Noninvasive Ventilation in Severe Hypoxemic Respiratory Failure: A Randomized Clinical Trial

Miquel Ferrer, Antonio Esquinas, Miguel Leon, Gumersindo Gonzalez, Antonio Alarcon, and Antoni Torres

Unitat de Vigilancia Intensiva Respiratoria, Institut Clinic de Pneumologia i Cirurgia Toracica, Institut d’Investigaciones Biomèdiques August Pi i Sunyer, Hospital Clinic, Universitat de Barcelona, Barcelona; Unidad de Cuidados Intensivos, Hospital Morales Meseguer, Murcia; and Unidad de Cuidados Intensivos, Hospital Arnau de Vilanova, Lleida, Spain

The efficacy of noninvasive ventilation (NIV) to avoid intubation and improve survival was assessed in 105 patients with severe acute hypoxemic respiratory failure (arterial O2 tension or saturation persistently 60 mm Hg or less or 90% or less, respectively; breathing conventional Venturi oxygen at a maximal concentration [50%]), excluding hypercapnia, admitted into intensive care units of three hospitals. Patients were randomly allocated within 24 hours of fulfilling inclusion criteria to receive NIV (n = 51) or high-concentration oxygen therapy (n = 54). The primary end-point variable was the decrease in the intubation rate. Both groups had similar characteristics. Compared with oxygen therapy, NIV decreased the need for intubation (13, 25% vs. 28, 52%, p = 0.010), the incidence of septic shock (6, 12% vs. 17, 31%, p = 0.028), and the intensive care unit mortality (9, 18% vs. 21, 39%, p = 0.028) and increased the cumulative 90-day survival (p = 0.025). The improvement of arterial hypoxemia and tachypnea was higher in the noninvasive ventilation group with time (p = 0.029 each). Multivariate analyses showed NIV to be independently associated with decreased risks of intubation (odds ratio, 0.20; p = 0.003) and 90-day mortality (odds ratio, 0.39; p = 0.017). The use of noninvasive ventilation prevented intubation, reduced the incidence of septic shock, and improved survival in these patients compared with high-concentration oxygen therapy.

Keywords: acute respiratory failure; intensive care unit; noninvasive ventilation; controlled clinical trial

During the evolution of severe acute hypoxemic respiratory failure (AHRF), patients may require intubation and mechanical ventilation as a life-support measure while concomitant treatments for the underlying disease are instituted. In these patients, however, invasive mechanical ventilation is associated with an important incidence of complications and mortality (1–4).

The use of noninvasive ventilation (NIV) as an alternative to immediate intubation in these patients reduced the incidence of serious complications and length of stay in one study (5). More recently, NIV has shown to reduce the need for intubation in selected groups of patients with severe cardiogenic pulmonary edema (6), immunosuppression (7, 8), and respiratory failure after lung resection (9). A randomized clinical trial in noninvasive obstructive pulmonary disease (COPD) patients receiving NIV failed to find significant benefits in the subset of patients without hypercapnia after a post hoc analysis (10). However, this study was not specifically powered to assess the efficacy of NIV in patients with AHRF. Therefore, whether the systematic use of NIV in these patients is effective enough to prevent intubation as compared with oxygen therapy remains to be assessed.

We hypothesized that in patients with severe AHRF unable to achieve acceptable levels of arterial oxygenation using conventional oxygen therapy, the use of NIV, providing appropriate inspired oxygen concentrations, would prevent intubation as the primary end-point variable, hence averting the poor outcome associated with the need of invasive ventilation. Accordingly, we conducted a prospective, randomized controlled trial to assess the efficacy of NIV compared with a standard regime consisting of high-concentration oxygen therapy. Some of the results of this study have been previously reported in abstract form (11).

METHODS

Patients

A prospective, randomized controlled study was conducted in three intensive care units (ICUs). Patients with severe AHRF, defined as PaO2 persistently (more than 6 to 8 hours) less than 60 mm Hg or arterial oxygen saturation by pulse oximetry (Spo2) persistently less than 90% while breathing conventional Venturi oxygen at a maximal concentration (50%), were considered eligible for the study.

