EDITORIAL

Whether to Intubate During Cardiopulmonary Resuscitation
Conventional Wisdom vs Big Data

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For 60 years, health care professionals and lay bystanders have saved the lives of individuals with cardiac arrest through successful deployment of cardiopulmonary resuscitation (CPR). Although the 2010 American Heart Association CPR guidelines changed from the traditional "ABC" (airway-breathing-circulation) to "CAB" (circulation-airway-breathing) to ensure that rescue personnel are not unduly distracted from the prompt provision of optimal chest compressions, the core elements have largely remained unchanged.[1] The definitive approach to secure and protect the airway and hence deliver effective breathing is via emergency endotracheal intubation by a suitably trained professional followed by institution of artificial ventilation. If no individual skilled in endotracheal intubation is available, then airway management via a bag-valve-mask device is an acceptable interim alternative. Because of the large number of in-hospital cardiac arrests, hospitals arrange, often at considerable cost, to have around-the-clock emergency response teams capable of providing advanced cardiac life support (ACLS), including endotracheal intubation.

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The American Heart Association engages in considerable efforts to generate and disseminate updated evidence-based guidelines for ACLS. Many elements of the guidelines are informed by randomized clinical trials (RCTs). However, certain aspects of resuscitation are not easy to evaluate in an RCT. Notably, there has been little enthusiasm to randomize patients to be managed with or without endotracheal intubation—the conventional wisdom is that this question has been asked and answered. Nonetheless, observational studies, paradoxically, have suggested that patients who are intubated have greater morbidity and mortality. The problem, of course, is that patients who are intubated may have greater severity of illness in the first place, and efforts to adjust for severity of illness may fail to fully account for residual indication bias.

Confounding by indication is arguably the major limitation to the use of observational data for estimation of treatment effects. However, as health care becomes digitized, there is now considerable optimism that advances in data richness and analytic techniques ("big data") will permit more reliable estimation of therapeutic effectiveness.[2] This optimism led to inclusion in the 21st Century Cures Act of an explicit mandate for the US Food and Drug Administration (FDA) to consider real-world evidence, and not just RCT results, during regulatory approval decisions.[3]

In this issue of *JAMA*, Andersen and colleagues[4] provide a highly sophisticated analysis of the benefits and harms of endotracheal intubation during CPR. Their approach and findings are instructive both for the provision of ACLS and as a window to what lies ahead as regulators, clinicians, and researchers envision incorporation of evidence of treatment effectiveness from actual clinical practice settings.

The authors conducted their analysis using the Get With The Guidelines-Resuscitation (GWTG-R) registry, which includes extremely detailed records of patients who sustained cardiac arrest at several hundred hospitals across the United States. Selecting from 668 hospitals over a 15-year period (January 2000 through December 2014), Andersen et al identified 108 079 adults who had a cardiac arrest managed with chest compressions, had complete data, did not have prior do-not-resuscitate orders, and were not already intubated. Of these patients, 71 615 (66.3%) were intubated within 15 minutes of their cardiac arrest. The primary analysis consisted of generating a paired case-control study, matching patients at the minute they were intubated following cardiac arrest to a control patient who was not intubated during that same minute using a "propensity to be intubated" model. The investigators were able to match 43 314 (60.5%) of the intubated patients to suitable control patients and found that the intubated patients incurred lower likelihood of return of spontaneous circulation (57.8% vs 59.3%; $P < .001$), a lower rate of good neurological outcome (10.6% vs 13.6%; $P < .001$), and worse survival (16.3% vs 19.4%; $P < .001$). Extensive sensitivity and secondary analyses largely confirmed the primary findings.

There are considerable strengths to this study. The data set is large, generalizable, and richly detailed with information to permit sophisticated risk adjustment. The use of time-based propensity matching captures an added level of detail missing in prior studies. However, even though the data were gathered prospectively and were subject to audit checks, some elements are inherently difficult to capture or missing. For example, the data set records intubation, but intubation can take several minutes, and the recorders may not capture the same moment in the process either consistently or accurately. Furthermore, the control patients are individuals who are not intubated during the same minute that a "case" was intubated. However, these controls may become "cases" in subsequent minutes. In other words, this is a comparison of those intubated vs those who are either never intubated or not intubated yet.

This kind of "now vs later" question is common in medicine, yet not that easy to study. For example, the ideal design

would be to compare the outcomes of all patients for whom the clinician decides to intubate "now" vs those in the "maybe later" group. However, intent to intubate is not captured in the data. Therefore, Andersen et al were forced to define cases as patients who were successfully intubated, whereas patients for whom the intent to intubate was unsuccessful or took longer than expected ended up being in the pool of potential controls instead of cases. Data sets from clinical registries often lack critical nuance, such as what the clinician was thinking or wanted to do, and so researchers are forced to oversimplify the study question or design, with potentially important consequences. A solution in this instance could be to modify the data collection, but the existing data set took 15 years to accrue—waiting another 15 years for an updated analysis of even more detailed data is daunting.

So, should clinicians conclude that early intubation is harmful or, at least, ineffective and unnecessary? The act of intubation, especially in skilled hands, should not directly cause injury or death. However, distraction from effective chest compressions while intubation is performed could certainly be harmful. Intubation may also facilitate provision of higher oxygen concentrations, which have been associated with harm.[5] Moreover, patients in the "maybe later" group who recover without any intubation avoid the multiple potential complications of prolonged mechanical ventilation. But, an alternative explanation is that patients who were intubated had greater illness severity in ways for which the design did not account, despite the richness of the data. It is also possible that hospitals or physicians and other members of the resuscitation team with greater propensity to intubate patients are also more likely to provide other therapies or interventions that may inadvertently cause harm. The data set did not allow the authors to explore these possibilities more thoroughly.

In other words, intubation may or may not be harmful, although clear demonstration of benefit is lacking. This is hardly a ringing endorsement for such an established intervention that requires substantial cost to provide, considering both the training and staffing costs and the downstream costs of mechanical ventilation and intensive care that are incurred once the patient is intubated.

There are interesting implications from this study. First, it demonstrates that big data may not yet be big, or "rich," enough. Having data sets large enough and detailed enough to perform minute-by-minute time-based propensity matching exposes the crudeness, and vulnerability to unmeasured confounding, of past studies. Yet even data analyses of this size, detail, and sophistication are insufficient to exclude residual confounding. Second, study limitations notwithstanding, the lack of demonstrable benefit of intubation does challenge conventional wisdom, perhaps to the degree that would generate adequate equipoise for a future RCT. But, third, what would the RCT look like? The study by Andersen et al highlights that the consequences of a decision to intubate or not could change each minute during CPR, which means a clinically useful RCT likely would require multiple randomization points or treatment groups. For such a complicated RCT to be feasible, it should perhaps leverage the existing machinery of the GWTG-R registry to facilitate enrollment and lower data collection costs. Such an approach might appear counter to the hope that big data could supplant the RCT, but it was recently advocated by the FDA[6] and may be the only path to generate definitive evidence when analyses of big data generate findings at odds with conventional wisdom.

ARTICLE INFORMATION

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