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Prone positioning, systemic hemodynamics, hepatic indocyanine green kinetics, and gastric intramucosal energy balance in patients with acute lung injury

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Abstract *Objective*: To investigate the effects of prone positioning on systemic hemodynamics, intra-abdominal pressure (IAP), plasma disappearance rate of indocyanine green (PDR_{ICG}), and gastric intramucosal to arterial PCO_2 difference ($Pi\text{-}aCO_2$). *Design and setting*: Prospective randomized study in the intensive care unit of a university hospital. *Patients*: 12 mechanically ventilated, hemodynamically stable patients with acute lung injury. *Intervention*: Positioning supine and prone for 3 h in random order. *Measurements*: Systemic hemodynamics were determined by transpulmonary double-indicator dilution technique using an integrating fiber-optic monitoring system. The same monitoring system was used to measure PDR_{ICG}. IAP was measured in the urinary bladder and gastric intramucosal PCO_2 was evaluated by automated recirculation gas tonometry. *Results*: IAP increased from 10±3 in the supine to 13±4 mmHg in the prone position. Cardiac index increased from 3.8±0.9 (supine) to 4.2±0.6 l/m^2 per minute (prone), mean arterial pressure from 75±10 (supine) to 81±11 mmHg (prone), PaO_2/FIO_2 from 194±66 (supine) to 269±68 mmHg (prone), and oxygen delivery from 558±122 (supine) to 620±74 ml/m^2 per minute (prone). No other parameters, including PDR_{ICG} and $Pi\text{-}aCO_2$, differed between the two positions. *Conclusions*: Prone positioning in mechanically ventilated patients with acute lung injury, despite a small increase in IAP, does not negatively affect the hepatic capacity to eliminate ICG and gastric intramucosal energy balance when systemic blood flow and oxygenation are improved.

Keywords Prone position · Mechanical ventilation · Cardiovascular function · Indocyanine green clearance · Gastric tonometry · Intra-abdominal pressure

Introduction

Prone positioning is used increasingly to improve arterial oxygenation in patients with acute lung injury (ALI) when PaO_2 remains unacceptably low despite ventilation with high positive end-expiratory pressure (PEEP) and inspired fraction of oxygen (FIO_2) [1, 2, 3, 4]. Restriction of abdominal movement during prone positioning has been claimed to increase intra-abdominal pressure (IAP), compress the inferior vena cava, and effect cardiovascular instability [1]. We have previously demonstrated that when patients with ALI are mechanically ventilated in the prone position without efforts to relieve abdominal compression, IAP increases, but systemic blood flow and renal perfusion and function are not affected [5]. Prone positioning has been shown to reduce hepatic clearance of indocyanine green dye (ICG) in anesthetized patients during major surgery [6], thus suggesting that liver function would be impaired. This is of concern because inadequate hepatosplanchnic perfusion

Table 1 Demographic and clinical characteristics (*BMI* body mass index, *ALI* acute lung injury, *MV* mechanical ventilation duration before the study, *SAPS* Simplified Acute Physiology Score [11], *MOF* Multiple Organ Failure Score [10])

Patient no.	Sex	Age (years)	BMI	Cause of ALI	MV	SAPS (days)	MOF	Outcome
1	F	72	25	Lung contusion	10	16	6	Survived
2	M	52	33	Vertebral fracture, pneumonia	2	13	5	Survived
3	M	57	23	Pneumonia	14	13	4	Survived
4	F	75	27	Esophageal perforation	3	10	6	Survived
5	M	64	29	Abdominal surgery, pneumonia	7	12	5	Survived
6	M	30	22	Acute pancreatitis	2	11	7	Survived
7	M	59	29	Lung contusion	3	9	6	Survived
8	F	17	29	Hemorrhagic shock	1	10	4	Survived
9	M	54	28	Acute pancreatitis	2	11	9	Survived
10	M	44	23	Lung resection, pneumonia	3	11	5	Survived
11	M	72	26	Pneumonia	16	14	6	Survived
12	M	23	20	Lung contusion	1	10	7	Survived
Mean±SD		52±21	26±3.7		5±5	11.7±2.0	5.8±1.4	

is known to play a key role in the development and maintenance of bacterial translocation and systemic inflammatory response syndrome and has been claimed one of the main determinants of mortality in critically ill patients [7, 8]. However, it is not known whether prone positioning affects hepatosplanchnic function in patients with ALI.

