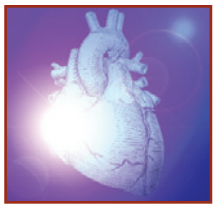

# Secondary Ventricular Fibrillation or Pulseless Ventricular Tachycardia During Cardiac Arrest and Epinephrine Dosing

By Andrew D. Straznitskas, PharmD, BCPS, Sylvia Wong, PharmD, Nicole Kupchik, RN, MN, CCNS, CCRN, and David Carlbom, MD

**Background** Development of ventricular fibrillation or pulseless ventricular tachycardia after an initial rhythm of pulseless electrical activity or asystole is associated with significantly increased cardiac arrest mortality.

**Objective** To examine differences in epinephrine administration during cardiac arrest between patients who had a secondary ventricular fibrillation or ventricular tachycardia develop and patients who did not.

**Methods** Data were collected for 2 groups of patients with in-hospital cardiac arrest and an initial rhythm of pulseless electrical activity or asystole: those who had a secondary ventricular fibrillation or ventricular tachycardia develop (cases) and those who did not (controls). Dosing of epinephrine during cardiac arrest and other variables were compared between cases and controls.

**Results** Of the 215 patients identified with an initial rhythm of pulseless electrical activity or asystole, 51 (23.7%) had a secondary ventricular fibrillation or ventricular tachycardia develop. Throughout the total duration of arrest, including periods of return of spontaneous circulation, the dosing interval for epinephrine in patients who had a secondary ventricular fibrillation or ventricular tachycardia develop was 1 mg every 3.4 minutes compared with 1 mg every 5 minutes in controls ($P$=.001). For the total duration of pulselessness, excluding periods of return of spontaneous circulation during the arrest, the dosing interval for epinephrine in patients who had a secondary ventricular fibrillation or ventricular tachycardia develop was 1 mg every 3.1 minutes versus 1 mg every 4.3 minutes in controls ($P$=.001).

**Conclusion** More frequent administration of epinephrine during cardiac arrest is associated with development of secondary ventricular fibrillation or ventricular tachycardia. (*American Journal of Critical Care.* 2015;24:e22-e27)


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In-hospital cardiac arrest is a prevalent problem, with an estimated 6.65 cases for every 1000 hospital admissions, and is associated with an exceedingly high mortality.[1] Survival to hospital discharge occurs in less than 20% of patients who experience in-hospital cardiac arrest.[1,2] Mortality is highly associated with the first identified rhythm of the arrest; pulseless electrical activity (PEA) and asystole are associated with a rate of survival to hospital discharge of about 10% whereas ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) are associated with a rate of survival to hospital discharge of about 35%.[2-4]

Although cardiac arrest with an initial rhythm of VF or VT has been associated with lower mortality rates than PEA or asystole, a secondary VF or VT after an initial rhythm of PEA or asystole has been associated with an increase in mortality.[5,6] In 1 study,[7] patients who did not have a secondary VF or VT develop had approximately 60% increased odds of survival to hospital discharge compared with patients who had a secondary VF or VT develop. No studies have been done to investigate what factors may increase a patient's risk of a secondary VF or VT developing.

Epinephrine is the cornerstone for the pharmacological management of cardiac arrest with the goal of increasing α-adrenergic mediated vasoconstriction, resulting in increased myocardial perfusion and oxygenation to facilitate return of spontaneous circulation (ROSC).[8] Current guidelines recommend the consideration of epinephrine at a dose of 1 mg every 3 to 5 minutes during PEA or asystolic cardiac arrest (class IIb recommendation; level of evidence: A).[9] Despite the fact that epinephrine has been associated with increased rates of ROSC, it has never been found to increase the rate of survival to hospital discharge.[10,11] Furthermore, epinephrine has been associated with the development of ventricular arrhythmias and disruption of the myocardial oxygen balance during cardiac arrest in animal models.[12,13]


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The objective of this retrospective study was to investigate differences in the frequency of epinephrine administration between patients with in-hospital cardiac arrest and an initial cardiac rhythm of PEA or asystole who had a secondary VF or VT develop and patients who did not. We hypothesized that, because of the proarrhythmic nature of epinephrine, the development of secondary VF or VT would be associated with an increased frequency of epinephrine administration.

## Methods

This retrospective, case-control study was approved by the institutional review board at the University of Washington. The data were collected from Harborview Medical Center, an urban, academic medical center in Seattle, Washington. The institution is a level 1 trauma center that maintains 400 beds and 89 critical care beds. It has approximately 19 500 admissions and more than 62 000 emergency department visits annually.

> Epinephrine of 1 mg every 3 to 5 minutes during pulseless electrical activity or asystole is recommended.

