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ORIGINAL RESEARCH

First Results of Our Local Practice Guide Used During the Late Phase of Resuscitation in Patients with Refractory VF in Out of Hospital Cardiac Arrest

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Objective: Treatment of refractory ventricular fibrillation (rVF) is a clinical challenge. If rVF is still present after standard advanced life support (ALS) guideline care, including amiodaron administration, other therapeutic options might be necessary. Based on the available evidence and expertise, our Helicopter Emergency Medical Service (HEMS) team developed a local practice guide for the prolonged resuscitation of patients in rVF and implemented this as standard HEMS care in March 2022.

Methods: This database study contains all patients treated with our local practice guide during out of hospital cardiac arrest (OHCA) with rVF beyond the fifth regular ALS shock-block. This local practice HEMS treatment algorithm consisted of, among others, cessation of epinephrine and alternating administration of esmolol and norepinephrine combined with enoximone. Data were derived from the HEMS database and the treating hospitals. Primary outcome was the return of spontaneous circulation. Secondary outcome was defined as survival to hospital discharge and cerebral performance. This outcome was compared to the literature to analyze for inferiority of treatment.

Results: In a 21-month period, HEMS was 761 times deployed for OHCA. Nineteen patients were treated with the local practice guide, nine patients (47%) were admitted to hospital with return of spontaneous circulation. Median resuscitation time was 22min. Hospital survival with good neurology was achieved in 42% vs 17% as expected. Exact Clopper-Pearson and logistic regression analysis revealed non-inferiority of the local practice guide. Withholding epinephrine was achieved in 84% of patients. A total of 79% and 90% of patients received esmolol and norepinephrine/enoximone mixture, respectively. Alternative defibrillation positions were indicated in 18 patients but applied in only 6 (33%).

Conclusion: In patients with persisting VF despite prolonged advanced life support care, a multifaceted bundle of care approach shows promising results and warrants further research. Alternative drug administrations were found to be substantially easier to achieve compared to alternative defibrillation positions.

Keywords: out-of-hospital cardiac arrest, ventricular fibrillation, cardiopulmonary resuscitation, emergency medical services, electric countershock, norepinephrine, enoximone

Introduction

Approximately 4–5% of all cardiac arrests and 20% of shockable arrests (pulseless ventricular tachycardia and ventricular fibrillation) are patients with *refractory* ventricular fibrillation (rVF).[1,2] This is defined by the contemporary European Resuscitation Council (ERC) Advanced Life Support (ALS) guideline as "ventricular fibrillation that persists after three defibrillations".[1] The duration of rVF is associated with poor outcome[3–6] and given the exponential decline in survival, early and effective treatment is crucial.[3,7]

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Treatment recommendations in the ALS guideline consist of optimizing standard defibrillation, using an escalating energy level or considering antero-posterior defibrillation pad position.[1] Acknowledging that repeating previous unsuccessful therapies does not contribute to favorable neurological outcome,[4] other treatment opportunities might be considered whenever the standard ALS algorithm falls short. Therapeutic options described in the literature can be categorized as follows:

Alternative defibrillation strategies, either a "vector change" (VC) to antero-posterior defibrillation resulting in a possible larger portion of the ventricles being depolarized or "dual synchronized external defibrillation" (DSED) with the delivery of more energy as well as a "conditioning shock" phenomenon, can increase the success rate of defibrillation.[8–12] *Reduction of adrenergic catecholamine drive*, can be achieved by the reduction of epinephrine administration,[13–15] beta-adrenergic blockade[16–19] and/or sedation.[20] Concerns around epinephrine in rVF focus on the negative effects mediated through beta-receptors and platelet's function, resulting in an increased myocardial oxygen demand, reduced subendocardial perfusion and exacerbated ischemic injury of the heart and brain.[21–24] Administration of epinephrine does not improve survival with good neurological outcome[2,15,25–27] and norepinephrine has therefore been studied as an alternative vasopressor.[22,28–32] *Mitigating ischemic effects* from phosphodiesterase inhibitors in (prolonged) cardiac arrest can benefit the cardiac function.[33–39] Niemann, Garner, Khaleeli and Lewis[36] compared the effects of milrinone and saline in an animal study, finding that milrinone facilitated resuscitation from rVF and attenuated left ventricular dysfunction. Evidence of *additional antiarrhythmic drugs* is limited, although lidocaine could be beneficial after ineffective administration of amiodarone in VF patients with Brugada syndrome.[40] Magnesium was reported successful in certain rVF cases,[41,42] although larger studies were unable to reproduce these findings.[43,44] *Finally, Extracorporeal-CardioPulmonary Resuscitation (E-CPR) can be a* "bridging" option in carefully selected patients,[45–49] eg until coronary revascularization is obtained.

Objective

We distilled a local practice guide from the available literature and introduced this as standard care for the later stage of VF by our HEMS service in March 2022. This analysis reports the results of our first patients and associated outcome data of this local practice guide. A comparison is made with reference data from the literature to analyze the outcome results and to check for non-inferiority.

Methods and Materials

Study Design

This was a database study evaluating standard of care using a local practice guide in patients with persisting VF beyond the fifth ALS shock-block in the presence of helicopter emergency medical service (HEMS).

