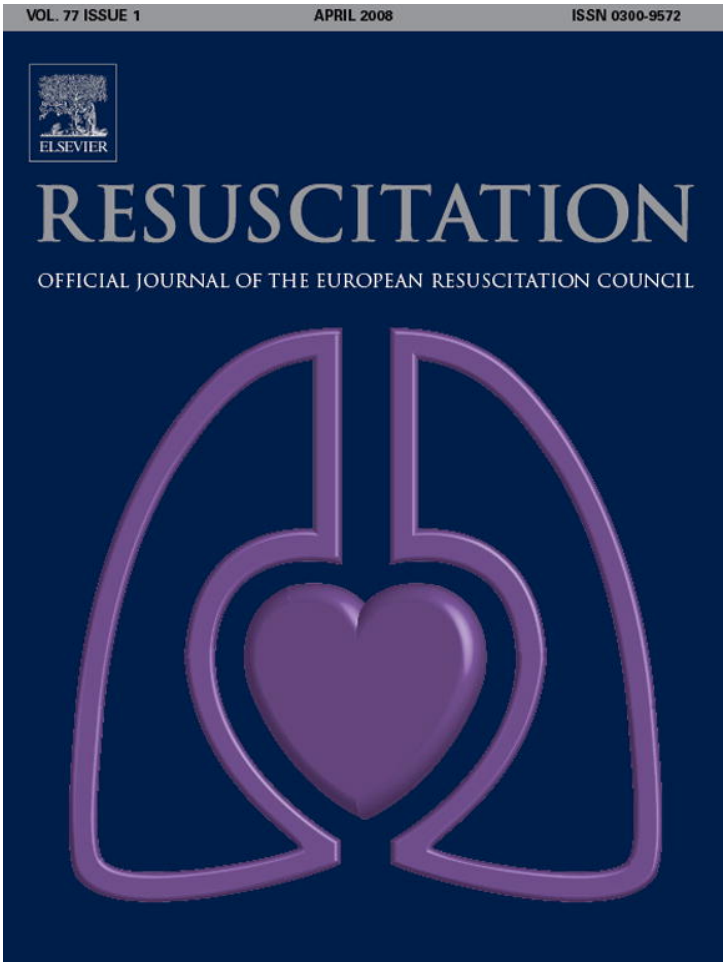

Resuscitation (2008) 77, 26—29

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/resuscitation

REVIEW ARTICLE

# Goal-directed hemodynamic optimization in the post-cardiac arrest syndrome: A systematic review☆,☆☆

Alan E. Jones[a], Nathan I. Shapiro[b], J. Hope Kilgannon[c], Stephen Trzeciak[c,d,*],

on behalf of the Emergency Medicine Shock Research Network (EMSHOCKNET) investigators

[a] *Department of Emergency Medicine, Carolinas Medical Center, Charlotte, NC, United States*
[b] *Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA, United States*
[c] *Department of Emergency Medicine, UMDNJ-Robert Wood Johnson Medical School at Camden, Cooper University Hospital, Camden, NJ, United States*
[d] *Department of Medicine, Division of Critical Care Medicine, UMDNJ-Robert Wood Johnson Medical School at Camden, Cooper University Hospital, One Cooper Plaza, Camden, NJ 08103, United States*

Received 19 October 2007; accepted 26 October 2007

**KEYWORDS**
Cardiac arrest;
Resuscitation;
Hemodynamics;
Cardiopulmonary resuscitation

**Summary**
*Aims:* The treatment recommendations from the 2005 International Consensus Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science (hosted by the American Heart Association) advocate a goal-directed treatment strategy for hemodynamic optimization after return of spontaneous circulation (ROSC) in post-cardiac arrest care. We performed a systematic review to (1) examine the available evidence for goal-directed hemodynamic support in the post-cardiac arrest syndrome, (2) determine the effect of such a treatment strategy on survival, and (3) define the specific hemodynamic goals, if any, that have been tested in clinical trials of post-cardiac arrest patients.
*Methods:* We conducted a systematic review of the Cochrane Library, MEDLINE, CINAHL, conference proceedings, clinical practice guidelines, and other sources using a comprehensive strategy to identify randomized controlled trials and quasi-experimental studies of goal-directed hemodynamic optimization in patients with ROSC after cardiac arrest.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2007.10.021.