We examined whether there is any impairment in systemic hemodynamics, hepatic capacity to eliminate ICG, and gastric intramucosal energy metabolism during prone positioning in critically ill patients with ALI when no attempt apart from using an air-cushioned bed is made to restrict or enhance the movement of the abdominal wall.

Materials and methods

Patients

After approval by the Bonn University Ethics Committee, informed consent for entry into the study was obtained from the next of kin in 12 mechanically ventilated patients with ALI. The criteria of the American-European Consensus Conference were used to define ALI [9]. Patients with unstable cardiovascular function requiring inotropic support and those who had undergone liver transplantation were excluded, as were patients with cerebral injury, unstable spinal fractures, and patients treated for peritonitis with an open-abdomen technique. The Organ Failure Score [10], the Simplified Acute Physiology Score [11], and the duration of mechanical ventilation were recorded on inclusion in the study (Table 1).

Routine clinical management of the patients included the use of a central venous catheter and a thermistor-tipped fiberoptic arterial catheter (Pulsiocath PV2024-4F, Pulsion Medical Systems, Munich, Germany) advanced via the femoral artery into the aorta.

Measurements

Mean arterial pressure (MAP) and central venous pressure (CVP) were transduced (Combitrans, Braun, Melsungen, Germany) and recorded. For cardiovascular pressure measurements a horizontal plane through the midaxillary line was taken as the zero reference point in the supine and prone position and was adjusted after each turning maneuver. Heart rate (HR) was obtained from the electrocardiogram. The transpulmonary double-indicator dilution method was used to measure cardiac output and intrathoracic blood volume as described previously [12]. ICG 25 mg (Becton Dickinson, Cockeysville, Md., USA) dissolved in 15 ml iced 5% dextrose solution was used as double indicator and injected into the right atrium via the central venous line. Simultaneous dilution curves for dye and temperature were recorded in the aorta with the thermistor-tipped fiberoptic arterial catheter. Cardiac output was measured by the Stewart-Hamilton method, and the mean transit time of the first pass of the thermal and dye (mtt_{ICG}) indicator was determined by computer (COLD-Z-021, Pulsion Medical Systems, Munich, Germany). An average was calculated for three measurements performed at random moments during the ventilatory cycle.

Arterial blood gases and pH were determined immediately after sampling in duplicate with standard blood gas electrodes (ABL 510, Radiometer, Copenhagen, Denmark). In each sample, hemoglobin concentration and oxygen saturation were analyzed using spectrophotometry (OSM 3, Radiometer). IAP was measured by transducing and recording the urinary bladder pressure (Combitrans) during transient clamping of the Foley catheter, as described previously [13]. The zero reference point for IAP measurements was set at the pubis level and adjusted after each turning maneuver.

The transpulmonary indicator dilution technique was used to determine the plasma disappearance rate of ICG (PDR_{ICG}) [12]. PDR_{ICG} is derived from the half-life time of ICG and reflects the percentage of the initial plasma dye level eliminated by the liver [12]. The downslope of the dilution curve for ICG recorded in the aorta with the thermistor-tipped fiberoptic arterial catheter was used to calculate PDR_{ICG} by computer (COLD-Z-021). This fiberoptic-based method for in vivo measuring ICG has been validated previously against photometric in vitro analysis of ICG concentration [14].

Gastric intramucosal CO_2 tension ($PiCO_2$) was measured by automated recirculation gas tonometry by a gastric tonometer (TRIP NGS-catheter, Tonometrics, Helsinki, Finland) connected to a capnometry monitor (Tonocap TC-200, Datex, Helsinki, Finland) [15]. The correct position of the gastric tube was confirmed by auscultation over the stomach while injecting air into the tube or by aspiration of gastric contents from it. After a 60- min equilibration period $PiCO_2$ and $PaCO_2$ were determined simultaneously.

Standard formulas were used to calculate cardiac index (CI), systemic vascular resistance index (SVRI), and oxygen delivery index (DO_2I). The intrathoracic blood volume index (ITBVI) was calculated as $CI \times mtt_{ICG}$ [12], PDR_{ICG} as $100 \times \ln 2 / t_{1/2(ICG)}$ [12], Pi-aCO_2 difference as $PiCO_2$–$PaCO_2$ [16].

