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Clinical paper

Goal-directed cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest in the emergency Department: A feasibility study



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Abstract

Aim: To describe the feasibility of prospective measurement of intra-arrest diastolic blood pressure (DBP) and goal-directed treatment of refractory out-of-hospital cardiac arrest (OHCA) in the emergency department (ED).

Methods: Retrospective case series performed at an urban, tertiary-care hospital from 12/1/2018 – 12/31/2019. We studied consecutive adults presenting with refractory, non-traumatic OHCA treated with haemodynamic-targeted resuscitation that entailed placement of a femoral arterial catheter, transduction of continuous BP during CPR, and administration of vasopressors (1 mg noradrenaline) and, if applicable, Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA), to achieve DBP \geq 40 mmHg. Feasibility was measured by the success rate and time to achieve arterial catheterization and BP transduction. Additional outcomes included the change in DBP with vasopressor administration and occurrence of sustained ROSC.

Results: Goal-directed treatment was successfully performed in 8/9 (89%) patients. Arterial access required 1.5 (interquartile range (IQR) 1–2) attempts and BP transduction occurred within 10.5 ± 2.4 minutes of patient arrival. Noradrenaline slightly increased DBP (pre 21.6 ± 8.3 mmHg, post 26.1 ± 12.1 mmHg, $p < 0.025$), but only 4/23 (17%) doses resulted in DBP \geq 40 mmHg. REBOA was attempted in 2/8 (25%) patients and placed successfully in both cases. Three (37.5%) patients achieved ROSC, but none survived to hospital discharge.

Conclusions: In ED patients with refractory OHCA, measurement of DBP during CPR and titration of resuscitation to a DBP goal is feasible. Future research incorporating this approach should seek to develop haemodynamic-targeted treatment strategies for OHCA patients that do not achieve ROSC with initial resuscitation.

Keywords: Cardiopulmonary resuscitation, Out of hospital cardiac arrest, Hemodynamics, Early goal-directed therapy, Emergency services

Introduction

Despite several decades of clinical research focused on enhancing the delivery of cardiopulmonary resuscitation (CPR), only 25–30% of out of hospital cardiac arrest (OHCA) patients achieve sustained return of spontaneous circulation (ROSC) in the prehospital setting with current advanced cardiac life support (ACLS) techniques^{1–3}. Many of the remaining patients with refractory OHCA are transported to the emergency department (ED), where until recently, cardiac arrest care was neither more sophisticated nor more successful than

that provided in the prehospital setting^{4,5}. The development of diagnostic and therapeutic point-of-care ultrasound (US) and the implementation of bedside extracorporeal cardiopulmonary life support (ECLS) at select centres for cases of refractory ventricular fibrillation/ventricular tachycardia (VF/VT) have expanded emergency physicians' capabilities in caring for refractory OHCA^{6,7}. Nevertheless, additional treatment strategies for this population are needed to improve outcomes from this highly morbid condition.

Preclinical studies demonstrate that achievement of ROSC after cardiac arrest is strongly associated with the adequacy of myocardial blood flow achieved with CPR^{8–10}. During closed-chest compres-

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sions, coronary artery blood flow occurs during diastole/decompression as a result of the coronary perfusion pressure (CPP), defined as proximal aortic pressure – right atrial pressure^{8,9,11}. In a seminal human study, Paradis *et al.* inserted central venous and aortic pressure-transducing catheters during ED resuscitation and retrospectively measured CPP in 100 patients with refractory OHCA treated with standard ACLS, confirming the association between maximal diastolic CPP achieved during CPR and attainment of ROSC¹². Subsequently, multiple animal experiments in which CPR technique and vasopressor administration are prospectively titrated to achieve a goal CPP (>20 mmHg) after induced cardiac arrest have shown improved rates of ROSC and survival compared to uniformly applied, non-titrated, guideline-based resuscitation^{13,14}. In fact, recent society guidelines on CPR quality recommend titration of intra-arrest resuscitation to physiological parameters such as CPP, if available^{15,16}.

