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Epinephrine Administration Intervals: Seeing the Forest for the Trees

The current pediatric and adult life support recommendations suggest an epinephrine administration interval (EAI) of 3–5 minutes during cardiopulmonary resuscitation (CPR) (1, 2). These recommendations are expert opinion based on the half-life of epinephrine in animal studies, but there are few clinical data about EAI during CPR. Adult observational data are inconsistent, reporting better outcomes with shorter EAI (3), longer EAI (4, 5), or neither (6). A practical approach uses a fixed 4-minute EAI that allows providers to synchronize with the 2-minute chest compressor change, rhythm check, and defibrillation. Thus, pediatric intensivists have a range of choices for a fixed or variable EAI and little evidence to guide their practice.

A 2017 retrospective review of 1,630 pediatric in-hospital cardiac arrests in a large national database related EAI to the rates of return of spontaneous circulation (ROSC) and survival to hospital discharge (7). They calculated EAI as the duration of CPR after the first epinephrine dose divided by the total number of epinephrine doses. ROSC and survival were better with EAIs from 5 to 8 minutes and best with EAIs from 8 to 10 minutes compared with the 1-to-5-minute EAI group. The duration of CPR was longer in the 5-to-8-minute group and longest in the 8-to-10-minute group. The time to first epinephrine administration was 2.4 minutes in all three groups. Worse outcomes were associated with total epinephrine dosage administered. The authors concluded that the administration of less epinephrine with less frequency was associated with better outcomes.

In this issue of the *Journal*, Kienzle and colleagues (pp. 977–985) provide contradictory findings on the association of EAI with outcomes in pediatric cardiac arrest (8). This 2021 retrospective review of an institutional database of 125 pediatric in-hospital cardiac arrests examined the effects of the EAI during CPR on the rates of ROSC, survival to hospital discharge, and return to neurologic baseline (8). Their method for determining the EAI was to round epinephrine administration times to the closest minute and average the intervals from the first epinephrine dose to the end of resuscitation. They compared the frequent administration of epinephrine (EAIs ⩽2 min) with standard EAIs (⩾3 min) and found that frequent epinephrine administration was associated with better rates of ROSC, survival, and return to neurologic baseline. They found that CPR duration was shorter in the frequent epinephrine group and was associated with better outcomes. The time to first epinephrine dose—1 minute in the frequent group and 2 minutes in the standard group—was not statistically different. The authors concluded that more frequent epinephrine dosing (⩽2-min intervals) was associated with better outcomes.

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The authors of both observational studies acknowledge that prospective clinical trials would better test the impact of EAI on pediatric resuscitation outcomes. The design and implementation of clinical trials will be exceedingly difficult not only because of the challenging clinical situation but also because of the large number of variables aside from EAI that might affect outcomes. Even evidence for whether to routinely administer epinephrine in adults and children remains low (1, 2). A trial would need to determine whether to remain within or to exceed guidelines, whether to use fixed or variable EAIs, when to administer the first dose, and what total dose to use. In addition, the etiology of arrest, the duration of arrest, the quality of CPR, the baseline condition of the patient, and the preparedness of the team all can modify outcome and treatment response.

Determining the effect of the EAI on outcome would help determine a more specific treatment guideline, but this question may be missing the forest for the trees. Perhaps there is not a single EAI that is best for all resuscitations, and investigators should focus on developing a personalized and responsive approach based on physiologic feedback that adapts to the situation and condition of the patient.

For example, a witnessed ventricular fibrillation arrest in an adult has electrocardiographic physiologic feedback that can confirm that myocardial energy stores are high (coarse fibrillation or increased amplitude spectral array) and may have invasive monitoring that shows that perfusion during CPR is good (high systolic and diastolic arterial pressures, high myocardial perfusion pressures, pulsations on saturation monitors, high end-tidal carbon dioxide levels). Reassured by this feedback and concerned for postresuscitation epinephrine effects on ischemic myocardium, an intensivist might delay the first and subsequent doses of epinephrine.

In contrast, an unwitnessed pulseless arrest due to a tracheostomy plug in a pediatric ICU may require a different approach to epinephrine administration. In a piglet asphyxial arrest model, diastolic blood pressure (a surrogate for coronary perfusion pressure associated with outcome in pediatric patients [9]) increased rapidly when the asphyxia duration was short (11 min) but had a delayed and smaller increase when the asphyxia duration was long (20 min) (10). These data suggest that an asphyxial arrest might require early epinephrine and a longer arrest might require more frequent epinephrine.