Protocol

The patients were placed on air cushion beds (MQ/VQ-TheraKair, KCI, Höchstadt, Germany); a continuous infusion of sufentanil and midazolam was adjusted to a Ramsay sedation score between 4 and 5 [17]. Adequate circulating blood volume was verified in all patients by assuring an ITBVI greater than 800 ml/m^2 prior to the study. Fluid replacement and all drug infusions were maintained unchanged throughout the study. Enteral feeding was discontinued, and H_2 blockade was induced with intravenous ranitidine 4 h prior to measurements. Pressure-limited, time-cycled mechanical ventilation was provided by a standard ventilator (SV 300, Siemens, Erlangen, Germany). Appropriate ventilatory settings were determined by the physician responsible for the care of the patient, and they were maintained unchanged throughout the study. Patients were then placed, in random order, supine and prone; each position was maintained for 180 min. A 60-min equilibration period followed turning maneuvers before measurements. Three sets of measurements performed at 60-min intervals were averaged for each position. In the prone position the head was turned laterally, and the arms were pronated and parallel to the body. No efforts apart from using an air-cushioned bed were made to alleviate the positional restriction of the abdomen or the thorax.

Statistical analysis

Results are expressed as mean ±standard deviation. Data were evaluated for normal distribution by Shapiro-Wilk's W test. The data obtained at the three time points during the supine or prone position were analyzed using one-way repeated-measures analysis of variance. Comparisons between the supine and prone positions were made using Student's paired *t* test. Differences were considered statistically significant if *p* was less than 0.05.

Results

Patients were ventilated with a PEEP of 11–20 cmH_2O (15±2 cmH_2O), an upper airway pressure limit of 23–35 cmH_2O (28±4 cmH_2O), a ventilator rate of 12–25/min (18±5/min), and an FIO_2 of 0.4–0.8 (0.58±0.17). Resulting tidal volumes [supine: 363–741 ml (493±245 ml), prone: 335–692 ml (472±208)] and minute ventilation (supine: 7.0–13.6 l/min (8.9±2.0), prone: 6.7–13.1 l/min (8.6±1.9 l/min) remained essentially unchanged between positions (n.s.). Similarly, mean airway pressure did not change between the supine (15–30 cmH_2O; 24±4 cmH_2O) and prone position (15–30 cmH_2O; 24±4 cmH_2O) (n.s.).

The IAP increased to 13±4 mmHg in the prone position, compared to 10±3 mmHg in the supine position ($p<0.05$).

Changes in cardiovascular and gas exchange variables are shown in Table 2. During the prone position CI and MAP increased ($p<0.05$), while HR, CVP, SVRI, and ITBVI remained unchanged (n.s.). Prone position resulted in an increased PaO_2/FIO_2 and higher DO_2I ($p<0.05$). Hemoglobin concentration, hematocrit, $PaCO_2$, and pH did not change between interventions (n.s.).

Hepatic function prior to the study was determined as part of the MOF-score classification system, where 0 points signified normal function, 1 point moderate dysfunction and 2 points severe dysfunction. Accordingly eight patients had normal hepatic function, four patients moderate hepatic dysfunction, and no patient severe hepatic dysfunction averaging 0.33±0.49 points. Individual changes in PDR_{ICG}, and Pi-aCO_2-difference are shown in Figs. 1 and 2. Neither the PDR_{ICG} (18.1±6.3% supine versus 19.2±6,4% prone), nor Pi-aCO_2-difference (10.9±15.1 mmHg supine versus 10.9±11.2 mmHg prone) were significantly altered by positioning. Repetition of measurements within a given position did not produce statistically significant changes in any variable.

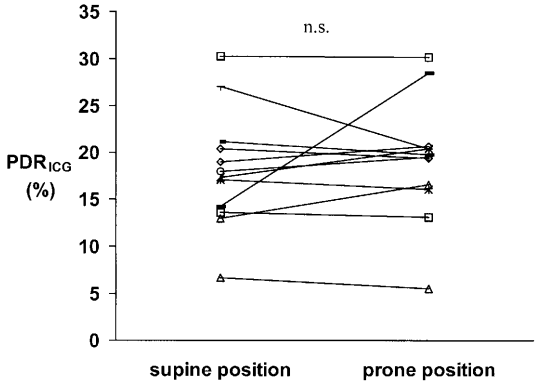

Fig. 1 Individual changes in the plasma disappearance rate of indocyanine green dye (PDR_{ICG}) between the supine and the prone position tested on a randomized basis. Each symbol represents one patient

Table 2 Cardiovascular and gas-exchange variables (*HR* heart rate, *CI* cardiac index, *MAP* mean arterial pressure, *CVP* central venous pressure, *SVRI* systemic vascular resistance index, *ITBVI* intrathoracic blood volume index, *DO_2I* oxygen delivery index)