Exclusion criteria were (1) hypercapnia (PaCO2 of more than 45 mm Hg) on admission; (2) need for emergency intubation; (3) recent cephalogal, facial, or cranial trauma or surgery; (4) severely decreased consciousness (a Glasgow coma score of 11 or less); (5) severe hemodynamic instability despite fluid replacement and use of vasopressive agents (6) a lack of cooperation; (7) trachocoele or other upper airway disorders; (8) severe ventricular arrhythmia or myocardial ischemia; (9) active upper gastrointestinal bleeding; (10) inability to clear respiratory secretions; and (11) more than one severe organ dysfunction in addition to respiratory failure. The study was approved by the ethics committee of the three institutions, and informed consent was obtained in all cases.

Study Design

Patients were randomly allocated within 24 hours of fulfilling inclusion criteria either to the noninvasive ventilation group or the control group. In the noninvasive ventilation group, patients were ventilated using the bilevel positive airway pressure mode (BiPAP Vision, Respirtronics Inc., Murrayville, PA). A face mask was used as the first choice, but the nasal mask was optionally used if patients did not tolerate face mask. FIO2 was set to achieve an SpO2 of more than 92% or a PaO2 of more than 65 mm Hg. NIV was continuously delivered after entry into the study as much time as possible. When patients received FIO2 of 0.50 or less, attempts to withdraw NIV were made if they achieved SpO2 of more than 92% or PaO2 of more than 65 mm Hg while spontaneously breathing Venturi oxygen at FIO2 of 0.50 or less.

In the control group, patients received oxygen using high concentration sources. The FIO2 was set to achieve SpO2 of more than 92% or PaO2 of more than 65 mm Hg. NIV to avoid intubation was allowed in

(Received in original form January 16, 2002; accepted in final form September 17, 2003) Supported by Grant 1999 SGR 00228, Red GIRA, Red Respira, and Carburos Metálicos, S.A.

Correspondence and requests for reprints should be addressed to Miquel Ferrer, M.D., Unitat de Vigilancia Intensiva Respiratoria, Institut Clinic de Pneumologia i Cirurgia Toracica, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain. E-mail: millefer@clinic.ub.es

This article has an online supplement, which is accessible from this issue’s table of contents online at www.atsjournals.org

Am J Respir Crit Care Med Vol 168, No 14 (Suppl), August, 2003

Original Published in Press as DOI: 10.1164/rcrm.200301-0722OC on September 16, 2003

Internet address: www.atsjournals.org

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
the control group if predefined criteria for spontaneous breathing failure occurred (see criteria in the online supplement) [12].

Definitions
Criteria for intubation were predefined (see criteria in the online supplement). The end of the protocol was defined as (1) clinical improvement, when patients could consistently achieve PaO2 of more than 65 mm Hg or SpO2 of more than 92% while breathing Venturi oxygen at FiO2 of 0.50 or less; (2) intubation; (3) death; (4) in the NIV group, withdrawal of NIV without intubation because of intolerance; and (5) in the control group, the use of NIV in the control group because of spontaneous breathing failure without intubation.

Data from patients were recorded, and follow-up was extended until 90 days after randomization. Respiratory frequency, heart rate, blood pressure, and arterial blood gases were recorded at baseline (before randomization) and after 1-2, 3-4, 6-8, 12, 24, 48, and 72 hours. At entry into the study, diagnosis of pneumonia [13], cardiogenic pulmonary edema [14, 15], and acute respiratory distress syndrome (ARDS) [16] were based on published criteria.

Clinical [13] and microbiologic [17] diagnoses of hospital-acquired pneumonia and septic shock and multiple organ failure [18, 19] were defined by published criteria (see criteria in the online supplement). Other relevant complications were recorded.

