Cardiovascular complications of prehospital emergency anaesthesia in patients with return of spontaneous circulation following medical cardiac arrest: a retrospective comparison of ketamine-based and midazolam-based induction protocols

Christopher King ,[1] Asher Lewinsohn,[1] Chris Keeliher,[1] Sarah McLachlan,[2,3] James Sherrin,[4] Hafsah Khan-Cheema,[4] Peter Sherren[1]

Handling editor Caroline Leech

[1]Essex & Herts Air Ambulance Trust, Essex, UK
[2]Research Department, Essex & Herts Air Ambulance, Essex, UK
[3]Department of Allied Health and Medicine, Anglia Ruskin University, Chelmsford, UK
[4]University College London Medical School, London, UK

Correspondence to
Dr Christopher King, Essex & Herts Air Ambulance Trust, Essex, Colchester CO6 2NS, UK; christopher.king2@nhs.net

Received 14 August 2020
Accepted 19 September 2021

To cite: King C, Lewinsohn A, Keeliher C, *et al*. *Emerg Med J* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/emermed-2020-210531

ABSTRACT

Background Hypotension following intubation and return of spontaneous circulation (ROSC) after cardiac arrest is associated with poorer patient outcomes. In patients with a sustained ROSC requiring emergency anaesthesia, there is limited evidence to guide anaesthetic practice. At the Essex & Herts Air Ambulance Trust, a UK-based helicopter emergency medical service, we assessed the relative haemodynamic stability of two different induction agents for post-cardiac arrest medical patients requiring prehospital emergency anaesthesia (PHEA).

Methods We performed a retrospective database review over a 5-year period between December 2014 and December 2019 comparing ketamine-based and midazolam-based anaesthesia in this patient cohort. Our primary outcome was clinically significant hypotension within 30 min of PHEA, defined as a new systolic BP less than 90 mm Hg, or a 10% drop if less than 90 mm Hg before induction.

Results One hundred ninety-eight patients met inclusion criteria. Forty-eight patients received a ketamine-based induction, median dose (IQR) 1.00 (1.00–1.55) mg/kg, and a 150 midazolam-based regime, median dose 0.03 (0.02–0.04) mg/kg. Hypotension occurred in 54.2% of the ketamine group and 50.7% of the midazolam group (p=0.673). Mean maximal HRs within 30 min of PHEA were 119 beats/min and 122 beats/min, respectively (p=0.523). A shock index greater than 1.0 beats/min/mm Hg and age greater than 70 years were both associated with post-PHEA hypotension with ORs 1.96 (CI 1.02 to 3.71) and 1.99 (CI 1.01 to 3.90), respectively. Adverse event rates did not significantly differ between groups.

Conclusion PHEA following a medical cardiac arrest is associated with potentially significant cardiovascular derangements when measured up to 30 min after induction of anaesthesia. There was no demonstrable difference in post-induction hypotension between ketamine-based and midazolam-based PHEA. Choice of induction agent alone is insufficient to mitigate haemodynamic disturbance, and alternative strategies should be used to address this.

Key messages

What is already known about this subject

- Patients with return of spontaneous circulation (ROSC) after cardiac arrest can have significant physiological derangement.
- It is not known what the optimal anaesthetic induction drug regime is for such patients in the resource-limited prehospital environment.
- Ketamine is a widely used prehospital induction agent, yet is traditionally avoided in hospital during cardiac anaesthesia due to potentially increased myocardial oxygen demand.

What this study adds

- In this retrospective study of prehospital emergency anaesthesia following cardiac arrest, hypotension occurred frequently.
- Both ketamine-based and midazolam-based anaesthetics showed similar incidence of hypotension within 30 min of anaesthetic induction.
- Alternative strategies to address post-induction hypotension should be employed, for example, anaesthetic dose reduction or co-administration of inotropes.

