The use of resuscitative endovascular balloon occlusion of the aorta (REBOA) for non-traumatic cardiac arrest: A review

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Abstract
Resuscitative endovascular balloon occlusion of the aorta (REBOA) has been proposed as a novel approach to managing non-traumatic cardiac arrest (NTCA). During cardiac arrest, cardiac output ceases and perfusion of vital organs is compromised. Traditional advanced cardiac life support (ACLS) measures and cardiopulmonary resuscitation are often unable to achieve return of spontaneous circulation (ROSC). During insertion of REBOA a balloon-tipped catheter is placed into the femoral artery and advanced in a retrograde manner into the aorta while the patient is undergoing cardiopulmonary resuscitation (CPR). The balloon is then inflated to fully occlude the aorta. The literature surrounding the use of aortic occlusion in non-traumatic cardiac arrest is limited to animal studies, case reports and one recent non-controlled feasibility trial. In both human and animal studies, preliminary data show that REBOA may improve coronary and cerebral perfusion pressures and key physiologic parameters during cardiac arrest resuscitation, and animal data have demonstrated improved rates of ROSC. Multiple questions remain before REBOA can be considered as an adjunct to ACLS. If demonstrated to be effective clinically, REBOA represents a potentially cost-effective and generalizable intervention that may improve quality of life for patients with non-traumatic cardiac arrest.

KEYWORDS
arrhythmias cardiac, cardiopulmonary resuscitation, endovascular procedures, heart arrest, intra-aortic balloon pumping, resuscitation, therapeutic occlusion
Cardiac arrest affects >500,000 adults each year in the United States and fewer than 10% survive to hospital discharge.\textsuperscript{1} Despite advances in technology and management of cardiac arrest over the past decades, patient-centered outcomes have remained frustratingly poor.\textsuperscript{1} During non-traumatic cardiac arrest (NTCA), traditional advanced cardiac life support (ACLS) interventions are frequently unable to achieve return of spontaneous circulation (ROSC).\textsuperscript{2} Chest compressions provide only 20%–30% of baseline cardiac output despite proper technique and ideal conditions.\textsuperscript{3} The limited blood flow generated during cardiopulmonary resuscitation (CPR) fails to adequately distend the aorta and sufficiently increase aortic diastolic pressure, the principal determinant of coronary perfusion pressure (CPP) and myocardial blood flow.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) was originally developed as a hemorrhage control technique to manage non-compressible truncal bleeding. It is most frequently employed to temporize the shock state of trauma patients with intra-abdominal hemorrhage.\textsuperscript{4} A balloon-tipped catheter is inserted into the femoral artery and advanced in a retrograde manner into the aorta. The balloon is then inflated to occlude the aorta to maximize perfusion to organs proximal to the balloon and minimize any distal flow to slow blood loss.\textsuperscript{5} REBOA is a less invasive alternative to resuscitative thoracotomy and aortic cross-clamping when used in traumatically injured patients, although the evidence surrounding its efficacy in trauma is mixed and lacking randomized trial data.\textsuperscript{6}

Aortic occlusion with REBOA may improve myocardial and cerebral blood flow by restricting cardiac output to the thoracic aortic vasculature. Given these advantageous physiologic changes, REBOA has been proposed as a novel intervention for treatment of NTCA. The use of REBOA in conjunction with closed chest CPR, shown in Figure 1, may improve aortic pressure, CPP, and cerebral blood flow. This would effectively increase the efficiency of CPR and would provide emergency physicians with a unique mechanism to optimize conditions for ROSC and neurologically intact survival.

This article reviews the use of REBOA during NTCA and animal and human data involving REBOA and discusses the future of REBOA for NTCA. The EMBASE and SCOPUS databases were searched for relevant articles published from 1946 to May 2020. Key words used in the search were composed of combinations of “aortic balloon occlusion,” “REBOA,” and “cardiac arrest.” Abstracts were evaluated by the last author and all relevant papers were included in this review. References for each paper identified were scrutinized for any articles involving the use of REBOA in NTCA that were not identified in the initial search. Given the growing experience of REBOA for use in trauma, it provides a relevant analogue for a discussion of NTCA and will be referenced. However, in light of the distinct differences in the epidemiology of pathophysiology of trauma and NTCA, the detailed use of REBOA for traumatically injured patients is outside the scope of this review.