	Supine position[a]	Prone position[a]
HR (beats min^{-1})	78±16	82±16
CI (l m^{-2} min^{-1})	3.8±0.9	4.2±0.6*
ITBVI (ml m^{-2})	1008±187	1036±180
MAP (mmHg)	75±10	81±11*
CVP (mmHg)	16±5	15±5
SVRI (dyne s^{-1} cm^{-5} m^{-2})	1308±363	1273±254
PaO_2/FIO_2 (mmHg)	194±66	269±68*
$PaCO_2$ (mmHg)	45±6	47±6
DO_2I (ml m^{-2} min^{-1})	558±122	620±74*
Hemoglobin (g l^{-1})	109±9	110±9
pH_a	7.42±0.05	7.40±0.07

*$p<0.05$ vs. supine position, *t* test for dependent samples
[a] Tested on a randomized basis

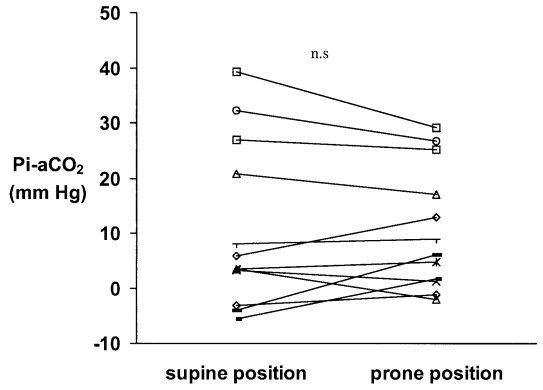

Fig. 2 Individual changes in the Pi-aCO_2-difference (*Pi-aCO_2*) between the supine and the prone position tested on a randomized basis. Each symbol represents one patient

Discussion

This study was designed to evaluate the effects of the prone position on cardiopulmonary and hepatosplanchnic function in patients with ALI. As changing volume load and inotropic support during the study period may have had confounding effects on systemic and regional blood flow, only hemodynamically stable patients being adequately resuscitated without any need for inotropic support were included in the study. When no effort apart from using an air-cushioned bed was made to minimize restriction of the abdomen or the thorax, prone positioning improved oxygen delivery by increasing both cardiac output and PaO_2. A small increase in IAP during prone position had no adverse effect on hepatosplanchnic function.

Arterial hypoxemia caused by venous admixture during ALI is directly correlated with the quantity of nonaerated tissue observed by computer tomography in dependent lung regions adjacent to the diaphragm [18]. Turning prone has been shown to increase the amount of aerated lung tissue, decrease venous admixture, and improve arterial blood oxygenation significantly in most patients with ALI [1, 2, 3, 4]. Pelosi and coworkers [4] recently observed that improvement in PaO_2 during prone positioning is correlated with a decrease in thoracoabdominal compliance. Similarly, in mechanically ventilated anesthetized pigs an increase in IAP during the prone position was associated with further improvement in PaO_2 [19]. These data support the contention that when turning patients with ALI prone, one should not attempt to minimize the restriction of the abdomen if a gain in arterial blood oxygenation is desired. The improvement in arterial blood oxygenation during prone positioning in our patients is in agreement with these data. However, patients with ALI rarely die of hypoxia and/or hypercarbia but commonly develop systemic inflammatory response syndrome with cardiocirculatory instability and impaired organ perfusion culminating in multiple organ dysfunction and death [20]. Hence improvement in oxygenation may not be desirable if it comes at the price of reduced regional blood flow to an essential organ.

When anesthetized patients are turned prone without an attempt to minimize abdominal compression, venous return and cardiac output decrease, presumably because IAP increases [21, 22, 23]. Apart from using an air-cushioned bed we made no effort to minimize restriction of the abdominal excursion during prone positioning. Unexpectedly, we observed only a moderate increase in IAP, from 10 to 13 mmHg. Results of previous studies suggest that free expansion of the abdominal wall is essential during prone position to avoid side effects caused by a marked increase in IAP [1, 2, 3, 4]. However, IAP appears to vary even in the supine position between patient groups; reports range from 6 mmHg in patients with acute respiratory distress syndrome of pulmonary cause to 16 mmHg in patients with the syndrome from extrapulmonary causes [24]. Experimental data suggest that if IAP is elevated from the usual ambient or subatmospheric level in spontaneously breathing subjects [13], hepatosplanchnic perfusion does fall [25, 26]. Therefore previously published data indicate that prone positioning may compromise systemic and regional blood flow and thereby promote hepatosplanchnic organ dysfunction in critically ill patients even if arterial blood oxygenation improves.