INTRODUCTION

Patients with return of spontaneous circulation (ROSC) can have significant physiological derangement driven by their primary pathology and the consequences of the ischaemic reperfusion injury as part of the 'post-cardiac arrest syndrome'.[1] Definitive airway management combined with treatment of the underlying aetiology and appropriate neuroprotection are a cornerstone of post-resuscitation care. However, emergency anaesthesia in such patients is not without significant risk given the observed haemodynamic instability. Hypotension following emergency intubation or ROSC is associated with increased mortality.[2 3] In patients with a sustained ROSC requiring emergency anaesthesia, there is limited evidence to guide anaesthetic practice. The ideal anaesthetic regime would induce an unconscious state smoothly, attenuate the sympathetic response to laryngoscopy, limit myocardial oxygen demand and maintain haemodynamic stability while optimising laryngoscopy conditions. Given some of the unique challenges of prehospital emergency medicine, consideration must also be

given to the simplicity of dosing, team familiarity, environmental stability and therapeutic drug index.

Ketamine is a commonly used induction agent in prehospital emergency medicine with a stable haemodynamic profile and desirable therapeutic index. While ketamine can have a direct myocardial depressant effect, the cardiac output is usually augmented through potentiation of catecholamines and direct stimulation of the sympathetic nervous system.[4] In healthy patients, this mechanism can be responsible for a 20%–25% increase in the BP,[5] however, this effect is a little more unpredictable in patients requiring anaesthesia for emergency surgery.[6 7] A high shock index (SI) in particular seems to be associated with a blunted hypertensive response and more frequent hypotension during prehospital emergency anaesthesia (PHEA).[8]

While the traditional 'cardiac anaesthetic' with gentle titration of high-dose opiates and low-dose hypnotic is ideal in elective anaesthesia with invasive cardiac monitoring, it may not suit the resource-limited and complex prehospital environment when combined with a cardiovascularly unpredictable patient.[9] Low-dose benzodiazepines may also fail to penetrate the brain effector sites quickly enough to be effective for a rapid sequence induction.[10] A prospective Japanese registry study showed lower rates of hypotension in haemodynamically unstable patients without preceding cardiac arrest when induced with ketamine, compared with either midazolam or propofol.[11] In hospitalised patients with ST-elevation myocardial infarction requiring intubation, midazolam use was again associated with a greater rate of hypotension when compared with ketamine.[12] However, our own service has demonstrated an acceptable cardiovascular profile following PHEA with a standardised fentanyl–midazolam–rocuronium induction.[13]

The objective of this study was to assess the haemodynamic stability of two different induction agents for post-cardiac arrest medical patients requiring PHEA.

METHODS

Essex & Herts Air Ambulance Trust (EHAAT) is a UK-based physician-paramedic helicopter emergency medicine service (HEMS) which responds to critically ill and injured patients of all ages. The team are available 24 hours a day 7 days a week, flying during daylight hours and driving on a rapid response vehicle after dark and in poor weather. Medical emergencies including cardiac arrests account for approximately 40% of the patient caseload. A HEMS paramedic working in the ambulance service control room screens calls and will task EHAAT to cardiac arrests where they feel the additional critical care resource would be advantageous.

The service offers PHEA guidance to clinicians in the form of a standard operating procedure (SOP). This outlines expectations on the prehospital management of anaesthesia in critically ill and injured patients. Indications for PHEA following ROSC in medical cardiac arrest include actual or impending airway compromise (including protection and maintenance); respiratory failure; and anticipated clinical course where the patient is expected to deteriorate rapidly or when intubation and ventilation will have a major impact on expediting life-saving intervention at hospital. The SOP allows some flexibility on the choice of hypnotic agent in medically ill patients. Haemodynamically stable patients receive a '3:2:1' induction with 3 µg/kg fentanyl, 2 mg/kg ketamine and 1 mg/kg rocuronium. Those patients with haemodynamic compromise or frailty receive a '1:1:1' induction with 1 µg/kg fentanyl, 1 mg/kg ketamine and 1 mg/kg rocuronium. Patient weights are estimated by the attending team. Clinical judgement is employed and dose reduction is encouraged in post-cardiac arrest patients. Rocuronium-only induction may take place in moribund patients as part of a 'crash intubation'. Clinicians are empowered to use alternative pharmacological doses and agents provided there is justification and team consensus. The service additionally carries the hypnotics midazolam and propofol. Propofol is only used in very specific circumstances given its narrow therapeutic window. Within the SOP, dosing of midazolam is left to clinician discretion within the range of 0.01–0.1 mg/kg. Titrated boluses or infusion of diluted epinephrine is used as an inopressor if required.

