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Editorial

Positioning of Prone Ventilation in the Management of Acute Respiratory Distress is Challenging

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Prone ventilation (PV) has been used for almost four decades in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). It improves oxygenation by recruiting more alveoli, reducing atelectasis, and possibly facilitating positional drainage [1].

Meta-analyses suggested survival benefits of PV only in patients with severe hypoxemia [2,3]. A recently published study, Proning Severe ARDS Patients (PROSEVA), is the first randomized controlled trial (RCT) that showed survival benefits in severely hypoxemic ARDS patients. The 28 and 90-day mortality rates were significantly lower with PV compared with conventional ventilation (hazard ratio 0.39 and 0.44 respectively, p<0.001) [4]. The PROSEVA study differed from previous RCTs in the duration and timing of PV [5-11]. Patient selection may have contributed to the difference in the results. The PROSEVA study recruited patients with the most severe hypoxemia with the mean partial pressure of arterial oxygen to the fraction of inspired oxygen ratio of 100 (Table 1).

Intensivists now face the current question of should PV be implemented for every patient who meets the inclusion criteria of the PROSEVA study? In other words, is the PROSEVA study a game changer believing that implementing PV sooner and longer in severely hypoxemic ARDS patients saves more lives?

Meta-regression analysis is a suitable tool to assess the association between predictors and outcomes. When all the RCTs are pooled and analyzed, age, severity of hypoxemia, duration and timing of PV, and SAPS II score do not appear to have a significant association with the survival benefit of PV (Table 2). Therefore, the difference in study protocol and patient population of the PROSEVA study may not be the reason for better outcomes. The demonstrated benefits may have happened by accident due to other confounders, such as an imbalance of patient characteristics between two groups. In addition, when the PROSEVA study was pooled with the previous RCTs, the survival benefits became no longer significant (Relative risk=0.86 [95% confidence interval 0.72 to 1.02] (Figure 1). A greater than 50% reduction in mortality seen in the PROSEVA study is something quite remarkable and unheard of in the ARDS literature. The possibility of type 1 error cannot be excluded.

Most of the clinical studies of PV were conducted in European countries (Table 1) where characteristics of ICU patients may differ from those in the US. The average body mass index in the PROSEVA study was 29.It is reported that as many as 25% of ICU

Table 1: Randomized controlled trials of prone ventilation in adult patients with acute respiratory distress syndrome.

Study [Reference]	Study site	Sample size	Age (mean)	PaO2/FiO2 (mean)	SAPS II score (mean)	Time from acute event to enrollment (mean, hour)	Duration of PV per session (mean)	Number of PV session (mean)
Gattinoni 2001 [5]	Italy and Switzerland	297	58	127	40	NR	7	9.4
Beuret 2002 [6]	France	21	55	326	50	14	4	6.0
Guerin 2004 [7]	France	790	62	152	46	51	8	4
Voggenreiter 2005 [8]	Germany	40	41	221	NR	107	11	NR
Mancebo 2006 [9]	Spain and Mexico	136	54	145	41	25	17	10
Fernandez 2008 [10]	Spain	40	55	118	38	< 48	>20	NR
Taccone 2009 [11]	Italy and Spain	338	60	113	41	< 72	18	8.4
PROSEVA 2013 [4]	France and Spain	466	59	100	46	32	17	4

PaO_2/FiO_2 = partial pressure of arterial oxygen to the fraction of inspired oxygen ratio; SAPS = simplified acute physiology score; PV= prone ventilation; NR= not reported

patients are obese in the US [12]. Repositioning of patients with a body mass index greater than 40 generally requires at least four staff members [13]. Although a recent study suggested that PV is feasible in obese patients and may improve oxygenation greater than in non-obese patients [14], implementing PV in morbidly obese patients would be a huge burden to staff members. Most aforementioned RCTs were conducted in centers experienced with PV at a minimum of 5 years. It remains to be seen if the same results can be reproduced when PV is implemented in centers where obesity is epidemic and staff members are not experienced with prone positioning.

Low tidal volume ventilation was found to decrease mortality in ALI/ARDS patients which is much easier to implement than PV, but its adoption in the clinical practice has been very slow despite its proven survival benefits [15]. Adopting PV in ARDS patients will likely be very slow due to its practicality and unclear reproducibility and generalizability of the survival benefits. There are only 10 studies registered at Clinicaltrials.gov for PV in ARDS as of June 2013. Ongoing studies are unlikely to answer the above question.

PV may follow the fate of selective digestive decontamination which is a striking example of very limited adoption, especially in the US, of an evidence- based therapy des pite its proven survival benefits [16]. The position of PV in the management of ARDS patients is by no means clear and a tiebreaker is desperately needed. While awaiting further evidence, a potential survival benefit seen in the PROSEVA study is hard to ignore.

Table 2: Univariate meta-regression analyses to examine the influence of prognostic factors on mortality.

Variables	No. of studies	Regression Coefficient	T score	P value
Age	8	0.033	1.03	0.34
PaO2/FiO2 ratio	8	0.00072	0.28	0.79
Duration of PV >10 hrs per day	8	-0.32	-2.29	0.062
Time to initiate PV < 48 hrs	7	-0.35	-2.48	0.056
SAPS II score	7	-0.023	-0.69	0.52

PaO_2/FiO_2 = partial pressure of arterial oxygen to the fraction of inspired oxygen; PV= prone ventilation; SAPS = simplified acute physiology score. A p value of less than 0.05 was considered significant. Analyses were performed using STATA 10.1.

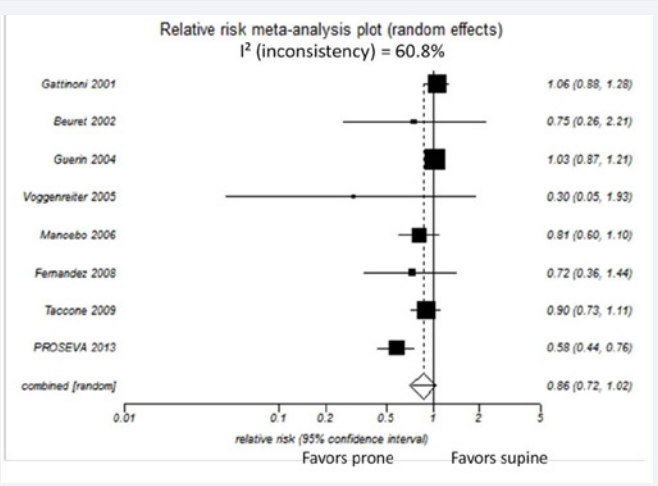

Figure 1 Forest plot showing the effect of prone position on mortality (at hospital discharge or the longest duration of follow-up).

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