Clinical paper

Out-of-hospital cardiac arrest complicated by hyperthermia

Timothy Edwardsa,*, Paul Reesb

Abstract

Background: The aims of this study were to establish epidemiology, clinical management and outcomes in cases of adult out-of-hospital cardiac arrest complicated by hyperthermia attended by the London Ambulance Service NHS Trust between January 2018 and December 2019. Where evidence is available in relation to this sub-set of cardiac arrest patients it is generally limited to small case series and we therefore we sought to improve knowledge and target therapeutic interventions.

Methods and results: Retrospective analysis of 253 cases was undertaken following abstraction from an established cardiac arrest database. Age ranged from 18-99 years with a median of 72 years (IQR 28) and 53.4% (n = 135) of patients were female. Overall thirty-day mortality was 94.5% (n = 239), with 48.2% (n = 122) of patients recognised life extinct in the out-of-hospital phase following termination of resuscitation. No significant differences in clinical characteristics stratified according to temperature group were identified. The presumed aetiology was infective in 62.8% (n = 159) of patients, and due to drug ingestion or heat illness in 7.5% (n = 19) and 2% (n = 5) respectively. In the remaining cases (27.7%, n = 70) it was not possible to determine the likely cause of the arrest.

Conclusions: Previous research relating to cardiac arrest complicated by hyperthermia is limited to case reports and small case series, suggesting that the current study represents the most comprehensive analysis of this sub-group of out-of-hospital cardiac arrest patients currently available. Most cases were associated with evidence of infection compared with drug related aetiologies and heat illness. Where indicated, cooling was applied infrequently using inconsistent methods.

Keywords: Cardiac arrest, Hyperthermia, Prehospital, Emergency medical services

Introduction

Cardiac arrest complicated by hyperthermia may occur due to a range of pathologies, most commonly infective, drug-induced and environmental aetiologies. In this setting, a temperature in excess of 37.7°C is generally regarded as supra-normal. There are fundamental differences in the mechanism of hyperthermia originating from pyrogenic infection versus other causes, with a central hypothalamic drive being a key trigger in the former. These differences are not addressed by current resuscitation guidelines. Although overall outcomes are poor, neurologically intact survival has been reported, even where temperatures historically regarded as fatal are encountered. Existing evidence regarding the epidemiology and management of out-of-hospital cardiac arrest associated with intra-arrest hyperthermia is largely confined to case reports focused almost exclusively on heat illness and drug-related presentations.

Resuscitation guidelines advocate active cooling in cases of hyperthermic cardiac arrest precipitated by heat illness or drug intoxication. Data from the era of mild therapeutic hypothermia (MTH) demonstrate that various methods of prehospital intra-arrest cooling are feasible, however efficacy in the presence of hyperthermia is unknown. As MTH is deemphasised in favour of targeted temperature management (TTM), prehospital cooling may become less available.

The London Ambulance Service NHS Trust (LAS) ranks amongst the largest Emergency Medical Services (EMS) globally, attending in excess of 10,000 cardiac arrest calls annually. The service maintains an established cardiac arrest registry spanning more than two decades, incorporating intra-arrest temperature recording from 2018 onwards. The aims of this study were to describe the epidemiology, clinical management and outcomes associated with out-of-hospital cardiac arrest complicated by hyperthermia utilising thirty-day survival as the primary outcome measure in patients with...
Return of Spontaneous Circulation (ROSC). Secondary objectives were to stratify odds of survival according to temperature range and compare clinical and demographic data according to likely aetiology, ROSC status and thirty-day survival.

