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ORIGINAL RESEARCH

Emergency Medical Services

Feasibility of prehospital esmolol for refractory ventricular fibrillation

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Abstract

Background: Esmolol may increase survival for patients with refractory ventricular fibrillation (RVF); however, information related to esmolol use in the prehospital environment is limited. We aimed to assess the feasibility of prehospital bolus dose esmolol for patients with RVF treated by a high-volume, ground-based emergency medical services (EMS) agency.

Methods: Esmolol (0.5 mg/kg single bolus) was added to the RVF protocol on December 10, 2018. Feasibility was defined as esmolol administration in >75% of RVF cases. Secondarily, we compared the proportion of patients with prehospital return of spontaneous circulation (ROSC), 24-hour survival, and survival to hospital discharge during the intervention period (December 10, 2018–June 10, 2020) to a historical control period (June 10, 2017–December 9, 2018) using chi-square tests.

Results: Before the protocol change, 63 patients with RVF were identified. After esmolol was added, 70 patients with RVF were identified and 61 (87%) received esmolol. Prehospital ROSC was higher in the esmolol group compared to the historical control group, though statistical significance was not reached (38% versus 24%, $P = 0.09$). Overall, few patients survived to 24 hours (esmolol n = 15, pre-esmolol n = 16) and fewer survived to hospital discharge (esmolol n = 5, pre-esmolol n = 5), precluding stable statistical comparisons.

Conclusion: Collectively, these findings suggest that EMS clinicians are able to accurately identify RVF and administer esmolol in the prehospital setting and that ROSC may be increased. Further large-scale studies are needed to determine the effect of prehospital esmolol for RVF as it relates to neurologically intact hospital discharge.

KEYWORDS
cardiac arrest, emergency medical services, esmolol, out-of-hospital cardiac arrest, prehospital, refractory ventricular fibrillation

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1 | INTRODUCTION

1.1 | Background

Refractory ventricular fibrillation (RVF) is characterized as cardiac arrest with persistent ventricular fibrillation despite initiation of American Heart Association advanced cardiac life support (ACLS), three defibrillations, three 1 mg doses of epinephrine and amiodarone administration.[1,2] RVF represents a specific subset of out-of-hospital cardiac arrest (OHCA) unlike the classic electrical storm described in the cardiology literature.[3,4] Outcomes for patients experiencing RVF are dismal, even when current standards of care are delivered.[5,6]

The Bottom Line

This before-and-after study evaluated an emergency medical services (EMS) protocol change for refractory ventricular fibrillation that added a bolus of intravenous esmolol. The authors found that the EMS system was able to successfully implement the protocol change. The results also suggested that patients treated with esmolol may have higher rates of return of spontaneous circulation, though this was not statistically significant and is a hypothesis to be tested in future studies.

1.2 | Importance

RVF is thought to result from adrenergic surge, often secondary to acute coronary occlusion and myocardial ischemia. Esmolol, an ultra-short acting beta-adrenergic antagonist, has been proposed as a treatment option for patients with RVF.[7] Two small hospital-based observational studies collectively totaling 66 patients[8,9] and earlier animal studies[10–12] have suggested increased survival in RVF with the addition of esmolol to standard ACLS care. However, RVF is often first encountered outside the emergency department or hospital environment, warranting examination of esmolol as a potential treatment option for use by emergency medical services (EMS) clinicians in the prehospital setting.

1.3 | Goals of this investigation

In this study, we sought to evaluate the feasibility of prehospital bolus dose esmolol for patients with cardiac arrest progressing to RVF within a high-volume, ground-based EMS agency. Secondarily, we compared prehospital return of spontaneous circulation (ROSC), 24-hour survival, and survival to hospital discharge between patients treated with esmolol and those treated during a historical control period immediately preceding the introduction of esmolol into the prehospital RVF protocol.

2 | METHODS

2.1 | Study design and setting

In this retrospective observational analysis, we examined the effects of introducing esmolol to the cardiac arrest with RVF protocol of a large, suburban, EMS agency in Texas. Montgomery County Hospital District (MCHD) is a ground-based EMS agency that employs approximately 250 advanced life support medics and provides medical direction for more than 1000 first responders. In a service area encompassing 1100 square miles, MCHD responds to more than 70,000 annual calls for service. This study was approved by the institutional review board at The Baylor College of Medicine and a waiver of informed consent was granted.

