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Letter from the Editor

Major advances in the care of cardiac arrest patients have been reported in the literature over the past decade, including better data on pharmacologic and airway management during the intra-cardiac arrest period and after return of spontaneous circulation. The collection of articles presented here highlights some of those advances.

Ventilator-associated pneumonia (VAP) is common in the post-cardiac arrest period and requires additional resources for testing, therapies, and cost. Hospital systems are evaluated on VAP occurrence as a measure of quality care. In the NEJM article *Prevention of Early Ventilator-Associated Pneumonia after Cardiac Arrest*, Francois and colleagues report on their trial of amoxicillin-clavulanate to prevent the development of VAP in post-cardiac arrest patients. Amoxicillin-clavulanate prevented VAP in this trial; however, even with a reduction in VAP, there were no measurable improvements in any patient-centered outcomes, such as ventilator-free days, ICU length of stay, or mortality. Practitioners and systems will have to decide if this intervention, even if it does not improve a patient-centered outcome, warrants widespread adoption. Decreased rates of VAP with no subsequent improvement in patient-centered outcomes is a common theme in the VAP prevention literature, which raises the concern that we are preventing a definition rather than a disease. Regardless of the shortcomings of the VAP definition, we and our patients can be reassured that with modern intensive care, the attributable mortality of VAP in patients who meet this definition is negligible.

The remaining three research summaries included in this collection highlight advances in immediate post-cardiac arrest care, assessment for extubation readiness, and how to support the recently extubated patient. Lascarrou and colleagues addressed targeted temperature management for nonshockable rhythms, which has been recommended in the past and now has high-quality evidence to support this practice. Subirà et al. showed that shorter spontaneous breathing trials are safe and increase the rate of successful extubation. Finally, accumulating evidence supports extubation of both high- and low-risk patients to noninvasive ventilation; the study by Thille and colleagues suggests that this practice decreases reintubation rates compared with extubation to lower levels of respiratory support.

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ORIGINAL ARTICLE

Prevention of Early Ventilator-Associated Pneumonia after Cardiac Arrest

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ABSTRACT

BACKGROUND

Patients who are treated with targeted temperature management after out-of-hospital cardiac arrest with shockable rhythm are at increased risk for ventilator-associated pneumonia. The benefit of preventive short-term antibiotic therapy has not been shown.

METHODS

We conducted a multicenter, double-blind, randomized, placebo-controlled trial involving adult patients (>18 years of age) in intensive care units (ICUs) who were being mechanically ventilated after out-of-hospital cardiac arrest related to initial shockable rhythm and treated with targeted temperature management at 32 to 34°C. Patients with ongoing antibiotic therapy, chronic colonization with multidrug-resistant bacteria, or moribund status were excluded. Either intravenous amoxicillin–clavulanate (at doses of 1 g and 200 mg, respectively) or placebo was administered three times a day for 2 days, starting less than 6 hours after the cardiac arrest. The primary outcome was early ventilator-associated pneumonia (during the first 7 days of hospitalization). An independent adjudication committee determined diagnoses of ventilator-associated pneumonia.

RESULTS

A total of 198 patients underwent randomization, and 194 were included in the analysis. After adjudication, 60 cases of ventilator-associated pneumonia were confirmed, including 51 of early ventilator-associated pneumonia. The incidence of early ventilator-associated pneumonia was lower with antibiotic prophylaxis than with placebo (19 patients [19%] vs. 32 [34%]; hazard ratio, 0.53; 95% confidence interval, 0.31 to 0.92; P=0.03). No significant differences between the antibiotic group and the control group were observed with respect to the incidence of late ventilator-associated pneumonia (4% and 5%, respectively), the number of ventilator-free days (21 days and 19 days), ICU length of stay (5 days and 8 days if patients were discharged and 7 days and 7 days if patients had died), and mortality at day 28 (41% and 37%). At day 7, no increase in resistant bacteria was identified. Serious adverse events did not differ significantly between the two groups.

CONCLUSIONS

A 2-day course of antibiotic therapy with amoxicillin–clavulanate in patients receiving a 32-to-34°C targeted temperature management strategy after out-of-hospital cardiac arrest with initial shockable rhythm resulted in a lower incidence of early ventilator-associated pneumonia than placebo. No significant between-group differences were observed for other key clinical variables, such as ventilator-free days and mortality at day 28. (Funded by the French Ministry of Health; ANTHARTIC ClinicalTrials.gov number, NCT02186951.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. François at Réanimation Polyvalente, CHU de Limoges, 2 Ave. Martin Luther King, 87042 Limoges, CEDEX, France, or at b.francois@unilim.fr.

*A list of investigators in the ANTHARTIC Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Reintubation Incidence After Extubation of High-Risk Patients

Noninvasive ventilation plus high-flow oxygen during breaks is a promising strategy.

Shortening the duration of mechanical ventilation has many benefits, including lowering risks for ventilator-associated pneumonia and delirium. Clinicians usually attempt extubation as soon as possible, with the knowledge that some extubated patients will require reintubation. In patients where risk for reintubation is particularly high, immediate support with noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC) oxygen has been studied, but no clear "best practice" has been established.