This was a retrospective database review using electronic notes on HEMSbase (Medic One Systems, Tadworth, UK). Five years of non-traumatic cardiac arrest patients attended by our service between 9 December 2014 and 8 December 2019 were reviewed. Patients were included if they had ROSC and PHEA with placement of an endotracheal tube, receiving either ketamine or midazolam as their induction agent. Patients were excluded if a pre-induction BP was unavailable, haemodynamic data were incomplete for the duration of anaesthesia or drug administration times were not recorded. Pre-administration of an induction agent at sedative doses was added to the induction dose to give a cumulative hypnotic dose. The cumulative dose was used for subsequent analysis. Midazolam administration as a sedative prior to PHEA did not preclude analysis within the ketamine group, nor did ketamine sedation in the group anaesthetised with midazolam. Doses and timings of drugs administered were recorded. Anaesthesia was maintained using an intermittent bolus regime of the clinicians' choosing, titrated to clinical effect. Patient observations were recorded on either the current Tempus Pro monitor (RDT, Basingstoke, UK) or previously on the Zoll X-series monitor (Zoll, Runcorn, England), and uploaded to an electronic patient record on HEMSbase. Non-invasive BP was measured at 2-minute intervals. ECG, oxygen saturation and end-tidal carbon dioxide were measured continuously.

When comparing the midazolam versus ketamine groups, the primary outcome measure was clinically significant hypotension post-PHEA. This was defined as a new systolic BP (SBP) less than 90 mm Hg within 30 min of induction or a 10% drop if SBP was less than 90 mm Hg before induction, a locally agreed standard used for clinical governance purposes. The time to lowest SBP within 30 min of induction was recorded. A number of secondary outcome measures were collected, including: the mean lowest and highest post-induction SBP within each group within 30 min; the mean percentage change in SBP between the pre-PHEA reading and the lowest reading within 30 min; maximum HR and the mean percentage change in HR between the pre-PHEA reading and maximum value within 30 min. Patient demographics, incident timings, triage location and drug doses were noted as well as airway management outcomes. Post-PHEA complications described in the notes were recorded, which included sustained arrhythmias, administration of resuscitation fluids and dilute epinephrine, anaesthetic awareness and re-arrest before arrival at hospital. The incidence of post-induction hypotension across groups was also compared, based on patient age, low flow duration and SI using thresholds from other studies.[14–16] Low flow was defined as time from collapse to ROSC, or 999 call time to ROSC if the time of collapse was not available.

Data were exported into a spreadsheet (Microsoft Excel, Washington, USA) and analysed with JASP V.0.11.1 (JASP team, Amsterdam, the Netherlands) and SPSS V.26 (IBM). X^2 testing was used to compare categorical outcomes between groups including the primary outcome. The independent samples t-test was used to compare continuous variables. Drug doses were compared between groups using the Mann-Whitney U test as the distributional assumptions of the independent samples t-test were not met. A p value

