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Response to the first awake prone positioning relates with intubation rate in SARS-CoV-2 patients suffering from acute respiratory failure with moderate to severe hypoxaemia: a retrospective study

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Summary

AIMS OF THE STUDY: Awake prone positioning (aPP) in non-intubated patients with severe SARS-CoV-2-related pneumonia improves oxygenation and reduces the intubation rate, but no early predictors for success or failure of the strategy have been described. The main objective of this study was to assess whether response to the first aPP in terms of PaO_2/FiO_2, alveolar-arterial gradient ($Aa-O_2$), respiratory rate and $PaCO_2$ could predict the need for intubation. As secondary objective, we assessed the effects of aPP on the same parameters for all the sessions considered together.

METHODS: Retrospective analysis of consecutive SARS-CoV-2 pneumonia patients suffering from acute respiratory failure with moderate to severe hypoxaemia for whom aPP was performed for at least 45 minutes based on the prescription of the clinician in charge according to predefined criteria. Respiratory rate, blood gases and oxygenation parameters (PaO_2/FiO_2 and $Aa-O_2$), before and after the first aPP were compared between patients who were subsequently intubated or not. Effects of all the aPP sessions together were also analysed.

RESULTS: One hundred and sixty-six patients were admitted for SARS-CoV-2 pneumonia during the study period. Among them, 50 received aPP lasting at least 45 minutes. Because 17 denied consent for data analysis and 2 were excluded because of a "do not intubate order", 31 patients (for a total of 116 aPP sessions without any severe adverse events reported) were included. Among them, 10 (32.3%) were intubated. Mean age ± standard deviation (SD) was 60 ± 12 years. At ICU admission, respiratory rate was 26 ± 7/minute, median PaO_2/FiO_2 94 (interquartile range [IQR] 74–116) mm Hg and median $Aa-O_2$ 412 (IQR 286–427) mm Hg (markedly increased). Baseline characteristics did not statistically differ between pa-

tients who subsequently needed intubation or not. During the first aPP, PaO_2/FiO_2 increased and $Aa-O_2$ decreased. When comparing patients who later where intubated or not, we observed, in the non intubated group only, a clinically significant decrease in median $Aa-O_2$, from 294 (280–414) to 204 (107–281) mm Hg, corresponding to a 40% (26–56%) reduction, and a PaO_2/FiO_2 increase, from 103 (84–116) to 162 (138–195), corresponding to an increase of 48% (11–93%). The *p value* is <0.005 for both. When all the aPP sessions (n = 80) were considered together, aPP was associated with a significant increase in PaO_2/FiO_2 from 112 (80–132) to 156 (86–183) mm Hg (p <0.001) and $Aa-O_2$ decrease from 304 (244–418) to 224 (148–361) mm Hg (p = 0.001).

CONCLUSIONS: Awake pronation in spontaneously breathing patients is feasible, and improves PaO_2/FiO_2 and $Aa-O_2$. Response to the first session seems to be associated with lower intubation rate.

Introduction

Severe hypoxaemia is frequent in SARS-CoV-2-related pneumonia and seems mainly related to ventilation/perfusion ratio mismatch with a variable potential for lung recruitment [1, 2]. Prone positioning in intubated patients with moderate to severe acute respiratory distress syndrome improves oxygenation and outcome [3]. Awake prone positioning (aPP) has been proposed for SARS-CoV-2 pneumonia to improve oxygenation and maybe avoid intubation [4]. The longer the duration of proning, the greater the benefit. However, the ideal duration remains unknown. There is growing evidence on feasibility and effects [5–7], but no early predictors for success or failure of the aPP strategy have been described.

The main aim of the study was to assess whether response to the first aPP in terms of oxygenation (ratio of the arterial

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partial pressure of oxygen to inspired fraction of oxygen [PaO_2/FiO_2 ratio] and alveolo-arterial oxygen gradient [$Aa-O_2$]), respiratory rate and arterial partial pressure of carbon dioxide ($PaCO_2$) could predict the need for intubation in patients suffering from SARS-CoV-2-related pneumonia with PaO_2/FIO_2 <200 mm Hg. Only patients who could be proned for at least 45 minutes were considered. As secondary objectives, we assessed for the same parameters the effects of aPP for all the sessions considered together. We also recorded the adverse events related to aPP to evaluate the feasibility of the treatment strategy.

