anaesthesia and a deep neuromuscular block with rocuronium. Patients were randomized to surgery under hypocapnic or hypercapnic conditions. During surgery, the surgical conditions were evaluated using the 5-point Leiden- surgical rating scale (L-SRS) ranging from 1 (extremely poor conditions) to 5 (optimal conditions) by the surgeon, who was blinded for the randomization allocation.

Results

Mean (SD) arterial carbon dioxide concentrations were 4.5 (0.6) kPa under hypocapnic and 6.9 (0.6) kPa under hypercapnic conditions. The L-SRS did not differ between groups: 4.84 (0.4) in hypocapnia and 4.77 (0.4) in hypercapnia. Ninety-nine percent of ratings were good or optimal irrespective of the treatment.

Conclusions

Deep neuromuscular block provides good to optimal surgical conditions in laparoscopic retroperitoneal urological surgery, independent of the level of arterial pCO_2.

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INTRODUCTION

Anaesthetists play an essential role in optimizing surgical conditions. This is especially true for procedures which are performed in a narrow space, such as laparoscopic retroperitoneal surgery and robot-assisted laparoscopic surgery.[1, 2] We recently showed that application of a deep neuromuscular block (deep NMB, 1-2 twitches post- tetanic- count) significantly improves surgical conditions in laparoscopic retroperitoneal prostatectomies and nephrectomies and greatly reduces the incidence of unacceptable conditions.[1] Similar observations were made by others for laparoscopic gynaecological procedures and laryngeal microsurgery.[3, 4] Despite the improvement of surgical conditions at deep muscle relaxation, the variation in surgical conditions is still high (>20%), indicating that there is still room for improvement.[1] Also other studies show that that during deep NMB suboptimal surgical conditions may persist. For example, Fernando et al. showed that at deep NMB (PTC values 1-2 twitches) diaphragmatic contractions still occur.[5] Causes of such diaphragmatic contractions include resistance to muscle relaxants (diaphragm relaxation is often less intense compared to relaxation of the adductor pollicis longus muscle) as well as efferent activation from brainstem respiratory centres due to high arterial CO$_2$ levels. The latter item is relevant as CO$_2$-insufflation with high intra-abdominal pressures during laparoscopic surgery coincides with high arterial CO$_2$ concentrations even when end-tidal concentrations suggest values in the normal range.

One possible method to reduce high CO$_2$-related diaphragm contractions is to hyperventilate the patient to (sub)normal arterial pCO$_2$ levels. Application of this technique has been used before to reduce the dose of anaesthetics and to improve surgical conditions when standard relaxation is applied (TOF 1-2 twitches).[6-8] Here we study the effect of hyperventilation to assess whether we can further improve surgical conditions during deep neuromuscular relaxation. We hypothesize that the induction of hypocapnia during laparoscopic surgery improves surgical conditions compared to hypercapnia.

METHODS

The study with acronym BLISS2 was carried out at Leiden University Medical Centre between February 2013 and September 2015 after approval was obtained of the protocol (protocol number P13.127) by the local medical ethics committee (Commissie Medische Ethiek). The protocol was registered at clinicaltrials.gov under number NCT01968447. The study was conducted in accordance with Good Clinical Practice and Good Research Practice guidelines. Eligible patients were approached in advance by one of the investigators and received oral and written information about the study. If a patient was willing

and able to participate, oral and written informed consent was obtained. The study had a randomized (hypocapnia against hypercapnia), double-blinded design (the surgical team and the investigators were blinded to treatment allocation; the attending anaesthetist was not blinded). Randomisation was performed using a computer-generated randomization list obtained from www.randomization.com. The attending anaesthetist, who received the randomization code just prior to induction of anaesthesia, was responsible for setting the desired tidal volume and respiratory rate on the anaesthesia ventilator (Primus, *Dräger Medical Netherlands BV,* Zoetermeer, the Netherlands).

