# Does β-Blockade for Treatment of Refractory Ventricular Fibrillation or Pulseless Ventricular Tachycardia Improve Outcomes?

## TAKE-HOME MESSAGE

β-Blockade may be associated with improved rates of return of spontaneous circulation and survival with favorable neurologic outcome in patients with refractory ventricular fibrillation or pulseless ventricular tachycardia.

## METHODS

### DATA SOURCES

Meta-analysis authors performed a search of PubMed, Scopus, the Cumulative Index of Nursing and Allied Health, the Latin American and Caribbean Health Sciences Literature database, Google Scholar, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials. They included studies published between database inception through September 2, 2019, that evaluated β-blockade treatment in patients with refractory ventricular fibrillation or pulseless ventricular tachycardia. Meta-analysis authors evaluated the reference lists of all retrieved articles to identify other relevant studies. Authors also performed a search of ClinicalTrials.gov for any ongoing studies.

### STUDY SELECTION

Inclusion criteria for the meta-analysis consisted of all retrospective observational, prospective observational, or randomized controlled trials comparing β-blockade therapy (defined as β-blocker medication

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## Results

Comparison of outcomes in the β-blockade and control group.

| Outcome | No. of Studies (Patients) | β-Blockade, No. (%) | Control Group, No. (%) | OR (95% CI) | Certainty |
|---|---|---|---|---|---|
| Temporary ROSC | 2 (66) | 19/22 (86.5) | 14/44 (31.8) | 14.46 (3.63–57.57) | Low |
| Sustained ROSC | 2 (66) | 13/22 (59.1) | 10/44 (22.7) | 5.76 (1.79–18.52) | Very low |
| Survival to admission | 2 (66) | 13/22 (59.1) | 10/44 (22.7) | 5.76 (1.79–18.52) | Very low |
| Survival to discharge | 3 (115) | 26/49 (53.1) | 7/66 (10.6) | 7.92 (1.85–33.89) | Very low |
| Survival with a favorable neurologic outcome | 2 (66) | 6/22 (27.3) | 4/44 (9.1) | 4.42 (1.05–18.56) | Very low |

*OR*, Odds ratio; *CI*, confidence interval; *ROSC*, return of spontaneous circulation.

or sympathetic blockade) with a control group for the treatment of ventricular fibrillation or pulseless ventricular tachycardia refractory to traditional cardiac arrest therapies (eg, defibrillation, epinephrine, antiarrhythmic medications). The authors excluded case reports, case series, review articles, and nonhuman studies. Two investigators independently reviewed the abstracts of all identified articles and retrieved studies. They reviewed all abstracts meeting initial criteria as full articles. They included studies meeting eligibility criteria on full-text review by both investigators and resolved any discrepancies by consensus.

## DATA EXTRACTION AND SYNTHESIS

The primary outcome was return of spontaneous circulation.[1] Authors defined temporary return of spontaneous circulation as return of pulses for greater than 30 seconds but less than 20 minutes and sustained return of spontaneous circulation as return of pulses for greater than 20 minutes. Secondary outcomes included survival to admission, survival to discharge, survival with a favorable neurologic outcome, and adverse events. Two investigators independently abstracted data from the included studies. Authors obtained effect estimates from included studies by using odds ratios derived from multivariable models adjusting for measured confounders with 95% confidence intervals. The meta-analysis analyzed pooled data with the Mantel-Haenszel method. The authors assessed heterogeneity with $\chi^2$ and $I^2$ statistics. Two investigators also independently assessed studies for quality by using the Cochrane Collaboration Risk of Bias in Non-randomised Studies of

The meta-analysis included 3 studies comprising 115 patients. The setting was the emergency department (ED) for 2 studies,[4,5] whereas the other study did not clearly describe the clinical location.[6] One study was prospective and observational,[5] and 2 were retrospective and observational.[4,6] Two studies evaluated β-blockade in patients presenting with either out-of-hospital cardiac arrest or ED cardiac arrest with refractory ventricular fibrillation or pulseless ventricular tachycardia.[4,5] These studies used esmolol for the intervention.[4,5] One study evaluated post–myocardial infarction patients with electrical storm (defined as ≥20 episodes of ventricular fibrillation/ventricular tachycardia per day or ≥4 episodes per hour).[6] This study used esmolol, propranolol, or left stellate ganglion block as the intervention. Of the patients included in these 3 studies, the mean age was 56 years (SD 9.3 years), and 80.9% of patients were male. Two studies measured temporary and sustained return of spontaneous circulation and survival to admission and to discharge with a favorable neurologic outcome,[4,5] whereas all studies measured survival to discharge. β-Blockade use was associated with more favorable outcomes compared with that of the control group for all outcomes (Table). None of the studies assessed adverse events from therapy. In accordance with the ROBINS-I tool, investigators deemed 2 studies at overall serious risk of bias and 1 study at overall moderate risk of bias.[2] Based on the GRADE criteria, the overall certainty of the evidence was low to very low.[3]