Nevertheless, clinical trials of such “goal-directed resuscitation” in OHCA have not been performed, in part because the de-novo insertion of vascular catheters and prospective measurement of CPP during CPR, while maintaining coordinated and effective patient resuscitation, is technically and logistically quite challenging. Measurement of intra-arrest femoral arterial diastolic blood pressure (DBP), which is highly concordant with proximal aortic DBP, is more feasible and has been successfully performed *post-hoc* in several studies of OHCA resuscitation^{17–19}. While this only establishes the afferent aspect of CPP, our current treatments for cardiac arrest (CPR, vasopressors) primarily target arterial, rather than central venous, pressure and prior studies have shown the association of femoral arterial DBP with ROSC to be nearly as strong as that of CPP^{12,20–22}. Thus, measurement of femoral arterial DBP during CPR, if done in real-time during resuscitation, could allow for arrest treatments to be titrated to achieving maximal coronary perfusion and possibly increase the likelihood of ROSC²³.

Along these lines, we describe our initial experience treating patients presenting to the ED with refractory OHCA using measurement of intra-arrest femoral DBP and goal-directed resuscitation targeted to optimizing DBP during CPR.

Methods

Study design and setting

We performed a retrospective, observational, case series study at an urban, academic-affiliated, tertiary-care hospital (Einstein Medical Centre) located in Philadelphia, Pennsylvania. Annual ED census is ~ 100,000 visits and annual OHCA volume is ~ 150 cases. ECLS is not available for OHCA at our institution.

Selection of participants

We enrolled consecutive, adult (≥ 18 years old) patients presenting to our ED from December 1, 2018 – December 31, 2019 with refractory, non-traumatic OHCA (ongoing CPR at the time of ED arrival) that had been treated by one of the authors with goal-directed resuscitation as part of clinical care. Only patients treated by one of the authors that had such treatment initiated were included; patients treated by other emergency physicians and patients treated by one of the authors that achieved ROSC or expired prior to hemodynamic-targeted care were not included. There were no speci-

fic exclusion criteria. Patients were identified and all data was collected retrospectively. The study was approved by the Institutional Review Board with a waiver of informed consent.

Goal-directed CPR treatment

All patients received initial ED resuscitation according to existing guidelines, specifically including manual CPR and administration of 1 mg adrenaline [epinephrine] IV/IO every 3–5 minutes¹⁶. As this study was a retrospective case series, a pre-defined treatment protocol for goal-directed resuscitation did not exist. Nevertheless, all enrolled patients were treated in a similar fashion, as described below.

As soon as possible after arrival, a right common femoral arterial line was placed under direct US guidance without interruption in CPR and continuous, invasive BP monitoring was commenced (details in [supplementary materials](#)). Diastolic BP during chest compressions was visualized/recorded in real-time (details in [supplementary materials](#)) and goal-directed resuscitation was performed targeting a DBP ≥ 40 mmHg. In lieu of standard adrenaline dosing and based upon the immediate availability of medications in our department, serial doses of 1 mg noradrenaline [norepinephrine] (1 mg/ml) IV/IO were administered at 60 second intervals with the goal of increasing DBP to ≥ 40 mmHg (details in [supplementary materials](#)). If the DBP increased to ≥ 40 mmHg, no additional vasopressors were given and the DBP was reassessed every 60 seconds. If the DBP did not increase or subsequently dropped below 40 mmHg, additional noradrenaline was administered (up to maximum of 4 doses). DBP values were recorded immediately prior to vasopressor administration and after dosing, the maximum DBP value achieved within the next 60 seconds was noted. Manual CPR was performed throughout the resuscitation in concordance with current guidelines and monitored using real-time audio-visual feedback (CPR Dashboard™, Zoll Medical Corporation, Chelmsford, MA, USA); chest compressions were not specifically titrated to DBP.

If the patient remained in arrest and the DBP remained < 40 mmHg after titrated vasopressor administration as above, they were assessed for mechanical augmentation of DBP using Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). This was only employed in cases of refractory arrest with prognostic factors positively associated with potential neurologically intact survival (witnessed arrest, ≤ 5 minutes of no-flow time, initial and current rhythm not asystole, favourable pre-morbid health characteristics, and total low-flow time ≤ 45 minutes). In such cases, contralateral common femoral arterial access was obtained, and an ER-REBOA (Prytime Medical, Boerne, TX) catheter was deployed in Zone I in the standard fashion (details in [supplementary material](#)) again targeting a DBP of ≥ 40 mmHg.

