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Review article / *Articolo di revisione*

Prone positioning and noninvasive respiratory supports in acute hypoxemic respiratory failure

Posizione prona e supporti respiratori non invasivi nell'insufficienza respiratoria acuta ipossiemica

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Summary

Background. Prone Positioning (PP) is a non-pharmacological treatment used during invasive mechanical ventilation (IMV) for severe Acute Respiratory Distress Syndrome (ARDS). During PP, patients lay on their stomach rather than their back, improving the redistribution of lung density from dorsal to ventral areas, gas exchange, and reducing mortality. Prone positioning has received significant attention during the current COVID-19 pandemic due to the possibility of avoiding intubation and reducing the pressure on hospital critical care resources. We aim to conduct a mini-review to highlight the effect of awake PP during High Flow Nasal Therapy (HFNT) or Noninvasive Ventilation (NIV) on PaO_2/FiO_2 (P/F) improvements and the need for intubation in patients with mild-to-moderate ARDS.

Methods. We conducted a literature search in November 2020 with no restrictions on the publication date. Literature sources included: MEDLINE (Ovid), PubMed, Cochrane Library, LitCOVID, WHO COVID-19 Research Database, BMJ Best Practice, and Google Scholar. Eight papers fulfilled the inclusion criteria and were included for the final analysis.

Results. Four of the eight included studies analyzed patients with confirmed SARS-CoV-2 infection. Prone positioning maneuvers during HFNT or NIV significantly increased P/F and avoided intubation in the majority of patients. In most severe ARDS (P/F < 100), PP was insufficient to stabilize gas exchange. In this sub-group of patients, the rate of progression to mechanical ventilation was sensibly higher. PP was generally well tolerated across a wide range of maneuvers duration.

Conclusion. PP during HFNT or NIV could be a viable option in case of mild-to-moderate ARDS both in patients with and without COVID-19 infection. Further prospective studies (e.g., Randomized-Control Trials) with a larger cohort of patients are needed.

Key words: acute hypoxemic respiratory failure, prone positioning, high flow nasal therapy, noninvasive ventilation, COVID-19

Riassunto

Introduzione. *La posizione prona (PP) è utilizzata durante la ventilazione meccanica invasiva (IMV) nei casi di sindrome da distress respiratorio acuto (ARDS) grave. Durante la PP i pazienti sono distesi sul ventre piuttosto che sul dorso, migliorando così la ridistribuzione della densità polmonare dalle aree dorsali a quelle ventrali e lo scambio dei gas con conseguente riduzione della mortalità. La posizione prona ha attirato particolarmente l'attenzione durante l'attuale pandemia di COVID-19 grazie alla possibilità di evitare l'intubazione e ridurre la pressione sulle unità di terapia intensiva. Abbiamo quindi condotto una mini-review per evidenziare l'effetto della posizione prona da svegli sul rapporto PaO_2/FiO_2 (P/F) e sulla necessità di intubazione, durante ossigenoterapia ad alti flussi (HFNT) o ventilazione non invasiva (NIV), nei pazienti con ARDS lieve-moderata.*

Metodi. *A Novembre 2020 abbiamo eseguito una ricerca bibliografica, senza restrizione sulla data di pubblicazione, sui seguenti motori di ricerca: MEDLINE (Ovid), PubMed, Cochrane Library, LitCOVID, WHO COVID-19 Research Database, BMJ Best Practice e Google Scholar. Otto documenti rispettavano i criteri di inclusione e sono stati considerati in questa review.*

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Conflict of interest
The Authors declare no conflict of interest.

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Risultati. *Quattro degli otto studi inclusi hanno analizzato pazienti con infezione confermata da SARS-CoV-2. La posizione prona in corso di HFNT o NIV ha determinato un aumento significativo del P/F ed evitato l'intubazione nella maggior parte dei pazienti. Nei casi di ARDS più grave (P/F < 100), la PP non si è dimostrata sufficiente a stabilizzare gli scambi gassosi. In questi pazienti il tasso di progressione verso la ventilazione meccanica invasiva era sensibilmente più alto. La posizione prona è stata generalmente ben tollerata anche per periodi più prolungati.*
Conclusioni. *La PP durante HFNT o NIV potrebbe essere un'opzione praticabile in caso di ARDS, da lieve a moderata, nei pazienti con e senza COVID-19. Futuri studi prospettici con una più ampia coorte di pazienti sono comunque necessari.*

