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The effects of CO_2-insufflation with 5 and 10 mmHg during thoracoscopy on cerebral oxygenation and hemodynamics in piglets: an animal experimental study

Lisanne J. Stolwijk · Stefaan H. A. J. Tytgat · Kristin Keunen · Nutnicha Suksamanapan · Maud Y. A. van Herwaarden · Floris Groenendaal · Petra M. A. Lemmers · David C. van der Zee

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Abstract
Objective To evaluate the effect of CO_2-insufflation with 5 and 10 mmHg on cerebral oxygenation and hemodynamics in neonates.
Background An increasing percentage of surgical interventions in neonates are performed by minimal invasive techniques. Recently, concerns have been raised regarding a decrease of cerebral oxygenation in neonates during thoracoscopy as a result of CO_2-insufflation.
Methods This was an animal experimental study. Piglets were anesthetized, intubated, ventilated, and surgically prepared for CO_2-insufflation. Insufflation was done with 5 or 10 mmHg CO_2 during 1 h. Arterial saturation (SaO_2), heart rate (HR), mean arterial blood pressure (MABP), and cerebral oxygenation ($rScO_2$) were monitored. CFTOE, an estimator of cerebral oxygen extraction (($SaO_2 - rScO_2$)/SaO_2)), was calculated. Arterial blood gases were drawn every 15′: pre (T0), during (T1-T4) and after CO_2-insufflation (T5).
Results Ten piglets (4 kg) were randomized for 5 (P5) and 10 (P10) mmHg CO_2-insufflation. Two P10 piglets needed resuscitation after insufflation, none P5. Linear mixed-effect modeling of $paCO_2$, pH, and SaO_2 showed that values were dependent on time and time squared ($p < 0.001$) but were not different between the 5 and 10 mmHg groups. Analysis demonstrated significant changes over time in heart rate and MABP between the 5 and 10 mmHg groups, with a significant higher heart rate and lower blood pressure in the 10 mmHg group ($p < 0.001$). For $rScO_2$ and cFTOE, no group differences could be demonstrated, but a significant effect of time was found: $rScO_2$ increased and cFTOE decreased ($p < 0.001$).
Conclusions Insufflation of CO_2 during thoracoscopy with 10 mmHg caused more severe hemodynamic instability and seems to be related with a decrease of cerebral perfusion as represented by a higher oxygen extraction. CO_2-insufflation of 5 mmHg for thoracoscopy seems to have no adverse effects on cerebral oxygenation.

Keywords Thoracoscopy · CO2 · Cerebral oxygenation · Neonatal surgery · Esophageal atresia · Pediatric · Endoscopy

Nowadays, an increasing percentage of major surgical interventions in neonates are performed by minimally invasive techniques, such as thoracoscopic repair of esophageal atresia [1–3]. Thoracoscopy enables shorter duration of postoperative-assisted ventilation and less days of sedation use [4], whereas thoracotomy may be associated with detrimental musculoskeletal outcomes like weakness of the latissimus dorsi musculature, winging of the scapulae, and thoracic scoliosis [5, 6].

The mortality of patients with esophageal atresia decreased to <5 % and attention shifted to morbidity and long-term outcome, with mostly anastomotic stenosis and gastroesophageal reflux [7]. In recent years, however, concerns have been raised regarding impaired neurodevelopmental outcome in these patients. The cause of this neurologic impairment in these patients is currently

L. J. Stolwijk (✉) · S. H. A. J. Tytgat · N. Suksamanapan · M. Y. A. van Herwaarden · D. C. van der Zee
Department of Pediatric Surgery, Wilhelmina Children's Hospital, University Medical Center Utrecht, 3508 AB Utrecht, The Netherlands
e-mail: L.J.Stolwijk@umcutrecht.nl

L. J. Stolwijk · K. Keunen · F. Groenendaal · P. M. A. Lemmers
Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

unknown and most likely multifactorial [8, 9]. The neonatal brain is extremely vulnerable for external changes because of an immature autoregulatory system and hemodynamic instability, especially within the first days to weeks after birth in neonates [10].