Subsequently, in patients who remained in arrest after 4 doses of noradrenaline +/- REBOA placement, resuscitation continued according to ACLS guidelines with resumption of standard adrenaline administration. Resuscitative efforts were discontinued in the usual fashion, according to the overall clinical judgement of the attending physician and treatment team.

Measurements and data analysis

Retrospective review of enrolled subjects' medical records was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines²⁴.

Prehospital data was collected from the Cardiac Arrest Registry to Enhance Survival (CARES) database, in which our institution and emergency medical services providers participate²⁵. In-hospital data was collected from the hospital electronic medical record. Variables including Utstein data elements, patient comorbidities, resuscitative treatments and intra-arrest vital sign measurements were recorded²⁶.

The primary outcome of the study was the feasibility of completion of the intra-arrest DBP measurement and goal-directed resuscitation. Feasibility was measured by the number of arterial line insertion attempts, time from ED presentation to catheter insertion, time from ED presentation to BP transduction and overall success rate of intra-arrest BP monitoring, vasopressor administration and if applicable, REBOA placement. Secondary outcomes included the change in DBP with vasopressor administration, occurrence of sustained ROSC, survival to hospital admission and survival to hospital discharge.

Descriptive statistics are presented using appropriate parameters based upon the distribution of the data [mean \pm standard deviation or median (interquartile range (IQR))]. Mean pre- and post-noradrenaline DBP values were compared using the paired, two-sample, Student's *t*-test.

Results

We initiated goal-directed resuscitation on 9 patients with refractory OHCA over the 13-month study period. In 1 patient, arterial access was unsuccessful prior to termination of resuscitation (catheter inserted, but through artery into vein on US confirmation), but in 8/9 (89%) it was successful. Characteristics of the 8 patients [mean age 63 ± 20 years, 5/8 (63%) male] are shown in Table 1. Cardiac arrest was witnessed in 6/8 (75%) with immediate CPR performed in 5/8 (62.5%). Initial rhythm was non-shockable in 6/8 (75%).

Table 2 shows the patient characteristics, treatments, and outcomes after ED arrival. Arterial access was obtained with 1.5 (1–2) attempts, on average 7.9 ± 1.2 minutes after patient presentation. Successful BP transduction and recording began 10.5 ± 2.4 minutes after patient arrival. Fifty individual DBP measurements (range 5–53 mmHg, mean 24.4 ± 11.5 mmHg) were obtained during CPR, 8 (16%) of which were ≥ 40 mmHg. Each patient had an average of 6 ± 4 DBP values recorded, however 2/8 (25%) patients achieved ROSC immediately after the initial DBP measurement. Fig. 1 displays the association between individual DBP values and the occurrence of ROSC within 60 seconds.

Six (75%) of the eight patients received one or more doses of noradrenaline [range 1–4, median 4 (2–4)]. DBP response to the 23 individual doses is displayed in Fig. 2. While there was a statistically significant increase in mean DBP with noradrenaline (pre 21.6 ± 8.3 mmHg, post 26.1 ± 12.1 mmHg, $p < 0.025$), only 4/23 (17%) doses resulted in a DBP increase of $\geq 25\%$ and 4/23 (17%) resulted in a post-administration DBP ≥ 40 mmHg.

REBOA insertion was attempted and successfully performed in 2 patients, both within 30 minutes of presentation. Full aortic occlusion was not appreciated on tactile feedback at a balloon volume of 25 cc in either case. In one patient, DBP increased from 5 to 40 mmHg; in the second patient, BP proximal to the balloon could not be transduced due to occlusion of the catheter lumen, most likely by blood clot. ROSC was not achieved in either case.

Table 1 – Patient and Arrest Characteristics.

