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Title Page**Title:**

Prone positioning improves oxygenation in spontaneously breathing non-intubated patients with hypoxemic acute respiratory failure: a retrospective study

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All authors provided substantial contributions to the conception and design, acquisition of data, analysis and interpretation of findings. Dr. Scaravilli and Dr. Castagna retrospectively collected and performed analyses of data. Dr. Scaravilli, Dr. Grasselli, Dr. Castagna, Dr. Bellani and Dr. Zanella drafted the manuscript and all authors contributed substantially to revisions. All authors gave approval for the final version submitted for publication.

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Abstract

Purpose:

Prone positioning (PP) improves oxygenation and outcome of patients with acute respiratory distress syndrome undergoing invasive ventilation. We evaluated feasibility and efficacy of PP in awake, non-intubated, spontaneously breathing patients with hypoxemic acute respiratory failure (ARF).

Material and Methods:

We retrospectively studied non-intubated subjects with hypoxemic ARF treated with PP from January 2009 to December 2014. Data were extracted from medical records. Arterial blood gas analyses, respiratory rate and hemodynamics were retrieved 1 to 2 hours before pronation (step PRE), during PP (step PRONE), and 6 to 8 hours after resupination (step POST).

Results:

Fifteen non-intubated ARF patients underwent 43 PP procedures. Nine subjects were immunocompromised. Twelve subjects were discharged from hospital while 3 died. Only 2 maneuvers were interrupted, due to patient intolerance. No complications were documented. PP did not alter respiratory rate or hemodynamics. In the subset of procedures during which the same PEEP and FiO₂ were utilized throughout the pronation cycle (n=18), PP improved oxygenation (PaO₂/FiO₂ 124 ± 50 mmHg, 187 ± 72 mmHg and 140 ± 61 mmHg, during PRE, PRONE, and POST steps, respectively, p<0.001), while pH and PaCO₂ were unchanged.

Conclusions:

PP was feasible and improved oxygenation in non-intubated, spontaneously breathing patients with ARF.

Keywords:

Prone Position

Pulmonary Gas Exchange

Hypoxia

Pulmonary Ventilation

Noninvasive Ventilation

Retrospective Studies

Abbreviations

Acute respiratory failure (ARF), intensive care unit (ICU), mechanical ventilation (MV), ventilator associated pneumonia (VAP), chronic obstructive pulmonary disease (COPD), prone positioning (PP), arterial partial pressure of oxygen to inspired fraction of oxygen ratio ($\text{PaO}_2/\text{FiO}_2$), length of stay (LOS), continuous positive airway pressure (CPAP), fraction of inspired oxygen (FiO_2), positive end expiratory pressure (PEEP), heart rate (HR), central venous pressure (CVP), respiratory rate (RR), Richmond agitation sedation scale (RASS), high flow nasal cannulas (HFNC), standard deviation (SD), analysis of variance (ANOVA), oxygen saturation of arterial hemoglobin (HbO_2), arterial partial pressure of carbon dioxide (PaCO_2), ventilator induced lung injury (VILI).

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Introduction

Acute respiratory failure (ARF) is a common cause of intensive care unit (ICU) admission [1]. Patients with severe ARF are usually managed with intubation and invasive mechanical ventilation (MV), but their clinical course is frequently complicated by ventilator associated pneumonia (VAP) [2]. The risk of VAP is particularly high in patients with malignancies, immunocompromise and chronic obstructive pulmonary disease (COPD) [3–6]. Especially in these patient groups, VAP may adversely affect the clinical outcome [7,8]: thus, it is commonly suggested to avoid intubation and, whenever possible, to employ non-invasive ventilation (NIV) [9,10].

Prone positioning (PP) during invasive MV has been demonstrated to improve oxygenation and reduce mortality of the most severe ARDS patients [11–13]. In theory, these benefits should apply also to non-intubated patients, in whom PP may improve oxygenation while delaying or even avoiding the need for intubation. This may be particularly useful in patients at high risk of VAP [14].

Reports of the application of PP in spontaneously breathing, non-intubated adult patients are limited to few case reports [15–17].

In this retrospective observational study, we reviewed the 5-year experience of our ICU in the application of PP in awake, non-intubated, spontaneously breathing patients with hypoxemic ARF, describing the effect of PP on oxygenation, breathing patterns and hemodynamics.