Local Practice Guide

The initial draft of the local practice guide was designed according to the available literature by two anesthesiologists/ HEMS physicians (CS, LM) and subsequently discussed with all HEMS physicians until expert consensus was reached. Additional content validity was obtained by an independent cardiologist. The local practice guide includes alternating blocks with bolus administration of esmolol (0.5mg/kg) and "cardio-mixture" (norepinephrine 0.5mg, combined with enoximone 25mg), coupled with alternative defibrillation strategies and optional use of magnesium and/or lidocaine (Figure 1). This local practice guide was introduced as standard HEMS care in March 2022 for the prolonged phase of patients in persisting VF.

In- and Exclusion

All primary HEMS deployments for cardiac arrest between 1-3-2022 until 31-12-2023 were included in this analysis. Inclusion was set to adult patients (≥18 years) suffering from an out-of-hospital cardiac arrest (OHCA) with both an initial and persistent shockable rhythm beyond the fifth ALS block *and* presence of HEMS. If HEMS would arrive before the fifth ALS block, treatment would be continued according to the contemporary ALS guideline until after the fifth ALS

Block	Defibrillation	Medication
1-2	Anterior-lateral	-
3	Anterior-lateral	Epinephrine 1 mg Amiodarone 300mg
4	Anterior-lateral	-
5	Anterior-lateral	Epinephrine 1 mg Amiodarone 150mg
6	Anterior-lateral	Esmolol 0.5 mg/kg
7	Anterior-posterior	Withhold further epinephrine Norepinephrine 0.5mg /enoximone 25mg*
8	Anterior-posterior	Esmolol 0.5 mg/kg
9	Dual shock defibrillation	Norepinephrine/enoximone*
10	Dual shock defibrillation	Consider lidocaine (0.5-1 mg/kg) and/or magnesium (2gr) if not given already
	General considerations	Optimise BLS and minimise pre-shock delays; PM hypothermia, intoxication

Figure 1 Local practice guide for the treatment of persistent Ventricular Fibrillation by the Helicopter Emergency Medical Service Lifeliner. Advanced Life Support (ALS) resuscitation block 1–5 according to contemporary ALS guideline. *Dichotomous weight-based dosing 0.5mg/25mg (>50kg), 0.25mg/12.5mg (<50kg).

block ensuring that at least five antero-lateral defibrillations, 450mg of amiodarone and 2mg of epinephrine had been administered before initializing the local practice guide.

Cardiac arrests resulting from obvious traumatic etiology or intoxication were excluded. Patients in VF in whom E-CPR was performed were also excluded from the study.

Data Extraction

All receiving hospitals were contacted for relevant outcome data, being part of standard procedure after a HEMS deployment. Patient selection and data extraction from HEMS database was performed between 20th – 24th December 2023 by two independent researchers (CS, LM). Any discrepancies were discussed until consensus was reached. The final cohort was subsequently verified by an independent physician. During data collection age and date of resuscitation and hospital were known. The name and date of birth (only age remains) of our patients disappears out of our database after 24 hours. This is how we maintain and comply with relevant data protection and privacy regulations.

Outcome Parameters

The primary outcome was defined as “sustained return of spontaneous circulation” (ROSC) until hospital admission. The deceased group was defined as patient declared dead either on-scene or at the emergency department. Secondary outcomes were defined as survival to hospital discharge and associated cerebral performance category (CPC). Survival to hospital discharge was compared to reference data from the literature using the systematic review by Mandigers, Boersma, den Uil et al.[50] As a tertiary outcome, we reported local practice guide adherence.

Reported resuscitation time was derived from the number of ALS blocks, starting from the first documented defibrillation and stopped when resuscitation was terminated either because the patient was declared dead or ROSC had occurred.

Statistical Analysis

Data were analyzed using IBM Statistic Package for the Social Sciences (IBM Corp.© SPSS Statistics for Windows, Version 28.0.0.0). Continuous variables were reported as median and interquartile range (IQR), dichotomous variables as

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counts and percentages unless otherwise specified. Differences between those who died and those with sustained ROSC were tested using the Mann–Whitney *U*-test or Fisher's exact test for continuous and dichotomous variables, respectively. The exact binomial test with exact Clopper-Pearson 95% CI and univariable and multivariable logistic regression analysis was used to test hospital survival against the reference literature data.

Ethical Consideration

The Institutional Ethical Review Board, METC Oost-Nederland, approved the study of our local practice guide in patients with prolonged rVF in prehospital care (2023–16616) and waived the need for informed consent as the study was not subjected to Medical Research Involving Human Subjects (WMO). Study complies with the Declaration of Helsinki.

Results

During a 21-month period, 716 hEMS deployments for an OHCA occurred. In 24 cases VF persistent beyond the fifth ALS block in the presence of HEMS crew. Five cases were excluded for E-CPR as our HEMS service participates in the on scene trial (On-Scene trial – The First Nationwide PreHospital ECPR program), leaving 19 patients to be included in this analysis (Figure 2). Patient demographics and resuscitation details are shown in Table 1 and individual patient treatments are included in Figure 3.