☆☆ There was no other source of external funding for this study.

* Corresponding author at: UMDNJ-Robert Wood Johnson Medical School at Camden, Cooper University Hospital, One Cooper Plaza, D363 Camden, NJ 08103, United States. Tel.: +1 856 342 3342; fax: +1 856 968 8306.
*E-mail address:* trzeciak-stephen@cooperhealth.edu (S. Trzeciak).

0300-9572/$ — see front matter 
doi:10.1016/j.resuscitation.2007.10.021

*Results:* The comprehensive search yielded a total of 1184 potential publications and after a relevance screen, five studies were eligible for full article review. None of the studies were eligible for inclusion in the final analysis.
*Conclusions:* To date, no clinical trials have examined hemodynamic optimization in post-cardiac arrest patients. Although clinical acumen may support the concept that hemodynamic derangements after ROSC should be normalized, there is currently no evidence available to indicate the best strategy for goal-directed hemodynamic support. The current study indicates the need for future clinical investigations designed to determine both the efficacy of hemodynamic optimization in post-cardiac arrest patients and the best endpoints to target as part of a goal-directed strategy.


## Introduction

The concept of goal-directed hemodynamic optimization as a treatment strategy to improve clinical outcome in critically ill patients has been tested in numerous randomized clinical trials since the 1980s. The first report of efficacy data came from a clinical trial in heterogeneous peri-operative high-risk surgery patients,[1] but the strongest efficacy data to date, with respect to improvement in survival, was demonstrated in patients with severe sepsis and septic shock.[2] Given that after return of spontaneous circulation (ROSC), the immediate post-cardiac arrest period may be characterized by profound hemodynamic instability due to reversible myocardial stunning and a robust systemic pro-inflammatory response,[3–6] it is a logical hypothesis that post-cardiac arrest patients may benefit from a goal-directed hemodynamic optimization treatment strategy as part of post-resuscitation care.

The 2005 International Consensus Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations advocates a goal-directed hemodynamic support strategy for post-cardiac arrest patients.[7] The committee acknowledged that the data supporting this recommendation is extrapolated from other disease processes (i.e. Level of Evidence 7), most notably septic shock.[2] Although the recommendation did not explicitly state specific hemodynamic goals or endpoints of resuscitation that clinicians should target as part of a goal-directed treatment strategy, the recommendation did include a directive that ''providers should normalize oxygen content and oxygen transport'' variables (similar to goal-directed therapy for septic shock[2]).[7] The broad nature of such a directive potentially could be challenging for clinicians who, in an attempt to implement the consensus recommendation in practice, would need to select specific hemodynamic goals or endpoints of resuscitation (e.g. mixed venous oxygen saturation) to target as part of goal-directed hemodynamic optimization.

In this systematic review we aimed to (1) examine the available evidence for goal-directed hemodynamic support in the post-cardiac arrest syndrome, (2) determine the effect of such a treatment strategy on survival, and (3) identify the specific hemodynamic goals (e.g. optimization of cardiac filling pressure, arterial pressure, cardiac output, or oxygen transport variables), if any, that have been tested in clinical trials of post-cardiac arrest patients.

## Materials and methods

### Search strategy for identification of studies

We followed a written protocol that was finalized prior to beginning the study. We searched the Cochrane Library, MEDLINE (1965—July 2007) and CINHAL (1982—July 2007) using the search terms (''post-resuscitation'' or ''post cardiac arrest'' or ''cardiac arrest'' or ''critical care'') and (''hemodynamics'' or ''resuscitation'' or ''resuscitation endpoints'' or ''oxygen delivery'' or ''goal-oriented therapy'' or ''goal-directed resuscitation'' or ''early goal-directed therapy'') and ''clinical trial''. To identify potential unpublished data we contacted two experts in the field of cardiac arrest resuscitation, we reviewed published practice guidelines for post-resuscitation care from 2000 to 2007, and searched websites containing details for clinical trial registration.