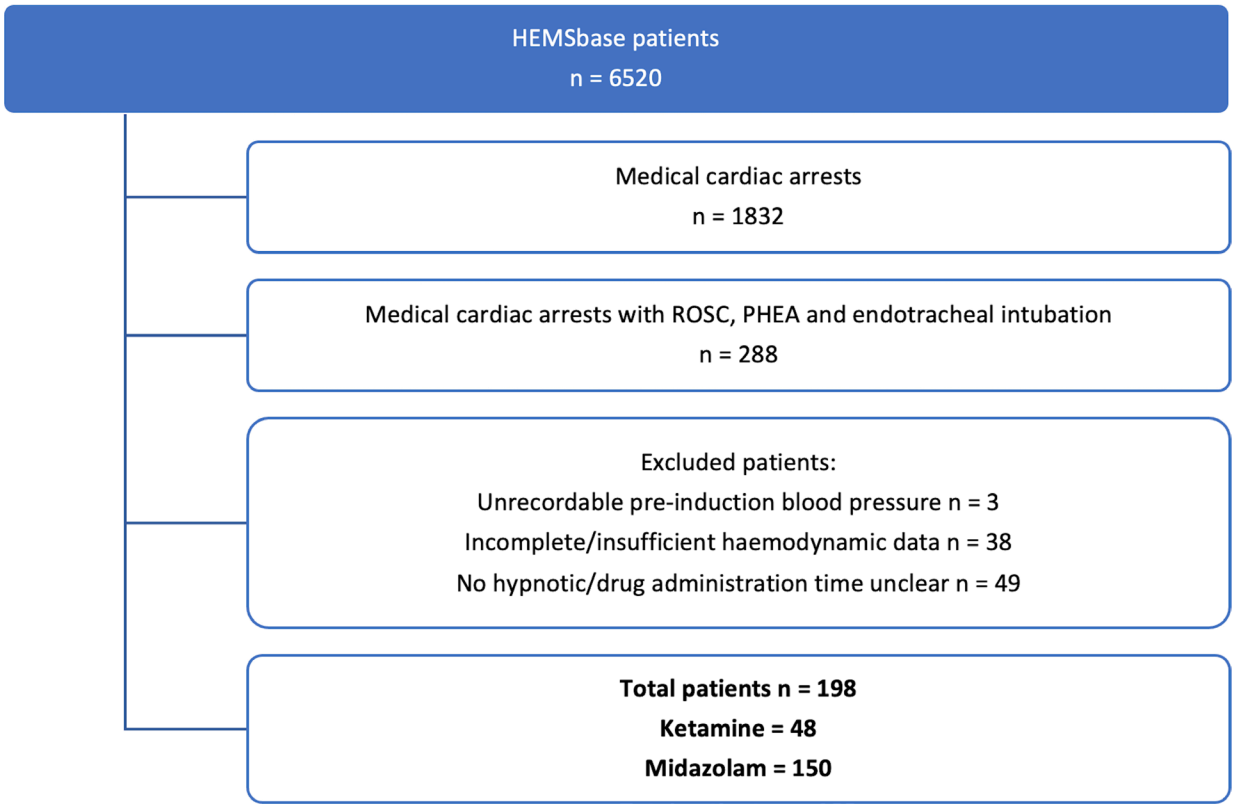

Figure 1 Patient flow chart showing selection of patients for inclusion in the analysis. PHEA, prehospital emergency anaesthesia; ROSC, return of spontaneous circulation.

of <0.05 was considered statistically significant. Given the collection of a reliable and complete data set was limited to the period that EHAAT has used the HEMSbase electronic patient record, a convenience sample based on all missions from this 5-year period was decided on.

Patient and public involvement

Patients were not involved in the design of the study. Our service employs patient liaison managers who regularly meet with our cardiac arrest survivors. Where appropriate, findings from this work will be shared directly with them to explain the continuous evolution of our clinical practice.

RESULTS

Over the 5-year study period, EHAAT attended 6520 patients, 1832 of whom were in cardiac arrest. Of these, 288 had ROSC and underwent PHEA with endotracheal intubation. Ninety met exclusion criteria (figure 1), leaving 198 patients. Group-specific demographics and baseline physiology immediately prior to PHEA are provided in table 1. Mean estimated weight was 83 kg (SD 15 kg) with 20% (41 of 198) weighing 100 kg or more. Cormack and Lehane laryngoscopy grade was I or II in 93% (184 of 198) of patients, with a 95% (188 of 198) first pass success rate of tracheal intubation. Twenty-five per cent (12 of 48) of patients receiving ketamine were transported by

Table 1 Baseline characteristics; mean (SD), number (proportion) or median (IQR)

	Ketamine (n=48)	Midazolam (n=150)	Difference (95% CI)	OR (95% CI)	P value
Age, years	56.7 (17.3)	59.5 (14.5)	−2.8 (−7.7 to +2.2)		0.273
Weight, kg	80.3 (19.2)	83.5 (13.5)	−3.2 (−8.2 to 1.8)		0.212
Sex, male	35 (72.9%)	116 (77.3%)		0.79 (0.38 to 1.66)	0.531
Witnessed cardiac arrest	44 (91.7%)	128 (85.3%)		1.89 (0.62 to 5.79)	0.258
Bystander CPR	29 (60.4%)	111 (74%)		0.54 (0.27 to 1.06)	0.074
Low-flow state duration, min	21.4 (10.2)	21.5 (12.8)	−0.2 (−4.3 to 4.0)		0.942
Shockable rhythm (VF/VT/AED shock)	33 (68.8%)	121 (80.7%)		0.53 (0.25 to 1.10)	0.087
SBP, mm Hg	130 (33)	132 (34)	−3 (−14 to 8)		0.634
HR, beats/min	99 (27)	105 (30)	−6 (−16 to 3)		0.189
SI, beats/min/mm Hg	0.80 (0.27)	0.84 (0.30)	−0.04 (−0.13 to 0.06)		0.443
SpO_2, %	93 (9)	94 (11)	0 (−4 to 3)		0.858
GCS	3 (3–6)	3 (3–5)			0.936

AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; SBP, systolic BP; SI, shock index; SpO_2, oxygen saturation; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2 Induction drug dose data; values are number (proportion) or median (IQR)

	Ketamine (n=48)	Midazolam (n=150)	P value
Midazolam use	11 (22.9%)	150 (100%)	
Midazolam total dose, mg/kg	0.04 (0.02–0.06)	0.03 (0.02–0.04)	0.165
Ketamine dose, mg/kg	1.00 (1.00–1.55)	Not applicable*	
Fentanyl use	39 (81.3%)	119 (79.9%)	0.773
Fentanyl dose, µg/kg	1.43 (1.00–2.82)	1.43 (1.00–1.88)	0.429
Rocuronium dose, mg/kg	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.520

*Value excluded as only single patient.

air compared with 29% (44 of 150) of those receiving midazolam. Median scene times were 35 (IQR 31–47) and 37 (IQR 30–45) min, respectively. PHEA to hospital times were the same for both groups at 39 min (IQR 29–50). Thirty-three per cent (65 of 198) of all patients were conveyed directly to a facility for primary percutaneous coronary intervention.

Forty-eight patients were induced with a combination including ketamine and rocuronium and 150 with midazolam and rocuronium. Drug dosing data are provided in table 2.

Haemodynamic consequences and adverse events following PHEA are outlined in figure 2 and table 3. Clinically significant hypotension within 30 min of PHEA, defined as an SBP less than 90 mm Hg or a 10% drop if SBP was less than 90 mm Hg before induction, occurred in 54.2% of the ketamine group and 50.7% of the midazolam group (p=0.673), with an OR of 1.15 (CI 0.60 to 2.21). The median time to SBP minimum was 13 min (IQR 8–20) across all patients.

Across both groups, fentanyl administration or omission did not significantly influence clinically significant hypotension (50.3% (20 of 39) vs 56.3% (67 of 119), respectively, p=0.495), maximum HR (121 vs 124 beats/min, p=0.664) or maximum SBP (154 vs 158 mm Hg, p=0.392).

There were no incidents of anaesthetic awareness reported in this study population.

An age of ≥70 years (p=0.041) and SI of ≥1.0 beats/min/mm Hg (p=0.046) were both associated with post-PHEA hypotension, with ORs of 1.96 (CI 1.02 to 3.71) and 1.99 (CI 1.01 to 3.90), respectively (table 4).

DISCUSSION

This retrospective study demonstrated no significant statistical difference in the rate of hypotension or tachycardia following PHEA with either ketamine or midazolam in patients with a ROSC following a medical cardiac arrest. The high rate of post-induction hypotension present in both cohorts exemplifies the inherent cardiovascular instability of patients with ROSC after cardiac arrest with a high prevalence of myocardial infarctions and ventricular stunning.[1] The primary outcome of hypotension was defined using a metric felt to be clinically significant by our organisation, representing the threshold at which end organ perfusion might reasonably be compromised. A value of SBP less than 90 mm Hg is widely used in the literature, but definitions are more varied for analysing patients already hypotensive below this value prior to induction.[13 16 17] Secondary outcomes using alternative definitions of hypotension also showed no significant difference between groups.

