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Review article

Systematic review and meta-analysis of hemodynamic-directed feedback during cardiopulmonary resuscitation in cardiac arrest☆

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ABSTRACT

Background/objective: Physiologic monitoring of resuscitative efforts during cardiac arrest is gaining in importance, as it provides a real-time window into the cellular physiology of patients. The aim of this review is to assess the quality of evidence surrounding the use of physiologic monitoring to guide cardiopulmonary resuscitation (CPR), and to examine whether the evidence demonstrates an improvement in patient outcome when comparing hemodynamic-directed CPR versus standard CPR.
Methods: Studies were obtained through a search of the PubMed, Embase and Cochrane databases. Peer-reviewed randomized trials, case–control studies, systematic reviews, and cohort studies that titrated CPR to physiologic measures, compared results to standard CPR, and examined patient outcome were included.
Results: Six studies met inclusion criteria, with all studies conducted in animal populations. Four studies examined the effects of hemodynamic-directed CPR on survival, with 35/37 (94.6%) animals surviving in the hemodynamic-directed CPR groups and 12/35 (34.3%) surviving in the control groups ($p < 0.001$). Two studies examined the effects of hemodynamic-directed CPR on ROSC, with 22/30 (73.3%) achieving ROSC in the hemodynamic-directed CPR group and 19/30 (63.3%) achieving ROSC in the control group ($p = 0.344$).
Discussion/conclusion: These results suggest a trend in survival from hemodynamic-directed CPR over standard CPR, however the small sample size and lack of human data make these results of limited value. Future human studies examining hemodynamic-directed CPR versus current CPR standards are needed to enhance our understanding of how to effectively use physiologic measures to improve resuscitation efforts and ultimately incorporate concrete targets into international resuscitation guidelines.

Introduction

Cardiac arrest is a life threatening medical emergency that continues to affect approximately 40,000 individuals in Canada each year.[1] While advancements have been made in recent years to improve resuscitation efforts, survival rates still remain low with only 10% surviving out-of-hospital cardiac arrests (OHCA) and 23% surviving in-hospital cardiac arrests (IHCA).[1] Since 2005, emphasis in resuscitative care has been placed on administering high-quality cardiopulmonary resuscitation (CPR) that meets international guidelines.[2] Chest compressions guided by feedback to ensure an adequate depth (≥5 cm) and rate (≥100 compressions min^{-1}) have been associated with increased survival based on large observational datasets.[2–4] However, the effect resuscitative efforts have on patient physiology, specifically on cardiac output and coronary and cerebral perfusion, is unclear. Physiologic monitoring at the time of an arrest is gaining in importance, as it provides a real-time window into the cellular physiology of the patient, and is likely to be sensitive to small changes that may more accurately guide resuscitative efforts.[5] They may have the potential to help improve patient outcomes through implementing therapeutic targets that can directly guide CPR efforts.

Currently, there are several physiological measures that can be monitored in real-time during CPR. Measures such as end-tidal carbon dioxide ($ETCO_2$), which is an indirect correlate of cardiac output, are commonly available to rescuers performing CPR in cardiac arrest patients,[6] while other monitoring tools such as near-infrared spectroscopy (NIRS) to measure cerebral perfusion have

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yet to be widely implemented.[4,7] Nonetheless, the 2010 American Heart Association (AHA) guidelines state that while $ETCO_2$ monitoring may help assess CPR quality and facilitate recognition of a return of spontaneous circulation (ROSC), no therapeutic targets are recommended as its relationship with survival and compression metrics, including chest compression depth, rate and fraction, is unclear.[8] Even less guidance is available for other physiologic monitoring tools due to poorer quality of evidence. This highlights a significant knowledge gap, as the use of physiologic monitoring to guide resuscitative efforts may be the next step forward in improving resuscitation strategies and patient survival. The aim of this review is to examine the quality of evidence surrounding the use of physiologic monitoring to guide CPR and to look at whether the evidence demonstrates an improvement in outcome (survival, ROSC, etc.) when comparing hemodynamic-directed CPR versus standard CPR.

Methods

This systematic review was carried out in accordance with the Preferred Reporting of Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) statement. Studies included in this review were obtained through a search of the PubMed (January 1946 to March 6, 2015), Embase (1947 to March 6, 2015) and the Cochrane Library (up to March 6, 2015). A comprehensive search strategy was designed to retrieve studies that were aimed at answering the following question: "Among individuals who are in cardiac arrest in any setting, does physiological feedback regarding CPR quality, compared with no feedback, change survival with favorable neurological/functional outcome at discharge and/or survival only at discharge and/or ROSC?" The search strategies used a combination of medical subject headings and keywords for cardiac arrest and cardiopulmonary resuscitation, combined using the Boolean operator "AND" with search terms such as physiologic monitoring, physiologic feedback, end-tidal carbon dioxide, near-infrared spectroscopy capnography, arterial diastolic pressure, hemodynamic directed, intrathoracic pressure, cerebral oximetry, and blood gas analysis. In order to locate cases where patient outcomes were assessed, search terms such as treatment outcome, survival, and ROSC were added. The complete search strategy used for each database can be found in Appendix A.