### Inclusion criteria

We considered studies eligible for review if they were randomized controlled trials or quasi-experimental studies (prospective before-and-after trials or controlled prospective before-and-after trials) in adults with ROSC after cardiac arrest who were treated with (1) a clearly defined intervention consisting of a structured cardiovascular resuscitation protocol administered to achieve pre-defined hemodynamic endpoints and (2) a control group in which subjects received standard of care therapy. We also included studies of pre-hospital, surgical and critical care populations in order to extract data on subpopulations of post-cardiac arrest patients if there were clearly definable criteria for cardiac arrest and data available for those subpopulations.

### Study selection and data abstraction

The titles and abstracts of identified studies were screened for eligibility by two independent reviewers (AEJ and ST). All studies deemed potentially relevant were obtained and the full manuscripts were reviewed for inclusion. Two reviewers abstracted data on patients, interventions and outcomes. Any disagreements in these processes were resolved by consensus.

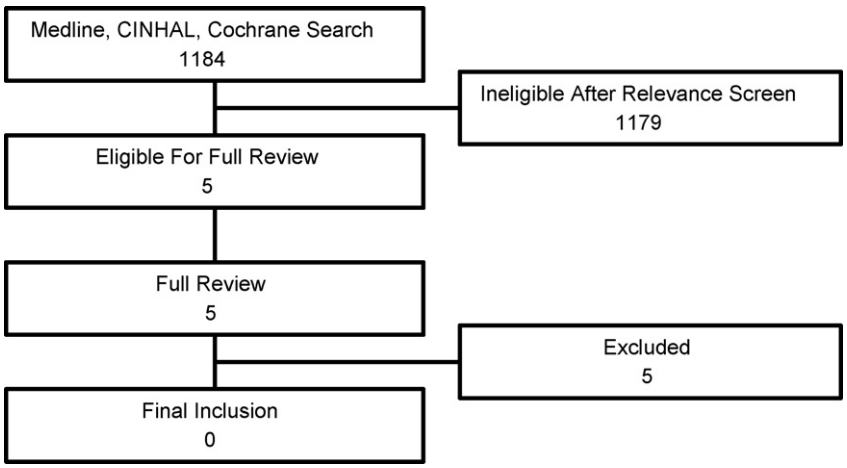


**Figure 1** Search, inclusion, and exclusion flow diagram.

### Assessment of quality

Study quality was assessed using two categories, (1) appropriate patient selection by identification of cardiac arrest using a standard definition and (2) the internal validity of the studies were assessed using the criteria proposed by Jadad et al. which evaluate quality of randomization, blinding and withdrawals.[8]

### Statistical analysis

The primary outcome of interest was in-hospital mortality. Thus, the raw data from each included study was used to calculate the effect size for each study. Heterogeneity was assessed using a Chi-square test, with $P < 0.10$ representing significance. The results were combined only if there was a lack of statistically significant heterogeneity among the included trials. A random-effects model was used to pool the results of only the randomized controlled trials included in the systematic review. Inter-observer agreement of the relevance screen was assessed using Cohen's kappa statistic.

## Results

The comprehensive search yielded a total of 1184 publications. After the relevance search (blinded inter-observer agreement $\kappa = 0.89$), we performed a complete article review on the remaining five studies. Four of the studies investigated hemodynamic optimization in critical care populations, but there were no identifiable cardiac arrest subpopulations. One study was a pre-hospital investigation that did not test a goal-oriented intervention. None of the studies were eligible for inclusion in the final analysis (Figure 1).

## Discussion

Post-cardiac arrest syndrome is a devastating disease with high morbidity and mortality.[9] After successful achievement of ROSC, $\geq$60% of patients do not survive to hospital discharge.[10] New research innovations such as therapeutic hypothermia for neuroprotection after cardiac arrest, applied after ROSC, have improved clinical outcome[11,12] including survival[11] in post-cardiac arrest patients. Due to this recent progress, a new concept for emergency cardiac care has emerged: post-ROSC interventions can be a vital link in the ''chain of survival'' from cardiac arrest.[13]

Post-cardiac arrest syndrome can manifest with hemodynamic instability due to (1) profound but reversible myocardial stunning[5] and (2) a robust systemic pro-inflammatory response secondary to global ischemia-reperfusion injury.[3,4] In other critically ill populations with major hemodynamic instability, most notably severe sepsis and septic shock, early goal-directed hemodynamic optimization targeting quantitative endpoints of resuscitation has improved survival.[2] Thus, it seems logical that hemodynamic optimization in the early post-ROSC phase of therapy potentially could improve clinical outcome in post-cardiac arrest patients.