Only scarce information is available about the effects of pneumothorax by insufflation of CO_2 on the cerebral oxygenation and perfusion during thoracoscopy in neonates [11]. Where it seems to be safe in adults, recently concerns have been raised about the application in neonates [12, 13] where high intrathoracic pressures up to 10 mmHg have been used. This is in contradiction to our normal clinical practice where a capnothorax in neonates is created using pressures of only 3 to a maximum of 5 mmHg and a flow of 1 L/min which seemingly does not result in the aforementioned disturbing effects.

Near infrared spectroscopy is a non-invasive method to continuously monitor the regional cerebral oxygen saturation ($rScO_2$) and is an estimator of cerebral tissue perfusion. $rScO_2$ is influenced not only by the arterial oxygen saturation but also by other parameters influencing cerebral hemodynamics and oxygenation like mean arterial blood pressure (MABP), mean airway pressure, hemoglobin concentration, and also $paCO_2$. Hypercapnia causes cerebral vasodilatation and increased perfusion, while hypocapnia causes vasoconstriction and decreased perfusion [14].

This study aimed to test the hypothesis that high-pressure insufflation of CO_2 with 10 mmHg during thoracoscopy in newborn piglets compromises the hemodynamic stability and the regional cerebral oxygen saturation ($rScO_2$) while insufflation with 5 mmHg, used in normal clinical practice in our hospital, will not.

Methods

This was an animal experimental study to test the difference in effect of creating a pneumothorax with 5 and 10 mmHg CO_2 in newborn piglets. The study protocol was approved by the Animal Experimental Board of the University of Utrecht, the Netherlands. Surgical preparation and veterinary care were given by a veterinary technician in the animal laboratory.

Surgical preparation and anesthesia of the piglets

Ten Dutch store piglets of 10–14 days of age were included.

A standard anesthesia protocol was used for all the piglets. The piglets were given premedication of 0.7 mg/kg midazolam i.m., 13 mg/kg ketamine i.m., and 0.05 mg/kg atropine i.m. Induction of anesthesia was given by administering a bolus of 4 mg/kg intravenous thiopental after an arterial catheter was inserted. For general anesthesia, 0.011 mg/kg/h sufentanil was given, 0.09 mg/kg/h cisatracurium and 1 mg/kg/h midazolam for maintenance. Tracheal intubation was performed after administering pain medication by meloxicam 0.4 mg/kg and lidocain locally. The oxygenation and ventilation were set to maintain a peripheral oxygenation of >90 %, pH 7.40–7.50, and $paCO_2$ 35–50 mmHg.

Monitoring of cerebral oxygenation and oxygen extraction

The $rScO_2$ measured by NIRS was used to monitor changes in the cerebral oxygenation. Although $rScO_2$ is not a robust quantitative measure of cerebral oxygenation, it can be reliably used to detect substantial changes in cerebral oxygenation. The $rScO_2$ reflects oxygen saturation in veins, capillaries, and arteries. The NIRS monitor (INVOS 5100-P Cerebral Oximeter; Covidien, Mansfield, Massachusetts) was used with the small adult sensor (Somanetics SomaSensor® no. 4100-SSA Adult/Disposable). This is a transducer containing a light emitting diode and two distant sensors that was attached to the frontoparietal side of the piglets head. The $rScO_2$ was calculated from the differential signals obtained from the two sensors [15].

The fractional cerebral tissue oxygen extraction (cFTOE) represents the balance between oxygen delivery and oxygen consumption. An increase in cFTOE might reflect an increase in oxygen extraction by the brain tissue, and a decrease in cFTOE suggests that there is less utilization of oxygen by brain tissue, in relation to the supply of oxygen [16, 17]. The cFTOE is formulated as a ratio by $((SaO_2 - rScO_2)/SaO_2))$ [18].

Experiment

The near infrared sensor was placed right frontoparietal on the shaved head of the piglet, after which premedication was given (Fig. 1). After induction of anesthesia, a 5 mm trocar was inserted in the fifth intercostal space of the right hemithorax. Insufflation was initiated with either 5 or 10 mmHg CO_2 during 1 h with continuous non-invasive NIRS-monitoring. The physiologic parameters end tidal CO_2 ($etCO_2$), arterial saturation, heart frequency (HF), and mean arterial blood pressure (MABP) were monitored. Arterial blood gases for paCO2 and pH were drawn every 15 min before, during and after insufflation of CO_2 (Fig. 2).

