Editorial Commentary

Closing the evidence gap for in-hospital cardiac arrest: a focus on advanced airway management

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Introduction

The 2020 American Heart Association (AHA) Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) guideline update assigns in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) their own respective chains of survival, citing significant differences between the two conditions in etiologies, processes, and outcomes (1). For OHCA, outcomes are more dependent upon community engagement and bystander responses, including early recognition of cardiac arrest, activation of local emergency response, bystander performance of cardiopulmonary resuscitation (CPR), and when indicated, use of an automated external defibrillator (AED) (1). For IHCA, outcomes are often dependent upon surveillance for and prevention of clinical decompensation; in the event of a cardiac arrest the responders are not bystanders but trained medical professionals who initiate and provide CPR, rapidly begin advanced life support (ALS) measures, defibrillate (when indicated), and continue care after return of spontaneous circulation (ROSC). As compared to OHCA, IHCA arrests are more likely to result from respiratory failure and occur in the setting of existing acute and chronic medical conditions (2).

Despite the differences between IHCA and OHCA, guidelines for management are nearly identical. This is due to a relative paucity of research devoted solely to IHCA; a systematic review of randomized controlled trials (RCTs) with more than 50 patients with cardiac arrest between 1995 and 2014 yielded 92 total studies (3). Of these, 81 trials were devoted solely to OHCA, 7 included mixed OHCA/IHCA populations, and only 4 were exclusively for IHCA.

In this review, we will discuss the implications of differences between IHCA and OHCA with respect to airway management, data from trials of airway management in the OHCA setting, recent observational trials in the IHCA setting, and the upcoming Hospital Airway Resuscitation Trial (HART, NCT05520762) and Airways-3 (ISRCTN17720457) trials of airway management during IHCA.

Physiologic and practical considerations regarding airway management during cardiac arrest

The progressively severe hypoxemia, hypercarbia, and acidemia that occurs during cardiac arrest results in increased pulmonary vascular resistance, decreased systemic vascular resistance, and decreased cardiac contractility (4). While ventilation during cardiac arrest allows for oxygenation and removal of carbon dioxide, it is not without risks. Hyperventilation increases intrathoracic pressure and induces hypocarbia, decreasing preload, cardiac output, coronary perfusion pressure, and through hypocarbia-induced cerebral vasoconstriction, cerebral perfusion pressure (5,6). Perhaps because of these mechanisms, hyperventilation has been shown to decrease survival rates in animal models and in observational studies (5,6). Hypoventilation, which generates lower tidal volumes and mean airway pressures, promotes atelectasis and decreased lung volume, resulting in hypoxia and hypercapnia (5,6). Thus, the management of ventilation during cardiac arrest

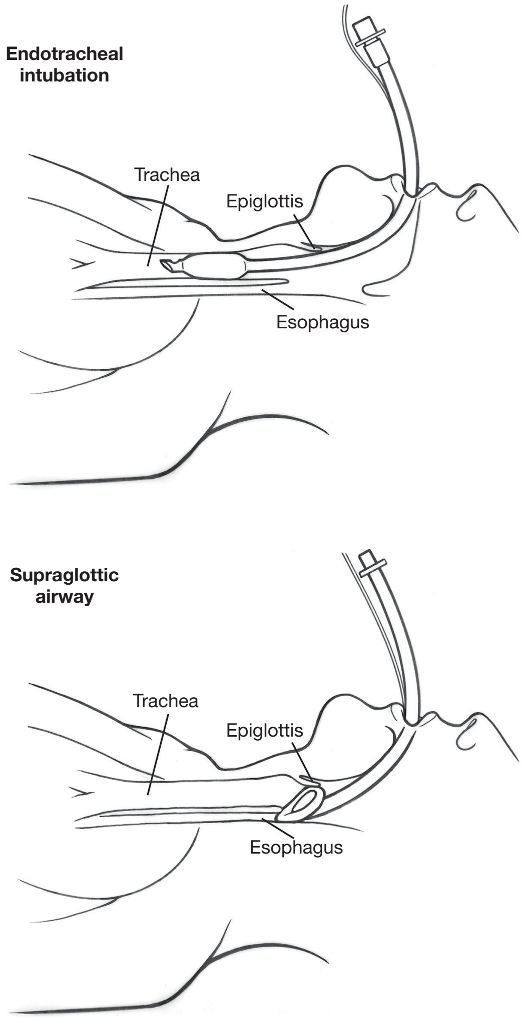

Figure 1 Endotracheal intubation and supraglottic airway.