Patients were identified by using the institution's internal cardiac arrest database. This database retains information on all in-hospital cardiac arrests and contains data including initial cardiac rhythm, date and time of arrest, patient's age and sex, hospital unit, shocks delivered, medications administered, immediate outcome of cardiac arrest, and discharge disposition. This database is used to monitor trends and outcomes for quality improvement within the institution. Study data were collected from this database and the electronic medical record according to Utstein definitions.

This database was used to identify patients who had in-hospital cardiac arrest between January 2008 and June 2011. Patients were included in the study if the initial cardiac rhythm was documented as PEA or asystole. Patients were excluded if they were less

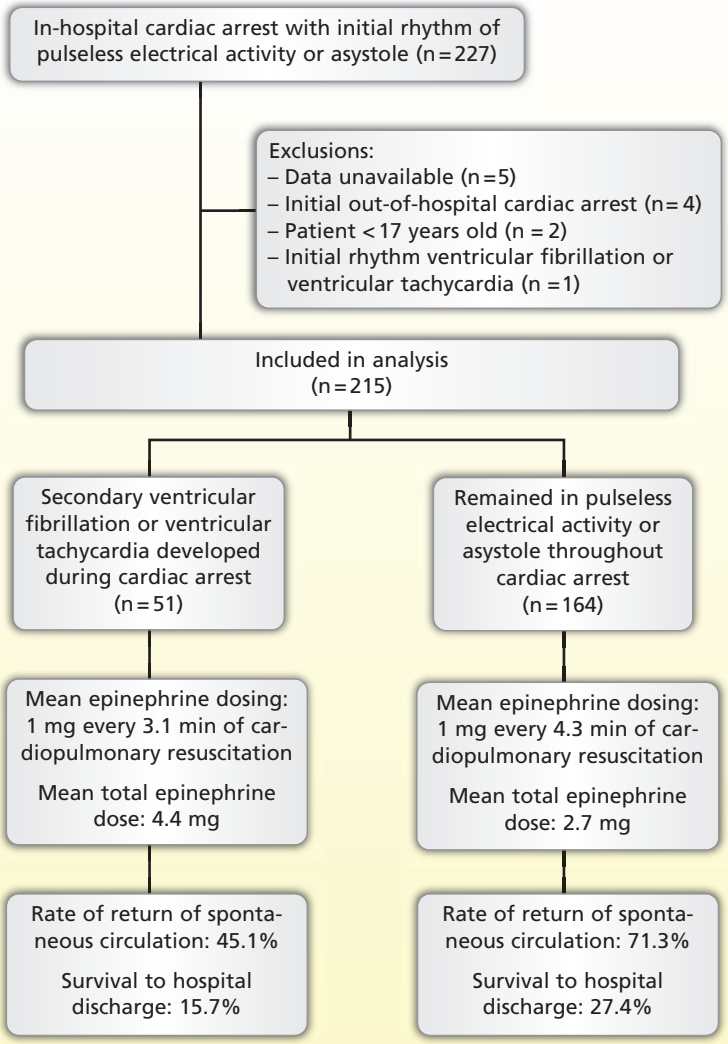


**Figure** Flow of patients identified with in-hospital cardiac arrest and an initial rhythm of pulseless electrical activity or asystole through study analysis.

**Table 1**
**Characteristics of patients**

| Characteristic | Secondary ventricular fibrillation or tachycardia | | *P* |
|---|---|---|---|
| | Present | Absent | |
| Age, mean (95% CI), y | 59.6 (54.1-65) | 57.2 (54.4-60) | .44 |
| Weight, mean (95% CI) , kg | 86.4 (77.6-95.2) | 86.2 (81.4-91) | .97 |
| Race, % of patients | | | .73 |
| Asian | 11.8 | 14 | |
| Black | 15.7 | 17.1 | |
| Hispanic | 7.8 | 4.3 | |
| White | 62.7 | 59.2 | |
| Other | 2 | 5.4 | |
| Sex, % of patients | | | .06 |
| Male | 58.8 | 72.4 | |
| Female | 41.2 | 27.6 | |
| Hospital location, % of patients | | | .45 |
| Intensive care unit | 64.7 | 73.2 | |
| Acute care/emergency department | 35.3 | 26.8 | |

than 17 years of age, experienced recent out-of-hospital cardiac arrest (within 2 hours of admission), or had experienced recent VF or VT cardiac arrest (within 2 hours of study event). Patients were not excluded on the basis of the suspected cause of the cardiac arrest. Secondary VF or VT was defined as a transition to VF or VT occurring at any point during the cardiac arrest. Sustained ROSC was defined as a period of ROSC lasting at least 2 hours.