Statistical analysis

Data from the monitor were extracted to Excel workbooks. The mean (SD) or median (range) of all parameters was calculated for every 15-min block.

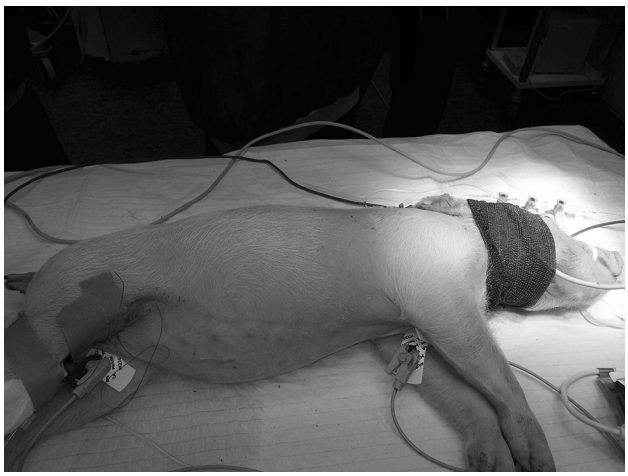

Fig. 1 Set-up of experiment

Data were analyzed using a linear mixed-effect model (R-software version 2.15.0; package nlme) with time, squared time, and group (5 vs. 10 mmHg) as independent variables, including interactions with time and squared time, and individual pig as a random factor. A p value of 0.05 was considered significant. Models were simplified using Occam's Razor based on Akaike Information Criterion.

Results

Ten piglets ($\approx$4 kg) were included in this study and were randomized into two different pressure groups, either CO_2-insufflation with 5 mmHg (P5) or CO_2-insufflation with 10 mmHg (P10).

At baseline, the vital parameters between P5 and P10 were not different and within normal limits. (Table 1). Also $rScO_2$ and cFTOE were not different between the groups; the $rScO_2$ was 42 % $\pm$ 3 with a cFTOE of 0.58 $\pm$ 0.02 in P5; and the $rScO_2$ was 37 % $\pm$ 8 in P10 with a cFTOE of 0.61 $\pm$ 0.06.

The procedure was terminated prematurely in two P10-piglets (piglets 2 and 8) due to the need of resuscitation. Termination of the procedure occurred in none of the P5.

Table 1 Baseline characteristics of P5 and P10

T0	P5	P10	p value
HR	172 $\pm$ 31	152 $\pm$ 18	NS
MABP (mmHg)	78 $\pm$ 13	84 $\pm$ 8	NS
SaO_2 (%)	97.9 $\pm$ 0.4	97.4 $\pm$ 0.3	NS
$paCO_2$ (mmHg)	36 $\pm$ 4	35 $\pm$ 5	NS
pH (AU)	7.46 $\pm$ 0.03	7.43 $\pm$ 0.04	NS
$rScO_2$ (%)	42 $\pm$ 3	37 $\pm$ 8	NS
cFTOE	0.58 $\pm$ 0.02	0.61 $\pm$ 0.06	NS

Variables in mean $\pm$ SD

NS not significant

After the experiment, all the piglets, including those in which the procedure was terminated prematurely, were thoracoscopically examined, and in none of the animals, damage or hemorrhages were present.

Piglets 5 mmHg

The vital parameters of the P5 showed a stable arterial saturation, heart rate, and MABP during CO_2-insufflation and after desufflation and were within normal limits (Fig. 3).

The $paCO_2$ increased, and the pH decreased significantly. The $rScO_2$ (%) increased, and the cFTOE decreased over time.

Piglets 10 mmHg

In 3 piglets in P10, a complete registration was obtained; in two piglets, there were missing monitor results at T4 during the resuscitation in which we stopped the insufflation of CO_2. Consequently, we report the results of the resuscitated piglets in the 10 mmHg group individually.

The vital parameters of three non-resuscitated P10-piglets showed a decrease in arterial saturation. The $rScO_2$ (%) increased, and the cFTOE decreased over time (Fig. 4). The heart rate and $paCO_2$ increased significantly, and the MABP and pH decreased.