American Society of Anesthesiologists (ASA) class I-III patients were included if they had prostatic or renal disease requiring elective laparoscopic retroperitoneal surgery. Patients were excluded if they were < 18 years of age, ASA class > III, had a known or suspected neuromuscular disorder, allergies to medication to be used during anaesthesia, a (family) history of malignant hyperthermia, renal insufficiency (as defined by glomerular filtration rate of < 30 mL.h^{-1}), previous retroperitoneal surgery at the site of the current surgery, a body mass index > 35 kg.m^{-2} or chronic obstructive pulmonary disease GOLD 2 or higher.

Perioperative protocol

All patients received total intravenous anaesthesia with propofol, remifentanil and rocuronium; the patients inhaled 40% oxygen in nitrogen. Monitoring was according to local practice and consisted of ECG, blood pressure and EEG monitoring (BIS module, *Philips,* Eindhoven, the Netherlands). Throughout surgery BIS values were kept between 45-55. A 22-gauge arterial cannula was placed in the radial artery of the left or right wrist and connected to a Vigileo advanced minimally invasive monitoring system (*Edwards Lifesciences*, USA) for hemodynamic monitoring. The arterial cannula was further used to obtain blood samples for arterial pCO$_2$ measurements at 15 min intervals.

Neuromuscular monitoring was performed using the TOF cuff device (*RGB Medical Devices,* SA, Madrid, Spain).[9] The TOF cuff is an upper arm cuff that was applied contralateral to the blood pressure cuff. The cuff incorporates two electrodes that stimulate the ulnar nerve. The evoked neuromuscular activity is recorded by measuring the pressure change induced by the muscular activity from stimulation. In comparison with mechanomyography (gold standard), the TOF cuff has an acceptable bias and limits of agreement, which compares to acceleromyography.[9] In a few patients we compared the TOF cuff with the TOF watch and observed similar results. Hence, we contend that using the TOF cuff resulted in a reliable assessment of neuromuscular function during anaesthesia. The TOF cuff is easier to use in patients in the lateral position or when the arm is hidden below the surgical drapes.

The TOF cuff was calibrated after induction but before administration of rocuronium. Thereafter, rocuronium 1.0 mg.kg^{-1} was given and a continuous rocuronium infusion was started at 0.2-0.6 mg.kg^{-1}.h^{-1}. The depth of neuromuscular block was closely monitored and aimed at 1-2 twitches post-tetanic count (PTC; *i.e.* a deep NMB). At the end of surgery, the deep NMB was reversed with a bolus dose of sugammadex 4 mg.kg^{-1}. The patient was extubated when the TOF ratio was > 0.9 and the patient was breathing spontaneously and opened his/her eyes on request. For postoperative pain relief, morphine 0.15-0.2 mg.kg^{-1} was given at least 45 min before surgical closure.

All patients were randomized before induction of anaesthesia and the "time out" procedure. Allocation to treatment was performed just prior to intra-abdominal insufflation of carbon dioxide. Patients were randomly assigned to one of two treatment groups. *Group 1:* hypocapnia during surgery (arterial pCO$_2$ range 3.5 to 4.5 kPa or 26 to 34 mmHg). The tidal volume of the ventilator was set at 7 mL.kg^{-1} and the respiratory rate at 16 min^{-1}; *Group 2:* hypercapnia during surgery (arterial pCO$_2$ range 6.5 to 7.5 kPa or 49 to 53 mmHg). The tidal volume of the ventilator was set at 7 mL.kg^{-1} and the respiratory rate at 11 min^{-1}. Insufflation rates were adjusted such that the target arterial pCO$_2$ was maintained throughout the laparoscopic procedure. However, the attending anaesthetist could deviate from the protocol at his/her discretion. In both treatment groups PEEP values were kept constant during anaesthesia at 5 mmHg.

