Changes in Oxygenation and Clinical Outcomes with Awake Prone Positioning in Patients with Suspected COVID-19 In Low-Resource Settings: A Retrospective Cohort Study

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Abstract
Introduction: This study aimed to describe the use of awake prone positioning (APP) and conventional oxygen therapy (COT) in patients with suspected coronavirus disease (COVID-19) and respiratory failure in a limited-resource setting.

Methods: This was a retrospective cohort study of hospitalized patients aged ≥18 years old who were placed in an awake prone position due to hypoxemic respiratory failure and suspected COVID-19. The patients were selected from a tertiary center in Cartagena, Colombia, between March 1, 2020, and August 31, 2020. Demographic, clinical, and laboratory variables were collected, and all the variables were compared between the groups.

Results: The median age of the participants was 63 (IQR, 48.8-73) years (survivors: 59 [IQR, 43.568] years vs. non-survivors: 70 [IQR, 63-78] years, P ≤.001). Of the 1470 patients admitted for respiratory symptoms, 732 (49.8%) were hospitalized for more than 24 h, and 212 patients developed respiratory failure and required COT and APP (overall hospital mortality, 34% [73/212]). The mean rank difference in PaO2/FiO2 before and after APP was higher in the survivors than in the non-survivors (201.1-252.6, mean rank difference = 51.5, P = .001 vs. 134.1-172.4, mean rank difference = 38.28, P = .24, respectively).

Conclusion: While using COT in conjunction with APP can improve respiratory failure in patients with suspected COVID-19 in low-resource settings, persistent hypoxemia after APP can identify patients with higher mortality risk. More evidence is needed to establish the role of this strategy.

Keywords
awake prone position, oxygenation, respiratory failure, COVID-19, mortality, resources

Introduction
A few weeks after being confirmed as a pandemic, the coronavirus (COVID-19) outbreak changed medical practice. The COVID-19 infection can lead to progressive hypoxemia, respiratory failure, and acute respiratory distress syndrome (ARDS), requiring admission of affected patients to the intensive care unit (ICU).1,2 An update of interventions for ARDS has been summarised in recent guidelines.3 Prone positioning (PP), a low-risk and straightforward technique that has been described more than 20 years ago,4 has garnered more attention owing to the growing evidence that confirms its benefit and impact on mortality in patients intubated for ARDS.5 Before the pandemic, some reports described the utility of PP for the improvement of oxygenation in awake patients with hypoxemic respiratory failure.6,7 Due to the lack of resources for the ventilation of patients during the COVID-19 pandemic, different strategies, including awake prone positioning (APP), are used to improve hypoxemia. APP is usually combined with a high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV).8 Currently, the literature describes that APP might

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improve oxygenation, but it is conflicting yet the impact on mortality, with some describing even an increase in mortality.

Additionally, little is known about the impact of APP in limited-resource scenarios where HFNC and/or enough ventilators are not available. Traditional Nasal Cannula (NC) and face mask (FM) (collectively referred to as conventional oxygen therapy or COT) can achieve flow rates of up to 15 L/min\(^6\)\(^{10}\) and is frequently the first option when oxygen therapy is required. We aimed to describe the clinical results of APP coupled with COT for the treatment of patients with suspected COVID-19 and respiratory failure in a limited-resource setting.

Materials and Methods

Study Design

This was a retrospective cohort study of patients hospitalized for acute respiratory failure and suspected COVID-19 at a tertiary referral center in Cartagena, Colombia, between March 1, 2020, and August 31, 2020. Institutional review board approval was obtained for this study. Informed consent was not considered necessary given the retrospective nature of the study.

Patients

We included patients aged ≥ 18 years old who were hospitalized for acute respiratory failure and suspected COVID-19. We defined respiratory failure as PaFiO\(_2\) < 300 mm Hg\(^{11}\)\(^{12}\) All the patients used APP and COT with a nasal cannula or face mask with a reservoir. We excluded patients who were referred to another institution or whose hospital stay was less than 24 h.

Awake Prone Positioning Protocol

The APP strategy was protocolized from the start of the pandemic to guarantee patient compliance and tolerability, with position changes alternating between full decubitus, left and right lateral decubitus, and supine decubitus\(^13\) (Supplemental material 1). The protocol was considered for all patients independently of the location (ER, general ward, or ICU).