Investigators in France randomized 641 patients at high risk for extubation failure (i.e., age, >65 or underlying cardiac or pulmonary disease) to 48 hours of either HFNC alone or NIV plus HFNC during breaks from NIV. Reintubation criteria were protocolized. Patients who received HFNC alone were significantly more likely to be reintubated within 7 days after extubation (18% vs. 12%). Similar results were found at 24 or 48 hours after extubation. The difference between groups was most pronounced in patients with partial pressure of carbon dioxide ($PaCO_2$) >45 mm Hg at extubation.

COMMENT

Many clinicians routinely extubate patients with hypercarbic respiratory failure (most commonly due to underlying chronic obstructive pulmonary disease) to NIV. This study would broaden that approach to patients at high risk for reintubation (defined quite broadly in this study), regardless of gas exchange abnormalities. Use of HFNC during breaks from NIV is an interesting new strategy. Many patients don't tolerate NIV well, but NIV with support during breaks with HFNC is worth trying. ***— Patricia Kritek, MD***

Dr. Kritek is Professor of Medicine, Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, and Associate Editor, *NEJM Journal Watch General Medicine.*

Thille AW et al. Effect of postextubation high-flow nasal oxygen with noninvasive ventilation vs high-flow nasal oxygen alone on reintubation among patients at high risk of extubation failure: A randomized clinical trial. **JAMA** *2019 Oct 2; 322:1465. (https://doi.org/10.1001/jama.2019.14901)*

Telias I and Ferguson ND. Added benefit of noninvasive ventilation to high-flow nasal oxygen to prevent reintubation in higher-risk patients. **JAMA** *2019 Oct 2; 322:1455. (https://doi.org/10.1001/jama.2019.14609)*

Therapeutic Cooling of Patients with Arrest After Nonshockable Rhythms

Survivors who were cooled were more likely to have favorable neurological outcomes.

Early studies of out-of-hospital arrest after a shockable rhythm (i.e., ventricular tachycardia or fibrillation) demonstrated benefit for therapeutic temperature management (TTM). Subsequent investigations have yielded mixed results, and meta-analyses have demonstrated benefit, harm, or no effect of TTM. The population for which we have the least guidance are those who have arrest with nonshockable rhythm (i.e., pulseless electrical activity [PEA] or asystole).

French investigators randomized 581 patients after resuscitation with nonshockable rhythm to either 24 hours of hypothermia (active cooling to 33°C with gradual rewarming) or 48 hours of normothermia (maintenance of 36.5–37.5°C). Three quarters of patients had out-of-hospital arrest; two thirds were from noncardiac causes. Patients with >10-minute delays in cardiopulmonary resuscitation were excluded. A protocol for prognostication or guidance on withdrawal of life support was not specified.

More than 80% of patients died during follow-up, most commonly due to withdrawal of life support. Patients in the hypothermia group were more likely to have cerebral performance category scores of 1 (good function) or 2 (moderate disability) at 3 months' follow-up (10% vs. 6%; P=0.04). Mortality and intensive care unit lengths of stay were similar between groups, as were adverse events.

COMMENT

This is the best examination to date of patients with asystole or PEA, and it shows a small benefit for TTM to 33°C for 24 hours. The numbers for in-hospital arrest are small; although cooling patients who arrest out of hospital might make sense, the data are less convincing for hospitalized patients. ***— Patricia Kritek, MD***

Lascarrou JB et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. **N Engl J Med** *2019 Oct 2; [e-pub]. (https://doi.org/10.1056/NEJMoa1906661)*

Less-Taxing Spontaneous Breathing Trial Was Better for Liberating Patients from the Ventilator

More patients were extubated successfully after a 30-minute trial of pressure support ventilation.

The spontaneous breathing trial (SBT) is the standard of care for assessing readiness to be liberated from mechanical ventilation; however, SBTs vary in duration (30–120 minutes) and degree of ventilatory support. The most common options are a T-piece, which provides only supplemental oxygen through the endotracheal tube, or low-level pressure support ventilation (PSV) to overcome the tube's resistance. Investigators in Spain randomized 1150 mechanically ventilated patients who met specific weaning criteria to SBTs that were less demanding (30 minutes of PSV with 8-cm H_2O pressure support and no positive end-expiratory pressure; PSV group) or highly demanding (120 minutes of T-piece ventilation; T-piece group). Criteria for SBT failure included anxiety, agitation, tachypnea, increased work of breathing, tachycardia, hypotension, or arrhythmia.

Significantly more patients were extubated successfully and free of mechanical ventilation at 72 hours in the PSV group than in the T-piece group (82% vs. 74%). More patients in the PSV group passed the initial SBT (93% vs. 84%); reintubation rates and length of stay in the intensive care unit and hospital were similar between groups.

COMMENT

This study demonstrates that a less-taxing SBT results in more patients being extubated without excess risk for reintubation. The findings are consistent with current American Thoracic Society and American College of Chest Physicians guidelines (*Am J Resp Crit Care Med* 2017; 195:115) and reinforce that standard practice should be a 30-minute SBT with low-level ventilatory support.

— Patricia Kritek, MD

Subirà C et al. Effect of pressure support vs T-piece ventilation strategies during spontaneous breathing trials on successful extubation among patients receiving mechanical ventilation: A randomized clinical trial. **JAMA** *2019 Jun 11; 321:2175. (https://doi.org/10.1001/jama.2019.7234)*

Girard TD and Burns KEA. Revisiting, reframing, and casting a new light on liberation from mechanical ventilation. **JAMA** *2019 Jun 11; 321:2167. (https://doi.org/10.1001/jama.2019.7364)*