2.2 | Intervention

A single 0.5 mg/kg bolus of esmolol was added to the prehospital cardiac arrest treatment protocol for RVF on December 10, 2018. Before December 10, 2018, the treatment protocol for RVF followed standard ACLS recommendations including high-quality cardiopulmonary resuscitation (CPR), epinephrine administration, 3 defibrillations, antiarrhythmic administration, and advanced airway management with either an endotracheal tube or supraglottic device. Dual sequential defibrillation (DSD) was available and encouraged but not required.

Approximately 1 month before the deployment of esmolol, all MCHD paramedics underwent a mandatory 2-hour training session that included a review of cardiac arrest physiology, focused didactic instruction on the pathophysiology and clinical findings in RVF, and an introduction to specifics of esmolol pharmacology and the updated RVF treatment protocol. Medics demonstrated an understanding of RVF and the esmolol treatment protocol through both written and psychomotor examinations at the conclusion of the mandatory training session. This knowledge was then reinforced by a dedicated RVF podcast, produced in house, which was available and promoted for the duration of the study period.

2.3 | Selection of participants

The prehospital electronic patient care record (ePCR) system was queried for all 9-1-1 encounters with cardiac arrest and 3 or more defibrillations by EMS. EMS patient care records were then individually and independently reviewed by 2 physician authors (C.P. and R.D.) to determine presence of true RVF as defined by shock resistance with persistent ventricular fibrillation, and no degeneration into pulseless electrical activity or asystole, during the initial ACLS treatment phase. Cardiac arrests with traumatic etiologies were excluded from this

analysis as traumatic cardiac arrest has a lower incidence, substantially lower rates of survival, and distinct definitive interventions compared to cardiac arrest with medical etiologies.

2.4 | Measures

Data elements were abstracted directly from the prehospital ePCR and hospital electronic medical records by a 2-person expert review panel consisting of 1 physician (CP) and 1 paramedic (BW) using a standardized data collection form including patient demographic information, prehospital medications, prehospital interventions, and hospital disposition.

We defined feasibility based on criteria often used as acceptability thresholds for pragmatic pilot studies.[13] Feasibility was defined as >75% of patients meeting RVF criteria receiving prehospital esmolol. Secondary outcome measures included presence or absence of ROSC during the EMS encounter, 24-hour hospital survival, and survival to hospital discharge. ROSC was ascertained using the prehospital electronic patient care record and survival measures were obtained from the hospital electronic health record.

2.5 | Data analysis

We evaluated the effects of adding esmolol to the prehospital protocol between December 10, 2018 and June 10, 2020. A historical control period between June 10, 2017 and December 9, 2018 was selected for secondary comparisons of the proportion of patients with prehospital ROSC, 24-hour survival, and survival to hospital discharge.

Descriptive statistics were calculated with frequencies and percentages for categorical variables and continuous variables summarized using medians and interquartile ranges (IQR). Patient and encounter characteristics were compared between the cohort of patients receiving esmolol and those in the control period using Wilcoxon Rank Sum tests for non-normally distributed continuous variables and chi-square tests for categorical variables. Comparisons of the proportion of patients experiencing prehospital ROSC, surviving to 24 hours after hospital arrival, and surviving to hospital discharge between patients receiving esmolol and those in the historical control period were made using chi-square tests. For all comparative tests, we set an alpha level of 0.05 as the threshold for determining statistical significance. Multivariable logistic regression modeling was used to assess the association between esmolol and outcome variables while controlling for patient age, sex, and initial rhythm. All analyses were completed using Stata IC Version 15.1 (StataCorp LLC, College Station, TX).

3 | RESULTS

During the control period before the addition of esmolol to the out-of-hospital cardiac arrest protocol, there were 527 EMS responses for patients with cardiac arrest and 87 patients received 3 or more defibrillations in the prehospital setting. After physician review, 24 cases were excluded, leaving 63 patients with cardiac arrest and RVF in the analysis. After implementation of esmolol, there were 781 EMS encounters for patients in cardiac arrest, of which 105 patients received at least 3 prehospital defibrillations. Physician review excluded 33 patients as non-RVF. Two patients with traumatic arrest etiologies were also excluded, leaving 70 patients with RVF eligible for esmolol. Among the 70 eligible patients with cardiac arrest and RVF, 61 (87%) received esmolol in the prehospital setting (Figure 1).