The Leiden - Surgical Rating Scale (L-SRS)

During the laparoscopic procedure, the surgical field was rated by one surgeon (RB), with ample experience in laparoscopic retroperitoneal renal and prostatic surgery, using the Leiden - surgical rating scale (L-SRS).[1] The L-SRS is a five-point scale, which covers the quality of the surgical field from extremely poor to optimal conditions (see Table 1 in Ref. 1 for a detailed description of the L-SRS). If the rating was 3 or lower, the surgeon and anaesthesia team would negotiate ways to improve the surgical working field. For example, a bolus of rocuronium 15 mg could be given in case of suboptimal neuromuscular block and the infusion rate increased by 20% or propofol 30 mg in case of high BIS values. The L-SRS is currently used in multiple studies to assess the influence of anaesthesia on the surgical field in retroperitoneal, laparoscopic, thoraco-laparoscopic and microlaryngeal surgeries.[1, 2, 10, 11]

Sample size calculation

The primary end-point of this study is the L-SRS. Our previous study yielded a mean surgical rating score of 4.7 during deep NMB. [1] However, in that study, arterial pCO$_2$ was not controlled resulting in hypo- or hypercapnic conditions in some patients. Also, depth of anaesthesia was not controlled, possibly resulting in deep levels of anaesthesia (BIS <

40), which may have confounded the study outcome to some extent. A realistic *a priori* estimation of the L-SRS in the current study was 4.1-4.3 in the hypercapnic group and 4.8-4.9 in the hypocapnia group. The estimated mean difference between the treatment groups was therefore conservatively estimated to be 0.5. Assuming a standard deviation of 0.45, a sample size of at least 19 subjects would provide at least 90% power to observe the expected difference at alpha = 0.05.

Data and statistical analysis

The following clinical variables were collected on the case record form: surgical variables (L-SRS, retroperitoneal pressure), anaesthesia variables (BIS, TOF or PTC, drug dosages), hemodynamic variables (arterial blood pressure, heart rate, cardiac index) and respiratory variables (arterial and end-tidal pCO_2, tidal volume, respiratory rate, inspiratory pressure, PEEP). Repeated measurements were made at 15 min intervals.

Data analysis was based on an intent-to-treat basis. A linear mixed model with an autoregressive covariance structure was used to determine the effect of hypocapnia against hypercapnia on the primary end-point, L-SRS. Secondary end-points were the effect of hypocapnia against hypercapnia on cardiorespiratory variables. These variables were averaged over time to get an indication of their mean value. Treatment effects were evaluated on the average data by *t*-test. The data were analyzed with SPSS (v. 22; *IBM corporation*, Armonk, NY, USA0). All data are presented as mean ± SD unless otherwise stated. p-values < 0.05 were considered significant.

RESULTS

The flow chart of the study is given in Figure 1. After randomization, three randomized patients were not studied due to inability to insert an arterial line ($n = 2$) and a decision to perform open surgery at the pre-surgical "time-out". These three patients were replaced. In total 40 patients in both groups received the allocated treatment and were analyzed. Patient characteristics and data obtained at screening did not differ between groups (Table 1).

Anaesthesia, pCO_2 and neuromuscular blockade

The use of anaesthetics and opioids did not differ between groups. Also, post-tetanic-count values were comparable (3.2 - 3.8), indicative of a similar deep NMB in both treatment groups (Table 2). Figs. 2A and B show the individual profiles of the end-tidal pCO_2 over time for the two study groups and the individual mean end-tidal and arterial pCO_2 values. The end-tidal pCO_2 differed by 2.3 kPa between treatments: hypocapnia 3.4 (0.2)