Material and Methods

The study protocol was approved by the local Ethics Committee. Written informed consent was not deemed necessary due to the retrospective design of the study. The medical records of patients admitted to the general ICU of San Gerardo Hospital (Monza, Italy) from January 2009 to December 2014 were retrospectively screened for the following inclusion criteria: (1) arterial partial pressure of oxygen to inspired fraction of oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) lower than 300 mm Hg; (2) at least one application of PP in absence of endotracheal intubation.

Demographic data (i.e. gender, age), comorbidities, diagnosis at ICU admission, severity scores (i.e. Acute Physiology and Chronic Health Evaluation II score - APACHE II and Simplified Acute Physiology Score II - SAPS II of the first 24 hours of ICU stay), ICU length of stay (LOS), hospital LOS, outcome at hospital discharge as well as incidence of endotracheal intubation after the application of PP were recorded. Subjects undergoing immunosuppressive therapies (including long-term or high-dose steroids) or suffering from hematological or advanced solid malignancies were defined as "immunocompromised".

To evaluate feasibility, the duration of each PP procedure was recorded, as well as occurrence of known complications of PP (i.e. displacement of indwelling catheters, facial edema, pressure sores, pressure neuropathies, compression of nerves and retinal vessels, vomiting and intolerance to the maneuver) [18] as recorded in the medical and nursing charts.

To evaluate the clinical effects of PP, during each pronation procedure 3 different time points were identified: 1 to 2 hours before pronation (step PRE), the last hour of PP (step PRONE) and 6 to 8 hours after resupination (step POST). At each time point the following variables were recorded: type of respiratory device (i.e. oxygen supply mask, high-flow nasal cannulas, helmet continuous positive airway pressure - CPAP, NIV mask), respiratory setting

(i.e. fraction of inspired oxygen - FiO_2 , positive end expiratory pressure - PEEP), arterial blood gas analyses, $\text{PaO}_2/\text{FiO}_2$ ratio, heart rate (HR), arterial blood pressure, central venous pressure (CVP), respiratory rate (RR), dosage of vasopressors and sedative drugs as well as Richmond Agitation Sedation Scale (RASS). Finally, the daily Nurse Activity Score (NAS) [19] was recorded. PEEP delivered by high flow nasal cannulas (HFNC) was considered equal to 4 cmH_2O [20].

Statistical Analyses

Data are presented as mean \pm standard deviations (SD) or median (interquartile range), when appropriate. For normally distributed variables, one-way analysis of variance (ANOVA) for repeated measurement with a post hoc Tukey's correction was used to compare data of the different steps. For non-normally distributed variables, the Kruskal-Wallis test was performed. A p-value below 0.05 was considered statistically significant. Statistical analysis was performed using the JMP 11 statistical software (SAS, Cary, NC).

Results

From January 2009 to December 2014, 15 non-intubated patients (5 females and 10 males) with $\text{PaO}_2/\text{FiO}_2$ less than 300 mmHg were treated with PP. Patients' characteristics are summarized in Table 1. Fourteen patients were adults (median age was 66 (52.5-78.5) years old) while one patient was 16 years old. Nine patients were immunocompromised. Five had previous COPD diagnosis and 4 suffered from malignancies. The median value of SAPS II and APACHE II score were 42 (30.25-49) and 17.5 (15-21.25), respectively. Median ICU LOS was 9 (7-9) days, while the median hospital LOS was 26 (18-31) days. Only 2 subjects (13%) required intubation during the ICU stay. Three subjects died in the ICU, while the other 12 were discharged from the hospital (survival rate 80%).

During the study period, a total of 43 PP procedures were performed, with a median of 2 (1-3) procedures per subject. PP was applied for the first time after a median interval of 2 days (1-3) from admission. The median duration of PP cycles was 3 (2-4) hours and the longest procedure lasted 8 hours.

Patients were managed with different respiratory devices, PEEP and FiO_2 levels, as shown in Table 2. In 18 PP procedures the same respiratory support (i.e. type of device, PEEP and FiO_2) was utilized before, during and after the pronation cycle. In 10 of those 18 PP procedures non-invasive positive pressure ventilation was applied with the same setting (i.e. type of device, PEEP and FiO_2) before, during and after the pronation cycle.