In piglet 2, the MABP dropped from 95 to 68 mmHg (Fig. 5), and the heart rate increased to 206 beats per minute after insufflation. The ventilation had to be adjusted frequently.

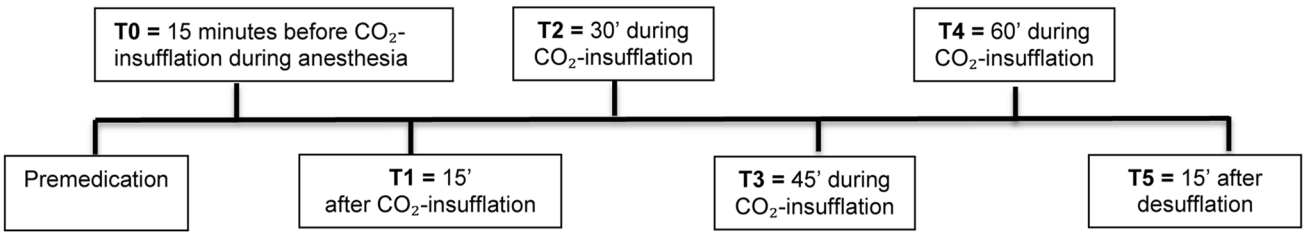

Fig. 2 Timeline experiment

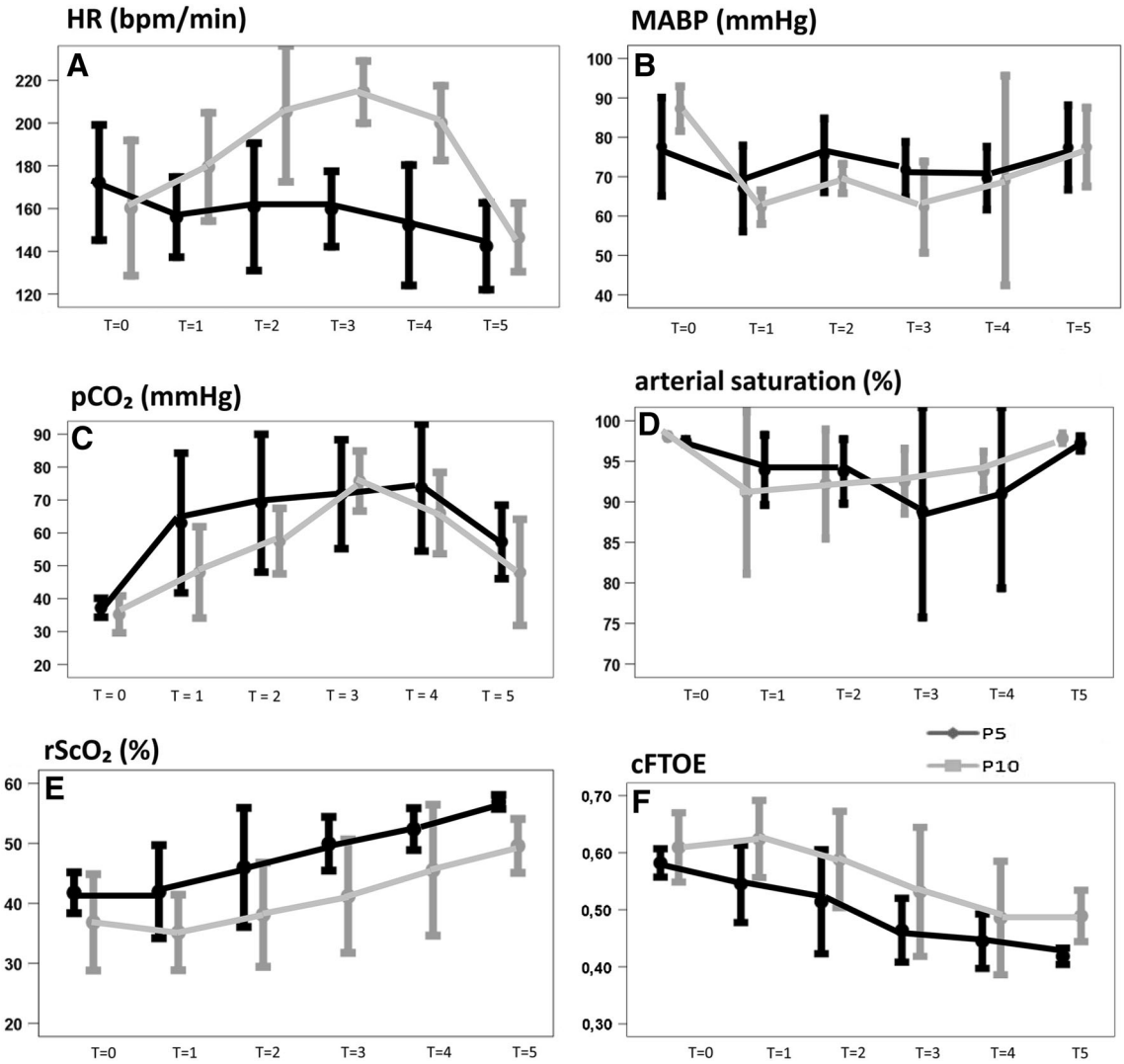

Fig. 3 Vital parameters of P5 and P10. *Note*: Vital parameters of the two groups, 5 mmHg CO_2-insufflation (*dark gray line*), and 10 mmHg (*light gray line*). The mean values of heart rate (HR, **A**), mean arterial blood