Patient and encounter characteristics were similar for between the cohort that received prehospital esmolol and the historical control period cohort (Table 1). The median age was 67 years in both groups and approximately 28% were female. Bystander CPR was noted in more than 75% of cases. Approximately 87% of patients in both groups presented with an initial rhythm of either ventricular fibrillation or ventricular tachycardia. Median time to the first dose of epinephrine was 4 minutes in both groups. The median number of epinephrine doses was slightly higher in the historical control group (5 doses) compared to the group that received esmolol (3 doses). The median EMS scene time was 35 minutes (IQR: 30–41 minutes) in the esmolol group compared to 32 minutes (IQR: 26–41 minutes) in the control group. The median on scene arrival time to esmolol administration was 17 minutes (IQR: 13–22 minutes). More patients in the control period received lidocaine or magnesium sulfate compared to patients receiving esmolol.

After esmolol administration 38% (n = 23) of patients achieved prehospital ROSC compared to 24% (n = 15) of patients from the control period, though this difference did not reach statistical significance ($P = 0.09$). Survival at 24 hours was similar for those who received esmolol (25%, n = 15) and those from the control period (25%, n = 16). In total, 5 patients (8%) from the esmolol group and 5 patients (8%) from the control group survived to hospital discharge (Table 2).

After adjusting for patient age, sex, and initial rhythm, there was a 2-fold increase in odds of ROSC during the EMS encounter (odds ratio: 1.99, 95% confidence interval: 0.89-4.47) for patients treated with esmolol compared to patients who were not administered esmolol, though statistical significance was not reached.

4 | LIMITATIONS

This study was limited by its retrospective nature, small sample size, and the single-agency study setting. Further, small sample size and lack of standardization surrounding the timing and use of dual sequential defibrillation limited the ability to draw inferences related to the effects of prehospital esmolol on overall RVF morbidity and mortality. The use of prehospital ePCR data to evaluate ROSC precluded the assessment of rearrest, an important variable to consider in future study. Further, the small sample size resulted in too few hospital survival events to generate stable estimates. The hospital data obtained did not allow us to evaluate other important clinical outcomes included the proportion of patients who presented with ST-segment–elevation myocardial infarction and subsequently received emergent percutaneous coronary intervention.