Effect of PP on $\text{PaO}_2/\text{FiO}_2$ is shown in Figure 1. In the subset of PP procedures without changes in respiratory support ($n=18$): mean $\text{PaO}_2/\text{FiO}_2$ was significantly higher during PRONE step (187 ± 72 mmHg), as compared to PRE (124 ± 50 mmHg) and POST steps (140 ± 61 mmHg) ($p < 0.001$). Similarly, in the subset of procedures performed during non-invasive positive pressure ventilation ($n=10$), mean $\text{PaO}_2/\text{FiO}_2$ was significantly higher during PRONE step (214 ± 71 mmHg), as compared to PRE (157 ± 44 mmHg) and POST steps (160 ± 69 mmHg) ($p < 0.001$). Among the overall population, mean $\text{PaO}_2/\text{FiO}_2$ was significantly higher during PRONE step (186 ± 72 mmHg), as compared to PRE (127 ± 49 mmHg) and POST steps (141 ± 64 mmHg) ($p < 0.05$).

Effect of PP on arterial blood gas analyses is represented in Table 3. In the subset of PP procedures without changes in respiratory support ($n=18$), PaO_2 was significantly higher during PRONE step than during PRE and POST steps, while oxygen saturation of arterial hemoglobin (HbO_2) was significantly higher during PRONE step as compared to PRE step but not to POST step. In the subset of patients undergoing PP while on non-invasive positive pressure ventilation ($n=10$), similar statically significant differences in PaO_2 and HbO_2 were

observed. Among the overall population, PaO₂ and HbO₂ were significantly higher during PRONE step as compared to PRE and POST steps. At variance, arterial pH, arterial partial pressure of carbon dioxide (PaCO₂), bicarbonate ions concentration and Base Excess were not affected by the positional change in any subset of patient.

PP did not affect RR (26 ± 10, 25 ± 11 and 25 ± 10 breaths for minute during PRE, PRONE and POST steps, respectively) (p = 0.28).

Hemodynamic parameters (HR, blood pressure and CVP) were not affected by the application of PP, as shown in Table 4. Only 2 subjects (4 PP procedures) were receiving a vasopressor infusion (dobutamine), and no dosage adjustment was required during pronation. The median RASS value was 0 (0-0) and was not affected by the application of PP (p = 0.75). Three subjects were sedated with a low dosage of remifentanyl (0.06 ± 0.04 mcg/kg/min), and no dosage adjustment was required during pronation.

Two procedures were interrupted due to patient intolerance after 30 minutes from PP start: in one subject helmet CPAP was utilized, while the other subject was wearing an oxygen mask. No other complications, such as displacement of indwelling catheters, facial edema, pressure sores, pressure neuropathies, compression of nerves and retinal vessels or vomiting, were documented.

Median daily NAS value was 70% (62-84%).

Discussion

The application of PP in patients with ARF has been associated to many benefits: it improves oxygenation by reducing lung ventilation/perfusion mismatch [21] and promoting recruitment of non-aerated dorsal lung regions of the lung [22,23]. Moreover, it has been hypothesized that PP may help to prevent ventilator induced lung injury (VILI) [24]. Recently,

a randomized controlled trial [13] and two meta-analyses [11,12] demonstrated that PP significantly improves survival of the most severe ARDS patients. These evidences are restricted to intubated patients undergoing invasive MV. We hypothesized that PP could be beneficial also in non-intubated patients. To the best of our knowledge, literature on the use of PP in non-intubated patients is limited to few case-reports. Feltracco et al. described a cohort of 5 patients with lung transplantation complications managed by PP in association with NIV [16,17]. In another paper, Valter et al. documented the application of PP in 4 patients with ARF [15] and observed improvement of oxygenation during pronation.

In the present paper, we describe the application of PP in 15 awake, spontaneously breathing, non-intubated patients with hypoxemic ARF. A total of 43 PP procedures were performed. Our findings indicate that pronation was associated with a significant improvement in oxygenation. The reliability of our results may be affected by the fact that the type of respiratory device and/or the PEEP and FiO_2 levels were changed during a large number of the procedures. However, the improvement in oxygenation was confirmed even when the analysis was restricted to those procedures during which the same respiratory device and PEEP levels were applied before, during and after the PP cycle. Moreover, similar results were confirmed in the subset of patients undergoing non-invasive positive pressure ventilation while being pronated. Interestingly, the oxygenation improvement observed during PP did not persist after pronation: blood gas analyses and PaO_2/FiO_2 returned to baseline 6 hours following resupination, as previously reported [25]. A potential explanation for this finding is that pronation did not determine stable recruitment of dorsal lung regions, being the oxygenation improvement during PP mainly due to a reduction in ventilation/perfusion mismatch.

