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Editorial

Which PART of the question are you asking?

Several recent papers have suggested that the timing of intravenous adrenaline administration may be important in the resuscitation of out-of-hospital cardiac arrest victims.[1–4] In a recent cluster-randomized clinical trial, the PART team demonstrated better survival from out-of-hospital cardiac arrest with an initial airway management strategy of laryngeal tube (LT) placement than with endotracheal intubation (ETI).[5] The team noted that patients in the LT group were much less likely to require three or more attempts at airway placement (4.5% vs 18.9%) or to suffer unsuccessful initial airway placement (11.8% vs 44.1%), and also that the interval from EMS arrival to first airway attempt was 2.7 min shorter on average in the LT group than in the ETI group. They thus postulated that perhaps at least some of the survival benefit seen in the LT group was due to earlier epinephrine administration, with the crew able to complete airway management and move on to other aspects of care sooner. Accordingly, they conducted a secondary analysis of their data, focusing on timing of first adrenaline dose, published in this issue of *Resuscitation*.[6] They examined the relationship between timing of first adrenaline dose and initial airway strategy (as randomized, via intention-to-treat analysis), but also the relationship between timing of first adrenaline dose and survival at 72 h, dichotomizing the adrenaline timing to $\leq$10 min vs $>$10 min. While no differences were found in time to initial adrenaline administration between the LT and ETI groups, even when the data were stratified by duration of airway attempt of number of attempts, a survival benefit was seen when adrenaline was given in $\leq$10 min (OR 1.36, 95% CI 1.05–1.77).

It is important to note that PART was a study of airway management *strategies*, not airway management *devices*. It may be that the survival benefit seen in the LT group in PART was due to overall efficiencies or other differences in care, rather than anything specific to the LT device itself. On the one hand, the original PART found that patients in the LT group had fewer insertion attempts, higher first attempt success, and shorter intervals from arrival to first airway attempt. On the other hand, the PART secondary analysis published here did not find that these efficiencies were associated with shorter times to first dose of adrenaline, suggesting that perhaps it was some aspect of care other than adrenaline where the LT patients benefitted. When patients were stratified by whether the first dose of adrenaline was given before or after the first airway attempt, minor ($<$1 min) differences in overall time to adrenaline administration emerged, but the significance of this is unclear.

While some studies have shown a benefit to early adrenaline administration, others have not. A study of four years' worth of OHCA patients ($>$32,000 in total) with initial nonshockable rhythms from the Resuscitations Outcome Consortium found 18% lower survival when adrenaline was given $\geq$10 min after EMS arrival, compared to when it was given in $<$10 min.[3] The authors noted that each additional minute from EMS arrival to adrenaline administration was associated with a 4% decrease in survival and a 6% decrease in neurologically intact survival. Another retrospective study, examining 686 patients in a suburban EMS system in the USA, found higher rates of return of spontaneous circulation, but not survival to hospital admission or discharge, among patients given adrenaline within 10 min of the 9-1-1 call, compared to those given adrenalin more than 10 min after the call.[2] Note that this study uses a different interval than the ROC study: time from 9-1-1 call to adrenaline, vs time from EMS arrival to adrenaline. A Japanese study examined both the interval between the call to dispatch and arrival of EMS at the patient's side ('response interval') and the interval between reaching the patient and giving the first dose of adrenaline ('adrenaline interval'). This retrospective study of over 13,000 patients examined survival at 1 month with CPC 1 or 2. Among patients with a response interval $<$8 min, those with an adrenaline interval $<$10 min had a better survival rate (OR 2.12, 95% CI 1.54–2.92) than those with an adrenaline interval of $\geq$10 min. Similarly, among those with a response interval between 8 and 16 min, those with an adrenaline interval of $\leq$10 min did better (OR 2.66, 95% CI 1.97–3.59) than those with an adrenaline interval of $\geq$10 min. Finally, a large study from Japan of 2634 patients receiving adrenaline in a much larger study of OHCA management noted that only 17 received adrenaline within 10 min of the call to dispatch, forcing the investigators to use other time intervals. Later adrenaline was associated with lower rates of ROSC and 1-month survival among patients with nonshockable presenting rhythms; this association was not found in those patients with shockable presenting rhythms.[4]

Why the differences in these findings? Study methodology heterogeneity likely plays a role: differences in EMS system types, resuscitation protocols, and definitions used, as well as factors adjusted for in multivariate analysis, all likely help account for the differences. On a broader basis, asking whether early adrenaline is better than late adrenaline is likely an oversimplificiation, and in fact this may be the wrong question to ask. As Wang et al. suggest in their discussion of the PART secondary analysis, there are a number of potentially interacting factors to consider, both physiological (adrenaline has both positive and negative physiologic effects on the OHCA victim's macro and microphysiology) and logistical/operational (many other things, including airway management, are going on at the same time adrenaline is being given). It is well established that substantial variation exists in OHCA outcomes (as well as incidence and patient characteristics) on the basis of geography alone,[7,8] as well as

socioeconomic status.[9,10] Some of these complex factors can be controlled for (both in studies and in actual OHCA resuscitations), but many cannot. There is almost certainly not a one-size-fits-all answer to the question of adrenaline timing; it is also likely that the interplay with other factors such as airway management affects both process and outcome variables. The PART team is continuing to look at this interplay, and many other researchers across the globe are contributing their efforts as well. Having more data may not necessarily enable to answer questions, though: we need to be sure we are asking the right questions first.

Conflict of interest statement

I attest that I have no pertinent financial or other conflicts of interest related to the editorial piece "Which PART of the question are you asking?".

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