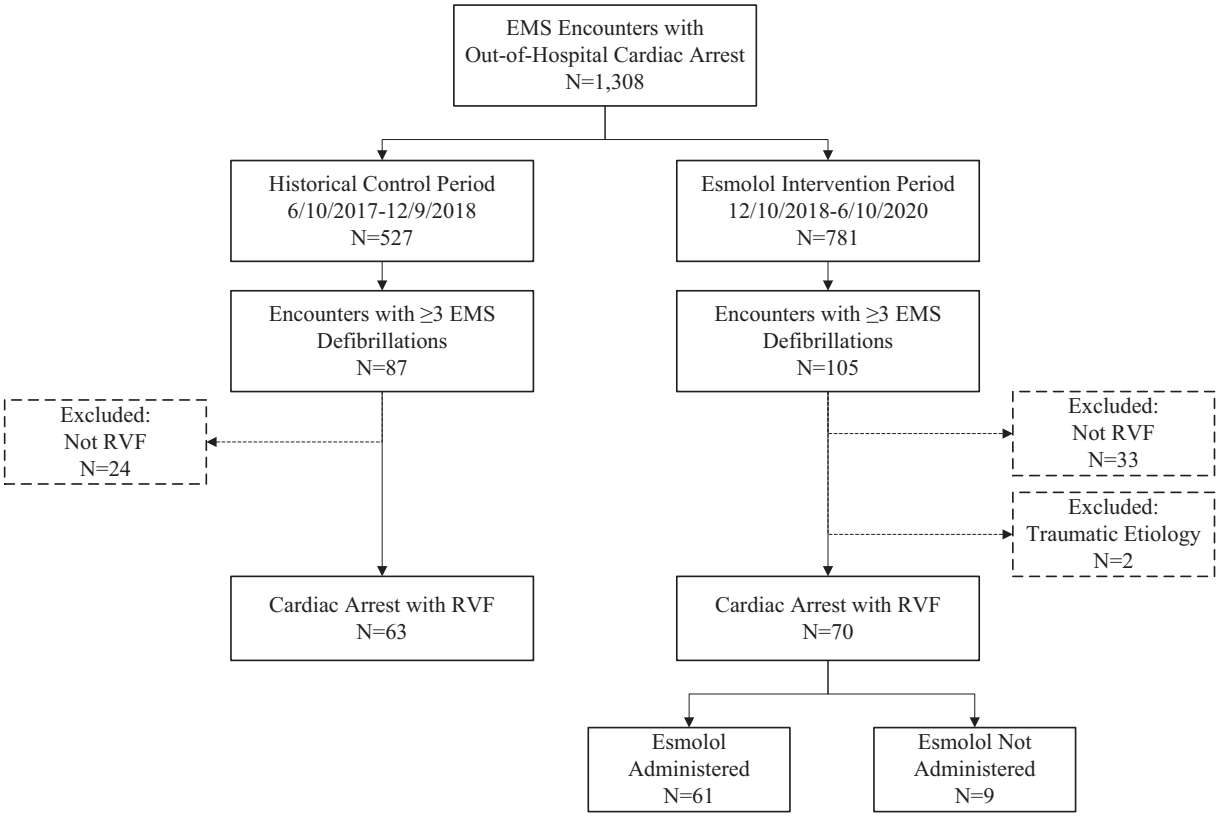

FIGURE 1 Inclusion of patients in analysis sample. Abbreviations: EMS, emergency medical services; RVF, refractory ventricular fibrillation

Although esmolol was not intended to replace any of the recommended ACLS treatments, a lower proportion of patients received antiarrhythmic medications after the addition of esmolol to the prehospital RVF protocol. Nevertheless, in our sample, antiarrhythmic medication was not associated with ROSC during the EMS encounter and adding this variable to the multivariable model did not meaningfully alter the findings. We also observed a difference in EMS transport rates between the intervention and control periods, with a lower rate of transport observed in the intervention period. There was no obvious explanation for this change; however, it is possible that the first months of the COVID-19 pandemic during the intervention period may have affected patient presentations and clinician decision-making. Randomized studies with larger sample sizes are needed to further investigate the effects of prehospital esmolol on patient morbidity and mortality in patients with RVF.

5 | DISCUSSION

In this pragmatic study of patients with RVF encountered by EMS, administering esmolol in the prehospital setting was feasible and non-inferior to standard ACLS treatment. After the protocol update, esmolol was administered in nearly 90% of eligible patients and no increases in scene time were observed. Though no statistical differences were noted, there appeared to be a trend toward higher ROSC for RVF patients administered esmolol. Overall, few patients survived to 24 hours and fewer survived to hospital discharge, making comparisons between groups challenging.

More patients who were administered prehospital esmolol experienced ROSC compared to those treated before the introduction of esmolol into the EMS protocol for RVF. This finding is consistent with 2 small in-hospital studies evaluating esmolol for patients with OHCA and RVF.[8,9] Although ROSC does not directly translate to survival, reestablishing circulation and perfusion in the prehospital setting before patient transport may help preserve neurologic function while allowing EMS to safely route the patient to appropriate continued care and advanced interventions. Recently, extracorporeal membrane oxygenation assisted CPR programs have shown benefit for RVF[14]; however, these programs largely take place in specific, specialized hospital settings. Early ROSC and immediate EMS transport of RVF patients to extracorporeal membrane oxygenation assisted CPR capable facilities may be beneficial within some systems of care where these resources exist.

Overall survival of patients with RVF was low throughout the study period. These findings are in line with overall poor outcomes observed for patients presenting with RVF.[4–6] Prehospital OHCA patients presenting with RVF are a complex, heterogenous patient population with a multifaceted clinical management pathway. This complexity makes true standardization between patients exceedingly difficult in the EMS setting. For example, although available and encouraged