pressure (MABP, **B**), arterial CO_2 ($paCO_2$, **C**), arterial saturation (%, **D**), regional cerebral oxygen saturation ($rScO_2$, **E**), and cerebral fractional tissue oxygen extraction (cFTOE, **F**). At T4, missing values of piglets 2 and 8 are presented

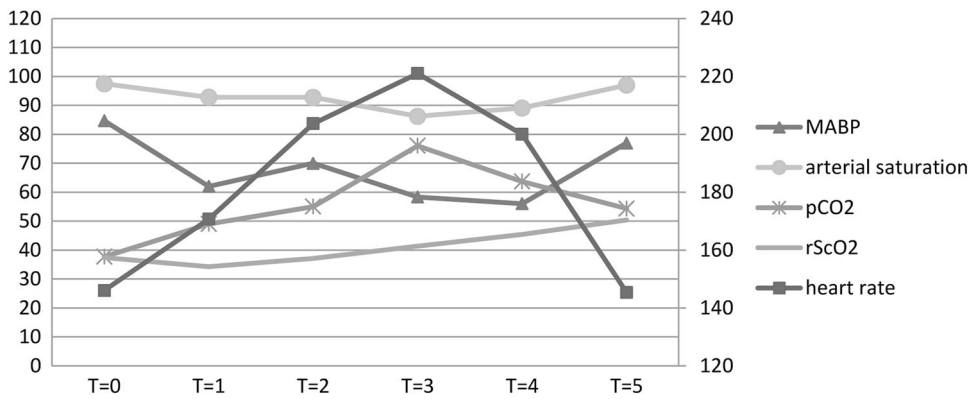

Fig. 4 Vital parameters and $rScO_2$ of P10. *Note*: MABP in mmHg, heart rate beats per minute, arterial saturation (%), $rScO_2$ (%), $paCO_2$ (mmHg). $^*p < 0.05$ versus baseline within the same group