Materials and methods

Study design, setting and eligibility criteria

We performed a retrospective analysis of all the consecutive patients admitted with SARS-CoV-2 pneumonia in the adult intensive care unit (ICU) of the University Hospital of Lausanne, Switzerland, from 13 March to 29 October 2020 (first wave and period between the first and second waves of the pandemic), who had moderate to severe hypoxaemia defined as PaO_2/FiO_2 ratio lower than 200 mm Hg, did not require early intubation for severe respiratory distress or rapid clinical deterioration, agreed for data utilisation, received aPP lasting at least 45 minutes according to predefined criteria and had no "do not intubate" order. At that time, in the Lausanne ICU, awake proning was considered for as long as possible in all non-intubated patients with PaO_2/FiO_2 <200 mm Hg without criteria for early intubation. From a practical point of view, eligible patients were invited to change position from supine to prone by the nursing staff, in autonomy or with healthcare assistance under close monitoring for safety reasons (risk of equipment displacement in particular). The tolerability of the position was a major concern and particular attention was payed to making the patient comfortable, adapting the bed position, adding pillows, and providing recreational means, primarily music. Painkillers were administered prior to the procedure if indicated. Intubation was performed based on clinician judgment, following our ICU standard procedure for COVID-19 patients: worsening or persistent tachypnoea (respiratory rate >35/min), inability to protect airways, important agitation and haemodynamic reasons. Isolated hypoxaemia was not a criterion.

Data collection, variables, calculations and outcomes

Respiratory rate and results of blood gas analyses were collected from the clinical database before and at the end of each pronation. The time of the last blood gas analysis before each session was recorded. PaO_2/FiO_2 and $Aa-O_2$ were computed for each time point. FiO_2 was estimated as in daily clinical practice in our ICU using a bedside conversion table. Practically, the table is used by the nurses to estimate delivered FiO_2 according to the interface and set oxygen flow. FiO_2 estimated this way is entered manually into the clinical information system for each change of oxygen interface or flow. In the table, the conversion formula applied for low flow systems without reservoir bag is: FiO_2 (%) = 4 x oxygen flow (l/min) + 20, up to a flow of 5 l/min [8]. For greater flow and use of a non-rebreather mask with reservoir, the delivered FiO_2 is esti-

mated according the American Association for Respiratory Care (AARC) guidelines for oxygen therapy [9].

Favourable response to aPP in terms of oxygenation was defined as an increase of at least 20% in PaO_2/FiO_2 at the end of the proning session compared with the most recent PaO_2/FiO_2 available in the supine position before aPP [10]. A clinically relevant decrease in $Aa-O_2$ and increase in PaO_2/FiO_2 was arbitrarily considered as a minimum 20% change compared with baseline.

Statistics

Data before and after proning were compared using paired t-tests or Wilcoxon/Mann Whitney U-tests as appropriated according to data distribution. Intubated and non-intubated patients were compared for their baseline characteristics and regarding physiological response to the first aPP using t-tests or Mann Whitney tests as appropriate according to the data distribution. A p-value <0.05 was considered as significant. Statistical analysis was performed with IBM SPSS 27.

Results

From 13 March to 29 October 2020, 166 patients were admitted with SARS-CoV-2-related pneumonia into the adult ICU of the Lausanne University Hospital, Switzerland. Among them, 59 patients (35.5%) were intubated early because of disease severity at admission or because of rapid clinical deterioration, following the relatively early intubation strategy that was the standard of care in our ICU at the time of the study. These 59 patients were thus not considered eligible for an aPP trial. Seven other patients were transferred from another hospital already intubated. Among the remaining 100 patients, 50 patients could be proned for more than 45 minutes. Nineteen out of them were excluded from the final analysis, 17 because they denied consent for data utilisation and 2 because they had a "do not intubate" order. The total number of aPP sessions of more than 45 minutes performed was 116, with an average of 3 (interquartile range [IQR] 1–6) sessions per patient (range 1–12 sessions). No adverse events were reported related to the 116 aPP sessions.