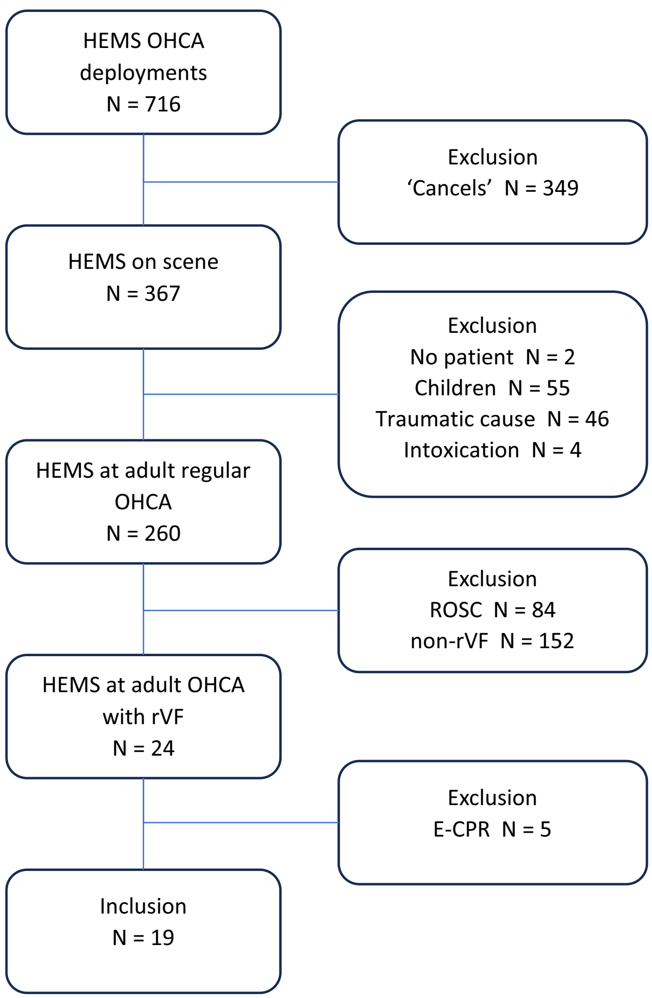

Figure 2 Overview of patients.

Table 1 Patient Demographics and Resuscitation Details

		Total
Number of individuals (N)		19
Demographics		
Gender	Male (N, %)	15 (79%)
	Female (N, %)	4 (21%)
Age years [median, IQR]		52.0 [10]
Resuscitation event		
Witnessed (N, %)		15 (79%)
CPR delay min [median, IQR]		0 [0]
Bystander CPR (N, %)		12 (63%)
AED used (N, %)		10 (53%)
Mech. chest compression used (N, %)		10 (53%)
Flight time min [median, IQR]		16 [5]
HEMS arrival in ALS block [median, IQR]		8 [2]
Resuscitation time min [median, IQR]		22 [16]
Pharmacological therapy given		
Epinephrine (N, %)		19 (100%)
Epinephrine dosage [median, IQR]		2 [1]
Amiodarone (N, %)		19 (100%)
Esmolol (N, %)		15 (79%)
1st Esmolol administered in ALS block [median, IQR]		8 [1]
Norepinephrine/enoximone (N, %)		17 (90%)
1st norepinephrine/enoximone administered in ALS block [median, IQR]		9 [2]
Magnesium (N, %)		8 (42%)
Lidocaine (N, %)		3 (15%)
Defibrillations given		
Total defibrillations [median, IQR]		10 [4]
Alternative defibrillator position (N, %)		6 (32%)
Outcome		
Survival to hospital discharge (N, %)		8 (42%)
Survival with CPC 1–2 (N, %)		8 (42%)
Deceased (N, %)		11 (60%)

Abbreviations: ROSC, return of spontaneous circulation; IQR, interquartile range [75–25%]; N, number; %, percentage; CPR, cardiopulmonary resuscitation; AED, automatic external defibrillator; ALS, advanced cardiac life support; CPC, cerebral performance category.