Consistent with our previous findings [5], turning prone effected an increase in CI in our patients, even though ITBVI and CVP, which we used as surrogates for preload, remained unchanged. Consequently, prone positioning improved oxygen delivery by effecting increases in both cardiac output and oxygen content. Our observations contradict the findings of decreased venous return [21, 22] and cardiac output [23] in patients under general anesthesia during prone positioning but are supported by data from small, nonrandomized studies performed in intensive care patients in whom global cardiac output was not negatively affected by prone positioning regardless of whether abdominal wall movement was restricted [27, 28] or not [3]. The most likely explanation for the differences between our study in critically ill patients and previous investigations in patients under general anesthesia is intravascular volume. Elevated IAP is most likely to effect alterations in venous return and cardiac output when intravascular volume is low [29], as is often the case in patients coming to surgery after an overnight fast and possible bowel preparation. However, this role of intravascular volume cannot be verified because available perioperative studies do not report whether participating patients were sufficiently volume-resuscitated prior to positioning.

Hepatosplanchic perfusion and function can be measured using ICG, a substance which is eliminated nearly unaltered by the liver into the bile [12]. We used a fiberoptic-based method for measuring ICG blood concentrations. This technique has been validated against photo-

metric determination of ICG blood levels [14] and shown useful in the bedside assessment of hepatic capacity to eliminate ICG in critically ill patients [30, 31]. During liver transplantation PDR_{ICG} has been demonstrated reliably to detect rapid variations in liver function caused by sudden changes in the hepatosplanchnic blood flow [12]. Since hepatic perfusion must be at least as high as the ICG clearance, PDR_{ICG} is related to the minimum of real hepatic blood flow. However, as PDR_{ICG} is, in addition to liver perfusion, also influenced by hepatocellular indocyanine green uptake [12, 32], measuring hepatic blood flow exactly requires hepatic vein catheterization and determination of hepatic ICG extraction [32]. Although none of our patients suffered from severe hepatic dysfunction prior to the study as indicated by the MOF score a significant change in hepatocellular uptake of ICG dye during the relatively short duration of our study cannot completely be ruled out. Thus it is one of the main limitations of our study that PDR_{ICG}, although being closely related to, does not solely reflect hepatic blood flow.

In our patients prone positioning was not associated with a change in PDR_{ICG} despite moderately elevated IAP. In anesthetized patients the prone position has been observed to impair hepatic ICG clearance; these changes have been attributed to a decrease in cardiac output [6]. Several experimental and clinical studies have revealed a close correlation between total hepatic blood flow and cardiac output [33]. It is possible that the unchanged PDR_{ICG} in the current study is a result of a direct depression of hepatic perfusion by a moderately elevated IAP offset by the small increase in systemic blood flow. Hence fractional hepatic blood flow, the ratio of hepatic blood flow to systemic blood flow, might have decreased during the prone position. Therefore maintaining adequate systemic blood flow is important to keep hepatic blood flow constant during prone positioning, even if the increase in IAP is small.

A gastric intramucosal to arterial PCO_2 difference has been proposed as a reliable measure of gastric mucosal perfusion in critically ill patients [16, 30, 34]. Prone positioning in our patients consistently was not associated with a change in the Pi-aCO_2 difference. This finding is supported by preliminary data in healthy volunteers in whom prone position did not affect Pi-aCO_2 difference [35]. Furthermore, this finding is in agreement with the PDR_{ICG} data. Apparently, prone positioning is not likely to affect hepatosplanchnic function as long as systemic cardiovascular function remains stable in patients with moderately elevated IAP. Thus based on our data we cannot rule out that prone positioning worsens hepatosplanchnic function in patients with preexisting abdominal hypertension or cardiovascular instability.

The results of this study demonstrate that resting patients with ALI on their thoraces and abdomens during prone positioning, although associated with a moderate increase in IAP, improves arterial oxygenation and systemic blood flow. Despite fractional hepatosplanchnic blood flow may decrease hepatosplanchic function is not likely to be affected when systemic blood flow improves during prone positioning. Therefore, apart from using an air-cushioned bed, special support to allow free chest and abdominal movement does not seem necessary when mechanically ventilated, adequately volume-resuscitated patients are turned prone to improve gas exchange. It should be noted, however, that these conclusions may not be applicable to patients with cardiovascular instability or severe abdominal hypertension.

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