Patients included in the study were divided into 2 groups: those who developed a secondary VF or VT (cases) and those who did not (controls). Cases were compared with controls in univariate analysis by using a Student *t* test for continuous variables and a $\chi^2$ test for categorical variables. In order to assess the association of variables on the rate of secondary VF or VT, information on medication administration for cases was collected from the beginning of cardiac arrest until the first onset of a secondary VF or VT. For controls, these data were collected from the beginning of cardiac arrest until the end of the event, either sustained ROSC or death.

## Results

A total of 215 patients were identified as having in-hospital cardiac arrest with an initial rhythm of PEA or asystole during the study period (see Figure). Secondary VF or VT occurred in 51 patients (23.7%). Patients' characteristics at the time of arrest are displayed in Table 1. No significant differences were detected between groups for the characteristics investigated in this study. However, the proportion of females was higher among cases than controls (41.2% vs 27.6%, *P*=.06).

Epinephrine results are reported as a mean dosing interval per 1-mg dose administered during cardiac arrest. As for the total duration of cardiac arrest, including periods of ROSC during the arrest, the mean dosing interval for epinephrine among patients who had a secondary VF or VT develop was 3.4 (95% CI, 2.9-4.1) minutes compared with 5 (95% CI, 4.4-5.7) minutes among controls (*P*=.001). This difference persisted when looking at epinephrine administration during the total duration of pulselessness, excluding periods of ROSC, during the arrest. The mean dosing interval for epinephrine among patients who had a secondary VF or VT develop was 3.1 (95% CI, 2.6-3.6) minutes compared with 4.3 (95% CI, 3.8-5) minutes in controls (*P*=.001).

The mean total dose of epinephrine from the beginning of the cardiac arrest until the first development of secondary VF or VT (for cases) and until the end of the arrest (for controls) was 2.6 mg and 2.7 mg (*P*=.70), respectively. However, when looking

**Table 2**
**Dosing interval for medications administered during cardiac arrest**

| Medication | Secondary VF/VT | | No secondary VF/VT | | *P* |
|---|---|---|---|---|---|
| | Mean dosing interval | 95% CI | Mean dosing interval | 95% CI | |
| **Total duration of cardiac arrest, min** | | | | | |
| Epinephrine 1 mg | 3.4 | 2.9-4.1 | 5.0 | 4.4-5.7 | .001 |
| Atropine 1 mg | 15.3 | 11.0-25.0 | 12.6 | 10.1-16.9 | .48 |
| Bicarbonate 50 mEq | 14.2 | 10.6-21.7 | 16.9 | 13.7-22.2 | .44 |
| Calcium chloride 10% 10 mL | 17.6 | 12.8-28.6 | 29 | 22.2-43.5 | .06 |
| **Total duration of pulselessness excluding periods of return of spontaneous circulation during arrest, min** | | | | | |
| Epinephrine 1 mg | 3.1 | 2.6-3.6 | 4.3 | 3.8-5.0 | .001 |
| Atropine 1 mg | 12.5 | 9.3-18.9 | 10.7 | 8.8-13.7 | .52 |
| Bicarbonate 50 mEq | 10.9 | 8.2-16.4 | 12.5 | 10.1-16.4 | .54 |
| Calcium chloride 10% 10 mL | 15 | 11.2-22.2 | 23.2 | 17.9-33.3 | .07 |

at the entire duration of cardiac arrest, regardless of time of onset of secondary VF or VT, cases received a significantly larger total dose of epinephrine than controls received, 4.4 mg compared with 2.7 mg ($P < .001$). This comparison does not account for differences in duration of cardiac arrest between cases and controls.

Patients who had secondary VF or VT develop had a significantly longer duration of cardiac arrest compared with patients who did not (33 vs 20.5 minutes, $P = .004$). For patients who had a secondary VF or VT develop, the mean time until the first onset of VF or VT was approximately 14.5 minutes. This duration was not significantly different from the total duration of cardiac arrest among the control group ($P = .14$).

As for the immediate outcome of cardiac arrest, patients who had a secondary VF or VT develop achieved sustained ROSC at a rate of 45.1% compared with 71.3% in controls ($P = .001$). Longer-term mortality, defined as survival to hospital discharge, was not significantly different between groups. Among patients who had a secondary VF or VT develop, survival to hospital discharge was 15.7% compared with 27.4% for controls ($P = .09$).

Differences were not detected between laboratory values before and during cardiac arrest. Before cardiac arrest, potassium levels were significantly higher among patients who had a secondary VF or VT develop; however, the mean for each group was within normal limits (cases 4.8 mEq/L vs controls 4.4 mEq/L).

The dosing intervals for other commonly used medications during cardiac arrest are reported in Table 2. Table 2 reports the dosing intervals both with respect to the total duration of cardiac arrest, including periods of ROSC, and with respect to the total duration of pulselessness, excluding periods of ROSC during the arrest. No significant differences in dosing interval were identified among any other medications administered during cardiac arrest. Calcium chloride was used more often among patients who had a secondary VF or VT develop; however, this difference was not statistically significant.