involves a delicate balance between promoting oxygenation and gas exchange, avoiding both hyperventilation and hypoventilation, and minimizing interruptions to chest compressions.

For nearly 50 years, CPR management was governed by the ABC principle described by Peter Safar and others, with the letter A signifying airway securement, B signifying breathing (or ventilation), and C signifying circulation (or chest compressions) (7). Safar described a stepwise approach consisting of opening the airway, initiating intermittent positive pressure inflation attempts via mouth-to-mouth or bag-mask ventilation (BMV), clearing any potential airway obstruction, inserting a tracheal tube, and delivering 100% concentrated oxygen. Arguments for early endotracheal intubation (ETI) centered on improved airway control, protection against airway obstruction, decreased risk for aspiration, improved oxygenation, and improved removal of carbon dioxide, although this is balanced by the potential risks of cerebral vasoconstriction due to hypocarbia and poorer overall survival with hyperventilation (7). The ABC paradigm endured from the first AHA cardiac arrest guidelines in 1966 until 2010, when the AHA shifted to a C-A-B principle focusing on quality chest compressions, citing improved outcomes from decreased interruptions to chest compressions (and thus an increased chest compression fraction) (8,9).

One alternative to ETI is the supraglottic airway (SGA). A visual comparison of the two modalities is detailed in *Figure 1*.

Identifying knowledge gaps

A review of literature on advanced airway management during adult cardiac arrest yielded 89 trials that compared the effects of ≥2 airway modalities on survival and neurological recovery with at least 10 patients in each group (10). Only 11 were controlled trials (both randomized and non-randomized), of which only three (all published in 2018) included a study population of more than 500 patients. The remainder (78/89) were observational studies which were generally at risk of several biases—perhaps most importantly resuscitation time bias. The authors of this manuscript conducted an updated literature review, searched Medline for relevant papers, reviewed the citations for recent AHA and European Resuscitation Council (ERC) guidelines, and selected the most pertinent for inclusion in this manuscript.

Resuscitation time bias as a special case of immortal time bias in observational studies of advanced airway management during cardiac arrest

A common method of performing an observational study is to retrospectively compare outcomes for two groups of patients: one group that received an intervention or had an exposure, and one group that did not. A frequently overlooked limitation for these observational studies is the bias resulting from the time it takes for the exposure or intervention to occur. For the intervention group, there is a period of time leading up to the intervention during which it is impossible to experience the outcome of interest (because the intervention has not occurred yet); however, for the control group, the outcome can occur at any time.

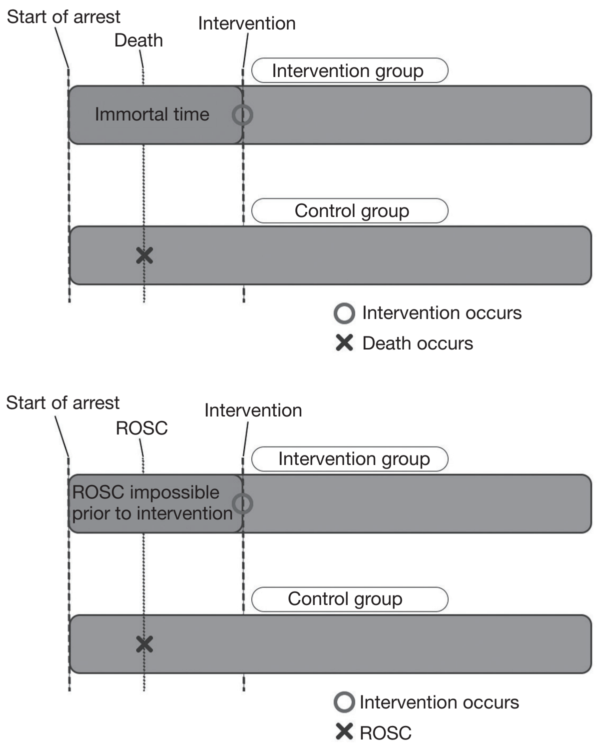

Figure 2 Immortal time bias. ROSC, return of spontaneous circulation.

