

## Duration of Cardiac Arrest Resuscitation: Deciding When to “Call the Code”

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Since the advent of cardiopulmonary resuscitation (CPR) >50 years ago,<sup>1,2</sup> progress has been made in the initial treatment of cardiac arrest, yet the diagnostic and monitoring modalities available to clinicians during resuscitation have lagged behind. As the science of cardiac arrest care continues to evolve, a key clinical dilemma remains unanswered: when is it acceptable to stop resuscitation, and based on what diagnostic criteria? Given that >300 000 adults in the United States will suffer from emergency medical services (EMS)-assessed out-of-hospital cardiac arrest (OHCA) each year,<sup>3</sup> the decision to stop resuscitation efforts has an enormous impact on thousands of lives.

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### Article, see p 1386

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In this issue of *Circulation*, Nagao and colleagues<sup>4</sup> have attempted to add clarity to the important question of when to stop resuscitation for OHCA victims in a retrospective analysis of 282 183 adult patients with bystander-witnessed OHCA. Taking advantage of the “natural experiment” of resuscitation duration in the Japanese EMS system, in which termination of resuscitation (TOR) efforts is not allowed before hospital arrival, they determined that, to achieve a  $\geq 99\%$  sensitivity for favorable 30-day neurologic outcome, prehospital resuscitation efforts should be maintained for a minimum of 40 minutes from the time of EMS call placement and at least 33 minutes from the time of EMS scene arrival for all witnessed OHCA events. The authors argued that the time intervals were similar across all 4 stratified patient groups (shockable/non-shockable, bystander CPR present/absent), and, as such, the “shockable” rhythm group was used to determine the resuscitation time recommendations.

In the work by Nagao et al,<sup>4</sup> the 30-day favorable neurologic survival rate in patients with shockable arrest and bystander resuscitation was 20.0%, whereas the 30-day survival rate for witnessed shockable arrest was 28.6% for all patients included in the study, measured from 2005 to 2012. As a comparator, in a 2015 report from the American Heart Association (AHA),

survival to hospital discharge for bystander-witnessed ventricular fibrillation in the United States was 31.4%.<sup>3</sup> Because of differences in database structure, EMS care, patient demographics, institutional standards of care, and outcome measurement, direct comparisons between the patient populations in the study by Nagao et al<sup>4</sup> and other investigations are difficult. To a first approximation, however, similar outcomes are being achieved in witnessed, shockable OHCA in Japan compared with other North American studies.

Nagao et al<sup>4</sup> found that most patients that had favorable neurologic outcome (83.1%) had prehospital return of spontaneous circulation, whereas an initial shockable arrest rhythm had the highest adjusted odds ratio for favorable 30-day neurologic outcome (7.53; 95% confidence interval, 7.10–7.98). These data are similar to previous work by Reynolds et al,<sup>5</sup> who reported that 89.7% of all patients with good functional outcome achieved prehospital return of spontaneous circulation within 16.1 minutes of CPR.

The investigation by Nagao et al<sup>4</sup> has distinct strengths that distinguish it from previous works that examined the duration of OHCA care. Representing a nationwide population-based cohort, the number of patients included in the study far exceeds most published OHCA literature. Furthermore, because the EMS system in Japan does not allow for prehospital TOR, the risk of treatment bias is much lower compared with studies in jurisdictions with TOR rules in place. In the absence of prehospital TOR, there is a decreased likelihood of advanced age, presumed futility, or prearrest morbidity status determining whether or not a patient receives prolonged care as can be the case with robust TOR policies. TOR rules can establish a patient’s outcome at a point in time determined by EMS rescuers; in contrast, in the study by Nagao et al,<sup>4</sup> EMS providers were not allowed to cease efforts until hospital arrival, creating a unique environment to evaluate the effect of CPR duration on outcomes without this confounder in place. Additionally, using favorable neurologic outcome as the primary end point is an important feature of the investigation; defining an optimal resuscitation time for survival alone may have lead one to question whether or not a prolonged resuscitation period leads to significant neurologic compromise in survivors.

Notably, the work of Nagao et al<sup>4</sup> reflects previous work that examined the duration of resuscitation for in-hospital cardiac arrest patients. In their 2012 study, Goldberger et al<sup>6</sup> demonstrated that longer duration of resuscitation during in-hospital cardiac arrest was associated with higher rates of return of spontaneous circulation and survival to discharge. The work of both of these groups begs the question: can the appropriate duration of resuscitation efforts be determined with confidence?