Methods

Study design

Patients attended during January 2018 to December 2019 were retrospectively identified via the LAS Cardiac Arrest Registry. This is an established registry which captures information from a range of clinical and operational sources including patient clinical records, ambulance mobile data terminals, control room emergency call logs and defibrillator data. Collectively these data sources provide information on ambulance response and scene times, patient demographics, clinical observations and interventions, ROSC and receiving hospital where applicable. Patients of all ages who suffer cardiac arrest are included in the registry regardless of whether active resuscitation was attempted on arrival. Inclusion criteria were patients aged 18 years and above with a documented temperature ≥ 37.8 °C who received an active out-of-hospital Cardiopulmonary Resuscitation (CPR) attempt. Patients aged under 18 years and those who were recognised as life extinct with no active resuscitation attempted by responding ambulance staff were excluded. Records were reviewed by a single author to extract patient demographics and data relating to clinical observations and interventions. Likely aetiology was determined by retrospective review of the ambulance clinical record based on free-text notes recorded by responding paramedics and other ambulance staff. Where appropriate, thirty-day survival was determined by accessing the NHS summary care record. Ethical approval was not required as this study reports audit data via an established registry.

System overview

The LAS provides emergency medical services to a population of 8.2 million people within the Greater London area, operating from 69 ambulance stations covering 609 square miles. In excess of 1.5 million emergency calls are received annually and responded to by paramedics trained in advanced life support and other emergency ambulance staff trained in intermediate life support. Further critical care support is available via advanced paramedics and physician-paramedic helicopter emergency medical service. Clinical management is provided in accordance with the Joint Royal Colleges Ambulance Liaison Committee (JRCLAC) national clinical guidelines. Paramedics are authorised to terminate resuscitation autonomously in cases of asystole unresponsive to advanced life support and in other circumstances on a case-by-case basis with remote clinical support.

Data analysis

Data were entered into IBM SPSS version 26 (IBM Corp. Released 2019, IBM SPSS Statistics for Windows Version 26.0. Armonk, NY: IBM Corp). Demographic and clinical data were analysed using descriptive statistics including measures of central tendency. Outcome data were stratified according to temperature range, aetiology and presenting ECG rhythm to facilitate analysis via chi-square and odds ratios with accompanying 95% confidence intervals. Categorical data were analysed using Mann Witney U and Kruskal-Wallis tests for comparisons of two or multiple groups respectively with statistical significance set at $p < 0.05$.

Results

A total of 264 cases were retrieved. Following initial review, eleven were excluded due to age < 18 years ($n = 8$) or temperature < 37.8 °C ($n = 3$) yielding a final sample of 253 patients. Thirty-day mortality outcomes were available for 250. Age ranged from 18-99 years with a median of 72 years (IQR 28) and 53.4% ($n = 135$) of patients were female. The onset of cardiac arrest was witnessed in 66% ($n = 167$) of cases, and bystander CPR performed in 75% ($n = 190$). Median ambulance response time was 8 minutes (IQR 6). The first monitored ECG rhythm was shockable in 9.1% ($n = 23$) of cases and return of spontaneous circulation (ROSC) was achieved in 40.7% ($n = 103$). Intra-arrest temperature ranged from 37.8 °C-42.5 °C (mean 38.8 °C, SD 1.03). Overall thirty-day mortality was 94.5% ($n = 239$), with 48.2% ($n = 122$) of patients recognised life extinct in the out-of-hospital phase following termination of resuscitation.

No significant differences in clinical characteristics stratified according to temperature range were identified (Table 1). The presumed aetiology was infective in 62.8% ($n = 159$) of patients, and due to drug ingestion or heat illness in 7.5% ($n = 19$) and 2% ($n = 5$) respectively. In the remaining cases (27.7%, $n = 70$) it was not possible to determine the likely cause of the arrest. There was no significant variation in the proportions of patients in each temperature range and no single aetiology was associated with higher temperatures. In patients with drug intoxication, the likely causative agent was unknown in more than half of cases ($n = 10$) and identified as either Methyleneoxyamphetamine (MDMA) ($n = 3$) or cocaine ($n = 6$) in the remainder. Patients with presumed infective aetiolgies were significantly older (mean 74 years) than those with