We documented the possibility to manage severe non-intubated patients with a $\text{PaO}_2/\text{FiO}_2$ as low as 130 mm Hg by combining prone positioning with non-invasive respiratory support. It is worth noting that the majority of the patients included in our study were immunocompromised. Recent meta-analyses limit the role of non-invasive ventilation for the treatment of ARDS patients, suggesting NIV to be employed only in carefully selected patients [26]. Nevertheless, NIV is currently recommended as the initial treatment of ARF in critically ill immunocompromised patients [27], since their prognosis is particularly poor when intubation and invasive MV are required, due to the high risk of VAP. Similar considerations apply also to COPD patients. For these reasons, we believe that a trial of PP may be attempted in these patients' categories, with the goal of recruiting the lung and improve oxygenation while avoiding intubation. Indeed, although maintenance of spontaneous breathing activity can promote aeration of dorsal lung regions better than controlled MV [28,29], closure of small airways in the dependent areas of the lung may develop also in non-intubated, spontaneously breathing subjects [30]. In these patients, the application of high airway pressures to recruit the lung may be impractical or poorly tolerated. In contrast, PP may be an alternative way to recruit the dorsal lung regions, without the need for high ventilatory pressures. Clearly, we do not suggest PP as an alternative to intubation. In contrast, since PP may promote recruitment in non-intubated patients, PP may be useful to guarantee adequate oxygenation, while limiting or delaying the need for intubation.

We have shown that PP is a feasible procedure in non-intubated patients (see Figure 2). Only in two cases pronation was interrupted due to patient intolerance. An increased level of sedation was not necessary to allow the positional change and in all patients a RASS score of 0 ("alert and calm") was maintained. Moreover, no catheter displacement or other complications of PP (i.e. facial edema, pressure sores or neuropathies) were documented,

and this can be at least partially explained by the short duration (on average 3 hours) of PP cycles, as well as by the fact that awake patients can perform small movements and change the pressure points. Clearly, staff expertise plays a major role, and an experienced team is essential to carry out pronation in awake, non-intubated patients. While we refer the reader to an excellent paper for further details on how to perform pronation [31], we would like to underline some technical aspects of the procedure that may be particularly important in awake patients. In conscious cooperative patients pronation can be performed by 2 nurses and the attending physician, while in patients with impaired mobility up to 5 operators might be necessary. Evaluation of gastric residual volume is needed to reduce the risk of aspiration and application of appropriate skin protections (i.e. hydrocolloids dressings) is mandatory to avoid pressure sores. Finally, careful application of appropriate cushions is used to improve patient tolerance to the maneuver. Notably, PP did not result in an increased nursing workload: the daily NASS score was 70%, similar to that observed in a recent study performed in our ICU on ARDS patients [19].

Our study has several limitations. The most important resides in the retrospective design of the study and the lack of a formal protocol. The changes in respiratory support during the majority of pronation cycles limit our capability to assess the effects of pronation on oxygenation. Thus, extrapolation of these results to current clinical practice warrants further formal evaluations. Similarly, our study does not allow to determine the best duration and frequency of PP application. Moreover, the selection of patients was performed by the attending physician and this may have positively biased the study results. This might also explain the relatively low mortality rate observed in the cohort as PP was not performed in those patients in whom a full commitment to care was missing. Finally, the small sample size

does not permit the evaluation of the effect of PP on important clinical outcomes such as intubation ratio, ICU and hospital length of stay and mortality.

Conclusions

We have demonstrated that pronation of awake, spontaneously breathing, non-intubated patients with hypoxemic ARF is feasible, safe and associated with a significant benefit on oxygenation. Further prospective studies are warranted to confirm our results and to evaluate the effect of PP on other clinically relevant outcomes.

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Figure Legends

Figure 1. PaO₂/FiO₂ during the three study steps. PRE, 1 to 2 hours before pronation; PRONE, during prone positioning; POST, 6 to 8 hours after resupination. Panel A shows PaO₂/FiO₂ of the subset of pronation procedures without changes in respiratory device, PEEP and FiO₂ (n=18). Panel B shows PaO₂/FiO₂ of the subset of pronation procedures performed during non-invasive positive pressure ventilation (n=10). Panel C shows PaO₂/FiO₂ of all the performed pronation procedures. Data are represented as mean ± standard deviations. * p < 0.05 vs. PRE step and † p < 0.05 vs. POST step.