TABLE 1 Patient and EMS encounter characteristics

	Esmolol administered N = 61	Control period N = 63	*P* value
Age, years			
Median (IQR)	67 (57–76)	67 (57–77)	0.60[a]
Sex			0.93[b]
Female	27.9% (17)	28.6% (18)	
Male	72.1% (44)	71.4% (45)	
Race			0.56[b]
White	78.7% (48)	85.7% (54)	
Black	4.9% (3)	3.2% (2)	
Hispanic	13.1% (8)	6.4% (4)	
Other/unknown	3.3% (2)	4.8% (3)	
Bystander cardiopulmonary resuscitation			0.91[b]
Yes	77.1% (47)	76.2% (48)	
No	22.9% (14)	23.8% (15)	
Initial rhythm			0.24[b]
Ventricular fibrillation	83.6% (51)	82.5% (52)	
Ventricular tachycardia	3.3% (2)	4.8% (3)	
Pulseless electrical activity	3.3% (2)	9.5% (6)	
Asystole	9.8% (6)	3.2% (2)	
Dual sequential defibrillation			0.46[b]
Yes	24.6% (15)	19.0% (12)	
No	75.4% (46)	81.0% (51)	
Lidocaine			0.03[b]
Yes	22.2% (14)	8.2% (5)	
No	77.8% (49)	91.8% (56)	
Magnesium sulfate			<0.01[b]
Yes	39.7% (25)	18.0% (11)	
No	60.3% (38)	82.0% (50)	
Number of defibrillations			
Median (IQR)	5 (4-7)	6 (5-9)	0.12[a]
Total doses of epinephrine			<0.01[a]
Median (IQR)	3 (2-4)	5 (4-6)	
Time to first epi, minutes			
Median (IQR)	4 (3-5)	4 (2-6)	0.79[a]
EMS scene time, minutes			
Median (IQR)	35 (30-41)	32 (26-41)	0.21[a]
ED transport			0.01[b]
Yes	62.3% (38)	82.5% (52)	
No	37.7% (23)	17.5% (11)	
EMS transport time, minutes			0.51[a]
Median (IQR)	10.5 (8-15)	12 (8.5-17.5)	

[a]Wilcoxon rank sum test.
[b]Chi-square test.
Abbreviations: ED, emergency department; EMS,emergency medical services; IQR, interquartile range;

TABLE 2 Prehospital ROSC, 24-hour survival and survival to hospital discharge

	Esmolol administered N = 61	Control period N = 63	*P*-value
Prehospital ROSC			0.09
Yes	37.7% (23)	23.8% (15)	
No	62.3% (38)	76.2% (48)	
24-hour survival			0.92
Yes	24.6% (15)	25.4% (16)	
No	75.4% (46)	74.6% (47)	
Survival to hospital discharge			0.96
Yes	8.2% (5)	7.9% (5)	
No	91.8% (56)	92.1% (58)	

Abbreviation: ROSC, return of spontaneous circulation

throughout the study period, only ~20% of RVF patients in both the pre- and postesmolol groups received DSD. Although the current evidence for the efficacy of DSD in RVF is mixed,[15,16] it is possible that increased DSD use in conjunction with esmolol administration could potentially lead to improved outcomes. Also, because of relatively short EMS transport times and to minimize logistical complexities, we elected to defer initiation of an esmolol drip within our protocol. Two hospital-based studies suggesting improved outcomes with esmolol in RVF[8,9] used a 0.5 mg/kg loading dose bolus followed by a 0–100mcg/kg/min infusion. Future large-scale prospective EMS investigations of both the pairing of DSD with esmolol in addition to a protocolized initiation of an esmolol infusion after the initial bolus dose are warranted.

Finally, the role of prehospital administered epinephrine in OHCA for patients with RVF is unclear. Use of epinephrine for OHCA in general has been questioned with the results of the PARAMEDIC-2 trial[17] showing no increase in 30-day neurologically intact survival when using epinephrine in OHCA, as compared to placebo. Additionally, in consideration of patients with RVF, it is worth noting that fibrillated myocardium has significantly increased oxygen consumption relative to normal,[18,19] which exogenous catecholamines likely increase via beta adrenergic stimulation. With the underlying pathophysiology of RVF believed to be a result of endogenous catecholamine surge in response to active myocardial ischemia,[7] it bears consideration that an early esmolol administration protocol, without exogenous epinephrine, may be beneficial in OHCA, specifically for patients presenting with shockable rhythms and those who progress to RVF. In our study, the time from EMS arrival to esmolol administration was nearly 20 minutes, further evaluation of earlier B-blockade warrants future investigation.