Data at admission are presented in table 1. The mean age ± standard deviation (SD) of the included patients was 60 ± 12 years and 23 (74.2%) patients were men. The most prevalent comorbidities were hypertension (54.8%), cardiovascular disease (25.8%), diabetes (25.8%) and obesity (25.8%). Upon admission to the ICU, mean respiratory rate was 26 ± 7/minute, median PaO_2/FiO_2 was 94 (IQR 74–116) and median $Aa-O_2$ was markedly increased at 412 (286–427) mm Hg; the normal predicted value corrected for age, altitude and FiO_2 is 47 (35–52) mm Hg [11].

Out of the 31 included patients, 10 (32.3%) were ultimately intubated (7 after the first aPP, 1 after the third, 1 after the fifth and 1 after the tenth session). Two of these intubated patients (6.4%) died in the ICU. Data at admission for the ultimately intubated and non-intubated patients are also given in table 1. The two groups were not statistically different in terms of sex, age, comorbidities and respiratory parameters at admission. PaO_2/FiO_2 was, however, slightly lower and $Aa-O_2$ was slightly higher in the patients who subsequently were intubated.

Complete data before and at the end of aPP were available for 27 patients for the first aPP and for 80 of the 116 aPP sessions performed (68.9%). Median time between the last available blood gas analysis before aPP and the start of proning was 37 (23–64) min for the first session. Minimum and maximum times were 2 and 157 minutes, respectively.

Data describing the effects of the first aPP are shown in table 2 for all the patients and for the patients who subsequently were intubated or not. Following the first aPP, in the overall population, we observed a clinically significant Aa-O_2 decrease of 86 (3–180) mm Hg, corresponding to a 29% (1–53%) drop and a PaO_2/FiO_2 increase of 31 (1–80) mm Hg, corresponding to a percentage increment of 39% (1–79%). In the ultimately intubated group, the changes were minimal, with an Aa-O_2 decrease of 13 (–30 to 116) mm Hg corresponding to a 3% change (–7 to 27%), and a PaO_2/FiO_2 increase of 7 (–24 to 16) mm Hg corresponding to a 5% (–38 to 18%) change. In the non-intubated group we observed clinically significant improvement with an Aa-O_2 decrease of 132 (84–214) mm Hg, corresponding to a 40% (26–56%) reduction, and PaO_2/FiO_2 increase of 66 (16–87) mm Hg, corresponding to a percentage rise of 48% (11–93%). When decreases in Aa-O_2 and

increases in PaO_2/FiO_2, before and after the first aPP were compared between the patients who subsequently were intubated or not, the p-values were p = 0.043 and p = 0.018 for Aa-O_2 and PaO_2/FiO_2, respectively.

Individual patient data are provided in figure 1.

When all the aPP sessions (n = 80) were considered together, aPP was associated with a significant increase in PaO_2/FiO_2 from 112 (80–132) to 156 (86–183) mm Hg (p <0.001) and Aa-O_2 decreased from 304 (244–418) to 224 (148–361) mm Hg (p = 0.001). Twenty-four patients (77.4%) responded to pronation with an increase in PaO_2/FiO_2 of at least 20% in at least one session, representing 45 out of 80 sessions (56.2%). For all sessions, Pa-CO_2 and respiratory rate did not differ significantly before and after pronation. pH slightly decreased in the non-intubated group.

Discussion

Our retrospective study reports that aPP in spontaneously breathing patients is feasible, safe and improves oxygenation, as manifested by PaO_2/FiO_2 increase and alveolar-arterial gradient decrease. Moreover, it seems that the re-

Table 1:
Characteristics at admission for all patients and for the two groups intubated and non-intubated.