Figure 2. Pictures of 2 representative non-intubated, spontaneously breathing patients undergoing prone position. Panel A shows prone positioning in a patient with helmet continuous positive airway pressure. Panel B shows prone positioning in a patient with mask non-invasive ventilation.

Pat ien t	Age (year s)	Ge nde r	ICU Diagnosis	Immunoco mpromized	CO PD	20 Malign nancy	APA CHE II	SA PS II	Endotrache al Intubation	IC U L O S	Hospit al LOS	Hospital Outcome
1	75	M	Pneumonia	X	X	X	21	42		7	35	Discharg ed
2	71	F	Pneumonia	X			22	39		8	31	Discharg ed
3	14	M	Pneumonia				N.A	N.A		7	18	Discharg ed
4	36	M	Pneumonia	X			15	21		5	15	Discharg ed
5	58	M	Pneumonia		X		23	49		7	26	Discharg ed
6	61	M	Fascitis				18	28		4	21	Discharg ed
7	63	M	Pneumonia	X			15	46		9	27	Discharg ed
8	80	F	Pneumonia		X	X	17	59		8	30	Discharg ed
9	65	M	Pneumonia		X		15	24	X	5 0	80	Discharg ed
10	67	M	Pneumonia		X		11	40		8	13	Discharg ed
11	80	F	Pneumonia	X		X	19	55		5	7	Dead
12	78	M	Pneumonia				16	49		9	26	Discharg ed
13	80	M	Pneumonia	X			21	42		7	23	Discharg ed
14	19	F	Pneumonia	X		X	16	31		2 6	34	Dead
15	28	F	Sepsis of unknown origin	X			27	43	X	1 5	25	Dead

Table 1. Patients' characteristics. ICU, intensive care unit. COPD, chronic obstructive pulmonary disease. LOS, length of stay. APACHE II, Acute Physiology and Chronic Health Evaluation II score. SAPS II, Simplified Acute Physiology Score II.

	All procedures (n=43)			Procedures without changes in respiratory device, PEEP and FiO ₂ (n=18)
	PRE	PRONE	POST	
Oxygen mask	24	16	23	8
High flow nasal cannula	1	2	1	0
Helmet CPAP	11	12	10	5
Mask NIV	7	13	9	5
FiO₂ (%)	74 ± 18	70 ± 22	69 ± 20	72 ± 20
PEEP (cmH₂O)	0 (0-9)	9 (0-9)	4 (0-10)	8 (0-10)

Table 2. Ventilatory settings during the different study periods. PRE, 1 to 2 hours before pronation; PRONE, during prone positioning; POST, 6 to 8 hours after resupination. CPAP, continuous positive airway pressure. NIV, non-invasive ventilation. PEEP, positive end expiratory pressure. FiO₂ values are represented as mean ± SD. PEEP values are represented as median (interquartile range).