The searches were run on March 6, 2015 and included both animal and human studies, with no limitations placed on publication date, language or age. Peer-reviewed randomized trials, case–control studies, systematic reviews, and cohort studies were included, while case reports, editorials, letters and comments were excluded. Independently and in duplicate, two authors screened the titles and abstracts generated by the search to exclude any studies where CPR was not guided by physiologic measures, where outcomes such as ROSC or survival were not assessed, and where a control group that implemented standard CPR protocols not guided by physiologic measures was missing. After the initial screen, full manuscripts were reviewed to further exclude any studies that did not directly address the question being studied in this review. Due to the limited number of studies meeting the inclusion criteria, abstracts without full articles that directly addressed the question were also included in the analyses, along with studies that used pediatric populations. Several of the studies meeting inclusion criteria were carried out by the same research groups, however there was no overlap in subjects between these studies and therefore no subjects were included multiple times in the analyses.

A two-sample Student *t*-test for independent samples with the assumption of unequal variances was used to compare the effects of CPR with or without hemodynamic feedback on mean rates of ROSC and survival. A $p < 0.01$ was considered significant. The risk of bias across studies and quality of results generated from these studies were assessed based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.

Results

The search strategy used in this review generated a total of 2200 studies, and after duplicates were removed, a total of 1758 studies remained (Fig. 1). After the titles and abstracts were reviewed to determine inclusion, 37 studies were identified for full manuscript review. Kappa values for the two reviewers at the selection of abstracts and manuscripts were 1.00. Twenty-seven of the 37 studies were excluded due to having CPR protocols that were not directly targeted to physiologic measures, three studies were excluded on the basis of missing a control group that received standard CPR, and one study was excluded due to having duplicate study subjects used in a subsequent manuscript, leaving only six studies that met all inclusion criteria. Four of these six studies examined the effects of hemodynamic-directed CPR on survival,[9–12] while the other two studies examined the effects of hemodynamic-directed CPR on ROSC.[13,14] The characteristics of the studies meeting the inclusion criteria are outlined in Table 1.

The four studies examining effects of hemodynamic-directed CPR on survival all had identical CPR protocols implemented, as they were each carried out by the same research group, however different cohorts of animals were used in each study.[9–12] The hemodynamic-directed CPR groups had chest compression depth titrated to a systolic blood pressure (SBP) of 100 mmHg and administered vasopressors targeted to maintain a coronary perfusion pressure (CPP) >20 mmHg. The groups without physiologic feedback maintained chest compression depth at 51 mm and administered doses of epinephrine as per the 2010 AHA guidelines. The animals studied were 3-month-old female swine. In three of the four studies, ventricular fibrillation was induced for seven minutes before CPR commenced,[10–12] whereas in the remaining study, animals underwent seven minutes of asphyxia followed by induction of ventricular fibrillation and initiation of CPR.[9] Pooling the results across the four studies showed that survival was 35/37 (94.6%) in the hemodynamic-directed CPR groups and 12/35 (34.3%) in the control groups, a statistically significant difference (OR 21.28, 95% CI 5.48–82.69, $I^2 = 0\%$, $p < 0.001$).

The two studies that examined the effects of hemodynamic-directed CPR on ROSC were both carried out by Hamrick et al., however the two study protocols differed slightly.[13,14] In the earlier study (2011), the control group was blinded to $ETCO_2$ and administered chest compressions at a rate of 100 compressions min^{-1} and a depth correlating with 1/3 of the anteroposterior diameter, whereas in the later study (2014), the control group had chest compressions that were optimized with video and audio feedback to maintain current AHA standards of depth ≥ 5 cm and ≥ 100 compressions min^{-1}. In the hemodynamic-directed CPR group for both studies, compressions were administered to maximize $ETCO_2$, without any feedback on chest compression depth or rate. The animals used in both these studies were 2 kg piglets, representing a pediatric population. The total number of animals that achieved ROSC in these studies was 22/30 (73.3%) in the hemodynamic-directed CPR group and 19/30 (63.3%) in the control group, which was not a statistically significant difference (OR 1.59, 95% CI 0.53–4.75, $I^2 = 0\%$, $p = 0.344$). Since the protocol differed slightly in the control group, it is important to note that in the earlier study where compressions were not optimized by video and audio feedback, 6/10 (60%) animals in the control group achieved ROSC,[14] whereas in the later study that did have this chest