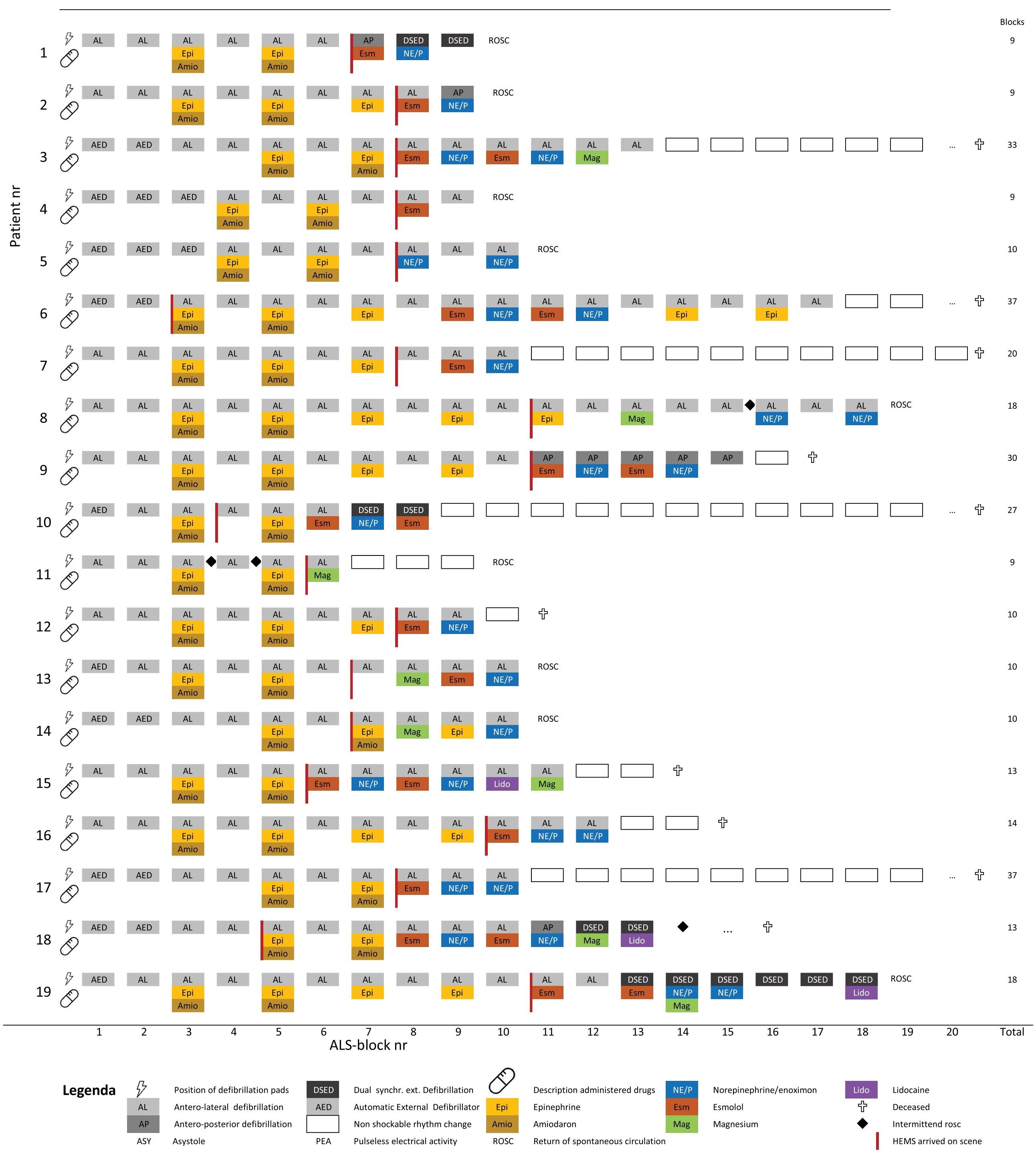

Figure 3 Individual patient treatments.

Primary Outcome

Most cardiac arrest were witnessed (79%), had bystander CPR (63%) and had an Automated External Defibrillator (AED) applied (53%). The overall median [IQR] age was 52.0 [10] All patients receiving ROSC did so prehospitally. The median [IQR] HEMS flight time was 16.0 [5] minutes, resulting in HEMS arrival in the 8th [2] ALS block. The overall median [IQR] resuscitation time was 22.0 [16]. All patients had been given amiodarone and epinephrine according to the contemporary ALS guideline before initiation of the local practice guide. Nine out of 19 patients (47%) arrived at hospital with ROSC.

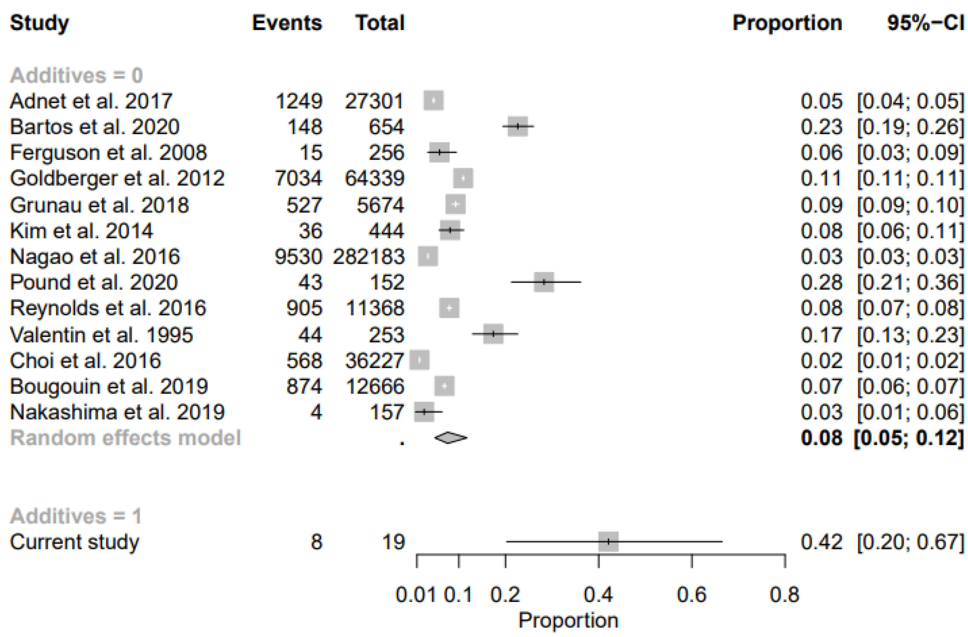

Figure 4 Forest plot survival with good neurology following Out of Hospital Cardiac Arrest. Forest plot for studies comparing out-of-hospital cardiac arrest survival with good neurology (CPC ≤ 2). Fourteen studies were included, n = 441.693 cases comparing standard ALS guideline care (n = 441.674) with additional local practice guideline care (n = 19). The size of the grey square reflects its weight in the analysis the grey diamond is the overall results of the meta-analysis. The horizontal lines represent confidential intervals.

Abbreviation: CI, confidence interval.