This period of time for the intervention group is referred to as immortal time (because the outcome is impossible) and can bias the study (*Figure 2*). Immortal time bias often biases an observational study in favor of the intervention because every patient in the intervention group has a period of immortality.

For studies of cardiac arrest, there is a specific type of immortal time bias that is especially prevalent: resuscitation time bias. In the case of resuscitation time bias, the outcome of ROSC is impossible for the intervention group prior to receiving the intervention. For example, when examining the effect of "intervention X" on ROSC during a cardiac arrest, the intervention group is unable to achieve ROSC from the time the arrest starts to the time that intervention X was performed (all patients who received an intervention would have to be resuscitated long enough without ROSC to allow adequate time for the intervention to be administered). Alternatively, those who have a shorter duration to ROSC, would never have a chance to receive the intervention and would therefore by definition be in the control group. This example is illustrated in *Figure 2* where the intervention group has a period of time during which ROSC is impossible because the intervention has not yet been administered. Inherently, the longer a resuscitation goes on during cardiac arrest, the longer amount of time there is for an intervention to take place, biasing the intervention group towards longer resuscitations. Since longer resuscitations are associated with poor outcomes, resuscitation time bias will bias an observational study in favor of the unexposed group. Simply adjusting for the duration of the cardiac arrest is not always possible since the interventions themselves often influence the duration of resuscitation, and early ROSC may be a mediator for the intervention on the outcomes such as survival.

An example of resuscitation time bias could be illustrated by the 649,654 patient observational study by Hasegawa *et al.* comparing neurologically favorable survival between either an advanced airway (ETI or supraglottic airway) or conventional BMV in OHCA (11). This study found lower odds of favorable neurological outcome for the intervention group of advanced airway placement (1.1% *vs.* 2.9%, OR =0.38; 95% CI, 0.36–0.39). BMV is typically initiated immediately, while the intervention of advanced airway takes time to prepare for, set up, and then complete the procedure; therefore the intervention group of advanced airway would have a period prior to completion of the intervention where ROSC is impossible, while the bag-valve-mask group could achieve ROSC at any time, and this resuscitation time bias favors bag-valve-mask. Although Hasegawa *et al.* attempted to address this bias in a sensitivity analysis including only those who survived to hospital arrival, the study is an illustrative case. Randomized clinical trials inherently protect against immortal time bias and resuscitation time bias as patients either need to survive long enough to undergo randomization or from randomization being pre-determined before the arrest occurs.

Clinical trials in advanced airway management for OHCA

As above, biases—including resuscitation time bias—have limited the evidence base in cardiac arrest advanced airway management. During the past 5 years, however, three relatively large randomized trials have begun to close the important knowledge gap regarding the optimal approach to airway management during resuscitation. The design and results of these trials can be seen in *Table 1*. Cardiac arrest airway management (CAAM) by Jabre *et al.* (n=2,043) was a multicenter trial that compared ETI to BMV at participating centers in Belgium and France, with crossover

Table 1 Overview of randomized controlled trials for airway management in out-of-hospital cardiac arrest