The inconsistent findings from retrospective reviews of EAI may indicate that resuscitation teams are already using clinical signs to guide drug administration. There is significant variability in the EAI used in adult cardiac arrests and in pediatric ICUs, but the reasons that resuscitators chose to deviate from guideline recommendations are not known. Observational studies assume that this variation is a random effect when trying to posit a causal relationship between EAI and outcomes. This approach is very limited if the EAI was based on some physiologic feedback or clinical impression that revealed that this patient responded better to more frequent or less frequent administration.

Ideally, intensivists would individualize epinephrine dosing on the basis of physiologic feedback such as diastolic blood pressure response. Clinical trials using physiologic feedback such as diastolic blood pressure or other monitoring to direct epinephrine administration would be a better next step than trials of different EAIs. The authors of the current study have already laid groundwork for these clinical trials by previously showing the use of hemodynamic directed CPR in animal models (11, 12) and determining clinical target values for diastolic blood pressure during CPR in infants (25 mm Hg) and children (30 mm Hg) (9). ■

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Philips Respironics Recall of Positive Airway Pressure and Noninvasive Ventilation Devices

A Brief Statement to Inform Response Efforts and Identify Key Steps Forward

On June 14, 2021, Philips Respironics issued a voluntary recall notification in the United States and a field safety notice internationally of the vast majority of models of continuous positive airway pressure (CPAP), bilevel PAP (BPAP), and mechanical ventilator devices produced over the last decade. The goal was to "ensure patient safety in consultation with regulatory agencies" (1) because of *1*) risk of exposure to particulates released from polyester-based polyurethane sound abatement foam and *2*) off-gassing of potentially toxic or carcinogenic concentrations of volatile organic compounds (VOCs). High environmental humidity and use of unauthorized ozone-based cleaning devices may accelerate degradation of foam. Potential symptoms listed by the manufacturer include rhinitis and sinusitis, upper airway irritation, cough, chest pressure, headache, or dizziness, which were reported by 11 (0.03%) patients in 2020 (2). The U.S. Food and Drug Administration (FDA) advised on July 22, 2021, that more than 1,200 complaints and 100 injuries were reported on this issue (3). The duration of exposure necessary to produce symptoms has not been reported or is unknown. For example, Philips has not clarified whether a one-time overnight exposure, such as a 2- to 8-hour period for a split-night or full-night titration sleep study, would impose unacceptably high risk. Exposure-related cancer and deaths have not been reported thus far.

The guidance from the manufacturer (current as of August 15, 2021) is that *1*) patients using recalled life-sustaining mechanical ventilator devices should continue therapy as prescribed until discussion with the healthcare provider and *2*) patients using recalled CPAP and BPAP devices should discontinue use and work with the healthcare or durable medical equipment provider to determine next steps. A timeline for replacement or repair by Philips remains unclear. Devices from other manufacturers are not reported to be affected by this recall.

Logistical Impact of the Recall Is Vast and Unprecedented in Scope

The recall notice impacts 3–4 million devices worldwide, resulting in exceedingly high population attributable and public safety risk of untreated sleep-disordered breathing (SDB) and pulmonary disease if device usage is discontinued without replacement or alternative therapy (4). The majority have underlying SDB (i.e., obstructive sleep apnea, central sleep apnea, or hypoventilation disorders). Thus, the scale and logistical impact of this recall far exceed that of the field safety notice of adaptive servo-ventilators that followed the release of results from the SERVE-HF (Treatment of Sleep-disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure) trial with implications focused on central sleep apnea (5, 6). One challenge is that many PAP users may not be aware of the recall or whether their device is affected. In addition, ongoing supply chain shortages for replacement devices are posing a global threat to many patients in sleep, pulmonary, and critical care medicine. Even ongoing (e.g., ADVENT-HF [Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure] NCT01128816) and planned clinical trials have been affected. Finally, given the lack of guidance for sleep laboratories using these devices, patients who need but who are not yet using recalled devices are also affected by delays in care.

Three immediate conundrums emerged:

1. The need to qualify the recommendation by Philips Respironics to discontinue CPAP and BPAP therapy immediately;
2. The need to relay this voluntary recall notification in a timely manner to the millions of afflicted patients; and
3. The need to determine how sleep laboratories that use recalled equipment for titration studies should manage their clinical testing needs.

This editorial aims to summarize current knowledge and offer suggestions for clinical decision-making.

Immediate Discontinuation of PAP Therapy May Harm Some Patients

For patients who use mechanical ventilators for immediate life-sustaining reasons, the decision to continue therapy is clear, as the

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