Secondary Outcome

Of the nine patients admitted to hospital, one was diagnosed with a cerebral etiology for the arrest and treatment was withdrawn. Of the remaining eight patients (42% of the total population), all were discharged from hospital with good neurological outcome (CPC 1 or 2).

The expected *hospital* survival derived from a median resuscitation time of 22min according to the systematic review by Mandigers, Boersma, den Uil et al[50] was 17% for adults suffering an OHCA due to a shockable rhythm. An exact binomial test with exact Clopper-Pearson 95% CI showed a significant higher survival (42%) in our sample with a 95% CI of 20.3% to 66.5%, p = 0.009. Logistic regression analysis revealed an OR of 8.7 (95% CI 1.2–61.5), p = 0.030 for survival with good neurology with additional care, according to the local practice guide (Figure 4). The effect of the local practice guide adjusted for age and gender resulted in an OR of 6.8 (95% CI 0.45–101.7), p = 0.165. These results suggest non- inferiority of the local practice guide.

Tertiary Outcome

Withholding epinephrine was achieved in 84% of patients. Esmolol and cardio-mixture were administered in 79% and 90% of patients respectively. Four patients were withheld esmolol because of intermittent underlying bradycardia or VF was already terminated after preceding drug administration (magnesium or norepinephrine/enoximone). A total of 42% of patients received magnesium and 15% were given lidocaine. Alternative defibrillation positions were indicated in 18 patients but applied in only 6 (33%).

Discussion

Local Practice Guide Design Reflection

Given the a priori expected low survival in extended resuscitations, we chose a parallel approach with alternating medications and defibrillations per ALS block. Given the reported effects of esmolol,[18,51] we put extra emphasis on beta-blockade administration. The observed effect in our study was, however, much smaller compared to the initial studies[18,51] and more in line with the recent published beta-arrest trial.[52] Both findings led to a more stringent indication and dose reduction for future patients.

Despite the study by Lindner and Ahnefeld[31] showing comparative effects of norepinephrine and epinephrine, we were concerned that high-dose norepinephrine could be deleterious to the ischemic heart when given without inotropic support in the late resuscitation phase. Given the reported positive effects of milrinone,[33,35–37,39] we therefore combined norepinephrine with enoximone, a phosphodiesterase-inhibitor that can be administer as a push dose.[53]

Contrary to case-reports, larger studies failed to demonstrate the benefit of magnesium in rVF,[43,44] which was the reason we placed magnesium optionally at the end of our local practice guide. A rather large portion of patients was given magnesium, which resulted from HEMS physicians' interpretation of polymorphic ventricular tachycardia as Torsades de Pointes.

Primary and Secondary Outcome Reflection

Survival with good neurology from VF declines rapidly to approximately 7% at 30min and 1–2% at 45min.[3,6,7,50,54] As inclusion was set to cases of persisting VF beyond the fifth ALS block, selection bias was inevitable present. The natural course of VF is, however, gradual with 40% of untreated cardiac arrests patients still in VF after 20 minutes.[3] Although in theory, E-CPR would not have to preclude additional rVF treatments, we did not combine these interventions and therefore E-CPR prevailed above the local practice guide, thereby excluding five rVF cases. Given the stringent criteria for E-CPR within our service (age 18–50 years, witnessed and shockable arrest with adequate bystander CPR, etCO2 > 10mmHg and time to initiation of E-CPR <45min after collapse), this selection was likely to attenuate survival.

Survival rates differ between true refractory and recurrent VF.[9,55] Given the high workload in the prehospital setting, limited diagnostic opportunities and often short intervals of terminated VF in recurrent cases, we could not differentiate between these two entities.[56,57] The majority of persisting VF, according to the ALS guideline definition, appears to be recurrent VF with only 4% being truly refractory VF.[57] Acknowledging this distribution, searching for alternative medication strategies as suggested in the local practice guide might be even more important compared to achieving alternative defibrillation positions.

To limit the overestimation of the effect, we purposefully derived the resuscitation time from the actual number of ALS blocks as AEDs and ambulance monitors keep track of time in an objective manner. This is, however, an underrepresentation of the actual resuscitation time as it does not incorporate no-flow and low-flow time before the first defibrillation.[58]

Tertiary Outcome Reflection

The pharmacological interventions from the local practice guide appear to be well implemented in the prehospital setting.[17] Alternative defibrillation on the other hand, seems much more difficult to achieve. Other observational studies achieved success rates of 78–89%.[10,12] Hypotheses for this discrepancy might be the concomitant tasks-/workload, the administration of alternative medications, the unavailability of equipment, unfamiliarity with the procedure and/or technical difficulty. The later might be particularly relevant to the Netherlands where, compared to the other studies, mechanical CPR is regularly used prehospitally.

Limitations

This study incorporated alternative pharmacological and defibrillation options for the later stage of shockable arrest. The well-organized resuscitation system in the Netherlands with eg dispatch-center initiated CPR instructions, the activation of citizen assistance ("near-bystander") CPR and public availability of AEDs are relevant to the survival outcome in this study. This study has limitations regarding sample size, data omissions and selection bias. We tried to minimize these by using independent researchers, by analyzing all HEMS deployments and by combining data from multiple sources as well as by providing detailed individual patient information. Furthermore, we calculated duration of resuscitation in a restrictive manner, thereby attenuating the effects of the local practice guide. We acknowledge the shortcomings of this study and underscore the necessity of more robust future research for confirmation of the study results.