	All patients (n = 31)	Ultimately intubated (n = 10, 32%)	Not intubated (n = 21, 68%)	p-value
Age	60 ± 12	62 ± 12	60 ± 13	0.679
Female sex	8 (25.8%)	3 (30%)	7 (23.8%)	0.517
BMI (kg/m^2)	28.3 ± 5.7	29.5 ± 6.3	27.7 ± 5.5	0.466
Cardiovascular disease	8 (25.8%)	4 (40%)	4 (19%)	0.208
Hypertension	17 (54.8%)	6 (60%)	11 (52.4%)	0.497
Diabetes	8 (25.8%)	3 (30%)	5 (23.8%)	0.517
Respiratory comorbidities	6 (19.4%)	2 (2%)	4 (19%)	0.650
Immunosuppression	3 (9.7%)	2 (20%)	1 (4.8%)	0.237
Obesity	8 (25.8%)	3 (30%)	5 (23.8%)	0.517
FiO$_2$	0.80 (0.60–0.80)	0.80 (0.80–0.80)	0.70 (0.52–0.80)	0.268
SpO$_2$ (%)	93 ± 3	93 ± 5	93 ± 3	0.723
PaO$_2$ (mm Hg)	65 (59–71)	65 (55–75)	65 (60–70)	0.758
Aa-O$_2$ (mm Hg)	412 (286–427)	415 (382–427)	295 (235–437)	0.313
PaO$_2$/FiO$_2$	94 (74–116)	90 (69–97)	103 (74–118)	0.261
pH	7.46 ± 0.03	7.45 ± 0.03	7.47 ± 0.03	0.220
PaCO$_2$ (mm Hg)	32.9 ± 5.1	34.4 ± 5.2	32.1 ± 5.0	0.263
RR (breath/min)	26 ± 7	25 ± 6	27 ± 7	0.396
Sessions of aPP	3 (1–6)	1 (1–3)	3 (2–7)	0.028*
Deceased	2 (6.5%)	2 (20%)	0 (0%)	0.97

BMI: body mass index; FiO$_2$: inspired fraction of oxygen; SpO$_2$: peripheral oxygen saturation; PaO$_2$: arterial partial pressure of oxygen; Aa-O$_2$: alveolar-arterial gradient of oxygen; PaCO$_2$: arterial partial pressure of carbon dioxide; aPP: awake prone positioning.
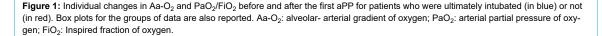
Table 2:
Physiological parameters before and after the first pronation session in the global patient population with blood gas analyses available for the first aPP (n = 27), in the subgroup of patients who did not later require intubation and in the subgroup of patients who were intubated.
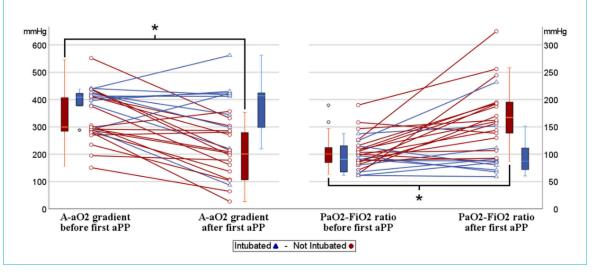
	All patients (n = 27)			Ultimately Intubated (n = 10, 37%)			Non intubated (n = 17, 63%)		
	Before	After	p-value	Before	After	p-value	Before	After	p-value
FiO$_2$	0.65 (0.60–0.80)	0.55 (0.36–0.80)	0.001*	0.80 (0.80–0.80)	0.80 (0.60–0.80)	0.340	0.60 (0.60–0.80)	0.50 (0.36–0.60)	<0.001*
SpO$_2$ (%)	92 ± 3	93 ± 3	0.058	92 ± 4	93 ± 4	0.416	92 ± 2	94 ± 3	0.092
PaO$_2$ (mm Hg)	64 (59–75)	69 (60–78)	0.315	64 (54–78)	65 (57–70)	0.401	65 (59–72)	73 (64–78)	0.074
Aa-O$_2$ (mm Hg)	340 (290–422)	242 (149–351)	<0.001*	422 (382–427)	412 (298–425)	0.445	294 (280–414)	204 (107–281)	<0.001*
PaO$_2$/FiO$_2$	99 (81–115)	150 (90–193)	0.001*	80 (67–115)	87 (71–111)	0.646	103 (84–116)	162 (138–195)	<0.001*
pH	7.46 ±0.04	7.44 ±0.04	0.011*	7.44 ±0.04	7.43 ±0.04	0.054	7.47 ±0.03	7.45 ±0.03	0.042*
PaCO$_2$ (mm Hg)	32.9 ±5.3	33.9 ±6.0	0.202	34.8 ±4.6	34.4 ±5.0	0.663	31.8 ±5.5	33.6 ±6.7	0.101
RR (breath/min)	28 ±6	26 ±6	0.299	28 ±5	27 ±7	0.523	28 ±6	26 ±6	0.406