Although there is limited published literature reporting anaesthesia in comparable high-acuity cohorts, our cardiovascular data compare favourably with what is available; in particular, the low rate of peri-intubation cardiac arrest.[12 18] Prehospital data published previously by our own organisation reported a lower rate of hypotension following PHEA with fentanyl–midazolam–rocuronium (31.2%), however, BP measurements were only observed for the first 9 min following induction. The

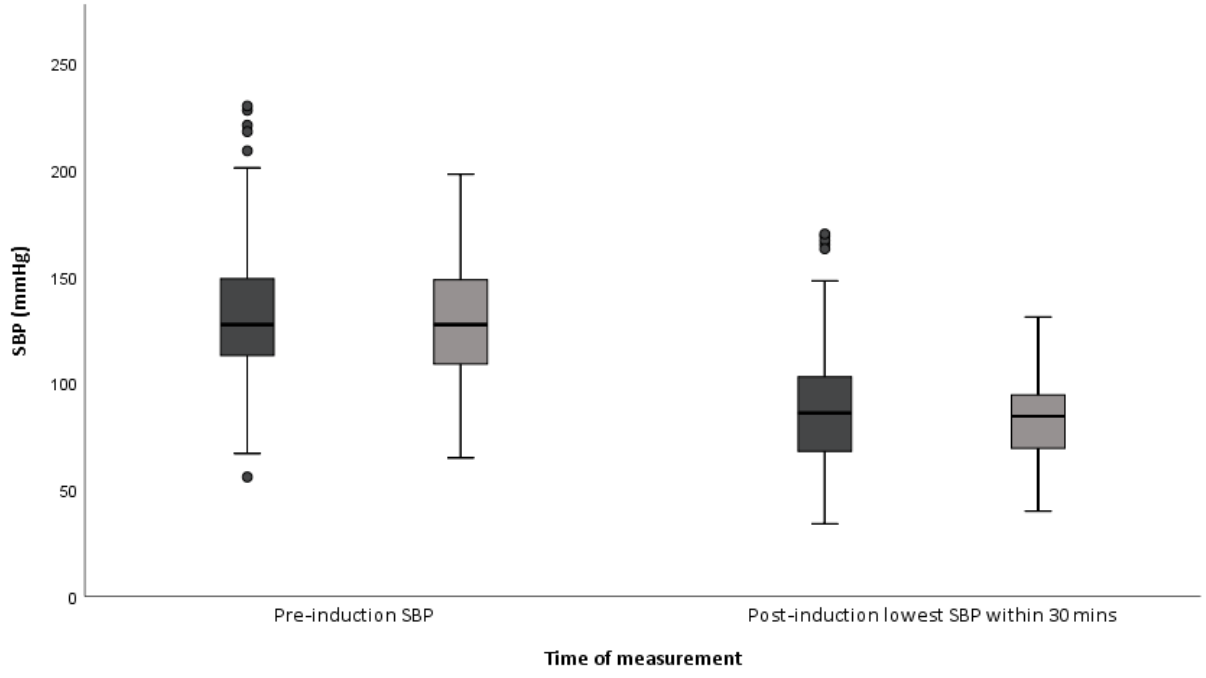

Figure 2 Boxplot of systolic blood pressure (SBP) immediately pre-induction and lowest value within next 30 min post-induction for patients anaesthetised with either ketamine (light grey) or midazolam (dark grey).

Table 3 Haemodynamic consequences within 30 min of anaesthetic induction and adverse events; number (proportion), mean (SD) or median (IQR)

	Ketamine (n=48)	Midazolam (n=150)	Difference (95% CI)	OR (95% CI)	P value
BP					
New SBP <90 mm Hg or a 10% drop if SBP <90 mm Hg before induction	26 (54.2%)	76 (50.7%)		1.15 (0.60 to 2.21)	0.673
Minimum SBP, mm Hg	85 (21)	88 (28)	−2.9 (−11.7 to 5.9)		0.512
Minimum SBP percentage change from pre-induction value, %	−32.3 (16.7)	−30.2 (26.0)	−2.1 (−10.0 to 5.7)		0.592
Time to minimum SBP, min	12 (5–20)	13 (8–20)	−1.3 (−3.9 to 1.4)		0.285
Maximum SBP, mm Hg	153 (29)	155 (31)	−2.5 (−12.5 to 7.6)		0.628
HR					
Maximum HR; beats/min	119 (31)	122 (32)	−3.1 (−13.6 to 7.4)		0.523
Maximum HR percentage change from pre-induction value, %	+25.0 (51)	+21.6 (39)	3.4 (−10.5 to 17.2)		0.632
HR ≥120 beats/min	19 (39.6%)	78 (52.0%)		0.60 (0.31 to 1.17)	0.134
Adverse events					
Arrhythmias					
All	4 (8.3%)	10 (6.7%)		1.27 (0.38 to 4.26)	0.695
SVT	2 (4.1%)	0			
AF	0	2 (1.4%)			
VT	0	4 (2.7%)			
VF	1 (2.0%)	1 (0.7%)			
Unspecified	1 (2.0%)	3 (2.0%)			
Cardiac arrest before hospital handover	5 (10.4%)	9 (6.0%)		1.82 (0.58 to 5.73)	0.299
Resuscitation fluids administered	17 (36.2%)	57 (38.0%)		0.89 (0.45 to 1.76)	0.748
Epinephrine administered	9 (18.8%)	27 (18.0%)		1.05 (0.46 to 2.42)	0.907