Statistical Analysis
Sample size estimation. We estimated at least 51 subjects in each group with an expected intubation rate of 58% in the control group and a 50% reduction in the NIV group (confidence level [1 - α] 95%, power level [1 - β] 80%).

Comparisons between the two groups. Qualitative or categoric variables were compared with the chi-square test or the Fisher’s exact test. Quantitative continuous variables were compared using the unpaired Student’s t test or the Mann-Whitney test. The overall time course of respiratory frequency, heart rate, blood pressure, and arterial blood gas variables was compared using a two-way analysis of variance for repeated measures. Differences between the two groups at each time point were compared with Student’s t test and Bonferroni correction. The cumulative probability of remaining on spontaneous breathing and the 90-day survival were compared with the Kaplan-Meier estimate of survival and the log-rank test to compare the two groups. All analyses were in intention to treat, and the level of significance was set at 0.05.

Risk factors for intubation. Univariate and multivariate analyses of risk factors for intubation were performed with logistic regression. Predictors of 90-day survival. Univariate and multivariate analyses of 90-day survival were performed with the Kaplan-Meier estimate of survival and Cox proportional hazard regression, respectively. To correct for collinearity in all multivariate analyses, a conditional stepwise forward model was chosen (p < 0.05). Adjusted odds ratios and 95% confidence intervals were computed for variables independently associated with intubation or survival.

RESULTS
Patients
One hundred five consecutive patients were studied (Figure 1): 51 were allocated to the NIV group and 54 to the control group. General clinical characteristics and physiologic parameters of patients at entry into the study are summarized in Table 1. Additional information of patients is shown in Table E1 of the online supplement. No significant differences between the two groups were shown in age, sex, severity of illness, presence of pulmonary infiltrates, underlying diseases, respiratory frequency, heart rate, blood pressure, arterial blood gases, and causes of AHFR.

NIV was delivered for a period of 3.5 ± 2.6 days (mean ± SD) (range, 1-13) in this group. The levels of inspiratory and expiratory positive airway pressure were 16 ± 3 cm H2O (range, 10-24) and 7 ± 2 cm H2O (range, 4-12), respectively, during the first day. Fourteen patients were ventilated with nasal mask because of better tolerance than face mask. Patients from the control group needed high-concentration oxygen therapy for a period of 3.2 ± 2.0 days (range, 1-10).

Intubation, Length of Stay, and Complications
The intubation rate and causes of intubation are summarized in Table 2. Compared with the control group, the intubation rate was lower in the NIV group (p = 0.010). Moreover, the probability of remaining without intubation with time was higher in the NIV group (p = 0.006; Figure 2). In two patients from the control group, the use of NIV because of spontaneous breathing failure spared intubation. NIV intolerance without intubation before achieving criteria for clinical improvement occurred in one patient from the NIV group. Separate analyses of patients by groups showed that the significant reduction in the intubation rate persisted in the subset of patients with pneumonia as the cause of respiratory failure (p = 0.017; Table 2). Multivariate analyses showed that NIV was independently associated with a decreased risk of intubation (Table 3). In addition, cardiogenic pulmonary edema and ARDS as the cause of respiratory failure were independently associated with a decreased risk and an increased risk of intubation, respectively.

ICU and in-hospital stays in the overall population did not change between the two groups (Table 2), but in-hospital stay among ICU survivors decreased in the NIV group (p = 0.043).

Complications diagnosed after entry into the study are summarized in Table 4. There was a nonsignificant trend to decrease the incidence of hospital-acquired pneumonia in the NIV group (p = 0.093). The incidence of other severe infections and barotrauma was not different between the two groups. In contrast, septic shock was more frequent in the control group (p = 0.028). The specific complications associated with NIV are shown in Table 4.