2 CARDIAC ARREST PHYSIOLOGY

Normally, coronary blood flow occurs primarily during diastole and is largely regulated by local tissue oxygen demand and microvascular autoregulatory mechanisms over the physiologic range of aortic pressure.\textsuperscript{7} In cardiac arrest states, profound tissue hypoxia results in complete microvascular dilatation and the principal driver of coronary blood flow is the pressure gradient across the coronary vasculature.\textsuperscript{8} This CPP is defined as the aortic pressure minus the right atrial pressure.\textsuperscript{9} Although an absence of myocardial contractions allows for
continuous coronary blood flow, research has shown CPP is greatest during the relaxation phase of chest compressions.9-11

During NTCA, cardiac output ceases, blood pools within the venous system, and peripheral arteries progressively dilate as CPP drops toward zero. The goal of traditional ACLS interventions is to increase CPP to promote ROSC. Studies have demonstrated that a sustained CPP above 15 mmHg during NTCA is highly predictive of increased rates of ROSC and survival.9,12,13 Traditional interventions are often unable to generate a CPP >15 mmHg even under optimal conditions.14 CPR blood flow is marginal; it can take up to 60 seconds of CPR to generate a positive CPP and 90 seconds to obtain a CPP >15 mmHg.9,15 Furthermore, intravenous epinephrine, recommended to increase CPP, has not yielded improved neurologic outcomes.16,17 Given these shortcomings, NTCA mortality rate has been largely unchanged for decades.18 The dearth of effective standard therapies, combined with improvements in intravascular device technology, has driven researchers to consider novel therapies such as REBOA as adjuncts to traditional ACLS.5

3 | REBOA DEPLOYMENT DURING CPR

REBOA catheterization can be performed while the chest, head, and upper extremities remain accessible to others to perform CPR and ACLS interventions.19 The common femoral artery is accessed using point-of-care ultrasonography and Seldinger technique.5 In the hands of an experienced practitioner, REBOA can be deployed by a single physician in approximately 5 to 10 minutes.20

The REBOA catheter is advanced retrograde into 1 of 3 zones of the aorta: Zone 1, the descending thoracic aorta between the left subclavian artery and the celiac axis; Zone 2, the paravisceral aorta from the celiac axis to the renal arteries; and Zone 3, the infrarenal aorta.21 Zone 1 placement is currently suggested for NTCA, as shown in Figure 2. The ER-REBOA catheter (Prytime Medical, Boerne, TX), the most common device currently in use, can be placed without fluoroscopy based upon an estimated distance using markers integrated into the catheter shaft.22 By contrast, over-the-wire catheters, such as the Coda Balloon Catheter (Cook Medical, Bloomington, IN) or REBOA Balloon Kit (Reboa Medical, Norway), are inserted after the depth of a guidewire tip has been confirmed radiographically.23,24 Blind placement technique using anatomic landmarks and estimated distance has been developed for the use of REBOA in trauma patients.25,26 This blind technique is likely adequate for use during NTCA and is currently in use in a Phase 1 clinical trial at Yale University.27

Once in the desired position the balloon at the tip of the REBOA catheter is inflated with a radiopaque solution, fully occluding the aorta. The radiopaque solution allows physicians to confirm REBOA placement on fluoroscopy or plain film imaging, although confirmation may be possible using ultrasound.28,29 If ROSC is obtained the balloon can be deflated with the REBOA catheter remaining in place. After the catheter is removed, the arterial introducer sheath may be used for arterial pressure monitoring and cardiac catheterization or upsized for extracorporeal membrane oxygenation (ECMO). For large REBOA catheters (>8 Fr), vascular repair may be required once removed, although this is much less likely for smaller catheters.30

4 | REBOA IN ANIMAL NON-TRAUMATIC CARDIAC ARREST

The majority of REBOA research is performed in swine models of ventricular fibrillation, as swine cardiac and aortic anatomy is similar to humans.31 The hemodynamic benefits of REBOA in CPR were
first outlined over 20 years ago.\textsuperscript{32,33} Multiple studies have shown thoracic aortic occlusion improves cerebral and coronary perfusion pressures, coronary blood flow, end-tidal carbon dioxide, and overall mortality.\textsuperscript{32,34-39} In one notable study of adult swine, during alternating periods of intra-aortic balloon inflation and deflation, balloon inflation increased CPP by an average of 13.7 mmHg (60%) and coronary blood flow increased by 15.5 mL/min (8.5%).\textsuperscript{35} Of note, there is substantial variance in response to REBOA during cardiac arrest despite laboratory models attempting to control for factors that influence hemodynamics during CPR.

Traditionally animal studies have utilized Zone 1 placement of REBOA, as a more proximal level of occlusion would theoretically result in maximal hemodynamic benefit. Recent animal studies have further divided Zone 1 into 3 subzones (a-c). Occlusion in Zone 1c (at the level of the diaphragm) augmented proximal arterial pressures and reduced arterial lactate concentrations better than occlusion in Zone 1b (at the level of the heart).\textsuperscript{40} This may be because of impaired ventricular expansion due to the location of the balloon directly deep to the heart, although it is unclear if this finding will translate to human physiology.