Number of patients	8
Age, years	63 ± 20
Male	5 (63%)
Race	8
African American	(100%)
Arrest Location	3
Residence	(37.5%) 3
Street	(37.5) 2
Ambulance	(25%)
Witnessed Arrest	6 (75%)
Immediate CPR	5 (62.5%)
Initial rhythm	2
VF/VT	(25%) 3
PEA	(37.5%) 3
Asystole	(37.5%)
Prehospital airway	4
ETT	(50%) 2
SGA	(25%) 2
BVM	(25%)
Prehospital vascular access	3
IV	(37.5%) 3
IO	(37.5%) 2
None	(25%)
Prehospital adrenaline dose, mg	3.8 ± 3.1
Prehospital time, minutes	30 ± 23
Prehospital transient ROSC	2 (25%)
Data expressed as mean \pm standard deviation or median (interquartile range).	
CPR = cardiopulmonary resuscitation, VF/VT = ventricular fibrillation/ventricular tachycardia, PEA = pulseless electrical activity, ETT = endotracheal tube, SGA = supraglottic airway, BVM = bag-valve mask, IV = intravenous, IO = intraosseous, ROSC = return of spontaneous circulation	

Overall, sustained ROSC was achieved in 3/8 (37.5%) patients. Five (62.5%) patients achieved a maximum DBP ≥ 40 mmHg, of which 2 achieved ROSC. Three (37.5%) patients did not achieve a maximum DBP ≥ 40 mmHg, of which 1 achieved ROSC. There were no hospital survivors.

Discussion

In this limited case series, we found that prospective measurement of femoral arterial DBP during CPR was feasible in ED patients with refractory OHCA undergoing resuscitation in a real-world environment. Further, our results illustrate one possible individualized, haemodynamic-directed, treatment strategy targeted to achieving optimal intra-arrest DBP, with the goal of concurrently raising CPP and possibly increasing the likelihood of ROSC.

Measurement of invasive haemodynamic parameters during CPR in humans has been described in the intensive care unit (ICU), where arterial/venous catheters are already in place at the time of arrest^{19,20,27}. However, de-novo insertion of vascular pressure-transducing catheters in the ED for refractory OHCA has

Table 2 – Emergency Department Resuscitation, Treatment and Outcome.

Number of patients	8
Initial ED rhythm	2
VF/VT	(25%) 3
PEA	(37.5%) 3
Asystole	(37.5%)
ED airway management	4
Prehospital ETT	(50%) 4
ED ETT	(50%)
Arterial line insertion	1.5
Number of attempts	(1–2)
Time to insertion, min [^]	7.9 ± 1.2
Time to transduction, min [^]	10.5 ± 2.4
Total adrenaline dose prior to first DBP measurement, mg	5.9 ± 3.2
Initial DBP, mmHg	
Range	9–50
Mean	26 ± 13.7
Time from arrest to initial DBP, min [*]	31 ± 26
Noradrenaline dose, mg	4 (2–4)
Noradrenaline administration site	n = 6
Upper extremity IV	2 (33%)
Upper extremity IO	2 (33%)
Lower extremity IO	2 (33%)
Maximum DBP, mmHg	
Range	19–53
Mean	38.6 ± 12.7
Time from arrest to maximum DBP, min [*]	31 ± 28
REBOA Insertion	2 (25%)
Time to REBOA insertion, min [^]	24 ± 1.4
ED ROSC	3 (37.5%)
Hospital admission	3 (37.5%)
Hospital survival	0 (0%)

Data expressed as mean ± standard deviation or median (interquartile range). ED = emergency department, VF/VT = ventricular fibrillation/ventricular tachycardia, PEA = pulseless electrical activity, ETT = endotracheal tube, IV = intravenous catheter, IO = intraosseous needle, DBP = diastolic blood pressure, REBOA = resuscitative endovascular balloon occlusion of the aorta, ROSC = return of spontaneous circulation. [^]Times from ED presentation to associated events. ^{*}Only for witnessed arrests with known time of onset (n = 6).