Parole chiave*: insufficienza respiratoria acuta ipossiemica, posizione prona, ossigenoterapia ad alti flussi, ventilazione noninvasiva, COVID-19*

Introduction

Prone Positioning (PP) is a non-pharmacological treatment used during invasive mechanical ventilation for severe Acute Respiratory Distress Syndrome (ARDS), where patients lay on their stomach rather than their back. The hypothesis on the rationale of PP being able to improve oxygenation includes alveolar recruitment, redistribution of ventilation toward dorsal areas that remain well perfused, homogenization of tidal volume distribution as a result of a better fitting of the lungs with the chest wall, and redirection of compressive force exerted by heart weight on lungs toward the sternum [1-3]. In contrast to PP for intubated mechanically ventilated patients with ARDS, no randomized control trials examined the role of awake PP for non-intubated patients with acute hypoxemic respiratory failure (AHRF), and only anecdotal reports, case series, and small prospective studies are available. Notably, PP has received great attention during the current COVID-19 outbreak [4] due to the possibility of avoiding intubation and, therefore, less burden on hospital critical care resources [5]. However, there is no evidence that regular PP in awake patients impacts relevant clinical outcomes. To further explore this topic, we identified and synthesized the studies examining the effect of awake PP on patients with AHRF, including those with ARDS and/or COVID-19.

Methods

We included studies with the following criteria: 1) hospitalized patients managed with High Flow Nasal Therapy (HFNT) and/or Noninvasive Ventilation (NIV); 2) AHRF, including ARDS and other potentially relevant conditions; 3) use of PP; 4) report of intubation, survival rate, and adverse events; 5) change in respiratory parameters; 6) observational or randomized control trial. The search was conducted in November 2020 with no restrictions on publication date. Literature sources searched included: MEDLINE (Ovid), PubMed, Cochrane Library, LitCOVID, WHO COVID-19 Research Database, BMJ Best Practice, and Google Scholar. Publications in a language other than English were excluded. Studies involving patients on helmet CPAP were also excluded. Our search produced 67 results. According to our criteria, 8 studies were eligible for this review. Interestingly, 51 out of 67 were published in 2020, and the majority (43/51) were based on COVID-19 patients.

Awake prone positioning in moderate-to-severe ARDS

The available evidence retrieved are showed in Table 1. The first evidence on PP in spontaneously breathing awake adult patients was published by Valter et al. in 2003 [6]. The authors reported four consecutive cases of AHRF, treated with NIV. Patients were placed in PP while breathing spontaneously, for a minimum of 50 minutes to a maximum of 5 hours to avoid intubation. FiO_2, set to maintain SpO_2 > 90% or PaO_2 > 55 mmHg, decreased from a median of 0.70 (0.60-0.70) in supine to 0.40 (0.30-0.50) during PP. At the same time, Respiratory Rate (RR) was reduced from a median of 31 min -1 (26-38) to 20 min-1 (18-21); as a result, intubation was avoided in all four patients. No significant complications were registered. A larger retrospective-cohort study was published in 2015 by Scaravilli et al. [7], including fifteen patients (10/15 males, 9/15 immunocompromised) with P/F < 300 mmHg, treated with a total of 43 PP procedures, from January 2009 to December 2014. The median duration of PP cycles was 3 (2-4) hours, and the longest procedure lasted 8 hours. Patients were managed with HFNT and NIV. Mean supine P/F and RR were 127 ± 49 mmHg and 26 ± 10 min-1, respectively. During PP, P/F has significantly improved to 186 ± 72 mmHg ($p < 0.05$), and RR reduced to 25 ± 11 min-1. Two patients out of 15 (13.3%) were intubated. No displaced catheters, pressure sores, neuropathy, vomiting, change in hemodynamics were reported. Two patients were non-tolerant, and 3 died without intubation. In 2020 Perez-Nieto et al. [8] retrospectively studied 6 patients (4 male) with severe non-infectious ARDS (including thoracic trauma with pulmonary contusions, lupus pneumonitis, bone marrow transplantation, and atelectasis of unknown cause) with a P/F < 100, managed with HFNT and/or NIV between 2017 and 2018. Prone positioning was applied for 2-3 hours, two times daily, for two days. Median supine P/F was 80 (67-91) versus 116 (101-131) in PP. Two patients (33.3%) were intubated, and 1 (17%) died. Ding et al. [9] conducted a small prospective cohort study in two teaching hospitals and studied 20 non-in-

Table I. Characteristics of studies examining awake prone positioning in high flow nasal therapy or noninvasive ventilation.