Conclusions

In this study on patients with persisting VF despite full amiodaron administration and multiple standard defibrillation attempts, a multifaceted, bundle of care approach shows promising results regarding survival with favorable neurological outcome and requires further research. Alternative pharmacologic interventions seem feasible in the prehospital environment, although alternative defibrillation strategies pose more of a challenge and require further exploration.

Highlights

- Alternative treatments can benefit survival in persistent ventricular fibrillation.
- Pharmacologic interventions are easier implemented than alternative defibrillation positions.

Abbreviations

CPR, Cardiopulmonary resuscitation; HEMS, Helicopter emergency medical service; rVF, refractory ventricular fibrillation; OHCA, Out-of-hospital cardiac arrest; ROSC, Return of spontaneous circulation; ALS, Advanced life support; E-CPR, Extracorporeal-cardiopulmonary resuscitation; CPC, cerebral performance category; AED, Automated External Defibrillator.

Data Sharing Statement

All distilled information from the individual patient records is included in this publication. Data can be shared on a reasonable request.

Declaration of Generative AI in Scientific Writing

The authors did not use a generative artificial intelligence (AI) tool or service to assist with the preparation or editing of this work. The author(s) take full responsibility for the content of this publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report there are no competing interests to declare for this work.

References

1. Soar J, Bottiger BW, Carli P, et al. European resuscitation council guidelines 2021: adult advanced life support. *Resuscitation*. 2021;161:115–151. doi:10.1016/j.resuscitation.2021.02.010
2. Bell SM, Lam DH, Kearney K, Hira RS. Management of refractory ventricular fibrillation (Prehospital and Emergency Department). *Cardiol Clin*. 2018;36(3):395–408. doi:10.1016/j.ccl.2018.03.007
3. Holmberg M, Holmberg S, Herlitz J. Incidence, duration and survival of ventricular fibrillation in out-of-hospital cardiac arrest patients in Sweden. *Resusc*. 2000;44:7–17.

4. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? *Circulation*. 2013;128(23):2488–2494. doi:10.1161/CIRCULATIONAHA.113.002408
5. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest. A 3-phase time-sensitive model. *JAMA*. 2002;288(23):3035–3038. doi:10.1001/jama.288.23.3035
6. Goto Y, Funada A, Maeda T, Goto Y. Time boundaries of the three-phase time-sensitive model for ventricular fibrillation cardiac arrest. *Resusc Plus*. 2021;6:100095. doi:10.1016/j.resplu.2021.100095
7. Holmen J, Hollenberg J, Claesson A, et al. Survival in ventricular fibrillation with emphasis on the number of defibrillations in relation to other factors at resuscitation. *Resuscitation*. 2017;113:33–38. doi:10.1016/j.resuscitation.2017.01.006
8. Hajjar K, Berbari I, El Tawil C, Bou Chebl R, Abou Dagher G. Dual defibrillation in patients with refractory ventricular fibrillation. *Am J Emerg Med*. 2018;36(8):1474–1479. doi:10.1016/j.ajem.2018.04.060
9. Cheskes S, Wudwud A, Turner L, et al. The impact of double sequential external defibrillation on termination of refractory ventricular fibrillation during out-of-hospital cardiac arrest. *Resuscitation*. 2019;139:275–281. doi:10.1016/j.resuscitation.2019.04.038
10. Cheskes S, Verbeek PR, Drennan IR, et al. Defibrillation strategies for refractory ventricular fibrillation. *N Engl J Med*. 2022;387(21):1947–1956. doi:10.1056/NEJMoa2207304
11. Bero M, Sochor M, Wong S, Brady W. Changing the management of refractory ventricular fibrillation: the consideration of earlier utilization of dual sequential defibrillation. *Am J Emerg Med*. 2020;38(3):545–548. doi:10.1016/j.ajem.2019.05.048
12. Cheskes S, Dorian P, Feldman M, et al. Double sequential external defibrillation for refractory ventricular fibrillation: the DOSE VF pilot randomized controlled trial. *Resuscitation*. 2020;150:178–184. doi:10.1016/j.resuscitation.2020.02.010
13. Mion G, Rousseau JM, Selcer D, Samama CM. Cardiac arrest: should we consider norepinephrine instead of epinephrine? *Am J Emerg Med*. 2014;32(12):1560e1–2. doi:10.1016/j.ajem.2014.05.046
14. Oshima K, Sawada Y, Isshiki Y, Ichikawa Y, Fukushima K, Aramaki Y. The association between ventricular fibrillation and serum catecholamine levels. *Cureus*. 2023. doi:10.7759/cureus.43252
15. Fernando SM, Mathew R, Sadeghirad B, et al. Epinephrine in out-of-hospital cardiac arrest: a network meta-analysis and subgroup analyses of shockable and nonshockable rhythms. *Chest*. 2023;164(2):381–393. doi:10.1016/j.chest.2023.01.033
16. Killingsworth CR, Wei -C-C, Dell'Italia LJ, et al. Short-acting β-adrenergic antagonist esmolol given at reperfusion improves survival after prolonged ventricular fibrillation. *Circulation*. 2004;109(20):2469–2474. doi:10.1161/01.cir.0000128040.43933.d3
17. Patrick C, Crowe RP, Ward B, Mohammed A, Keene KR, Dickson R. Feasibility of prehospital esmolol for refractory ventricular fibrillation. *J Am Coll Emerg Physicians Open*. 2022;3(2):e12700. doi:10.1002/emp2.12700
18. Driver BE, Debaty G, Plummer DW, Smith SW. Use of esmolol after failure of standard cardiopulmonary resuscitation to treat patients with refractory ventricular fibrillation. *Resuscitation*. 2014;85(10):1337–1341. doi:10.1016/j.resuscitation.2014.06.032
19. Gottlieb M, Dyer S, Peksa GD. Beta-blockade for the treatment of cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia: a systematic review and meta-analysis. *Resuscitation*. 2020;146:118–125. doi:10.1016/j.resuscitation.2019.11.019
20. Eifling M, Razavi M, Massumi A. Evaluation and management of electrical storm. *Tex Heart Inst J*. 2011;38(2):111–121.
21. de Oliveira FC, Feitosa-Filho GS, Ritt LE. Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: a systematic review. *Resuscitation*. 2012;83(6):674–683. doi:10.1016/j.resuscitation.2012.01.025
22. Paradis NA, Wenzel V, Southall J. Pressor drugs in the treatment of cardiac arrest. *Cardiol Clin*. 2002;20(1):61–78, viii. doi:10.1016/s0733-8651(03)00065-1
23. Ristagno G, Tang W, Huang L, et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation. *Crit Care Med*. 2009;37(4):1408–1415. doi:10.1097/CCM.0b013e31819cedc9
24. Dhanjal TS, Medina RA, Leem J, Clark JE, Southworth R, Curtis MJ. Trapped platelets activated in ischemia initiate ventricular fibrillation. *Circ Arrhythm Electrophysiol*. 2013;6(5):995–1001. doi:10.1161/CIRCEP.113.000591
25. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med*. 2018;379(8):711–721. doi:10.1056/NEJMoa1806842
26. Paradis NA, Koscove EM. Epinephrine in cardiac arrest: a critical review. *Ann Emerg Med*. 1990;19(11):1288–1301. doi:10.1016/S0196-0644(05)82289-9
27. Zhong H, Yin Z, Kou B, et al. Therapeutic and adverse effects of Adrenaline on patients who suffer out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Eur J Med Res*. 2023;28(1):24. doi:10.1186/s40001-022-00974-8
28. Woodhouse SP, Lewis-Driver D, Eller H. Catecholamines during cardiopulmonary resuscitation for cardiac arrest. *Resusc*. 1992;24:263–272.
29. Klouche K, Weil MH, Sun S, Tang W, Zhao DH. A comparison of alpha-methylnorepinephrine, vasopressin and epinephrine for cardiac resuscitation. *Resuscitation*. 2003;57(1):93–100. doi:10.1016/s0300-9572(02)00403-3
30. Srisurapanont K, Thepchinda T, Kwangsukstith S, et al. Comparing drugs for out-of-hospital, shock-refractory cardiac arrest: systematic review and network meta-analysis of randomized controlled trials. *West J Emerg Med*. 2021;22(4):834–841. doi:10.5811/westjem.2021.2.49590
31. Lindner KH, Ahnefeld FW. Comparison of epinephrine and norepinephrine in the treatment of asphyxial or fibrillatory cardiac arrest in a porcine model. *Crit Care Med*. 1989;17(5):437–441. doi:10.1097/00003246-198905000-00012
32. Lindner KH, Ahnefeld FW, Grünert A. Epinephrine versus norepinephrine in prehospital ventricular fibrillation. *Am J Cardiol*. 1991;15:427–428. doi:10.1016/0002-9149(91)90055-P
33. Zoerner F, Lennmyr F, Wiklund L, Martijn C, Semenas E. Milrinone and esmolol decrease cardiac damage after resuscitation from prolonged cardiac arrest. *Acta Anaesthesiol Scand*. 2015;59(4):465–474. doi:10.1111/aas.12480
34. Overgaard CB, Džavík VR. Inotropes and Vasopressors. *Circulation*. 2008;118(10):1047–1056. doi:10.1161/circulationaha.107.728840
35. Rao YJ, Xi L. Pivotal effects of phosphodiesterase inhibitors on myocyte contractility and viability in normal and ischemic hearts. *Acta Pharmacol Sin*. 2009;30(1):1–24. doi:10.1038/aps.2008.1
36. Niemann JT, Garner D, Khaleeli E, Lewis RJ. Milrinone facilitates resuscitation from cardiac arrest and attenuates postresuscitation myocardial dysfunction. *Circulation*. 2003;108(24):3031–3035. doi:10.1161/01.CIR.0000101925.37174.85
37. Sandroni C, Cavallaro F, Caricato A, Scapigliati A, Fenici P, Antonelli M. Enoximone in cardiac arrest caused by propranolol: two case reports. *Acta Anaesthesiol Scand*. 2006;50(6):759–761. doi:10.1111/j.1399-6576.2006.01026.x