only been described in a few prior studies, particularly by researchers at Henry Ford Hospital in the 1990s^{12,19,28,29}. There, a two-person, on-call research team performed catheter insertion (internal jugular or subclavian vein - landmark-guided, percutaneous Seldinger technique; femoral artery - open cutdown or landmark-guided, percutaneous Seldinger technique) while a separate clinical team managed ongoing resuscitation. They reported success rates of 87% (20/23) and 73% (22/30) for combined aortic/central venous catheterization and pressure transduction, requiring an average of 12–16 ± 6–7 minutes^{28,29}. For isolated arterial catheterization and BP transduction, performed by clinical personnel simultaneously managing the ongoing resuscitation, Sainio *et al.* reported 66% (69/104) success using landmark-guided, percutaneous Seldinger technique at either the radial or femoral artery, primarily in the setting of in-hospital cardiac arrest. Specific to the femoral artery location, catheterization time was 13 (IQR 9 – 18) minutes¹⁹. Our rate of success and time to femoral arterial catheterization and BP transduction were slightly better than reported previously under similar scenarios, possibly because of the use of real-time US guidance and specific provider training in emergent vascular access skills^{30,31}.

While intra-arrest CPP is the ideal haemodynamic parameter upon which to target goal-directed resuscitation, prospective CPP measurement was not feasible in our environment. Insertion of upper body central venous catheters during manual CPR is challenging due to the proximity of the introducer needle to the compressors' moving hands and it requires a separate, procedurally skilled provider from the individual obtaining femoral arterial access if it is to be accomplished in a timely fashion. Additionally, prospective display of CPP requires monitoring technology capable of digitally subtracting central venous from arterial pressure waveforms in real-time, which is not available at the bedside. Hence, we chose to obtain and measure only arterial DBP during CPR to guide goal-directed resuscitation. Further, we employed only manual CPR, and not mechanical, to allow for accurate prospective measurement of end-diastolic blood pressure, which is very challenging to perform with the naked eye with the BP waveform characteristic of most mechanical compression devices (details in [supplementary materials](#))^{11,18}.

As this was a feasibility study, interpretation of the haemodynamic values and their response to our goal-directed treatment algorithm is limited by the small sample size. Our initial DBP

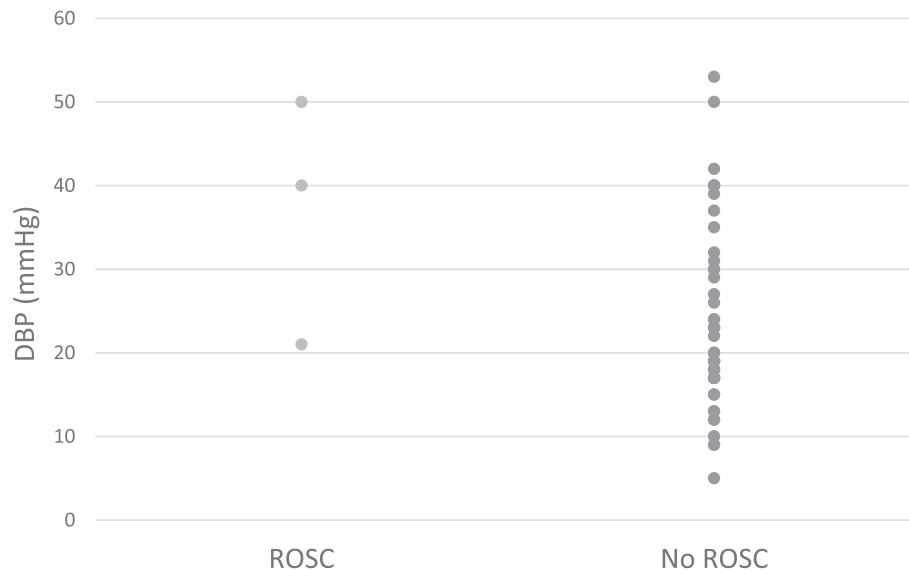


Fig. 1 – Association between diastolic blood pressure and return of spontaneous circulation. DBP = diastolic blood pressure, ROSC = return of spontaneous circulation. Occurrence of ROSC classified immediately after a given diastolic blood pressure measurement (n = 50 measurements).