Author	Year	N	Inclusion criteria	Oxygen delivery mode	Duration of prone positioning	Supine P/F and RR	Prone P/F and RR	Intubation rate	Adverse event
Valter et al. [6]	2003	4	Hypoxemia	NIV	1-5 h	FiO_2: 0.70 (0.60-0.70) RR: 31 (26-38)	FiO_2: 0.40 (0.30-0.50) RR: 20 (18-21)	0/4	Not reported
Scaravilli et al. [7]	2015	15	P/F < 300	HFNT or NIV	3 (2-4)	P/F: 127 (49) RR 26 (10)	P/F: 186 (72) RR: 25 (11)	2/15	2 non-tolerant, 3 died
Perez-Nieto et al. [8]	2020	6	ARDS, P/F<100	HFNT or NIV	2-3h	P/F 80 (67-91)	P/F 116 (101-131)	2/6	1 died
Ding et al. [9]	2020	20	ARDS, P/F<200	HFNT or NIV	2h	Success group P/F: 151 Failure group P/F: 83	Success group P/F: 125 Failure group P/F: 119	9/20	2 non-tolerant, 1 died
Sun et al. [13]	2020	n/a	Not reported	HFNT or NIV	Not reported	Not reported	Not reported	Not reported	Not reported
Slessarev et al. [14]	2020	1	COVID-19 infection, Hypoxemia	HFNT	16-18h	100	250	0/1	1 nosebleed
Xu et al. [15]	2020	10	COVID-19 infection PF < 300 mmHg	HFNT	4-6 h	P/F range: 89-228	P/F range: 200-325	0/10	No adverse events reported
Sartini et al. [16]	2020	15	COVID-19 infection SpO_2 < 94% FiO_2 0.6, PAP 10 cmH_2O	NIV	3h (1-6)	P/F range: 58-117 RR 21-31	P/F range: 114-122 RR 18-27	1/15	1 died

Abbreviations: N: number of subjects; NIV: Non-Invasive Ventilation; HFNT: High Flow Nasal Therapy; P/F, PaO_2:FiO_2; RR, Respiratory Rate. Values are reported as numbers, mean (SD) and median (IQR).

tubated patients with moderate-to-severe ARDS (according to the Berlin criteria - 10 moderate and 10 severe ARDS) mostly having viral pneumonia. Patients with a P/F < 200 while on NIV with CPAP 5 cmH_2O and FiO_2 of 0.5 were enrolled. Patients with altered mental status, agitation, or respiratory distress were excluded. All the patients started with High Flow Nasal Therapy (HFNT) alone (flow rate up to 60 L/min and FiO_2 max 0.9) and were escalated to HFNT combined with PP or NIV (CPAP or BiPAP and oro-nasal mask) or NIV combined with PP to maintain SpO_2 > 90%. Prone positioning was applied at least twice per day for a minimum of 30 minutes per session, with an average of 2 hours per session, for 3 days without sedation. The primary outcome was the rate of avoidance for endotracheal intubation (ETI). The secondary outcome included improvement in P/F with the combination of PP+HFNT/NIV. 55% [10] of patients avoided ETI, and 45% [9] were intubated. In this group, the median initial P/F was lower in comparison with non-intubated patients (83 *vs.* 151). P/F in HFNT+PP or NIV+PP was significantly higher in the success group than in the failure group (125 ± 41 mmHg *vs.* 119 ± 19 mmHg, p = 0.043). Three intubated patients underwent extra-corporeal membrane oxygenation, and 1 (5%) died. Two patients were defined as non-tolerant to PP.

Prone positioning combined with HFNT or NIV in COVID-19 related ARDS

The current COVID-19 pandemic presents a consider-

able challenge to healthcare systems worldwide [11]. Emerging evidence suggests that COVID-19 patients develop atypical ARDS with relatively preserved lung mechanics [10] despite severe hypoxemia due to shunt fraction [12]. Several studies explored the feasibility, efficacy, and tolerance of PP in improving oxygenation and reducing shunt fraction in awake patients with COVID-19 outside the ICU, as shown in Table I.

Sun et al. [13] reported their experience in the early phase of the COVID-19 pandemic in China. They described a better outcome than national data, and they partly attributed this to a combined approach of early awake PP, NIV, and restrictive fluid resuscitation. Still, the paper lacked clinical data on the enrolled patients and the P/F values.