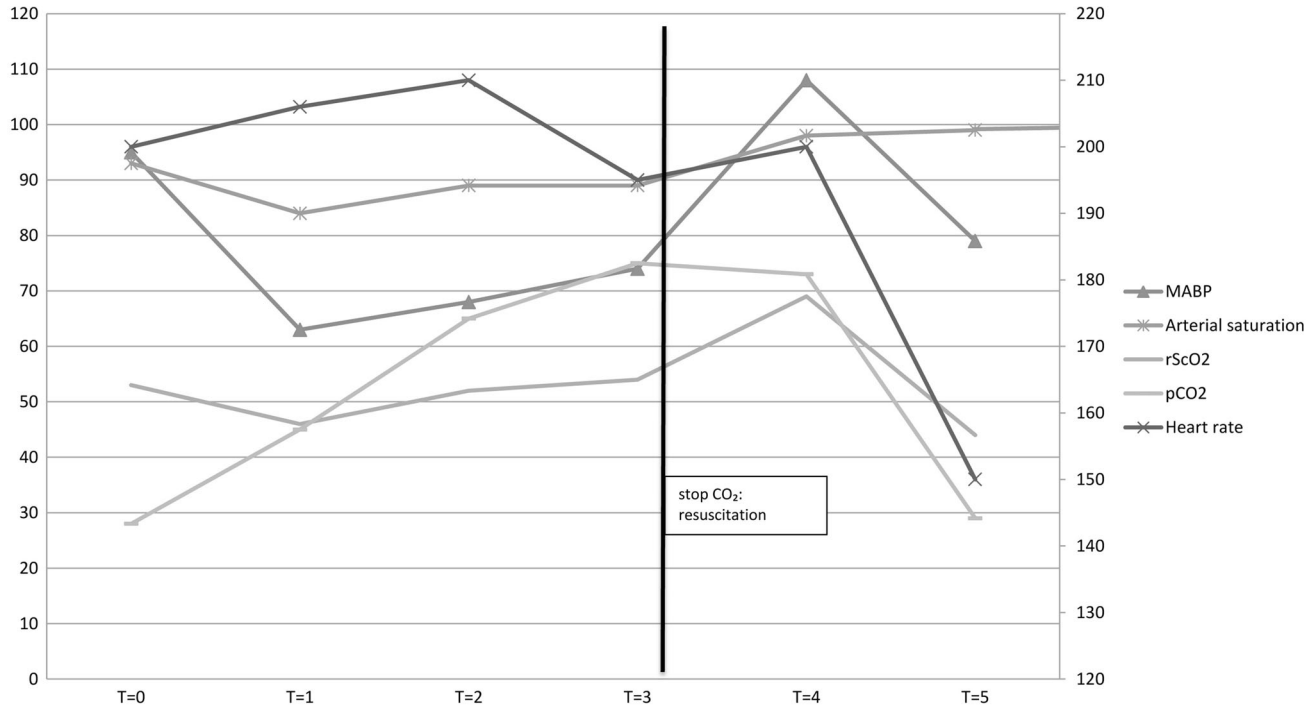

Fig. 5 Vital parameters and $rScO_2$ of piglet 2 (10 mmHg). *Note*: MABP in mmHg, heart rate beats per minute, arterial saturation (%), $rScO_2$ (%), $paCO_2$ (mmHg). After CO_2-insufflation, the heart rate increases, and the MABP drops. The ventilation had to be adjusted frequently. Due to a ventilation problem, the insufflation had to be stopped, and the piglet needed resuscitation after T3

After a new ventilation problem occurred, the CO_2-insufflation had to be stopped and resuscitation started after T3.

The heart rate of piglet 8 increased from 169 beats per minute to 258. The insufflation of CO_2 was stopped prematurely because of the severe decrease in MABP (73–22 mmHg); there were no measurements at T4. The piglet needed resuscitation (Fig. 6).

P5 versus P10

Analysis using the mixed-effect model demonstrated significant changes over time in heart rate and MABP between the P5 and P10 groups, with a significant higher heart rate and lower blood pressure in the P10 group ($p < 0.001$).

For $rScO_2$ and cFTOE, no group differences could be demonstrated, but a significant effect of time was found: $rScO_2$ increased and cFTOE decreased ($p < 0.001$).

Linear mixed-effect modeling of $paCO_2$, pH, and SaO_2 showed that values were dependent on time and time squared ($p < 0.001$) but were not different between the P5 and P10 groups.

Discussion

The results of this animal experimental study show that intrathoracic CO_2-insufflation with 10 mmHg causes a severe loss of hemodynamic stability, even resulting in resuscitations in contradiction to stable hemodynamic parameters in piglets insufflated with 5 mmHg. Nevertheless, in this study, we observed a cerebral oxygenation that increased during thoracoscopy with 5 and 10 mmHg CO_2-insufflation. In P10, there was an increased $paCO_2$ up to 70 mmHg observed during procedure with a severe acidosis, where in P5, a milder acidosis was observed, although no significant difference was demonstrated. In both groups, the ventilation was adjusted where needed to maintain normal values.