| Temperature Range | 37.8–38.9 °C ($n = 169$) | 39.0–39.9 °C ($n = 51$) | 40.0–40.9 °C ($n = 28$) | 41.0–41.9 °C ($n = 8$) | >42 °C ($n = 5$) | p |
|-------------------|--------------------------|------------------------|------------------------|------------------------|-----------------|---|
| Median Age (IQR) | 74 (27.50) | 71 (30.00) | 60 (23.00) | 75 (31.25) | 65 (39.50) | <0.05 |
| Male Gender | 78 (46.2%) | 20 (39.2%) | 12 (63.2%) | 4 (50.0%) | 4 (46.6%) | 0.38 |
| Witnessed Arrest | 113 (66.9%) | 35 (68.6%) | 11 (57.9%) | 5 (62.5%) | 3 (50.0%) | 0.83 |
| Bystander CPR | 124 (73.4%) | 40 (78.4%) | 13 (68.4%) | 7 (87.5%) | 6 (100%) | 0.45 |
| Shockable | 18 (10.7%) | 4 (7.8%) | 1 (5.3%) | 0 (0.0%) | 0 (0.0%) | 0.68 |
| ROSC | 76 (45.0%) | 19 (37.3%) | 6 (31.6%) | 2 (25.0%) | 0 (0.0%) | 0.13 |
| ROSR | 30 (17.5%) | 5 (9.8%) | 1 (5.3%) | 0 (0.0%) | 0 (0.0%) | 0.19 |
| ROSC to Hospital | 52 (54.7%) | 14 (51.9%) | 2 (25.0%) | 1 (50.0%) | 0 (0.0%) | 0.21 |
| 30 day survival | 9 (5.4%) | 1 (2.0%) | 1 (5.3%) | 0 (0.0%) | 0 (0.0%) | 0.78 |
heat illness (mean 58 years), or drug related presentations (mean 42 years).

The majority of patients were asystolic on arrival of the ambulance service (n = 155, 61.3%), with the remainder presenting in PEA (n = 75, 29.6%) or VF or pulseless VT (n = 23, 9.1%). There was no significant variation between temperature groups in the proportions of patients presenting in each ECG category, however no shockable rhythms were observed in any case with a temperature ≥ 41 °C. Significantly higher proportions of patients achieved ROSC in the prehospital phase where the cardiac arrest was witnessed (47.9%, n = 80 versus 26.7% n = 23, 95% CI 1.43–4.43, p < .001) and where bystander CPR was performed (44.2%, n = 84 versus 30.2% n = 19, 95% CI 1.00–3.38, p = .049). A significantly higher proportion of shockable ECG rhythms were observed in survivors (18.2%, n = 4 versus 3.1% n = 7, 95% CI 1.88–26.24, p < .001). Unadjusted odds of survival did not vary significantly between temperature groups (Table 2).

Patients achieving ROSC had a significantly shorter median scene time, were administered lower doses of adrenaline and normal saline, and exhibited higher End Tidal Carbon Dioxide (ETCO2) and blood glucose levels alongside a lower median temperature (Table 3). Similarly, patients alive thirty days post event had significantly shorter arrival at scene to ROSC and total prehospital times and were administered lower doses of normal saline (Table 4). In the majority of survivors (90%, n = 9) no intra-arrest adrenaline was administered. Documented evidence of cooling was observed using a passive approach in one patient and active methods in a further two, all of whom were drug-related cases.

### Table 2 – Unadjusted odds of survival stratified by temperature range.

| Temperature Range                        | Unadjusted OR | 95% CI Lower | 95% CI Upper |
|-----------------------------------------|---------------|--------------|--------------|
| 39.0–39.9 °C versus 37.8–38.9 °C         | 0.42          | 0.07         | 2.76         |
| 40.0–40.9 °C versus 39.0–39.9 °C         | 1.86          | 0.44         | 7.85         |
| >40.0 °C versus < 40 °C                  | 0.70          | 0.11         | 4.67         |