Variables and Data Collection

The information was extracted from the electronic medical records of patients after admission to the emergency room (on day 1). The collated information included demographic variables (age, sex, and pre-existing conditions), laboratory variables (haemoglobin, haematocrit, leukocytes, neutrophils, lymphocytes, platelets, lactate, transaminases, bilirubin, lactate dehydrogenase [LDH], procalcitonin, and ferritin levels; reverse transcription polymerase chain reaction [RT-PCR] severe acute respiratory syndrome coronavirus 2 test results; and arterial blood gas [ABG] levels), and clinical variables (oxygen saturation, respiratory rate, ROX index [which includes oxygen saturation, respiratory rate, and inspired oxygen fraction], and Sepsis-related Organ Failure Assessment [SOFA] score). The respiratory rate was measured, and pulse oximetry was performed before and after using the APP. The PaO\(_2\), FiO\(_2\), and PaFiO\(_2\) values were recorded on admission and soon after using the APP.

Evaluation of Clinical Course Variables

The other clinical variables, such as time (in days) from the onset of symptoms to hospital admission, were estimated. The time from hospital admission to admission to the ICU and time from the start of APP to the start of invasive ventilation or discontinuation of APP were measured, and the length of hospital stay was quantified and recorded.

Sampling Method and Statistical Analysis

We included all consecutive patients admitted to the hospital and described the continuous variables as means (± standard deviations) or medians (25th-75th centile or quartiles). The nominal variables were summarised as counts and percentages. We selected hospital mortality as the primary outcome. The differences between the groups (survivors and non-survivors) were analyzed using the t-test and rank-sum tests to compare the continuous variables and the Chi-square or Fisher’s exact test for the categorical variables. The change in PaO\(_2)/FiO\(_2\) index before and after APP was assessed via one-way analysis of variance (ANOVA) followed by Dunnett’s multiple comparisons test. Finally, the association between clinical and laboratory variables to mortality in patients under APP was analyzed, including sensitivity, specificity, positive and negative predictive value, the area under receiver operator curve, and Youden’s index from the best cut-off.

All the analyses were performed using STATA software, version 15.0 (Stata Corp., College Station, TX). The one-way ANOVA and Dunnett’s multiple comparisons test were performed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California, USA.). A P-value < .05 was considered to be statistically significant.

This report was written according to the Enhancing the Quality and Transparency Of health Research (EQUATOR) STROBE guidelines.

Results

Participants

During the study period, 1470 consultations for respiratory symptoms and suspected COVID-19 were recorded in the emergency department. Only 732 (49.8%) patients stayed in the hospital for more than 24 h. Two hundred and fifteen patients used APP; however, three (1.3%) patients were lost to follow-up. Thus, a total of 212 patients were included in the final analysis (overall mortality, 73 [34%] patients) (Figure 1).
Descriptive Data

The median age of the patients was 63 years (interquartile range [IQR], 48.8-73 years), and most of them were male (142 patients, 67%). The survivors were younger than the non-survivors (median age: 59 [IQR 43.5-68] years vs. 70 [IQR 63-78] years; \( P = .001 \)), respectively. The most frequent pre-existing conditions were hypertension and diabetes. We found no differences between the groups regarding the frequency of hypertension (56 [40.3%] vs. 43 [58.9%, \( P = .22 \)); diabetes (27 [19.4%] vs. 20 [27.4%], \( P = .22 \)); or obesity (5 [3.6%] vs. 6 [8.2%]; \( P = .19 \)) among survivors and non-survivors, respectively. Only 46 (21.7%) patients had positive RT-PCR results; however, no differences were observed between the groups (31 [22.3%] vs. 15 [20.5%]; \( P = .76 \)), respectively (Table 1).

Clinical Course

The overall median time from onset of symptoms to hospital admission was 6 (IQR, 3-9.2) days. The median time from onset of symptoms to hospital admission was higher for the survivors (seven [IQR, 4-10] days) than for the non-survivors (four [IQR, 2-7] days) \( (P < .001) \). The rate of ICU admission differed between the survivors (50, 36%) and the non-survivors (62, 84.9%) \( (P < .001) \). There were no differences between groups concerning the time from hospital admission to ICU admission (1 [IQR, 0-2] day vs. 1[IQR, 1-3] day, \( P = .5 \)); hospital stay [9.5 [IQR, 1.2-16.8] days vs. 7 [IQR, 4-10], \( P = .68 \)); and duration of ICU stay [9 [ IQR, 2-17] days vs. 9 [IQR, 6-14]; \( P = .51 \)], respectively [Table 1].