In 2005, the International Consensus Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations made the following recommendation in the ''postresuscitation care'' guideline:

> Data extrapolated from a study of goal-directed therapy for sepsis (Level of Evidence [LOE] 1 for sepsis[2]; LOE 7 [extrapolated] for cardiac arrest) suggests that providers should try to normalize oxygen content and oxygen transport.[7]

Since the publication of this recommendation, some institutions have successfully implemented a goal-directed treatment strategy for post-cardiac arrest care (e.g. targeting normalization of central venous oxygen saturation[14]). However, one potential challenge facing clinicians trying to implement the consensus recommendation in practice is the broad nature of this directive. It leaves the clinician with the burden of selecting specific hemodynamic goals or endpoints of resuscitation to target as part of goal-directed hemodynamic optimization. Thus, our objectives in performing this review were to not only examine the available evidence supporting a goal-directed hemodynamic support strategy in the post-cardiac arrest syndrome, but

also to define the specific hemodynamic goals that clinicians should target. Using a comprehensive search strategy, we were unable to identify any clinical trials that have examined the effect of hemodynamic optimization on outcome in post-cardiac arrest patients. Furthermore, we were unable to identify any available data to guide the selection of predefined hemodynamic endpoints of resuscitation post-ROSC. Although clinical acumen supports the concept that hemodynamic derangements after ROSC should be normalized, there is currently no evidence available to indicate the best strategy and endpoints for goal-directed hemodynamic support. Even if it is assumed reasonable to extrapolate about the efficacy of hemodynamic optimization from the available evidence in other disease processes, the optimal hemodynamic variables to target remain unknown.

This study highlights the need for future controlled clinical trials designed to determine both the efficacy of hemodynamic optimization in post-cardiac arrest patients as well as the optimal endpoints of resuscitation that, when coupled with current state-of-the-art post-ROSC interventions,[11,12] could improve survival beyond what is presently observed.

## Conclusions

To date, no clinical trials have examined hemodynamic optimization in post-cardiac arrest patients, and there is currently no evidence available to indicate the best strategy for goal-directed hemodynamic support. The current study indicates the need for future controlled clinical trials designed to determine both (1) the efficacy of hemodynamic optimization in post-cardiac arrest patients and (2) the best endpoints to target as part of a goal-directed strategy.

## Conflict of interest

None.

## Acknowledgements

Dr. Jones and Dr. Shapiro are supported by grants from the National Institute of General Medical Sciences [K23GM76652 (Jones) and 1P50GM076659-01 (Shapiro)]. Dr. Trzeciak is supported by a grant from the American Heart Association (0530152N).

## References

1. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988;94(6):1176—86.
2. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368—77.
3. Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a ''sepsis-like'' syndrome. Circulation 2002;106(5):562—8.
4. Adrie C, Laurent I, Monchi M, Cariou A, Dhainaou JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? Curr Opin Crit Care 2004;10(3):208—12.
5. Laurent I, Monchi M, Chiche JD, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 2002;40(12):2110—6.
6. Vasquez A, Kern KB, Hilwig RW, Heidenreich J, Berg RA, Ewy GA. Optimal dosing of dobutamine for treating post-resuscitation left ventricular dysfunction. Resuscitation 2004;61(2):199—207.
7. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: Part 7.5. Postresuscitation support. Circulation 2005;112(Dec):IV-84—8.
8. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1—12.
9. Negovsky VA. The second step in resuscitation—the treatment of the post-resuscitation disease. Resuscitation 1972;1(1):1—7.
10. Stiell IG, Wells GA, Field B, et al. Advanced cardiac life support in out-of-hospital cardiac arrest. N Engl J Med 2004;351(7):647—56.
11. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549—56.
12. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346(8):557—63.
13. Langhelle A, Nolan J, Herlitz J, et al. Recommended guidelines for reviewing, reporting, and conducting research on post-resuscitation care: the Utstein style. Resuscitation 2005;66(3):271—83.
14. Center for Resuscitation Science (University of Pennsylvania). Post-cardiac arrest early goal-directed therapy. Accessed December 5, 2007, at http://www.med.upenn.edu/resuscitation/hypothermia/images/HypothermiaDiagrams.pdf.