3

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┌─────────────────────┐
│   Assessed for      │
│ eligibility: n=49   │
└─────────────────────┘
          ┆          ┌──────────────────────────────────────────┐
          ┆ ─ ─ ─ ─ ─│ Not meeting inclusion criteria:   n=2    │
          ┆          │ Declined participation:           n=4    │
          ▼          └──────────────────────────────────────────┘
┌─────────────────────┐
│   Randomized:       │
│      n=43           │
└─────────────────────┘
          ┆          ┌──────────────────────────────────────────┐
          ┆ ─ ─ ─ ─ ─│ No arterial line inserted:        n=2    │
          ┆          │ Immediate conversion to open:     n=1    │
          ▼          └──────────────────────────────────────────┘
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Allocated to group 1: n=20	Allocated to group 2: n=20
Analyzed: n=20	Analyzed: n=20
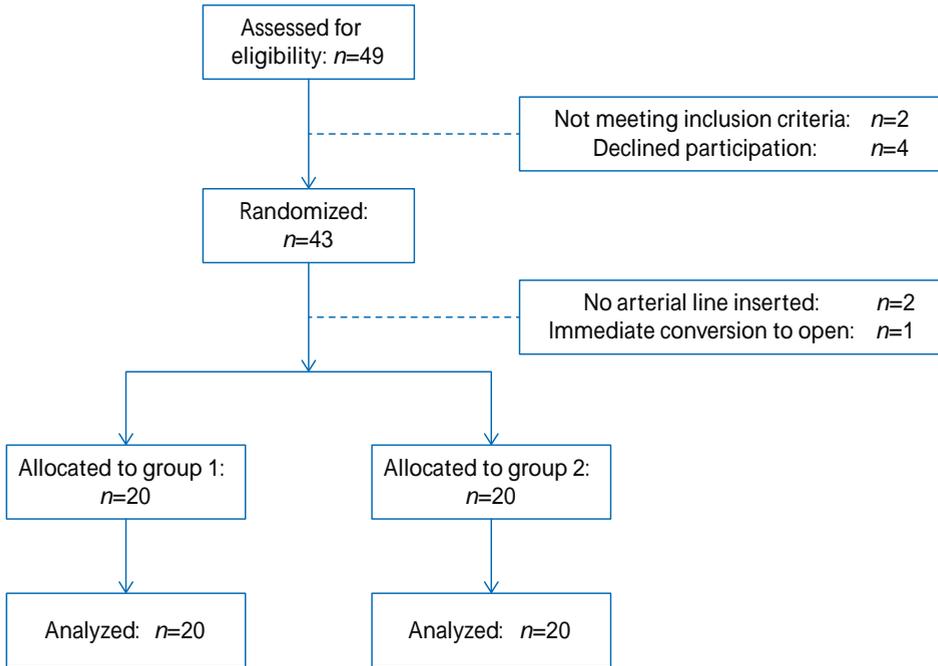
Figure 1. Study flow chart

Table 1. Patient characteristics and data obtained at screening.

	Hypocapnia (n=20)	Hypercapnia (n=20)
Prostate surgery (n)	13	11
Renal surgery (n)	7	9
ASA class I (n)	8	3
ASA class II (n)	12	17
Gender M/F (n/n)	17/3	14/6
Age (years; median, range)	65 (22-80)	62 (25-72)
Weight (kg)	81 (12)	81 (17)
Height (cm)	176 (10)	175 (9)
BMI (kg.m^{-2})	26,1 (3.4)	26.3 (4.3)
BP systolic (mmHg)	137 (15)	139 (16)
BP diastolic (mmHg)	81 (11)	85 (12)
Heart rate (min^{-1})	77 (16)	74 (14)

Data are presented as mean (SD) unless stated otherwise.

Table 2. Measurements during anaesthesia and surgery.

	Hypocapnia	Hypercapnia
Duration (min)	184 (43)	170 (50)
BIS	41 (3)	43 (5)
Propofol (g)	1.7 (0.4)	1.5 (0.5)
Remifentanil (μg.kg^{-1}.min^{-1})	0.21 (0.06)	0.19 (0.08)
Rocuronium (mg)	223 (65)	201 (94)
Sugammadex (mg)	317 (77)	334 (96)
Post-tetanic-count	3.2 (2.4)	3.8 (3.3)
Retroperitoneal pressure (mmHg)	11 (1)	11 (1)
Leiden – surgical rating scale	4.84 (0.4)	4.77 (0.4)*
Mean arterial pressure (mmHg)	85 (10)	81 (9)
Heartrate (min^{-1})	68 (11)	69 (9)
Cardiac output (L.min^{-1})	3.9 (1.1)	4.4 (1.3)
Arterial pCO$_2$ (kPa)	4.5 (0.6)	6.9 (0.6)**
Arterial pCO$_2$ range (kPa)	3.8-5.6	6.1-8.1
End tidal CO$_2$ (kPa)	3.4 (0.2)	5.7 (0.5)**
Minute volume (L.min^{-1})	12.5 (2.1)	7.1 (1.3)**
Respiratory rate (min^{-1})	20.3 (3.0)	12.7 (1.6)**
Inspiratory pressure (cm H$_2$0)	25 (4)	22 (2)*
Peep (cm H$_2$0)	5 (0.6)	5 (0.3)