Two recent publications by Bishay show that thoracoscopy in infants with pressures as high as 10 mmHg is associated with an extended decrease of $rScO_2$, measured by near infrared spectroscopy (NIRS), and hypercapnia with extreme severe acidosis [12, 13].

The devastating results from these studies could not be reproduced in this animal experimental model. The former outcomes could greatly restrain the application of thoracoscopic procedures being performed in neonates, such as esophageal atresia repair. The initial values of cerebral oxygenation in this study were higher than normally observed in humans [19]. We suggest that this discrepancy is caused by a different sensor being used which gives a 10 % higher value or that it is due to a high FiO_2 during the induction of anesthesia [20]. Although in this study, the values always remained within the normal limits, it stresses

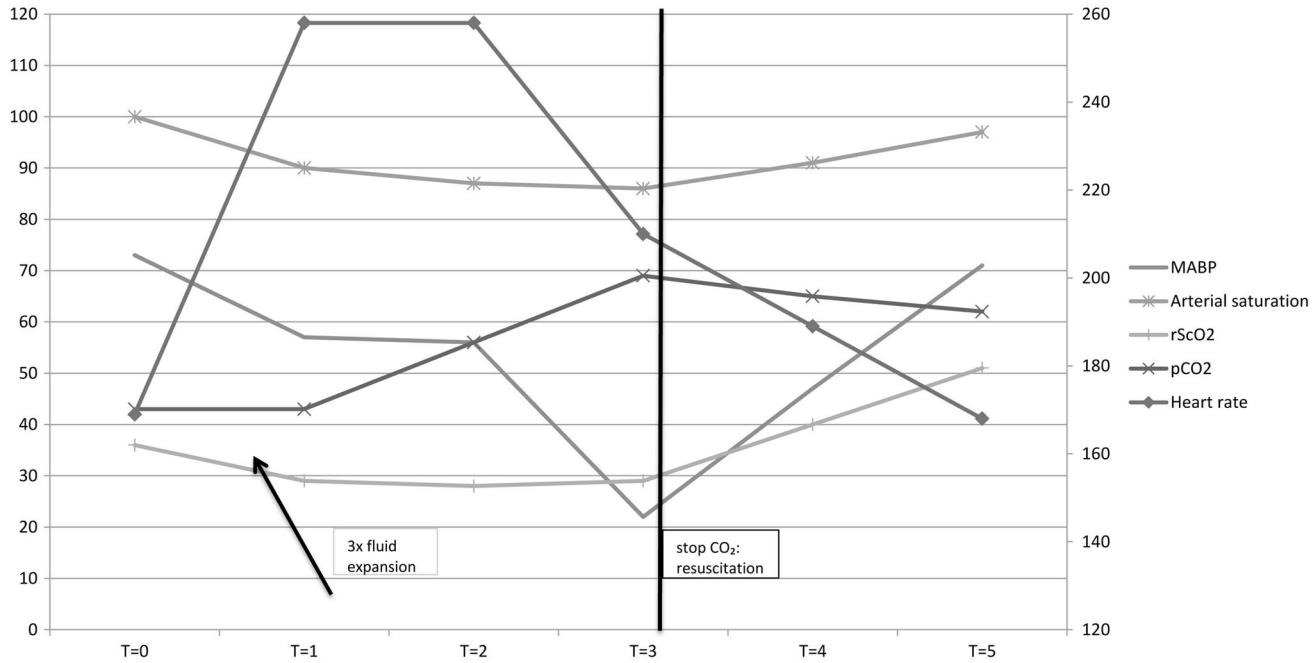

Fig. 6 Vital parameters and $rScO_2$ of piglet 8 (10 mmHg). *Note*: MABP in mmHg, heart rate beats per minute, arterial saturation (%), $rScO_2$ (%), $paCO_2$ (mmHg). The insufflation was stopped prematurely because of the severe drop in blood pressure, the piglet needed resuscitation after T3

the importance of starting the neuromonitoring preoperatively at the ward, to assess the normal values of the patient.