Two recent studies published in 2020 have demonstrated improved proximal physiology with Zone 1 placement when compared to Zone 3 placement.\textsuperscript{41,42} Although Zone 3 occlusion would benefit visceral perfusion and possibly prevent ischemic injury, any hemodynamic benefit was transient or did not translate to improved outcomes.\textsuperscript{41,42}

5 | REBOA IN HUMAN NON-TRAUMATIC CARDIAC ARREST

The literature surrounding the use of aortic occlusion in human patients is limited to case reports and one recent non-controlled feasibility trial.\textsuperscript{19} The first description of aortic occlusion, from Deakin et al in 1996, describes 2 patients who suffered cardiac arrests with an intra-aortic balloon pump in place. Both patients underwent aortic occlusion through the continuous inflation of the intra-aortic balloon pump and had immediate increases in systolic, diastolic, and coronary perfusion pressure. Neither patient survived.\textsuperscript{43} The generalizability of this report is limited as one patient had infective endocarditis and the other was immediately post coronary artery bypass graft.

Thirteen years later in 2009, Aslanger et al described a case that may be more representative of the majority of NTCA patients. A 74-year-old female was taken to the cardiac catheterization laboratory for an acute myocardial infarction and suffered from a cardiac arrest during the procedure.\textsuperscript{44} After 25 minutes of traditional ACLS, she underwent aortic occlusion with an intra-aortic balloon pump while in asystole, followed by sustained ROSC 1 minute later. She was discharged from the hospital eventually and made a “good recovery.”\textsuperscript{44}

In June 2019, Coniglio et al reported on the first case where a REBOA catheter was used in the emergency department for NTCA as a bridge therapy to an intra-aortic balloon pump.\textsuperscript{45} Following aortic balloon inflation in the ED, the patient’s ETCO\textsubscript{2} increased from 8–20 mmHg, hemodynamics stabilized, and sustained ROSC was achieved. The REBOA catheter was replaced with an intra-aortic balloon pump. Unfortunately, the patient developed a post-cardiac arrest coagulopathy and ultimately died. However, this report demonstrates the potential effectiveness of REBOA in NTCA to increase coronary perfusion and act as a bridge to a more definitive intra-vascular therapy. In November 2019, a Norwegian group reported out-of-hospital deployment of REBOA in 10 NTCA subjects treated by helicopter emergency medical services.\textsuperscript{19} Femoral artery cannulation for REBOA was successful on first attempt in 8 of 10 patients and on second attempt in the 2 remaining patients. The cohort consisted of 7 men and 3 women aged 50–74 years old. Mean time from dispatch to balloon occlusion was 45.6 minutes, procedural time ranged from 8–16 minutes, and ETCO\textsubscript{2} increased a mean of 13 mmHg after 60 seconds of occlusion ($P < 0.001$). Similar to laboratory studies, the graph of ETCO\textsubscript{2} measurements for individual patients showed substantial variability with some patients having large increases in ETCO\textsubscript{2} whereas others showed little effect. This is the first report to demonstrate that REBOA is temporally associated with improvements in CPR quality as measured by ETCO\textsubscript{2}. Six of the 10 enrolled patients achieved ROSC (60%), 3 patients (30%) were admitted to the hospital, and 1 survived to hospital discharge with good neurologic outcome. In the patient who survived with a favorable neurologic outcome, investigators did not achieve aortic occlusion until 60 minutes into his asystolic NTCA. REBOA was again used as a rapidly deployable bridge therapy to a more definitive intervention and was converted to ECMO later in the patient’s course.

Emergency medicine investigators at Yale University are currently enrolling subjects in the first United States Phase I clinical trial of REBOA in out-of-hospital NTCA patients presenting to the ED.\textsuperscript{27} Investigators will measure real-time diastolic blood pressure and patients will have no-flow times that are more typical of those seen in urban populations. Two of 5 initial subjects have been enrolled at the time of this writing, each with immediate and sustained improvements in ETCO\textsubscript{2} and mean arterial blood pressure and transient ROSC in one. Despite this, both patients were in ventricular fibrillation that was refractory to antiarrhythmics and defibrillation and did not survive to hospital admission.

6 | CHALLENGES AND UNKNOWNS

REBOA placement carries a risk of significant vascular and ischemic injury, even in the hands of experienced physicians. In a large prospective trial of REBOA for traumatically injured patients at level 1 trauma centers in the United States, outcomes were favorable.\textsuperscript{20} Aortic occlusion was obtained in an average of 6.6 minutes, there was a low complication rate (2.2% pseudoaneurysm and 4.3% distal embolism), and REBOA had a similar survival rate to more invasive surgical techniques.\textsuperscript{20} Several additional retrospective trials have shown improvement in mortality with REBOA with low complication rates.\textsuperscript{6,46,47}