Values are mean (SD). * $p>0.05$, ** $p<0.001$

kPa with a range of 3.0 to 3.7 kPa and hypercapnia 5.7 (0.5) kPa with a range of 4.9 to 6.8 kPa. Similarly, arterial pCO$_2$ differed by 2.4 kPa between treatments: hypocapnia 4.5 (0.6) kPa (range 3.8-5.6 kPa) and hypercapnia 6.9 (0.6) kPa (range 6.1 – 8.1 kPa). A clear difference between arterial and end-tidal pCO$_2$ was present during both hypocapnia and hypercapnia and averaged to 1.2 (0.1) kPa (Fig. 2). As is visible in panels C and D of Figure 2, the difference tended to slowly increase over time.

Rating of surgical conditions

We obtained 9 to 12 scores per patient. In Figure 3A, the mean scores over time are given for the two treatment groups. The scores did not differ between groups (p = 0.59). The mean of the mean L-SRS scores were: hypocapnia group 4.84 (0.4) against hypercapnia group 4.77 (0.4) (Fig. 3B). The distribution of the individual L-SRS scores is given in Figure 3C, showing that 99% of all scores were good or optimal, irrespective of the arterial pCO$_2$ conditions. There was no correlation between end-tidal pCO$_2$ and L-SRS (Fig. 3D, Pearson r = 0.02, p = 0.9) or between arterial pCO$_2$ and L-SRS (r = -0.08, p = 0.67).
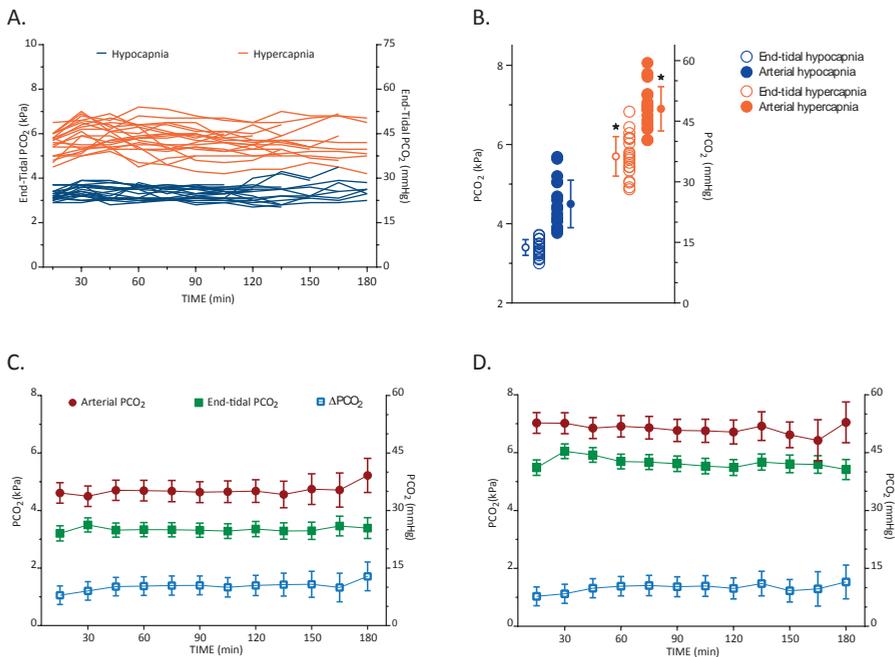
Figure 2. A. Individual end-tidal pCO$_2$ values over time. Blue lines hypocapnia, orange lines hypercapnia. **B.** Individual mean end-tidal and arterial pCO$_2$ values and mean of the means (SD). * p < 0.001. **C** and **D.** Profiles of the arterial pCO$_2$, end-tidal pCO$_2$ and difference between arterial and end-tidal pCO$_2$ (ΔpCO$_2$) under hypocapnic (**C**) and hypercapnic conditions (**D**). Data are mean ± 95% confidence interval.