Main Results

On admission, there were differences in the clinical variables between the survivors and the non-survivors, respiratory rates (23 [IQR, 20-26] vs. 27 [IQR, 24-34]), oxygen saturation (94% [IQR, 90-97] vs. 88% [IQR, 80-92]), and ROX indexes (5.7 [IQR, 4.75-10.2] vs. 4.1 [IQR, 3.03-4.6]) (all \( P < .001 \)), respectively. Furthermore, the SOFA score before APP of the non-survivor group was higher than that of the survivor group (five [IQR, 4-7] vs. three [IQR, 3-5]) \( (P < .001) \), respectively. The oxygen saturation after using APP was higher in the survivors than in the non-survivors (97% [IQR, 95-99] vs. 91% [IQR, 85-95]; \( P < .001 \)), respectively. The respiratory rate after using APP was lower in the survivors than in the non-survivors (22 [IQR, 20-23]rpm vs. 25 [IQR, 22-28]rpm; \( P < .001 \)), respectively. Additionally, we found differences between the survivors and the non-survivors in all the laboratory variables except for the ferritin level \( (P < .05) \) (Table 2).

The mean rank difference in \( \text{PaO}_2/\text{FiO}_2 \) ratio before and after using APP was higher in the survivors than in the non-survivors.
Table 1. Demographic Characteristics and Clinical Course of Patients Hospitalized for Suspected COVID-19 and Respiratory Failure That Were Treated with Awake Prone Positioning.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (N=212) n/N (%)</th>
<th>Survivors (n = 139) n/N (%)</th>
<th>Non-survivors (n = 73) n/N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics, median (IQR), and n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>63 (48.8-73)</td>
<td>59 (43.5-68)</td>
<td>70 (62-78)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>142 (67)</td>
<td>91 (65.5)</td>
<td>51 (69.9)</td>
<td>.54</td>
</tr>
<tr>
<td>Pre-existing conditions, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>99 (46.7)</td>
<td>56 (40.3)</td>
<td>43 (58.9)</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>47 (22.2)</td>
<td>27 (19.4)</td>
<td>20 (27.4)</td>
<td>.22</td>
</tr>
<tr>
<td>Asthma</td>
<td>6 (2.8)</td>
<td>4 (2.9)</td>
<td>2 (2.7)</td>
<td>.95</td>
</tr>
<tr>
<td>COPD</td>
<td>8 (3.8)</td>
<td>3 (2.2)</td>
<td>5 (6.8)</td>
<td>.12</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>10 (4.7)</td>
<td>4 (2.9)</td>
<td>6 (8.2)</td>
<td>.09</td>
</tr>
<tr>
<td>Obesity</td>
<td>11 (5.2)</td>
<td>5 (3.6)</td>
<td>6 (8.2)</td>
<td>.19</td>
</tr>
<tr>
<td>Timeline of clinical course and interventions, median (IQR), days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration from onset of symptoms to hospital admission</td>
<td>6 (3-9.2)</td>
<td>7 (4-10)</td>
<td>4 (2-7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of awake prone positioning before invasive mechanical ventilation</td>
<td>1 (1-3.2)</td>
<td>2 (1-3)</td>
<td>1 (0.25-3.75)</td>
<td>.88</td>
</tr>
<tr>
<td>Duration from the start of hospitalisation to ICU admission</td>
<td>1 (1-3)</td>
<td>1 (0-2)</td>
<td>1 (1-3)</td>
<td>.5</td>
</tr>
<tr>
<td>ICU admission</td>
<td>112 (52.8)</td>
<td>50 (36)</td>
<td>62 (84.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of stay in ICU</td>
<td>8 (4-15)</td>
<td>7 (4-10)</td>
<td>9.5 (1.2-16.8)</td>
<td>.68</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>9 (5-16)</td>
<td>9 (6-14)</td>
<td>9 (2-17)</td>
<td>.51</td>
</tr>
</tbody>
</table>

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

Table 2. Clinical and Laboratory Variables of Patients Hospitalized for Acute Respiratory Failure and Suspected and Treated with Awake Prone Positioning and Conventional Oxygen Therapy.