measurements (26 ± 13.7 mmHg) were similar to those obtained in prior studies of refractory OHCA ^{12,19,28,29}. The association between DBP and subsequent ROSC quantifiable from our data is limited by the scarcity of ROSC occurrence (Fig. 1). We chose to target a $DBP \geq 40$ mmHg based upon the mean DBP attained by subjects that achieved ROSC in the Paradis *et al.* study (35.2 ± 11.5 mmHg), but the optimal DBP or CPP target during CPR is currently unknown. Both animal and human data indicate a minimum CPP threshold (15–20 mmHg) below which ROSC is very unlikely to occur, but a similar cut-off for DBP and to what extent CPP/DBP should be raised to optimize the chance of ROSC has not been fully elucidated ^{8,10,12,15,16,22,27,32,33}. It is likely that such a true optimal target varies significantly depending on the cause of arrest, pre-existing patient comorbidities and the manner in which it is achieved ^{9,34}.

The treatments we employed for haemodynamic-targeted resuscitation were chosen by what was immediately available at the bedside in our ED. We used noradrenaline as the vasoconstricting agent because our patients with refractory OHCA would have already received large amounts of adrenaline (Table 2), which likely loses effectiveness with prolonged resuscitation, and because we did not have immediate access to vasopressin, which may be a better alternative as its efficacy does not diminish as significantly with extended down-times ^{35–38}. While the mean DBP increase with noradrenaline among our patients was statistically significant, it was not likely clinically significant. Furthermore, it was somewhat heterogenous (Fig. 2), which was also noted by the Henry Ford group with CPP response to adrenaline and vasopressin after prolonged arrest in humans ^{39,40}. This significant variation in BP response to vasopressors during cardiac arrest may explain why many prior clinical trials of uniformly prescribed, novel vasopressor regimens in humans have been unsuccessful and why an approach targeting vasopressor administration to individual-patient physiology may be more effective ^{13,14,16}.

Pharmacological treatment is not the only means of augmenting coronary perfusion during cardiac arrest; mechanical occlusion of the

descending thoracic aorta is known to improve cardio-cerebral blood flow during CPR and is routinely employed in the treatment of traumatic haemorrhagic arrest ^{41,42}. While emergent aortic occlusion was only previously feasible via thoracotomy, development of an easily deployable REBOA catheter for use in trauma has made non-surgical aortic occlusion during closed-chest CPR possible for medical cardiac arrest. Two recent pilot studies have successfully employed REBOA in the setting of OHCA resuscitation in the pre-hospital and ED setting ^{43,44}. From our extremely limited experience in this series, catheter deployment was achievable, but notably did not produce complete aortic occlusion using the ER-REBOA device, which has a maximal balloon diameter of 32 mm. We hypothesize this could be due to profound vasoplegia in the setting of prolonged cardiac arrest resulting in a flaccid and dilated aorta not completely obstructed by this particular balloon. Nonetheless, our results add to the existing evidence suggesting REBOA is feasible in the treatment of refractory, non-traumatic OHCA. Whether it is efficacious requires significant further study, which is currently being investigated (NCT03703453).

Our findings in this feasibility study are limited by the small sample size, lack of racial diversity amongst the subjects, unique training of the investigator(s) who performed the procedures, lack of availability of particular resuscitation adjuncts that could have been employed (transoesophageal echocardiography, vasopressin), and the inability to collect more complete haemodynamic data in real-time without dedicated support personnel or a prospective trial design. Further, the uses of noradrenaline and REBOA as modalities to increase intra-arrest DBP are atypical and not well studied, and their results may not be generalizable to other resuscitation strategies. Another limitation to external validity is the need to maintain the specific procedural skills for rapidly measuring intra-arrest arterial pressure over time with potentially infrequent case exposure. Finally, our study is far too small to provide any data on patient-oriented outcomes such as survival/neurologically intact survival.