Variable	PRE	PRONE	POST	p
Procedures without changes in respiratory device, PEEP and FiO ₂ (n=18)				
pH	7.42 ± 0.04	7.42 ± 0.03	7.42 ± 0.03	0.50
PaCO ₂ (mmHg)	47.8 ± 10.9	46.8 ± 9.8	47.1 ± 9.6	0.42
HCO ₃ ⁻ (mMol/L)	30.0 ± 5.7	30.0 ± 6.1	29.2 ± 4.2	0.84
PaO ₂ (mmHg)	88 ± 26	131 ± 60*†	91 ± 23	< 0.001
HbO ₂ (%)	95.1 ± 1.9	96.7 ± 1.5*	95.5 ± 253	0.01
Base excess (mMol/L)	4.8 ± 4.9	4.9 ± 5.2	4.1 ± 3.7	0.68
Procedures during non-invasive positive pressure ventilation (n=10)				
pH	7.43 ± 0.04	7.43 ± 0.03	7.43 ± 0.03	0.85
PaCO ₂ (mmHg)	44.8 ± 5.8	43.8 ± 4.8	44.0 ± 4.3	0.54
HCO ₃ ⁻ (mMol/L)	29.0 ± 4.2	28.5 ± 3.7	29.1 ± 3.5	0.48
PaO ₂ (mmHg)	97 ± 30	128 ± 48†	92 ± 20	0.02
HbO ₂ (%)	95.9 ± 1.1	97.0 ± 1.7	96.0 ± 1.8	0.04
Base excess (mMol/L)	4.1 ± 4.2	3.7 ± 3.6	4.3 ± 3.3	0.48
All procedures (n=43)				
pH	7.42 ± 0.03	7.42 ± 0.03	7.43 ± 0.03	0.80
PaCO ₂ (mmHg)	45.4 ± 9.6	45.7 ± 9.0	45.3 ± 9.0	0.64
HCO ₃ ⁻ (mMol/L)	28.7 ± 4.9	28.8 ± 5.0	28.5 ± 4.1	0.44
PaO ₂ (mmHg)	89 ± 28	124 ± 53*†	91 ± 42	< 0.001
HbO ₂ (%)	94.8 ± 2.7	96.6 ± 1.5*†	95.2 ± 2.3	< 0.001
Base excess (mMol/L)	3.8 ± 4.2	3.9 ± 4.3	3.6 ± 3.4	0.61

Table 3. Arterial blood gas analyses during the different study periods. PRE, 1 to 2 hours before pronation; PRONE, during prone positioning; POST, 6 to 8 hours after

resupination. HCO_3^- , bicarbonate ions concentration; HbO_2 , arterial oxygen hemoglobin saturation. PEEP, positive end expiratory pressure. Data are represented as mean \pm standard deviations. Right column shows ANOVA p value. Post hoc analysis: * p < 0.05 vs. PRE step and † p < 0.05 vs. POST step.

	PRE	PRONE	POST	p
Heart rate (bpm)	88 ± 15	88 ± 16	89 ± 17	0.88
Systolic arterial pressure (mmHg)	121 ± 19	123 ± 20	124 ± 21	0.53
Mean arterial pressure (mmHg)	87 ± 16	87 ± 14	87 ± 17	0.96
Diastolic arterial pressure (mmHg)	66 ± 15	67 ± 15	66 ± 17	0.89
Central venous pressure (mmHg)	4 ± 3	4 ± 4	4 ± 3	0.61

Table 4. Hemodynamic variables during the different study periods. PRE, 1 to 2 hours before pronation; PRONE, during prone positioning; POST, 6 to 8 hours after resupination. Data are represented as mean ± standard deviations. Right column shows ANOVA p value.