Measurements following surgery

NMB reversal was by sugammadex 4 mg.kg^{-1} and resulted in optimal extubation conditions (train-of-four ratio > 0.9) within 3 min in all patients. Postoperative pain scores were similar between groups (data not shown).

DISCUSSION

We tested the hypothesis that hypocapnia would improve surgical conditions during retroperitoneal laparoscopic surgery and deep muscle relaxation, as rated by the Leiden-surgical rating scale To emphasize any difference between the treatment groups, we compared hypocapnic conditions against hypercapnic (rather than normocapnic) conditions induced by differences in respiratory rate. We cannot reject the null-hypothesis as no differences were observed in L-SRS (mean L-SRS hypocapnia 4.84, hypercapnia 4.77; Figs. 3A-D) between the two CO$_2$ conditions.

A.

B.

C.

D.
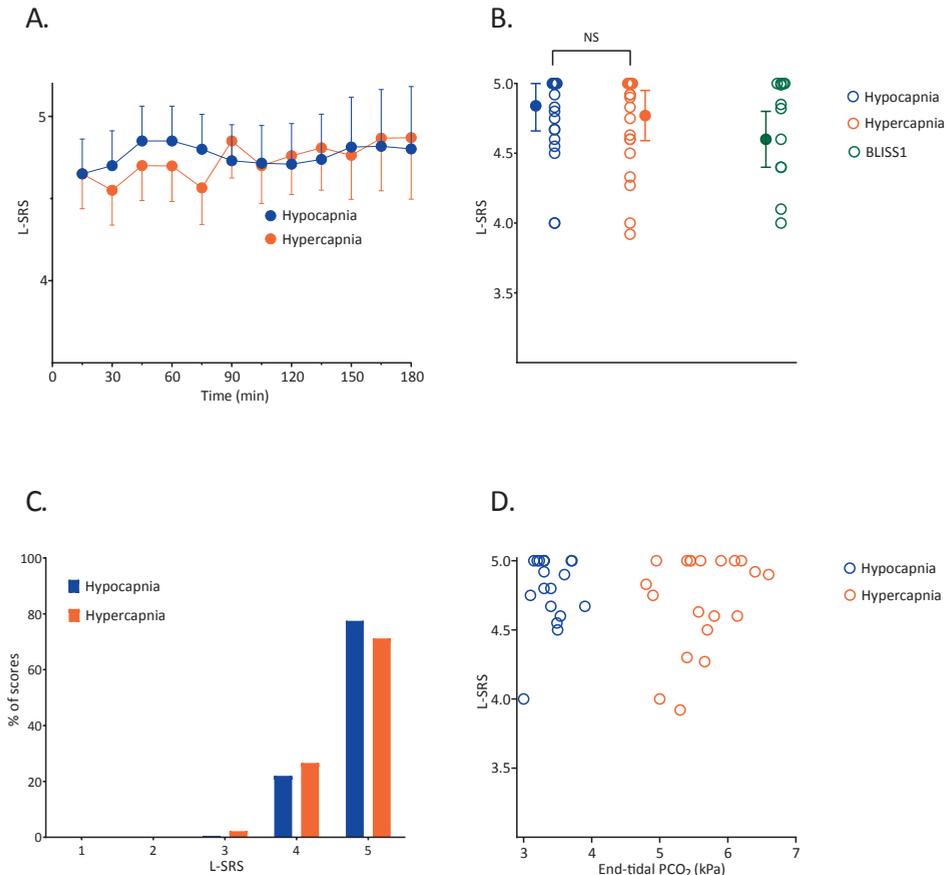
Figure 3. A. Mean (95% confidence interval) Leiden - surgical rating scale (L - SRS) scores *versus* time under hypocapnic (blue symbols) and hypercapnic conditions (orange symbols). **B.** Individual mean L - SRS scores (each symbol is the mean L - SRS of one patient) and mean of the means (SD). In green the results of the patients that had recieved a deep NMB (under normocapnic conditions) in the BLISS 1 study. **C.** Distribution of the surgical ratings under hypocapnic (blue bars) and hypercapnic (orange bars) conditions. **D**. Individual mean L - SRS scores *versus* mean individual end-tidal pCO_2 values in subjects treated with hypocapnia (blue symbol) and hypercapnia (orange symbol). Pearson $r = 0.02$, $p = 0.9$.