<table>
<thead>
<tr>
<th>Clinical variables, median (IQR)</th>
<th>All patients (N=212) n/N (%)</th>
<th>Survivors (n = 139) n/N (%)</th>
<th>Non-survivors (n = 73) n/N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROX index prior to APP, points</td>
<td>5.12 (4.1-7.25)</td>
<td>5.7 (4.75-10.2)</td>
<td>4.1 (3.03-4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SOFA score, points</td>
<td>4 (3.5-25)</td>
<td>3 (3.5)</td>
<td>5 (4-7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Respiratory rate prior to APP, rate per min</td>
<td>24 (22-28)</td>
<td>23 (20-26)</td>
<td>27 (24-34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pulse oximetry result prior to APP, %</td>
<td>92 (88-96)</td>
<td>94 (90-97)</td>
<td>88 (80-92)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Respiratory rate post-APP, rate per min</td>
<td>22 (20-24.3)</td>
<td>22 (20-23)</td>
<td>25 (22-28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pulse oximetry result post-APP, %</td>
<td>96 (92-98)</td>
<td>97 (95-99)</td>
<td>91 (85-95)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Laboratory values, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive RT-PCR result, n (%)</td>
<td>46 (21.7)</td>
<td>31 (22.3)</td>
<td>15 (20.5)</td>
<td>.76</td>
</tr>
<tr>
<td>D-dimer on day 1, ng/mL</td>
<td>1030 (650-2430)</td>
<td>870 (530-1550)</td>
<td>1990 (960-8084)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ferritin level on day 1, ng/mL</td>
<td>934 (646-1500)</td>
<td>930 (536-1392)</td>
<td>995 (775-1500)</td>
<td>.15</td>
</tr>
<tr>
<td>C-reactive protein level on day 1, mg/L</td>
<td>96 (32.6-192)</td>
<td>48 (24-96)</td>
<td>96 (96-192)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Arterial lactate level on day 1, mmol/L</td>
<td>1.8 (1.3-2.3)</td>
<td>1.7 (1.2-2.2)</td>
<td>2.1 (1.6-2.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDH level on day 1, U/L</td>
<td>813 (623-1012)</td>
<td>731 (562-886)</td>
<td>984 (821-1166)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Troponin level on day 1, ng/L</td>
<td>0.07 (0.05-0.16)</td>
<td>0.05 (0.05-0.12)</td>
<td>0.10 (0.05-0.28)</td>
<td>.006</td>
</tr>
<tr>
<td>Creatinine level on day 1, mg/dL</td>
<td>1.12 (0.93-1.46)</td>
<td>1.08 (0.91-1.29)</td>
<td>1.34 (1.03-2.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Procalcitonin level on day 1, ng/L</td>
<td>0.46 (0.09-0.99)</td>
<td>0.2 (0.05-0.49)</td>
<td>0.57 (0.45-2.17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Arterial blood gases, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph value on day 1</td>
<td>7.37 (7.33-7.41)</td>
<td>7.39 (7.36-7.42)</td>
<td>7.38 (7.32-7.41)</td>
<td>.002</td>
</tr>
<tr>
<td>PaO2 on day 1, mm Hg</td>
<td>70 (56-92)</td>
<td>76 (60-115)</td>
<td>73.5 (56.43-104)</td>
<td>.49</td>
</tr>
<tr>
<td>PaCO2 on day 1, mm Hg</td>
<td>30 (26-33)</td>
<td>30 (28-34)</td>
<td>30 (26-33)</td>
<td>.3</td>
</tr>
<tr>
<td>PaO2/FiO2 on day 1, mm Hg</td>
<td>142 (90-210)</td>
<td>160 (96.5-245)</td>
<td>100.7 (73.3-167)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; SOFA, Sepsis-related Organ Failure Assessment; APP, awake prone positioning; RT-PCR, real-time reverse transcriptase polymerase chain reaction; LDH, lactate dehydrogenase.
of invasive mechanical ventilation. This lack of difference in oxygenation; however, only the survivors showed a significant association with mortality. After APP, a respiratory rate ≥ of 24 rpm and oxygen saturation post APP ≤ 92% showed an association with mortality. Only LDH values ≥ 800 U/L were associated with mortality (see supplementary Table 1).