Given the advantages of minimal invasive surgery techniques, it is important to emphasize the possibilities of thoracoscopy with pressures up to 5 mmHg. Although in our experiment, suprafysiologic values of $paCO_2$ up to 70 mmHg and in a few cases a pH of 7.10 were observed, they are not near the extreme hypercarbia and hypercapnea of up to 120 reported earlier by Bishay. One should take into account by interpreting these results that the high pressures of up to 10 mmHg and 4 L/min flow were used during those procedures. Because a significant decrease in the $rScO_2$ can be damaging, we gave preference to evaluate the effects of CO_2-insufflation of up to 10 mmHg in this animal experimental model. Previous research showed that a nadir $rScO_2$ of less than 35 % [21] is associated with impairments in neurodevelopment [8, 10].

How can we explain our results? Even though we saw a severe loss of hemodynamic stability in the 10 mmHg group, we observed that cerebral oxygenation increased over time. The decrease in MABP could have been antagonized by the vasodilatating effect of the raised $paCO_2$. Kaiser et al. [22] showed that progressive hypercapnia results in a loss of autoregulation of the brain. We speculate that the difference in hemodynamic stability is caused by exceeding the central venous pressure which results in a decreased venous return and a compromised cardiac output [7]. Higher heart rate and lower mean arterial blood pressure suggest a loss of hemodynamic stability, apart from the necessity of resuscitations with this pressure.

We underline that it is important to be aware of extreme hypercarbia and acidosis during this procedure, by frequently drawing blood gases, also for the maintenance of cerebral autoregulation. In neonates, the end tidal CO_2 is no reliable estimator for arterial CO_2 like it is in adults [23]. In normal practice, the ventilation has to be adjusted after insufflation of CO_2, during this experiment as well, to maintain a normal saturation.

Although the differences were not significant, the cerebral tissue oxygen extraction (cFTOE) was higher in P10 at all time points in comparison to P5, which reflects a higher oxygen extraction in P10. The difference in cFTOE between P5 and P10 might have become significant during an extended procedure. This suggests that, although a high $paCO_2$ causes vasodilatation and thus increased cerebral perfusion, there was a mild and not significant decrease in cerebral perfusion as represented by a higher oxygen extraction in P10. A possible explanation is the exceeding of the central venous pressure with high intrathoracic pressure, which could compromise the cerebral perfusion.

The limitation of this study is the relative small number of piglets in each group. We do believe the harmful effect of CO_2-insufflation with 10 mmHg is so profound that a larger number of piglets will only mark the hemodynamic

instability more. In order to draw valid conclusions, we used conservative statistical tests, which all became highly significant. Furthermore, piglets are not the same as neonates, with a lower cerebral oxygenation like we observed according to Kurth et al. [24] and Chien et al. [25]. However, we do think these results are representative as the trend of the cerebral oxygenation is more important than the absolute value [19]. There was no continuous registration of all parameters; thus, the relation between blood pressure and $rScO_2$ as an estimator of autoregulatory ability could not be measured [10, 26]. In the future, a prospective, human study is required to confirm the effects of CO_2-insufflation with 5 mmHg on cerebral oxygenation hemodynamics and with neurodevelopmental follow-up. Such a study is currently underway in our hospital.

In conclusion, this animal experimental model shows that insufflation of CO_2 during thoracoscopy with a pressure of 10 mmHg caused a severe hemodynamic instability with a decrease in blood pressure and an increased heart rate. Although higher CO_2-levels are related with higher brain perfusion by cerebral vasodilation, insufflation with 10 mmHg seemed to be related with a decrease of cerebral perfusion as represented by a higher oxygen extraction.

Special attention should be given to the possible suprafysiologic $paCO_2$ values reached during CO_2-insufflation. CO_2-insufflation of 5 mmHg for thoracoscopy seems to have no adverse effects on cerebral oxygenation in this animal study.

Disclosures L.J. Stolwijk MD, S.H.A.J. Tytgat MD, K. Keunen MD, N. Suksamanapan MD, M.Y.A. van Herwaarden MD PhD, F. Groenendaal MD PhD, P.M.A. Lemmers MD PhD and D.C. van der Zee MD PhD have no conflict of interest or financial ties to disclose.

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