FiO$_2$: inspired fraction of oxygen; SpO$_2$: peripheral oxygen saturation; PaO$_2$: arterial partial pressure of oxygen; Aa-O$_2$: alveolar-arterial gradient of oxygen; PaCO$_2$: arterial partial pressure of carbon dioxide; RR: respiratory rate

Figure 1: Individual changes in Aa-O$_2$ and PaO$_2$/FiO$_2$ before and after the first aPP for patients who were ultimately intubated (in blue) or not (in red). Box plots for the groups of data are also reported. Aa-O$_2$: alveolar- arterial gradient of oxygen; PaO$_2$: arterial partial pressure of oxygen; FiO$_2$: Inspired fraction of oxygen.

sponse in term of oxygenation to the first aPP is correlated with intubation rate.

Our study has some limitations, mainly due to the retrospective nature of the design and the absence of a control group. First, FiO$_2$ was estimated according to the oxygen flow delivered using a bedside available conversion table [8, 9] and not measured by oximetry. As patients' inspiratory flow is unknown, delivered FiO$_2$ is thus only an approximate value. Second, even if the differences were not statistically significant, the patients who subsequently were intubated had slightly lower PaO$_2$/FiO$_2$ ratios and higher Aa-O$_2$ gradients at baseline. These differences could partly explain, independently from the physiological response to the first aPP, why these patients finally required intubation. Nevertheless, it is important to note that criteria for intubation at the time of the study in our ICU was not isolated hypoxaemia but worsening or persistent tachypnoea (respiratory rate >35/min), inability to protect airways, important agitation and haemodynamic reasons. As respiratory rate, pH and PaCO$_2$ were not different between the two groups at baseline, this suggests that patients who subsequently were intubated or not were relatively similar in terms of respiratory distress severity at baseline. For this reason the predictive value of responding to the first aPP in terms of oxygenation probably remains an important element to consider. Regarding intubation rate in our study, 10 patients out of 31 (32.3%) were intubated, which is in line with previously published data [12]. Third, we cannot exclude a selection bias, with longer aPP sessions performed in patients who particularly felt better in the prone position or where considered responders by the clinicians in charge. However, a 20% increase in the PaO$_2$/FiO$_2$ ratio was observed in only 45 sessions out of 80 (56.2%). Conversely, patients with a sudden desaturation are likely to have been encouraged to change position and described as responders even if another reason could explain the increase in oxygen saturation. Transient desaturations that do not reflect a global worsening of the clinical status can be explained by efforts, cough and secretions. In addition, we cannot exclude that the lack of response to pronation may have influenced the clinician in the de-

cision to intubate. However, according to the service protocol, hypoxaemia without respiratory distress was not an intubation criterion and the fact that 33.3% of non-intubated patients (7 out of 21) had FiO$_2$ of 60% or more after the first aPP, tends to confirm good adherence to the protocol.

In conclusion, improvement in alveolar arterial oxygen gradient and PaO$_2$/FiO$_2$ during the first aPP could be indicators of successful prone positioning in awake non-intubated SARS-CoV-2 pneumonia patients. Additional studies are required to confirm our findings and provide additional clinical evidence in favour of this strategy.

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