Study	Country	Intervention	Comparator	Primary outcome	ETI, first pass success rate (%)	72-hour survival rate		ROSC		Survival to hospital discharge		Favorable neurologic recovery	
						Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator
Jabre, 2018 (12)	Belgium, France	BMV	ETI	Favorable neurologic recovery (CPC ≤2)	98%	Not reported	Not reported	348/1,018 (34.2%)	397/1,022 (38.9%)	55/1,018 (5.2%)	54/1,022 (5.3%)	44/1,018 (4.3%)	43/1,022 (4.2%)
Benger, 2018 (13)[†]	United Kingdom	i-Gel	ETI	Functional neurologic recovery (mRS ≤3)	69%	664/4,872 (13.6%)	575/4,395 (13.1%)	1495/4,880 (30.6%)	1,294/4,404 (28.4%)	392/4,882 (8.0%)	372/4,407 (8.4%)	311/4,882 (6.4%)	300/4,407 (6.8%)
Wang, 2018 (14)	United States	LT	ETI	72-hour survival rate	51%	274/1,505 (18.3%)	230/1,495 (15.4%)	420/1,505 (27.9%)	365/1499 (24.3%)	163/1,504 (10.8%)	121/1,495 (8.1%)	107/1,500 (7.1%)	75/1,495 (5.0)

[†], 28-day survival rates reported. BMV, bag mask ventilation; ETI, endotracheal intubation; CPC, cerebral performance category; mRS, modified Rankin scale; LT, laryngeal tube.

to rescue ETI permitted in cases of suspected massive regurgitation or inability to perform BMV, and crossover to BMV permitted in cases of inability to intubate (12). The primary outcome (CPC score 1 or 2) was nearly identical (4.3% in the BMV group and 4.2% in the ETI group), but did not meet the *a priori* threshold for non-inferiority; the ETI group also demonstrated a higher rate of ROSC (38.9% *vs.* 34.2%) but there were no significant differences between the ETI and BMV groups for survival to hospital admission or at 28 days. The BMV group had more frequent rates of difficulty (18.1% *vs.* 13.4%), failure (6.7% *vs.* 2.1%) and regurgitation of gastric contents (15.2% *vs.* 7.5%). Of note, the ETI success rate was 98%, possibly due to the availability of emergency medicine physicians (who are among ALS first responders in France and Belgium) to supervise or intervene in ETI.

Airways-2 by Benger *et al.* (n=9,296), compared the iGel supraglottic airway (SGA) to ETI via direct laryngoscopy in a paramedic-based system in England (13). Paramedics (rather than patients) were randomized to either group, were allowed two attempts at their allocated strategy prior to pursuing the alternative, but were also allowed to deviate from their strategy based on clinical discretion. The primary outcome of functional neurologic recovery (modified Rankin score of 0–3) was 6.4% for the SGA group and 6.8% for the ETI group, though SGA demonstrated a greater rate of successful ventilation in ≤2 attempts (87.4% *vs.* 79.0%), a greater rate of airway loss (10.6% *vs.* 5.0%) and a lower rate of crossover due to paramedic discretion (2.0% of the SGA group were intubated *vs.* 14.0% of the ETI group received an SGA). While crossover between groups can bias towards the null hypothesis of no difference between interventions, such crossover between airway choice depending on clinical judgment is perhaps more reflective of real-world practice. The ETI success rate in Airways-2 was 69%.

PART (Effect of a Strategy of Initial Laryngeal Tube Insertion *vs.* Endotracheal Intubation of 72-Hour Survival in Adults with Out-of-Hospital Cardiac Arrest), by Wang *et al.* (n=3,004), was a cluster randomized controlled trial that compared the laryngeal tube (LT) SGA with ETI in a paramedic-based system in the United States (14). The primary outcome (72-hour survival rate) was 18.3% for the SGA group and 15.4% for the ETI group. The SGA group also showed a greater rate of ROSC (27.9% *vs.* 24.3%), survival to hospital discharge (10.8% *vs.* 8.1%), favorable neurologic recovery at discharge (7.1% *vs.* 5.0%), had nearly 3 min less time to successful airway placement, and lower rates of complications such as pneumothoraxes, rib fractures, and airway misplacement or dislodgement. The ETI success rate in PART was 51%, and the SGA success rate was 88%.