### Table 3 – Demographic and clinical data according to ROSC status for all patients.

| Variable                      | Yes (n = 103) | No (n = 150) | p value |
|-------------------------------|---------------|--------------|---------|
| Age (years)                   | 73.00 (30.75) | 71.00 (26.25)| 0.70    |
| Response time (minutes)       | 8.00 (6.00)   | 8.00 (5.00)  | 0.71    |
| Arrival to ROSC (minutes)     | 28.00 (24.00) | 23.50 (29.50)| 0.59    |
| Total intra-arrest adrenaline (mg) | 4.00 (5.00) | 6.00 (3.00)  | <0.001  |
| Total post ROSC adrenaline (mcg) | 300.00 (300.00) | 400.00 (NA) | 0.30    |
| Total volume saline (ml)      | 500.00 (750.00) | 287.50 (447.50) | <0.001 |
| Highest ETCO2 (kPa)           | 5.75 (4.30)   | 4.30 (3.98)  | <0.001  |
| Temperature (°C)              | 38.40 (1.08)  | 38.60 (1.45) | 0.02    |
| Blood glucose (mmol/l)        | 9.40 (6.30)   | 7.80 (6.08)  | 0.01    |

### Table 4 – Demographic and clinical data according to thirty-day survival status for all patients.

| Variable                      | Alive (n = 11) | Deceased (n = 239) | p value |
|-------------------------------|---------------|-------------------|---------|
| Age (years)                   | 56.00 (29.00) | 72.00 (26.00)     | 0.29    |
| Response time (minutes)       | 7.00 (6.00)   | 8.00 (5.00)       | 0.35    |
| Arrival to ROSC (minutes)     | 6.50 (31.75)  | 30.00 (21.00)     | 0.01    |
| Total intra-arrest adrenaline (mg) | 0.00 (N/A) | 6.00 (4.00)       | <0.001  |
| Total post ROSC adrenaline (mcg) | 200.00 (300.00) | 300.00 (N/A)     | 0.67    |
| Total volume saline (ml)      | 20.00 (277.50) | 345.00 (608.75)  | 0.02    |
| Highest ETCO2 (kPa)           | 3.90 (1.30)   | 4.90 (3.70)       | 0.36    |
| Temperature (°C)              | 38.10 (0.70)  | 38.50 (1.30)      | 0.13    |
| Blood glucose (mmol/l)        | 9.90 (1.90)   | 8.60 (6.73)       | 0.32    |

**Discussion**

Out-of-hospital cardiac arrest complicated by hyperthermia occurs infrequently with the majority of cases attributable to infective aetiologies in older patients. The mean age of participants (68 years) was similar to that reported in national8 (68.6 years, SD 19.6) and London datasets (65 years, SD 16.7)7. Higher rates of witnessed arrest (52.7% versus 66%), bystander CPR (75.0% versus 61.0%) and ROSC
A greater proportion of cases were asystolic on ambulance service arrival (61.3% versus 41.4%) with comparatively less patients presenting in a shockable rhythm (9.1% versus 20.6%).

In keeping with internationally recognised pre-arrival predictors of survival following OHCA, higher rates of ROSC were observed where the arrest was witnessed and bystander CPR was performed. In contrast, the only significant finding in relation to thirty-day survival was a higher proportion of shockable rhythms amongst survivors which was not replicated in findings relating to ROSC. Asystole is an uncommon finding in prior case reports relating to hyperthermic cardiac arrest, however these are exclusively based on patients transported to hospital as opposed to those where resuscitation was terminated in the field. As a consequence, the incidence of asystole in this patient group may be underestimated depending on variation in local guidelines and practices relating to cessation of resuscitation.

In most cases, cardiac arrest was preceded by infection as opposed to heat illness or drug ingestion, with no significant difference in temperature distribution between aetiological groups. This must be balanced against relatively limited numbers of heat illness or drug induced cases. Of note, cases with a temperature ≥ 41 °C were due exclusively to heat illness or drug intoxication and had universally fatal outcomes. This appears consistent with existing albeit limited literature addressing drug related hyperthermia which indicates a correlation between increasing temperature and mortality with hyperthermia ≥ 41.5 °C reportedly associated with mortality rates in excess of 60% in the context of MDMA. Similar trends are observed in relation to heat illness, with temperatures ≥ 41 °C associated with increased mortality. However, case reports suggest neurologically intact survival is possible following cardiac arrest with temperatures exceeding these thresholds from both drug aetiologies and heat illness.