Time Course of Respiratory Frequency, Heart Rate, Blood Pressure, and Arterial Blood Gases
Arterial hypoxemia, as assessed by the PaO2/FiO2 ratio, and respiratory frequency improved with time in the two groups (Figure

Figure 1. Trial profile. *The main exclusion criteria, as defined, were a lack of cooperation, including agitation and mild to moderate altered mental status (n = 45), the need for immediate intubation (n = 10), severely decreased consciousness (n = 5), and severe hemodynamic instability (n = 4).
The overall improvement of $P_{aO_2}/F_{O_2}$ with time (from baseline to 72 hours after randomization, $p = 0.029$) and respiratory frequency (from baseline to 6–8 hours after randomization, $p = 0.029$) were higher in the NIV group. In the NIV group, $P_{aO_2}/F_{O_2}$ and respiratory frequency became significantly higher and lower, respectively, 3–4 hours after randomization, and differences remained significant until 24 hours for $P_{aO_2}/F_{O_2}$ and 6–8 hours for respiratory frequency. There were no differences between the two groups in the time course of heart rate, blood pressure, arterial pH, and $P_{aO_2}$.

**Analyses of Mortality and Survival**

The ICU mortality was lower in the NIV group ($p = 0.028$; Table 2), and differences between the two groups persisted in the subset of patients with pneumonia ($p = 0.030$). Likewise, the cumulative survival probability after 90 days of randomization, as shown in Figure 4, was higher in the NIV group ($p = 0.025$). The causes of death within 90 days of randomization are summarized in Table 4.

The multivariate analyses of 90-day survival are summarized in Table 5. Two different analyses were done. When entering the same variables tested to predict the risk factors for intubation, allocation in the control group, ARDS as the cause of respiratory failure, and severity of illness (Simplified Acute Physiology Score-II of more than 37 on admission) were independent predictors of decreased 90-day survival. However, when also including the follow-up variables in the analyses, the need for intubation was the only independent predictor of decreased 90-day survival ($p < 0.001$).

**DISCUSSION**

The results of this study show that the use of NIV to avoid intubation in patients with severe AHRF decreased the need for intubation, the incidence of septic shock, and the levels of tachypnea and arterial hypoxemia, and improved ICU and 90-day survival compared with patients receiving high-concentration oxygen therapy.

Significant debate exists concerning the precise indications for NIV in patients with AHRF (20, 21), as NIV was initially shown to be of limited benefit to these patients (10, 22, 23). Initial evidence for the lack of efficacy of NIV in patients with AHRF was not supported by randomized clinical trials powered to address this question (10, 22). Subsequently, however, NIV has shown to be effective in preventing intubation in selected groups of patients with cardiogenic pulmonary edema (6), immunosuppression (7, 8), and acute respiratory failure after lung resection (9).

Despite the latter studies, the efficacy of the systematic use of NIV to avoid intubation in a general population of patients with severe AHRF, defined as the inability to achieve acceptable levels of arterial oxygenation using conventional oxygen therapy at maximal concentration and flow, has not been assessed yet in a randomized fashion. We used this inclusion criteria instead of $P_{aO_2}/F_{O_2}$, ratios below predefined thresholds because $P_{aO_2}/F_{O_2}$ is dependent on the levels of $F_{O_2}$ delivered. In addition, using predefined thresholds for $P_{aO_2}/F_{O_2}$ may not always reflect life-threatening consequences of the deterioration of oxygenation. These criteria selected patients with very severe hypoxemia, as
assessed by the baseline mean $P_{A}O_{2}/F_{O_{2}}$ ratios. In similar patients, NIV decreased the incidence of serious complications and length of stay when compared with immediate intubation and invasive ventilation (5). However, the efficacy of NIV in preventing intubation as compared with a conventional therapeutic approach was not assessed in the study mentioned (5).