Building largely on the above trials, the 2020 AHA CPR & ECC guidelines were updated to allow for either the use of BVM only or an advanced airway during resuscitation from cardiac arrest (1,15). When an advanced airway was selected, SGA was preferred in settings with low ETI success rate or with minimal training opportunities for ETI. In settings with a high ETI success rate and adequate training, either ETI or SGA was considered acceptable and left to the clinician's discretion. These recommendations, derived primarily from an OHCA evidence base, were generalized to IHCA where either advanced airway approach was considered acceptable.

More recently, a systematic review and network meta-analysis of 9 RCTs between 1986–2018 evaluating airway management strategies in OHCA did not find that any of the studied airway management methods (BMV, ETI, LT, Laryngeal Mask Airway, i-Gel, and Combitube) were superior in terms of ROSC, airway success rate, survival to hospital admission, or survival to hospital discharge in OHCA (16).

Emergency airway management during in-hospital cardiac arrest: the current state and the future

As compared to OHCA, where the evidence base remains thin, the evidence base used for creating recommendations in IHCA is even less robust. While several observational studies have been performed exploring approaches to advanced airway management in IHCA, these generally suffer from the same biases as those described above. Two observational studies worth highlighting however, are those conducted using the AHA nationwide Get With The Guidelines® (GWTG®) Resuscitation Quality Improvement Registry. In one study of adult patients suffering an IHCA between 2000 and 2016 among hospitals participating in the GWTG® registry, hospitals were categorized into quartiles based on rates of intubation during IHCA, and the risk adjusted odds ratio of survival between the lowest and highest quartiles was 0.81, though this association disappeared when controlling for those patients who had respiratory failure prior to their IHCA (17).

A time-based propensity matched cohort study by Andersen *et al.* of adult IHCA patients in the GWTG® registry demonstrated decreased survival (16.3% *vs.* 19.4%), decreased ROSC (57.8% *vs.* 59.3%), and decreased functional outcome (CPC <2) (10.6% *vs.* 13.6%) among those patients who were intubated compared with those who were not intubated during the first 15 min after experiencing an IHCA (18). These results were similar when applied to previously designated subgroups (initial shockable *vs.* non-shockable rhythm, illness category, pre-existing respiratory insufficiency, and event location) except for those with pre-existing respiratory insufficiency, for whom no statistically significant association between intubation and mortality was seen (though results trended towards increased mortality for those receiving ETI). Notably, patients with an initial shockable rhythm who were intubated had a survival rate 32% lower than those who were not intubated. The authors hypothesized that focusing on intubation during in-hospital cardiac arrest detracted attention from other actions such as early defibrillation and high-quality CPR. In a recent study by Schwab *et al.*, it was notable that rates of ETI during CPR have been decreasing over time—especially in relation to the focus on compressions introduced in the shift to a C-A-B resuscitation approach (19). Indeed ETI, when it is performed, is occurring later during the cardiac arrest.

Encouragingly, there are two upcoming RCTs that aim to fill the gap in evidence for airway management during IHCA. The first is AIRWAYS-3 (ISRCTN17720457) in the United Kingdom, a multi-center open-label pragmatic individually randomized parallel-group superiority trial comparing the effects of ETI *vs.* SGA during adult IHCA (20). The second is Hospital Airway Resuscitation Trial (HART, NCT05520762) in the United States, a cluster randomized pragmatic trial comparing the strategy of first choice SGA *vs.* first choice ETI (21). Both trials will be assessing the impact of airway choice during IHCA on patient centered outcomes and have recently begun enrollment. Airways-3 and HART will hopefully allow for future recommendations regarding airway management during IHCA with data developed in an IHCA population—a rarity in the resuscitation arena.

Conclusions

IHCA and OHCA, both common conditions and major public health concerns, are distinct entities with patients experiencing IHCA more likely to suffer a respiratory etiology of arrest, have a more rapid response, and be responded to by expert providers with a full range of advanced resuscitation equipment. Nevertheless, recommendations for IHCA put forth by national resuscitation councils largely draw off of evidence derived from OHCA patients. This phenomenon is highlighted in the approach to advanced airway management during cardiac arrest—which at present is largely built on an OHCA evidence base. Future trials of advanced airway management during IHCA are needed and are already being conducted.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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