Other large retrospective trials have shown poorer outcomes with REBOA. In 2019 Bellal et al published a large, multicentered, retrospective analysis of case-matched outcomes involving REBOA...
the SAAP catheter, like REBOA catheter, is inserted via a femoral artery to the thoracic aorta and provide heart and brain perfusion during cardiac arrest. Although the SAAP catheter, like REBOA catheter, is inserted via a femoral artery to the thoracic aorta and provide heart and brain perfusion during cardiac arrest. Although the SAAP catheter, like REBOA catheter, is inserted via a femoral artery to the thoracic aorta and provide heart and brain perfusion during cardiac arrest. The variability in response to REBOA during cardiac arrest, seen in both laboratory studies and the Norwegian out-of-hospital clinical study, does not presently have a clear explanation. REBOA may augment CPP during cardiac arrest, but the primary driver of blood flow is providing high-quality chest compressions. Factors, such as downtime before CPR, body habitus, CPR quality, volume status, and upper body peripheral arterial vasomotor tone, may significantly influence the effect of REBOA during CPR. This variance and its effect on outcomes need further investigation.

7 | THE FUTURE OF CARDIAC ARREST

REBOA is being investigated to treat NTCA along with other advanced technologies, including selective aortic arch perfusion (SAAP) and ECMO. SAAP utilizes a large-lumen balloon catheter to occlude the thoracic aorta and provide heart and brain perfusion during cardiac arrest. Although the SAAP catheter, like REBOA catheter, is inserted via a femoral artery to the thoracic aorta, SAAP is primarily an extracorporeal perfusion intervention. After aortic occlusion is obtained, an external pump infuses oxygenated perfusate into the aortic arch in to improve oxygen delivery to critical organs. Thus, SAAP has more in common with ECMO than REBOA. Aortic occlusion with SAAP is primarily to direct perfusate flow preferentially to the heart and brain to promote ROSC and favorable neurological recovery, respectively. Laboratory models of both ventricular fibrillation and hemorrhage-induced cardiac arrest have shown high rates of ROSC. SAAP is presently undergoing regulatory review for clinical trial initiation.

ECMO has been used to treat refractory cardiac arrest since the 1980s. Although ECMO is primarily used in the pediatric population, its use for extracorporeal cardiopulmonary resuscitation (ECPR) has expanded in recent years. In a large retrospective trial of ECMO in NTCA, survival to hospital discharge was an impressive 29%. Although these results are promising, none of the studies involving ECMO in NTCA have utilized a prospective control group, making it difficult to determine the efficacy of this intervention. ECMO is resource intensive, associated with significant cost and requires multispecialty expertise for placement and management. Recent literature suggests ECMO may be cost effective, but it is not yet generalizable to most community EDs where the majority of cardiac arrests are treated. REBOA, by contrast, is lower cost and requires a skillset already mastered by emergency physicians. As demonstrated by Brede and Coniglio et al, REBOA may have a role in bridging patients to more advanced interventions such as ECMO, an intra-aortic balloon pump, or cardiac catheterization.

8 | CONCLUSION

REBOA is a novel technique for the management of NTCA. Work with animal models has shown that REBOA placement improves CPP and cerebral perfusion pressure and leads to increased rates of ROSC. Early feasibility human trials have shown promise and Phase 1 trials for REBOA in NTCA are currently underway. Unlike more resource-intensive interventions, REBOA is relatively low cost and requires a technical skillset that most emergency physicians have already mastered, making its widespread dissemination more feasible. REBOA for NTCA remains in its infancy and numerous questions remain about its feasibility, efficacy, and safety. If aortic occlusion with REBOA for NTCA is demonstrated to be effective in humans, the potential for change in clinical practice and improvement in quality of life is substantial.

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AUTHOR CONTRIBUTIONS

Study concept and design (Craig D. Nowadly, M. Austin Johnson, James I. Daley); drafting of the manuscript (Craig D. Nowadly, M. Austin Johnson, Guillaume L. Hoareau, James E Manning, James I. Daley); critical revision of the manuscript (Craig D. Nowadly, M. Austin Johnson, Guillaume L. Hoareau, James E Manning, James I. Daley); and approval of final manuscript (Craig D. Nowadly, M. Austin Johnson, Guillaume L. Hoareau, James E Manning, James I. Daley).

CONFLICTS OF INTEREST

Craig D. Nowadly. reports no conflict of interest. M. Austin Johnson, is a founder and stockholder of Certus Critical Care, Inc. Guillaume L. Hoareau. reports no conflict of interest. James E. Manning, is a co-
founder and stockholder of Resusitech, Inc. James I. Daley has received grant funding from Prytime Medical Devices Inc. and the American Heart Association.

DISCLAIMERS
The views expressed in this material are those of the authors, and do not reflect the official policy or position of the U.S. Government, the Department of Defense, or the Department of the Air Force.

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