**Other Results**

After adjustment for age and before APP, clinical variables such as ROX index of ≤ 4.5 (3.22 [1.22-8.51]), a SOFA score of ≥ 6 (OR 7.82 [2.45-24.9]), and pulse oximetry ≤ 89%, were all associated with higher mortality. After APP, a respiratory rate ≥ of 24 rpm and oxygen saturation post APP ≤ 92% showed an association with mortality. Only LDH values ≥ 800 U/L were associated with mortality (see supplementary Table 1).

**Discussion**

**Key Results**

In this study, we evaluated the use of APP and COT to treat patients with suspected COVID-19 and respiratory failure. The present study is one of the most extensive Latin American studies to date on the use of APP in patients with hypoxemic respiratory failure during the COVID-19 pandemic. We found that high SOFA scores and respiratory rates, low ROX indexes, and low oxygen levels before using APP were associated with higher mortality. Additionally, higher d-dimer, lactate, procalcitonin, LDH, troponin on day one might be associated with high mortality.

We evaluated the impact of using the APP on the gas exchange in patients using COT. As reported in most of the previous studies, the use of APP was associated with improved oxygenation; however, only the survivors showed a significant change. Thus, we can consider that the lack of response after using APP may identify patients at the highest risk of mortality, thereby preventing delays in deciding to intubate. In the present study, there were no differences between the survivors and the non-survivors regarding the time before initiation of invasive mechanical ventilation. This lack of difference suggested that the decision to use APP in our study did not affect the clinical outcomes; other authors have reported similar results. The non-survivors in the present study had a significantly shorter time from onset of symptoms to hospital admission. A recent study reported that a time from the onset of viral COVID-19 symptoms to ICU admission of no longer than seven days was associated with a higher risk of death.

The most common pre-existing condition among non-survivors in the present study was hypertension. According to the SOFA scores, hospital admission was early in the non-survivors, a factor that could be related to the greater severity of the disease.

**Generalisability**

Like in many non-invasive strategies, APP aims to correct hypoxemia and possibly prevent the need for intubation. However, this procedure should be used with caution to avoid increased morbidity or mortality. Choosing patients who will benefit from the procedure is crucial, also analyze each case...
to predict possible success or failure. Our results show that regular clinical and laboratory variables can help identify patients with increased mortality while using APP and COT. These results may be of critical relevance in low- and middle-income countries (LMIC).

**Strengths and Limitations**

Our study had several strengths. To date, studies on APP have focused on the use of APP with HFNC and NIV in patients with respiratory failure and COVID-19. In our hospital, APP is used in conjunction with COT. To our knowledge, this is the first description of the use of APP with COT. Thus, our results apply to many centers in LMIC with resource situations similar to ours.23

The limitations of this study should be noted as well. Given that this was a retrospective and single-center cohort study validating the results globally might be challenging. However, our results significantly contribute to the existing body of research, especially in low-resource contexts. This is the first Latin American study to address the use of APP in patients with suspected COVID-19 and respiratory failure, reflecting the situation in countries that do not have HFNC and/or have a limited quantity of respirators.29

We also think that it might be helpful to detail changes in the inspired fraction of oxygen separately. This inclusion might highlight if the use of APP had any influence on oxygen demand. Given the retrospective data, we cannot describe this detail in our study. Thus, this might be an interesting addition to future research questions.

**Conclusion**

Our study showed that using COT with APP is feasible as an initial intervention for patients with suspected COVID-19 and respiratory failure in low-resource settings. Additionally, the presence of hyperinflammation and high SOFA scores, low ROX indexes, low oxygen levels before using APP, and persistent signs of hypoxemia after using APP can identify patients with a higher risk of mortality. More evidence is needed to establish the role of this strategy in the management of patients with acute respiratory failure and COVID-19.

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**Declaration of Conflicting Interests**

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**Ethical Approval**

Not applicable, because this article does not contain any studies with human or animal subjects.

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**Supplemental Material**

Supplemental material for this article is available online.

**References**