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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### TOR and Optimal CPR Duration

The current AHA guidelines are divided into basic life support (BLS) and advanced life support (ALS) systems, with different criteria for cessation of resuscitation in both categories.<sup>7,8</sup> It is important to note that the EMS system studied in the investigation by Nagao et al<sup>4</sup> is most comparable with the North American ALS system. The guidelines for continuing ALS care in the AHA guidelines and the inclusion criteria in the Nagao et al<sup>4</sup> article are similar; both protocols suggest that witnessed arrests require advanced cardiac life support without early prehospital termination.

The updated 2015 AHA guidelines do not explicitly include a suggested minimum duration for ALS CPR provision before ceasing resuscitative efforts. If the current study is confirmed in other EMS environments, it is possible that additional iterations of the AHA guidelines may need to define minimum resuscitation duration intervals for ALS systems. However, generalizing the optimal duration of resuscitation care for North American OHCA patients based solely on this Japanese study is challenging, especially for those patients being cared for by basic life support providers. The basic life support–TOR rule of Morrison et al<sup>9</sup> provides a robust clinical decision rule for CPR termination in OHCA patients. Although this rule, which has been incorporated into the AHA guidelines, has been demonstrated to be effective in North American populations,<sup>10</sup> a Japanese study suggested that it has a lower specificity and positive predictive value in a Japanese cohort than it did during the initial North American derivation and validation studies,<sup>11</sup> further illustrating the complex nature of determining optimal CPR duration across widely divergent EMS systems and probable confounders related to local protocols and available therapies.

### CPR Duration in the Future: A Role for Improved Monitoring?

Despite the progress represented by more quantitative studies of resuscitation care, such as the work by Nagao et al,<sup>4</sup> there are very few means by which to assess the probability of survival and resuscitation duration for an individual patient. Although other interventions in critical care have personalized physiologic and biologic end points based on monitoring, analogous approaches during CPR are lacking. For example, whereas vasopressor use during shock can be titrated to mean arterial pressure and duration of antibiotic therapy can be guided in part by white blood cell count or fever curve, real-time physiologic markers during CPR have not been well-validated to guide care or the duration of resuscitation efforts. The decision to stop resuscitative efforts in large part continues to rely on a provider's qualitative judgment that efforts have become futile.

However, the recognition that quantitative metrics are required to aid this decision making are gaining traction. The recent AHA guidelines recommended using end-tidal CO<sub>2</sub> measurements of <10 mmHg after 20 minutes of CPR as part of a multimodal approach to support the cessation of resuscitation efforts.<sup>12</sup> A recent study of pediatric in-hospital cardiac arrest demonstrated that altering CPR quality to real-time hemodynamic targets resulted in improved arterial blood

pressure, which may be a useful diagnostic approach to assess viability.<sup>13</sup> Although more experimental concepts, such as the use of tissue redox potential, have shown some promise as a novel strategy to assess resuscitation care,<sup>14</sup> such approaches have yet to be tested in the clinical environment. As additional therapies for extending the duration of CPR become more established (eg, extracorporeal membrane oxygenation and mechanical CPR devices), the need for such physiologic biomarkers and monitoring modalities will become increasingly relevant.

Finally, it is important to recognize that the optimal resuscitation duration for a given patient may evolve over time as new therapeutic options are established that may alter the CPR duration–survival relationship. The adaptation of mobile telephone technology to increase both quality and frequency of bystander CPR has shown great promise.<sup>15–17</sup> Recent studies have illustrated the potential effectiveness of extracorporeal membrane oxygenation for patients with refractory cardiac arrest, offering an aggressive care strategy that could lead to increased rates of return of spontaneous circulation and favorable neurologic outcome.<sup>18–20</sup> An ongoing trial is examining the role that a “hyperinvasive” approach to cardiac resuscitation, including early prehospital targeted temperature management, mechanical chest compressions, extracorporeal life support, and early coronary angiography, may play in neurologic survival when compared with a normal standard of care.<sup>21</sup> With continued technologic advancement, there exists a distinct possibility that code duration will increase and the duration–survival relationship will change. Improved real-time physiologic monitoring during CPR will be required to balance this shift.

After 50 years of progress in resuscitation science, one of the most basic questions in the field remains unanswered: when can we stop resuscitation efforts? The work by Nagao et al<sup>4</sup> is an interesting and provocative examination of the optimal duration of resuscitative efforts for witnessed OHCA, suggesting that overall survival may be increased with longer resuscitation efforts than are often experienced in North American EMS systems. Additional studies from other EMS environments will be required to confirm and clarify these findings before implementation of widespread protocol changes. With continued focus on the quantitative study of CPR delivery and resuscitation duration, it seems likely that the next few years will yield continued insights into how resuscitation care can be optimized during OHCA to improve both survival and favorable neurologic outcomes.

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