Interventions to promote cooling were initiated infrequently, regardless of whether these were active or passive. Cooling is recommended in both heat illness and drug induced non- pyrogenic hyperthermia. In these instances, anti-pyretics are not effective and prompt cooling is associated with prevention of deterioration and improved outcomes. Recommended methods such as cold water immersion are not routinely available outside the setting of pre-planned events, however a number of cooling devices have been successfully deployed in the prehospital phase.

Limited evidence exists in relation to cardiac arrest precipitated by infection, however use of antipyretics has not been shown to improve survival and may worsen outcomes in intensive care settings. Hepatic and renal toxicity associated with antipyretics such as NSAIDS and paracetamol are also compelling reasons not to administer such agents, especially in circumstances where preceding drug history is unknown and overdose may result. Adherence to standard sepsis guidelines is advocated in the context of cardiac arrest, with intravenous fluids and adrenaline forming the mainstay of treatment aside from antimicrobial therapy.

**Limitations**

The current study is subject to many of the limitations associated with retrospective chart review utilising data not primarily collected for research purposes. A single author abstracted data and determined likely aetiology based on free text clinical notes and emergency call log data, introducing the potential for bias. Identification of patients was also dependent on accurate coding of the clinical condition by the attending ambulance crew. It is possible that some patients attended prior to the onset of cardiac arrest may have been initially classified on the basis of their presenting complaint rather than subsequent cardiac arrest. Similarly, patients who suffered cardiac arrest after hospital arrival would also not have met study inclusion criteria.

Clinical notes were not sufficiently comprehensive to determine aetiology in more than a quarter of cases (27.7%, n = 70) limiting the extent to which generalisations relating to the entire study population can be made. The three patients in whom thirty-day survival could not be determined were all drug-related cases which may have further confounded outcome analysis. The study exclusively comprised patients who suffered cardiac arrest with evidence of hyperthermia as distinct from respiratory arrest or non-arrest hyperthermia cases with evidence of life-threatening illness. The study population therefore likely represents an underestimate of the prevalence of critical illness associated with hyperthermia in the host ambulance service.

With the exception of drug-related presentations, no further data relating to drug history including prescribed medication were collected. Use of medications such as anti-pyretics or steroids in the period preceding cardiac arrest may have resulted in lower temperature measurements than might otherwise have been the case. Similarly, no provision was made to collect data relating to previous medical history due to registry limitations. This includes factors such as day-to-day care requirements, smoking status or alcohol consumption as well as diagnosed medical conditions which may have influenced outcome.

Measurement of temperature was predominantly via tympanic thermometry. Although rectal thermometers are available it was not possible to consistently determine which device was used in each case. Outcome measures were limited to ROSC and thirty-day survival and no assessment of neurological function post event was undertaken. No data were available in relation to receiving hospital or in-hospital management and subsequent clinical course. Multiple confounders relating to the hospital phase of care may have influenced outcome in the current study, however these could not be accounted for or incorporated in the analysis.

**Conclusion**

Previous research relating to cardiac arrest complicated by hyperthermia is limited to case reports and small case series, suggesting that the current study represents the most comprehensive analysis of this sub-group of out-of-hospital cardiac arrest patients currently available. Most cases were associated with evidence of infection compared with drug related aetiologies and heat illness.

Where indicated, cooling was applied infrequently using inconsistent methods. Current improvised approaches limited to surface and passive cooling may prove inadequate in the context of hyperthermic cardiac arrest. Further guidance regarding optimal management in the small but potentially treatable sub-set of cardiac arrest patients where active cooling is indicated is required.