## Discussion

The results of this study demonstrate that patients who had a secondary VF or VT develop after an initial cardiac arrest rhythm of PEA or asystole received epinephrine more frequently, before the first onset of VF or VT, than did patients who did not have a secondary VF or VT develop. Both groups of patients, those who had a secondary VF or VT develop and those who did not, received epinephrine in adherence to the current guideline recommendation of 1 mg every 3 to 5 minutes. We also identified a larger total dose of epinephrine among patients who had a secondary VF or VT develop. However, this association may be explained by the longer duration of cardiac arrest and greater number of repeat doses seen in patients who had a secondary VF or VT develop.

Epinephrine is a nonselective catecholamine with potent α- and β-adrenergic effects.[12] Although the α-adrenergic activity of epinephrine increases myocardial perfusion and oxygen delivery, the β-adrenergic effects may increase myocardial workload, disrupting the balance between oxygen supply and demand and increasing the risk of ventricular arrhythmias.[13,14] In addition, pharmacokinetic alterations

that occur during cardiac arrest may provide a physiological explanation for the association seen in this study. In healthy persons, following intravenous administration of epinephrine, the circulating concentration of epinephrine is significantly decreased after approximately 2 to 3 minutes as a result of wide tissue distribution and extensive metabolism to inactive compounds.[15] Cardiac arrest and resuscitation are associated with significant impairments in systemic perfusion that result in decreased drug distribution and metabolism.[16] This decrease in tissue distribution and metabolism may result in an increased half-life of circulating epinephrine during cardiac arrest, potentially leading to accumulation of epinephrine with more frequent administration. These pharmacological characteristics of epinephrine may explain the association between the more frequent administration of epinephrine and the higher rate of secondary VF or VT developing that was seen in this study.

Those who had a secondary ventricular fibrillation or tachycardia received epinephrine more often.

An analysis of a randomized controlled trial comparing resuscitation with intravenous drug administration to resuscitation without intravenous drug administration demonstrated that patients who received epinephrine experienced more unstable cardiac arrests than did patients who did not receive epinephrine.[17] These patients experienced rhythm changes at 1.6 times the rate among patients who did not receive epinephrine. These changes were positive, transitioning to ROSC, as well as negative, transitioning to a pulseless rhythm.

Our results also suggest that epinephrine may be associated with more unstable cardiac arrests, shown through a higher rate of secondary VF or VT. Despite this association with an increased rate of transitioning to cardiac rhythms correlated with a worse prognosis, studies in patients with out-of-hospital cardiac arrest have demonstrated that epinephrine is also associated with improved rates of ROSC.[10,11] Further investigation is needed to evaluate what dose and dosing interval are ideal to maintain the beneficial effects of epinephrine (increased rates of ROSC), but avoid the potential deleterious effects (more unstable arrests and increased rates of secondary VF or VT).

Our study has several limitations. First, it is important to note that we are not able to determine the direction of association between increased epinephrine administration and the development of secondary VF or VT. Although it may be that increased epinephrine administration creates an increased risk of secondary VF or VT, it is equally plausible that secondary VF or VT is an independent poor prognostic marker that is associated with increased duration of cardiac arrest that leads to increased administration of epinephrine. Second, our small sample size may not have been adequate to accurately evaluate differences between groups for certain variables. Several factors approached statistical significance (calcium administration, sex, survival to hospital discharge), and with a larger sample size, these differences might have been statistically significant. Third, as data on factors that affect the incidence of secondary VF or VT are limited, we limited our analysis to a small number of variables that we hypothesized might affect this outcome. Several other factors may affect a patient's risk of secondary VF or VT, such as past medical history, cause of cardiac arrest, reason for hospitalization, and medications received before cardiac arrest. Last, our study relied on retrospective data collection. Most data were collected from written documentation during cardiac arrest, resulting in potential for human error.

## Conclusion

Our study demonstrated that patients with in-hospital cardiac arrest who had a secondary VF or VT develop after an initial cardiac rhythm of PEA or asystole received epinephrine more frequently than did patients who did not have a secondary VF or VT develop. Furthermore, patients who had a secondary VF or VT develop had longer duration of cardiac arrest and received a larger total dose of epinephrine. A true association between increased epinephrine administration during cardiac arrest and development of secondary VF or VT would need to be confirmed in prospective studies. If this association were to be confirmed, extending the dosing interval of epinephrine might result in improved outcomes among patients with cardiac arrest and an initial rhythm of PEA or asystole.

FINANCIAL DISCLOSURES
None reported.

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