## Commentary

Refractory ventricular fibrillation or pulseless ventricular tachycardia by definition does not respond to the standard advanced cardiac life support (ACLS) management of defibrillation, epinephrine, and antiarrhythmic agents. Two of the studies included in this meta-analysis defined refractory ventricular fibrillation and pulseless ventricular tachycardia as cardiac arrest from ventricular fibrillation or ventricular tachycardia not responsive to at least 3 defibrillation attempts, 3 mg of epinephrine, 300 mg of amiodarone, and at least 10 minutes of cardiopulmonary resuscitation.[4,5] Patients with refractory ventricular fibrillation or pulseless ventricular tachycardia can be difficult to manage, and they have worse outcomes compared with patients with ventricular fibrillation or pulseless ventricular tachycardia that is responsive to standard ACLS therapies.[7]

Epinephrine is a core treatment of ACLS care.[8] It leads to increased coronary perfusion through simulation of α-adrenergic receptors.[9] A recent meta-analysis of 15 randomized controlled trials evaluating the use of epinephrine versus controls in adults with out-of-hospital cardiac arrest concluded that standard or high doses of epinephrine should be used because epinephrine improves survival to hospital discharge.[10] However, the authors also concluded there was not an increase in favorable neurologic outcome with use of epinephrine.[10] Epinephrine therapy may have several

Interventions (ROBINS-I) tool.[2] The certainty of evidence was evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[3]

detrimental effects on patients in cardiac arrest. Through stimulation of α- and β-receptors, epinephrine results in an increase in sympathetic tone and may also contribute to increased myocardial oxygen consumption, myocardial dysfunction, new arrythmias, and an influx of calcium into the cytoplasm of myocardial cells.[9,11-15] β-Blockade may counteract some of these deleterious effects of β-adrenergic stimulation caused by repeated epinephrine dosing during ACLS resuscitation. The authors of this meta-analysis sought to evaluate whether β-blockade compared with control improved outcomes in patients in cardiac arrest caused by refractory ventricular fibrillation or pulseless ventricular tachycardia.[1]

Results of this meta-analysis suggest that β-blockade in patients with cardiac arrest caused by refractory ventricular fibrillation or pulseless ventricular tachycardia may lead to increased rates of return of spontaneous circulation, survival to discharge, and survival with a favorable neurologic outcome.[1] The agent used for β-blockade was esmolol in 2 of the studies,[4,5] with another study evaluating esmolol, propranolol, or left stellate ganglion block.[6]

This meta-analysis has several limitations.[1] There were no randomized controlled trials evaluating β-blockade versus control in patients with refractory ventricular fibrillation or pulseless ventricular tachycardia. All of the included studies were observational, significantly increasing the risk of confounding. Additionally, of the 3 studies identified, only 2 evaluated the use of β-blockade on ED patients with cardiac arrest from ventricular fibrillation or pulseless ventricular tachycardia refractory to standard ACLS therapies.[4,5] The other study evaluated post–myocardial infarction patients with electrical storm,[6] which may not be generalizable to an ED population. Although all studies assessed esmolol, one study also included left stellate ganglion block,[6] which may have introduced heterogeneity. Left stellate ganglion block is a foreign procedure to many emergency clinicians and is more commonly performed by cardiologists.[16] Not all patients received targeted temperature management, which is a vital component of post–cardiac arrest care. All included studies had relatively small sample sizes, with the largest including 49 patients,[6] leading to wide confidence intervals. Additionally, 81% of the patients in these studies were male, limiting the generalizability of these results in female patients. Given the observational design of these studies and small sample size, the meta-analysis authors determined all of the studies to be at moderate to serious risk of bias.

According to this meta-analysis, although the overall quality of evidence was low to very low, an association may exist between β-blockade and increased likelihood of return of spontaneous circulation, survival to discharge, and survival with a favorable neurologic outcome in patients presenting with cardiac arrest caused by refractory ventricular fibrillation or pulseless ventricular tachycardia. Given the paucity of studies found and included through screening of the literature in this meta-analysis and the low confidence of the results, further high-quality clinical investigations are necessary to evaluate the efficacy of β-blockade in refractory ventricular fibrillation and pulseless ventricular tachycardia before routine ED use.


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