NIV reduced the need for intubation in this study, and the beneficial effects were independent of other factors, as shown in the multivariate analyses. Interestingly, NIV was especially effective in the subset of patients in whom pneumonia was the cause of respiratory failure. Pneumonia is considered a predictor both of poor response to NIV when it causes an exacerbation of COPD as compared with other causes (24) and in patients with AHRF (25). However, a randomized controlled study in patients with pneumonia showed that NIV prevented intubation in those with underlying COPD and hypercapnic respiratory failure only (26). Therefore, this is the first study showing that NIV can reduce the rate of intubation in patients with pneumonia mainly without chronic respiratory disorders. Two reasons may explain the greater efficacy of NIV in this study in patients with

---

**TABLE 2. INTUBATION, LENGTH OF STAY, AND OUTCOME VARIABLES**

<table>
<thead>
<tr>
<th></th>
<th>Noninvasive Ventilation Group (n = 51)</th>
<th>Control Group (n = 54)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation rate, n, %</td>
<td>13 (25)</td>
<td>28 (52)</td>
<td>0.010</td>
</tr>
<tr>
<td>Pneumonia, n/tot</td>
<td>5/19</td>
<td>11/15</td>
<td>0.017</td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema, n/tot</td>
<td>1/15</td>
<td>2/15</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Thoracic trauma, n/tot</td>
<td>1/6</td>
<td>5/11</td>
<td>0.333</td>
</tr>
<tr>
<td>ARDS, n/tot</td>
<td>6/7</td>
<td>8/8</td>
<td>0.467</td>
</tr>
<tr>
<td>Other, n/tot</td>
<td>0/4</td>
<td>2/5</td>
<td>—</td>
</tr>
</tbody>
</table>

Indications for intubation and other relevant features at the time of intubation:

- Signs of exhaustion
- Neurologic impairment
- Respiratory pauses and gasping
- Severe hemodynamic instability
- Respiratory or cardiac arrest
- Aspiration
- Inability to clear secretions
- Major agitation
- Refractory hypoxemia
- Respiratory acidosis
- Metabolic acidosis
- Respiratory rate of more than 35 min$^{-1}$

ICU stay, d
- Among ICU survivors: 9.6 ± 12.6
- Among ICU survivors: 8.0 ± 7.6

Hospital stay, d
- Among ICU survivors: 20.7 ± 16.6
- Among ICU survivors: 21.1 ± 14.8

Intensive care unit mortality, n (%)
- Pneumonia, n/tot: 9/15
- Cardiogenic pulmonary edema, n/tot: 1/6
- Thoracic trauma, n/tot: 0/6
- ARDS, n/tot: 5/7
- Other, n/tot: 0/4

**Definition of abbreviations:** ARDS = acute respiratory distress syndrome, ICU = intensive care unit; n/tot = number of events/total number of patients.

---

**TABLE 3. MULTIVARIATE ANALYSES OF RISK FACTORS FOR INTUBATION**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive ventilation</td>
<td>0.20</td>
<td>0.07–0.58</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema</td>
<td>0.14</td>
<td>0.04–0.56</td>
<td>0.005</td>
</tr>
<tr>
<td>ARDS</td>
<td>28.5</td>
<td>3.2–249.8</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** ARDS = acute respiratory distress syndrome; CI = confidence interval.

* With the randomized groups (noninvasive ventilation or control), the variables tested for association to intubation are shown in the online supplement.
* Adjusted odds ratio and 95% confidence intervals below one mean a beneficial effect on intubation.

---

**Figure 2.** Kaplan-Meier curves for patients remaining without intubation after entry into the protocol. In the overall population, the cumulative probability of remaining without intubation was higher in the noninvasive ventilation (NIV) group (log-rank test). Time denotes the hours after patients were entered into the study.
TABLE 4. SERIOUS COMPLICATIONS DIAGNOSED AFTER PATIENTS WERE ENTERED INTO THE STUDY AND CAUSES OF DEATH WITHIN 90 DAYS AFTER ENTRY INTO THE STUDY