There are many physiological and pharmacological effects of hypocapnia that made us believe that lowered arterial CO_2 concentrations would improve surgical conditions. These effects include deepening of the anaesthetic state, enhanced muscle relaxation, inhibition of and abdominal muscle reflexes and a reduced efferent output from the brainstem to the diaphragm.[6-8, 12] Our inability to detect a significant difference between L-SRS scores does not imply that any of these effects of hypocapnia did not occur. It simply indicates that hypocapnia, irrespective of the physiological changes it causes, was without effect on the quality of the surgical field. We infer from our data that in case

of suboptimal surgical conditions, increasing ventilation is without effect and additional relaxation may be required.

We induced hypocapnia by increasing respiratory rates rather than increasing tidal volume. We did not allow high tidal volumes to prevent any pressure-related damage to the lungs.[13] Despite the relative high insufflation rates in hypocapnia peak inspiratory pressures were considered acceptable (Table 2) and none of the patients experienced any harm from the hypocapnic treatment.

Two recent studies from outside our institute have been published that use the L-SRS to assess the quality of the surgical field in deep NMB. Yoo and colleagues[2] observed a mean score of 4 (range 3-5) during deep NMB against a mean score of 3 (range 2-5) during a moderate block in robotic laparoscopic prostate surgery. Kim and colleagues[4] showed improved conditions during deep block compared to a moderate block in micro laryngeal surgery with 92% of patients with scores 4 or 5 at PTC 1-2 and 78% at TOF 1-2. Furthermore, just 3% of patients at deep NMB exhibited vocal cord movement during surgery compared to 39% of patients at moderate NMB. These studies indicate not only that a deep NMB is associated with superior surgical conditions in various complex surgeries but also show the practical usefulness of the L-SRS in scoring the quality of surgical field in different surgeries. Screening the various public clinical trial registries showed that additional studies that assess surgical conditions during anaesthesia using the L-SRS are underway, including one study on the effect of deep NMB in bariatric surgery (clinicaltrials.gov identifier NCT02553629). Apart from the 5-point L-SRS that we developed, other scoring systems were used in clinical studies, such as a 4-point scale by Dubois et al.[3] with similar end-points to those we used, a 4-point scale to assess the surgical space conditions by Staehr-Rye et al.[14] (only the worst score per case is reported), and a 100-point visual analogue scale by Blobner et al.[15] While we do not feel that one scoring system is superior to the other, we do express the need for a uniform scoring system that allows comparison between studies.

There are some limitations to our study. (1) The target pCO$_2$ at hypocapnia was not reached in all patients. Hyperventilation to relatively low levels of pCO$_2$ is more difficult in laparoscopic surgeries with continuous intracorporal CO$_2$ insufflation than in open surgeries. Greater ventilatory frequencies than applied would have been required to reach the target values. Since these high rates often hindered the surgeon we accept these deviations from target. (2) Scoring in our current and previous study was performed by one surgeon (RB), with large experience in the tested surgeries. This eliminates inter-observer variability but other surgeons may rate the surgical field differently, especially surgeons with less experience or surgeons trained in other subspecialties. This is illustrated by our previous observation that there was just moderate agreement between the ratings of our expert surgeon and eight other laparoscopy-skilled surgeons who rated video images of the surgical procedure.[1] Further validation of the L-SRS in

other specialties is therefore necessary. (3) The ability to effectively reverse a deep NMB in an acceptable time frame is essential in clinical practice. Sugammadex is currently the only reversal agent that allows rapid and safe recovery from a deep block without consequences such as residual curarization. However, the restricted use or availability of sugammadex in some hospitals makes application of a deep NMB not always practical.

In conclusion, our study shows that deep NMB provides good to optimal surgical conditions in laparoscopic retroperitoneal urological surgery, which were independent of the level of arterial pCO_2.

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