In summary, this evaluation demonstrated feasibility of esmolol use for RVF within a ground-based EMS prehospital setting. Although statistical significance was not observed in this exploratory study, comparison with a historical control period suggests a potential association of esmolol with higher ROSC rates. Future work at a larger scale is needed to determine the effect of prehospital esmolol for RVF on neurologically intact hospital discharge.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

The authors have made substantial contributions to the conception and design of the study (Casey Patrick, Remle P. Crowe, Brad Ward, Kelley Rogers Keene, Robert Dickson), acquisition of data (Casey Patrick, Brad Ward, Ali Mohammed), analysis and interpretation of data (Casey Patrick, Brad Ward, Remle P. Crowe), and drafting/revising it critically for important intellectual content (Casey Patrick, Remle P. Crowe). All authors have read and approved the submitted manuscript, the manuscript has been submitted elsewhere nor published elsewhere in whole or in part, except as an abstract. Casey Patrick, the corresponding author, takes responsibility for the paper as a whole.

REFERENCES

1. Miraglia D, Miguel LA, Alonso W. Esmolol in the management of prehospital refractory ventricular fibrillation: a systematic review and meta-analysis. *Am J Emerg Med*;38:1921-1934.
2. Koster RW, Walker RG, Chapman FW. Recurrent ventricular fibrillation during advanced life support care of patients with prehospital cardiac arrest. *Resuscitation*. 2008;78:252-257.
3. Gao D, Sapp JL. Electrical storm: definitions, clinical importance, and treatment. *urrO pin Cardiol*. 2013;28:72-79.
4. Eifling M, Razavi M, Massumi A. The evaluation and management of electrical storm. *Tex Heart Inst J*. 2011;38:111-121.
5. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics—2019 Up-date: a Report From the American Heart Association. *Circulation*. 2019;139:e56-528.
6. Sakai T, Iwami T, Tasaki O, et al. Incidence and outcomes of out-of-hospital cardiac arrest with shock-resistant ventricular fibrillation: data from a large population-based cohort. *Resuscitation*. 2010;81:956-961.
7. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med*. 1997;336:1629-1633.
8. Driver BE, Debaty G, Plummer DW, Smith SW. Use of esmolol after failure of standard cardiopulmonary resuscitation to treat patients with refractory ventricular fibrillation. *Resuscitation*. 2014;85:1337-1341.

9. Lee YH, Lee KJ, Min YH, et al. Refractory ventricular fibrillation treated with esmolol. *Resuscitation*. 2016;107:150-155.
10. Killingsworth CR, Wei CC, Dell'Italia LJ, et al. Short-acting beta-adrenergic antagonist esmolol given at reperfusion improves survival after prolonged ventricular fibrillation. *Circulation*. 2004;109:2469-2474.
11. Jingjun L, Yan Z, Weijie DongdongZ, Guosheng L, Mingwei B. Effect and mechanism of esmolol given during cardiopulmonary resuscitation in a porcine ventricular fibrillation model. *Resuscitation*. 2009;80:1052-1059.
12. Cammarata G, Weil MH, Sun S, Tang W, Wang J, Huang L. Beta1-adrenergic blockade during cardiopulmonary resuscitation improves survival. *Crit Care Med*. 2004;32:S440-3.
13. Lewis M, Bromley K, Sutton CJ, et al. Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back!. *Pilot Feasibility Stud*. 2021;7:40.
14. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet*. 2020;396:1807-1816.
15. Cheskes S, Dorian P, Feldman M, et al. Double sequential external defibrillation for refractory ventricular fibrillation: the DOSE VF pilot randomized controlled trial. *Resuscitation*. 2020;150:178-184.
16. Beck LR, Ostermayer DG, Ponce JN, Srinivasan S, Wang HE. Effectiveness of prehospital dual sequential defibrillation for refractory ventricular fibrillation and ventricular tachycardia cardiac arrest. *Prehosp Emerg Care*. 2019;23:597-602.
17. Perkins GD, Ji C, Deakin CD, Quinn T, et al. PARAMEDIC2 Collaborators. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med*. 2018;379:711-721.
18. Mc KW, Gregg DE, Canney PC. Oxygen uptake of the nonworking left ventricle. *Circ Res*. 1958;6:612-623.
19. Berglund E, Monroe RG, Schreiner GL. Myocardial oxygen consumption and coronary blood flow during potassium-induced cardiac arrest and during ventricular fibrillation. *Acta Physiol Scand*. 1957;41:261-268.

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