<table>
<thead>
<tr>
<th>Complications after patients were entered into the study</th>
<th>Noninvasive Ventilation Group (n = 51)</th>
<th>Control Group (n = 44)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-acquired pneumonia, n (%)</td>
<td>5 (10)</td>
<td>13 (24)</td>
<td>0.093</td>
</tr>
<tr>
<td>Catheter-related sepsis, n (%)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>—</td>
</tr>
<tr>
<td>Urinary tract-related sepsis, n (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>—</td>
</tr>
<tr>
<td>Abdominal-related sepsis, n (%)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>—</td>
</tr>
<tr>
<td>Bacteremia of unknown origin</td>
<td>—</td>
<td>1 (2)</td>
<td>—</td>
</tr>
<tr>
<td>Barotrauma, n (%)</td>
<td>—</td>
<td>2 (4)</td>
<td>—</td>
</tr>
<tr>
<td>Septic shock, n (%), causes:</td>
<td>6 (12)</td>
<td>17 (31)</td>
<td>0.028</td>
</tr>
<tr>
<td>Hospital-acquired pneumonia</td>
<td>3</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td>Pneumonia causing AHFR</td>
<td>1</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Abdominal-related sepsis</td>
<td>1</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Catheter-related sepsis</td>
<td>1</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Bacteremia of unknown origin</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Specific complications associated to noninvasive ventilation</td>
<td>13 (25)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mild to moderate nasal bridge injury</td>
<td>3 (6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gastric distention</td>
<td>1 (2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Causes of death within 90 days of randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock/multiple organ failure</td>
<td>6</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Refractory hypoxemia</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Do not resuscitate order</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviation: AHFR = acute hypoxic respiratory failure.

* Cases of septic shock (18) developed after patients were entered into the study; cases of shock on admission are not included in this table.
* Cases of pneumonia diagnosed after patients were entered into the study.
* Cases of pneumonia causing the episode of acute hypoxic respiratory failure.
* In one case from the control group, acute respiratory distress syndrome secondary to abdominal sepsis was the cause of acute hypoxic respiratory failure; in the remaining cases, abdominal sepsis was diagnosed after entry in the study.

In patients with thoracic trauma, pneumothorax, pneumomediastinum, or subcutaneous emphysema were not considered as barotrauma if present at entry into the study.

Because all of these patients had rib fractures, and in some cases flail chest, the use of positive-pressure ventilation could facilitate chest wall stabilization and consequently prevent spontaneous breathing failure during the initial days of hospital admission. However, conclusions about the latter subset of patients are limited by the small sample size.

The efficacy of continuous positive airway pressure has been compared with oxygen therapy in a population of patients with AHFR secondary to acute lung injury with or without preexisting cardiac disease, but with less severe levels of arterial hypoxemia (28). Despite an initial improvement of arterial hypoxemia, the use of continuous positive airway pressure did not result in changes of the intubation rate nor outcome variables in this study. In our study, the use of NIV was also associated with a higher improvement of arterial hypoxemia. A possible limitation of these differences could be an overestimation of the actual FIO2 and therefore underestimation of the PaO2/FI02 ratio in the control group because the peak inspiratory flow rate of patients with AHFR may exceed in some cases the flow rate delivered by the high-concentration oxygen sources, as shown in other populations (29), hence potentially magnifying the differences between the two groups. We think that in addition to applying positive pressure to the airways to improve the physiologic determinants of abnormal pulmonary gas exchange, as well as lung mechanics and heart function, providing inspiratory support is very relevant to support the high ventilatory demands and decrease the work of breathing. This is supported by the improvement of respiratory frequency in the NIV group (Figure 3), suggesting beneficial physiologic effects of this technique compared with a standard regime. However, although the effects of NIV in decreas-
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
improved survival. Our data provide strong evidence for the use of NIV as a first-line intervention in patients with severe AHF in the absence of contraindications for using this technique.

Conflict of Interest Statement: M.F. has no declared conflict of interest; A.E. has no declared conflict of interest; M.L. has no declared conflict of interest; G.G. has no declared conflict of interest; A.A. has no declared conflict of interest; A.T. has no declared conflict of interest.

Acknowledgement: The authors thank the nursing staff of the three ICUs for their cooperation in the development of this study.

References
14. American College of Cardiology/American Heart Association Task Force on Practice Guidelines: committee on evaluation and manage-