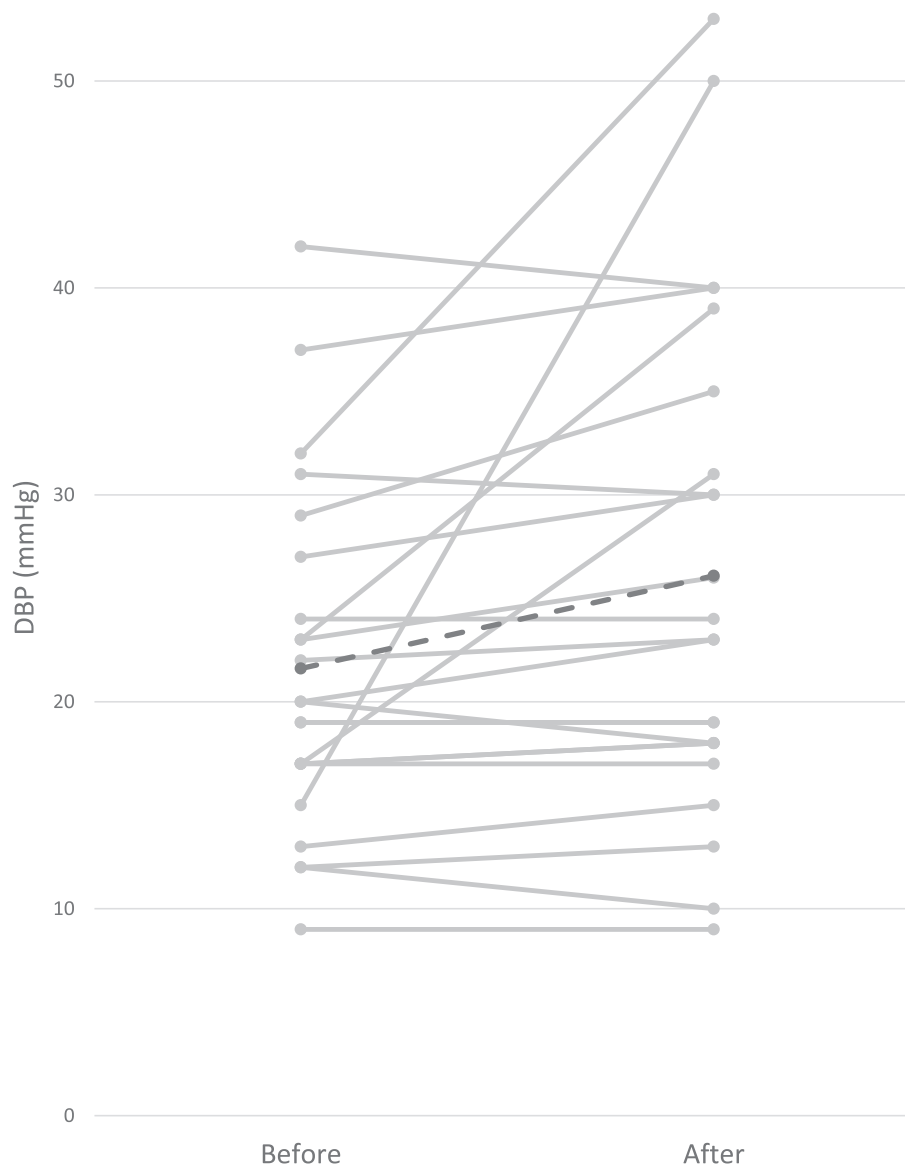


Fig. 2 – Change in diastolic blood pressure following administration of noradrenaline. DBP = diastolic blood pressure. N = 23 pre/post measurements. Dotted line represents mean value: before 21.6 ± 8.3 mmHg, after 26.1 ± 12.1 mmHg, $p < 0.025$.

Conclusions

We report a case series of prospective measurement of intra-arrest DBP and haemodynamic-targeted resuscitation for the treatment of refractory OHCA in the ED. If optimized and validated, this strategy has the potential to significantly expand the available treatment of patients with refractory OHCA and facilitate evidence-based evaluation of novel therapies' effectiveness compared with current guideline-based, one-size-fits-all care.

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CRedit authorship contribution statement

Byron C. Drumheller: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Joseph Pinizzotto:** Data curation, Writing - review & editing. **Ryan C Overberger:** Conceptualization, Data curation, Writing - review & editing. **Erin E. Sabolick:** Conceptualization, Data curation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resplu.2021.100159>.

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