Slessarev et al. [14] published the first report of a 68-yr-old self-proning patient affected by COVID-19, managed with HFNT (60 L/min, FiO_2 0.90) and instructed to self-prone via telephone by lying with his chest down as long as possible (approximately 16-18 hours per cycle). Initial supine P/F was 120 mmHg, but it greatly improved during each PP maneuver to around 250 mmHg. The P/F ratio failed to improve on the third cycle, and the care team found blood clots in his posterior nasal passages. Once cleared, his oxygenation improved again, and he was discharged from the ICU to a dedicated COVID-19 ward on day 4. Later on, Xu et al. [15] conducted a retrospective observational study in three hospitals in China involving 10 subjects (5 male, 50%) with moderate-to-severe COVID-19-related ARDS, recruited between January and April of the same year. Patients had P/F < 300 mmHg (lowest P/F ratio was 89 mmHg) and were managed using HFNT. The mean time of PP was 4-6 h per day. Target SpO_2 was > 90%. Supine P/F ranged from 89 to 228. After 3 days, during PP, P/F ranged from 200 to 325. Intubation was avoided in all patients, no significant complications were registered, and no deaths were reported.

Sartini et al. [16] published a cross-sectional survey on COVID-19 patients and ARDS in May 2020. They showed that NIV was used for 62 patients with mild-to-moderate ARDS. The study outcome assessed the proportion of patients with PaO_2 increase ≥ 20% from supine to PP, P/F, and patient comfort with NIV. Inclusion criteria were hypoxemia (SpO_2 < 94%), FiO_2 > 0.6 and CPAP 10 cmH_2O. Prone positioning was used in 15 patients (13 male) with poor response to NIV. Noninvasive ventilation in the prone position started after a median of 5 days. Compared with baseline, all patients had a reduction in RR during and after pronation ($p < 0.001$ for both). All patients had an improvement in SpO_2 and P/F during PP ($p < 0.001$ for both), 2 (13.3%) had the same value, and 1 (6.7%) worsened. On day 14 of follow-up, 9 patients were discharged home, 1 improved and stopped PP, 3 continued pronation, 1 patient was intubated and admitted to ICU, and 1 patient died.

Discussion

In this mini-review, we reported a series of studies involving hypoxemic patients treated with HFNT or NIV combined with PP. First, we analyzed 4 studies [6-9] involving hypoxemic patients with ARDS mostly of infectious etiology, except for the report of Perez-Nieto and coworkers [8]. The impact of prone positioning was evaluated on P/F or FiO_2 improvements and intubation rate. The duration of PP cycles ranged from a minimum of 1 hour to a maximum of 5 hours. The majority of the subjects showed significant improvement in oxygenation after PP, and 32/45 (71%) patients avoided intubation. However, in particularly severe ARDS patients, PP was insufficient to stabilize gas exchange. Indeed, 13 out of 18 patients with P/F < 100 mmHg did not improve enough to avoid ETI. Promising results were observed when the PP sessions were started early, maybe due to the availability of a higher proportion of potentially recruitable alveoli in the early stages of ARDS [17]. No significant complications associated with PP were reported in all the included studies. Only 4 patients were non-tolerant to PP due to discomfort, anxiety, and the inability to change position, and 5 died.

As shown in our results, we found that most studies in which PP was used were published during 2020. Indeed ARDS is one of the main complications of COVID-19 occurring in 20-40% of patients with severe disease [18]. As resources like ventilators and intensive care beds are limited, strategies to prevent intubation are needed. According to Slessarev [14], Xu [15], and Sartini [16], PP can be a useful tool to avoid intubation in mild-to-moderate COVID-19-related ARDS. The impact of prone positioning was evaluated on P/F or FiO_2 improvements and intubation rate. The duration of PP cycles ranged from a minimum of 1 hour to a maximum of 18 hours. Twenty-five out of 26 (96%) patients avoid intubation. Only 1 patient died, and 1 had a nosebleed. The included studies reported no major complications associated with PP. Overall, PP was well tolerated.

Conclusion

In patients with ARDS, awake PP combined with both HFNT and NIV may improve patients' outcomes, such as oxygenation (P/F) and the need for intubation. There are no formal guidelines for PP in non-intubated patients. However, protocolization may improve compliance and provide a time frame that may be helpful. Awake prone positioning presents a low risk, easy implementation

and may improve oxygenation early in the course of the disease. Nevertheless, prospective data with clear benefits are still lacking. This review has several limitations, such as the small number of papers reviewed, the relatively small cohorts of patients involved in the included studies, and the retrospective nature of the majority of studies enclosed.

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