**Conflicts of Interest**

None.
REFERENCES

1. Ogoina D. Fever, fever patterns and diseases called ‘fever’-a review. J Infect Public Health 2011;4:108–24.
2. O’Grady NP, Barie PS, Bartlett JG, Bleck T, Carroll K, Kalil AC, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med 2008;36:1330–49.
3. Walter E, Carraretto M. Drug-induced hyperthermia in critical care. J Intensive Care Soc 2015;16:306–11.
4. Voizeux P, Lewandowski R, Daily T, Ellouze O, Bouchot O, Bouhemad B, et al. Case of cardiac arrest treated with extra-corporeal life support after MDMA intoxication. Case Reports in Critical Care 2019:2019:7825915.
5. Lott C, Truhlar A, Alfonzo A, Barelli A, Gonzalez-Salvado V, Hinkelbein J, et al. European Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstances. Resuscitation 2021;161:152–219.
6. Lindsay PJ, Buell D, Scales DC. The efficacy and safety of pre-hospital cooling after out-of-hospital cardiac arrest: a systematic review and meta-analysis. Critical care (London, England) 2018;22:66.
7. Fothergill RT, Watson LR, Chamberlain D, Virdi GK, Moore FP, Whitbread M. Increases in survival from out-of-hospital cardiac arrest: a five year study. Resuscitation 2013;84:1089–92.
8. Hawkins C, Booth S, Ji C, Brace-McDonnell SJ, Whittington A, Mapstone J, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. Resuscitation 2017;110:133–40.
9. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2010;3:63–81.
10. Yan S, Gan Y, Jiang N, Wang R, Chen Y, Luo Z, et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Critical care (London, England) 2020;24:61.
11. Jiang J, Yuan Z, Huang W, Wang J, 2. 4-dinitrophenol poisoning caused by non-oral exposure. Toxicol Ind Health 2011;27:323–7.
12. Hall AP, Henry JA. Acute toxic effects of ‘Ecstasy’ (MDMA) and related compounds: overview of pathophysiology and clinical management. British J Anaesthesia 2006;96:678–85.
13. Armenian P, Mamantov TM, Tsutaoka BT, Gerona RR, Silman EF, Wu AH, et al. Multiple MDMA (Ecstasy) overdoses at a rave event: a case series. J Intensive Care Med 2013;28:252–6.
14. Sprague JE, Moze P, Caden D, Rusyniak DE, Holmes C, Goldstein DS, et al. Carvedilol reverses hyperthermia and attenuates rhabdomyolysis induced by 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) in an animal model. Critical Care Med 2005;33:1311–6.
15. Gowing LR, Henry-Edwards SM, Irvine RJ, Ali RL. The health effects of ecstasy: a literature review. Drug Alcohol Rev 2002;21:53–63.
16. Argaud L, Ferry T, Le OH, Marfisi A, Corba D, Achache P, et al. Short- and long-term outcomes of heatstroke following the 2003 heat wave in Lyon, France Arch Intern Med 2007;167:2177–83.
17. Marfisi A, Genty A, Ferry T, Martin O, Druzeau R, Robert D, et al. Fever as a prognostic factor for heat stroke. Presse medicale (Paris, France : 1983) 2008;37:406–11.
18. Ramirez O, Malyshyev Y, Sahni S. It’s Getting Hot in Here: A Rare Case of Heat Stroke in a Young Male. Cureus 2018;10:e3724.
19. Calabro L, Bougouin W, Cariou A, De Fazio C, Skrifvars M, Soreide E, et al. Effect of different methods of cooling for targeted temperature management on outcome after cardiac arrest: a systematic review and meta-analysis. Crit Care 2019;23:285.
20. Leoni D, Rello J. Cardiac arrest among patients with infections: causes, clinical practice and research implications. Clin Microbiol Infect 2017;23:730–5.
21. Drewry AM, Aborodepey EA, Murray ET, Stoll CRT, Izadi SR, Dalton CM, et al. Antipyretic therapy in critically ill septic patients: A systematic review and meta-analysis. Critical Care Med 2017;45:806–13.