38. Lozada Martinez ID, Bayona-Gamboa AJ, Meza-Fandino DF, et al. Inotropic support in cardiogenic shock: who leads the battle, milrinone or dobutamine? *Ann Med Surg*. 2022;82:104763. doi:10.1016/j.amsu.2022.104763
39. He Y, Wang G, Li C, Wang Y, Zhang Q. The protective effects of phosphodiesterase-5 inhibitor, sildenafil on post-resuscitation cardiac dysfunction of cardiac arrest: by regulating the miR-155-5p and miR-145-5p. *Scand J Trauma Resusc Emerg Med*. 2021;29(1):2. doi:10.1186/s13049-020-00819-5
40. Aleksandrowicz D. Amiodarone or lidocaine, that is the question - Pharmacological therapy of refractory ventricular fibrillation associated with Brugada syndrome. *Resuscitation*. 2021;169:76–77. doi:10.1016/j.resuscitation.2021.10.022
41. Tobey RC, Birnbaum GA, Allegra JR, Horowitz MS, Plosay JJ. Successful resuscitation and neurologic recovery from refractory ventricular fibrillation after magnesium sulfate administration. *Ann Emerg Med*. 1992;21(1):92–96. doi:10.1016/s0196-0644(05)82249-8
42. Baraka A, Ayoub C, Kawkabani N. Magnesium therapy for refractory ventricular fibrillation. *J Cardiothorac Vasc Anesth*. 2000;14(2):196–199.
43. Hassan TB, Jagger C, Barnett DB. A randomised trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation. *Emerg Med J*. 2001;19:57–62. doi:10.1136/emj.19.1.57
44. Allegra J, Lavery R, Cody R, et al. Magnesium sulfate in the treatment of refractory ventricular fibrillation in the prehospital setting. *Resusc*. 2001;49:245–249.
45. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a Phase 2, single centre, open-label, randomised controlled trial. *Lancet*. 2020;396(10265):1807–1816. doi:10.1016/S0140-6736(20)32338-2
46. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation*. 2015;86:88–94. doi:10.1016/j.resuscitation.2014.09.010
47. Belohlavek J, Kucera K, Jarkovsky J, et al. Hyperinvasive approach to out-of hospital cardiac arrest using mechanical chest compression device, prehospital intraarrest cooling, extracorporeal life support and early invasive assessment compared to standard of care. A randomized parallel groups comparative study proposal. "Prague OHCA study". *J Transl Med*. 2012;10:163. doi:10.1186/1479-5876-10-163
48. Rob D, Smalcova J, Smid O, et al. Extracorporeal versus conventional cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest: a secondary analysis of the Prague OHCA trial. *Crit Care*. 2022;26(1):330. doi:10.1186/s13054-022-04199-3
49. Kawakami S, Tahara Y, Koga H, Noguchi T, Inoue S, Yasuda S. The association between time to extracorporeal cardiopulmonary resuscitation and outcome in patients with out-of-hospital cardiac arrest. *Eur Heart J Acute Cardiovasc Care*. 2022;11(4):279–289. doi:10.1093/ehjacc/zuac010
50. Mandigers L, Boersma E, den Uil CA, et al. Systematic review and meta-analysis comparing low-flow duration of extracorporeal and conventional cardiopulmonary resuscitation. *Interact Cardiovasc Thorac Surg*. 2022;35(4). doi:10.1093/icvts/ivac219
51. Lee YH, Lee KJ, Min YH, et al. Refractory ventricular fibrillation treated with esmolol. *Resuscitation*. 2016;107:150–155. doi:10.1016/j.resuscitation.2016.07.243
52. Gelbenegger G, Jilma B, Horvath LC, et al. Landiolol for refractory ventricular fibrillation in out-of-hospital cardiac arrest: a randomized, double-blind, placebo-controlled, pilot trial. *Resuscitation*. 2024;201:110273. doi:10.1016/j.resuscitation.2024.110273
53. Zausig YA, Stowe DF, Zink W, Grube C, Martin E, Graf BM. A comparison of three phosphodiesterase type III inhibitors on mechanical and metabolic function in Guinea pig isolated hearts. *Anesth Analg*. 2006;102(6):1646–1652. doi:10.1213/01.ane.0000216290.74626.27
54. Hasegawa M, Abe T, Nagata T, Onozuka D, Hagihara A. The number of prehospital defibrillation shocks and 1-month survival in patients with out-of-hospital cardiac arrest. *Scand J Trauma Resusc Emerg Med*. 2015;23(1). doi:10.1186/s13049-015-0112-4
55. Nas J, Thannhauser J, Bonnes JL, Brouwer MA. Importance of the distinction between recurrent and shock-resistant ventricular fibrillation: call for a uniform definition of refractory VF. *Resuscitation*. 2019;138:312–313. doi:10.1016/j.resuscitation.2019.01.042
56. Nehme Z, Delorenzo A, Yates J, Bernard S, Smith K. 'Reply to:' Importance of the distinction between recurrent and shock-resistant ventricular fibrillation: call for a uniform definition of refractory VF. *Resuscitation*. 2019;138:306–307. doi:10.1016/j.resuscitation.2019.02.047
57. Verkaik BJ, Walker RG, Marx R, et al. Incidence of true refractory ventricular fibrillation in patients meeting a pragmatic definition of refractory ventricular fibrillation. *Circulation*. 2023;148:A419. doi:10.1161/circ.148.suppl_1.419
58. Mommers L, Slagt C, Coumou FC, van der Crabben R, Moors X, Dos Reis Miranda D. Feasibility of HEMS performed prehospital extracorporeal-cardiopulmonary resuscitation in paediatric cardiac arrests; two case reports. *Scand J Trauma Resusc Emerg Med*. 2023;31(1):49. doi:10.1186/s13049-023-01119-4