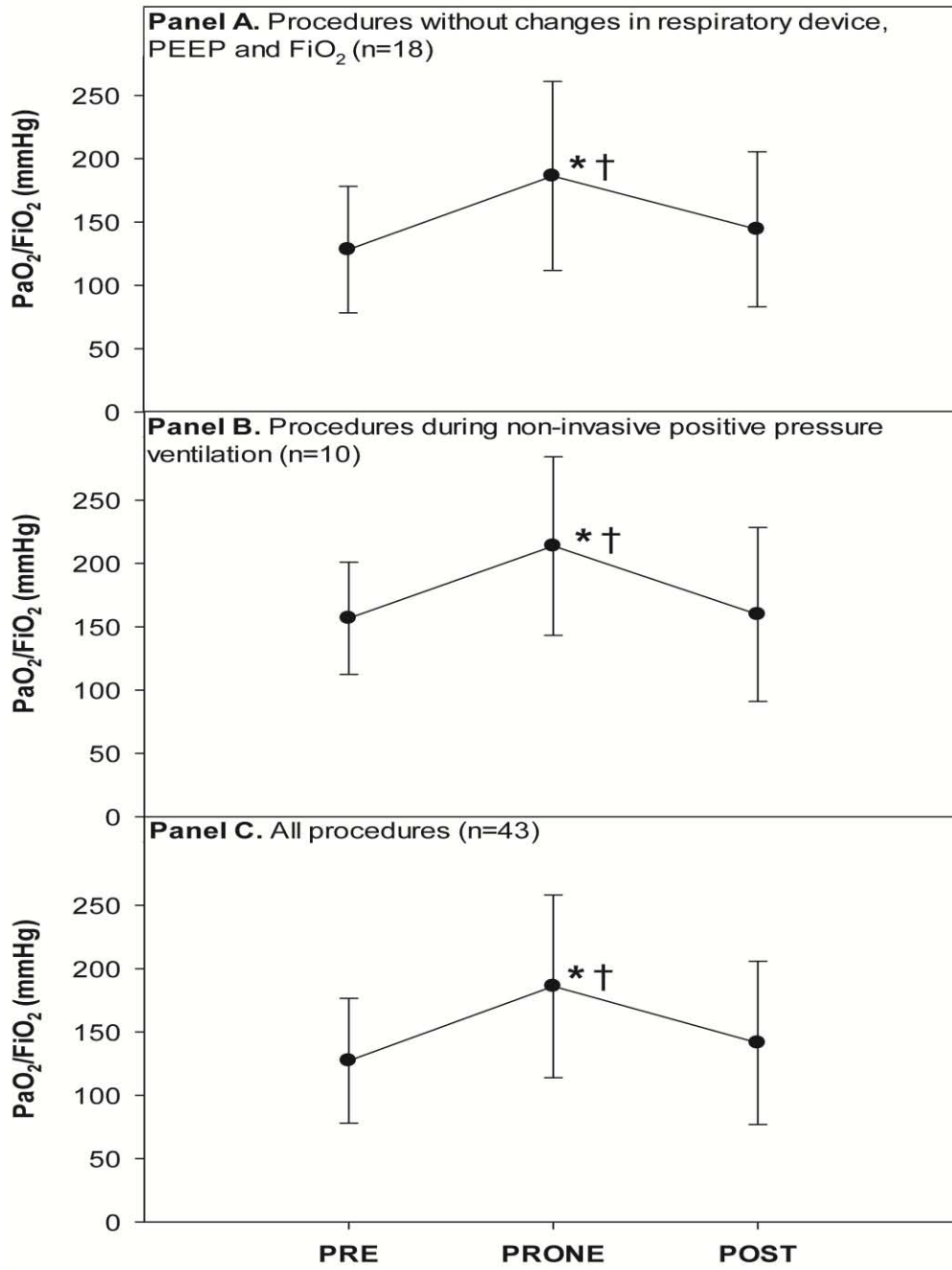


Figure 1

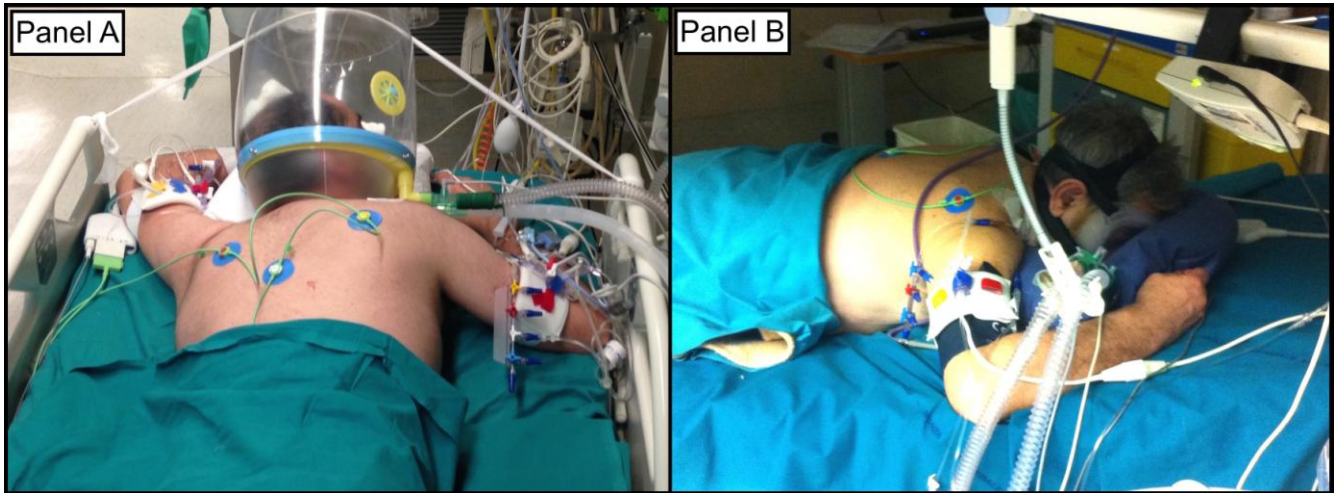


Figure 2