AF, atrial fibrillation; SBP, systolic BP; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

cumulative incidence of hypotension increased significantly over time, and within 3, 6 and 9 min was 6.2%, 15.6% and 31.2%, respectively.[13] Increasingly, the authors feel that studies reporting only early hypotension miss a significant number of patients in the 10–30 min window where the sympathetic simulation of laryngoscopy and packaging for transfer have abated. We demonstrate in this study a median time of 13 min to the lowest post-induction SBP.

Given the significant rate of hypotension observed, the authors were keen to identify variables that were related to post-induction hypotension to better guide clinical teams and inform future iterations of the local SOP. Age ≥70 years (OR 1.96, CI 1.02 to 3.71) and SI ≥1.0 beats/min/mm Hg (1.99, CI 1.01 to 3.91) were both significantly associated with post-induction hypotension.

Ketamine does not appear to display the relative cardiovascular stability hypothesised and expected. This may be because there truly is little haemodynamic difference between these two agents at the relatively low doses administered in this study. Alternatively, the reduced systemic vascular resistance from induction agents may not be the predominating cause for hypotension in this patient cohort. The transition to positive pressure ventilation, adversely influencing preload, afterload and ventricular compliance, may have a greater influence on haemodynamic stability and cardiac output.

Fentanyl use was similar in both groups (table 2). Its omission was not predictive of post-induction hypotension or hypertension though this is likely explained by concurrent adjustment of hypnotic dosing. The speed of drug onset for the midazolam group did not appear to have had any impact on intubating conditions as there were no statistically significant differences observed in first pass success rates. Percentage change in maximum HR and SBP within 30 min of induction compared with pre-induction was also similar between groups further reinforcing this observed assumption. Within these undifferentiated medical cardiac arrests, a significant proportion was likely caused by neurological events. These patients in particular would benefit from avoiding sudden elevations in intracranial pressure.

Resuscitation fluids and titrated epinephrine boluses were used infrequently during this study, 37.4% (74 of 198) and 18.2% (36 of 198), respectively, despite the high incidence of hypotensive episodes. Concerns over increased myocardial oxygen demand, dysrhythmias and a consistent association with increased mortality in a variety of acute cardiomyopathies may explain the reluctance to use such β−1 adrenoreceptor agonists.[19] The combination of a busy prehospital environment, relatively short transfer times and the prioritisation of timely transfer for evidence-based percutaneous coronary intervention has limited the use of central lines, syringe drivers and more novel inotropes.[20] Since this study, the α_1-adrenoreceptor agonist metaraminol has been introduced to our service as an additional pharmacological agent. Greater emphasis is placed on augmentation of BP post-induction, particularly in elderly patients or those with an elevated SI. Given the low pre-induction GCS of many

Table 4 Patient variables (both groups combined) and rates of post-PHEA hypotension; number (proportion)

		Post-PHEA hypotension	OR (95% CI)	P value
Age, years	≥70	34/54 (63.0%)	1.95 (1.03 to 3.71)	0.041
	<70	67/144 (46.5%)		
Duration of low flow, min	≥30	22/46 (47.8%)	0.97 (0.50 to 1.87)	0.921
	<30	73/150 (48.7%)		
Shock index, beats/min/mm Hg	≥1.0	30/47 (61.7%)	1.99 (1.01 to 3.90)	0.046
	<1.0	71/151 (47.7%)		

PHEA, prehospital emergency anaesthesia.

patients, there may be a case for omission of hypnotic entirely. However, rocuronium-only inductions and their haemodynamic consequences were not included in this study.

A fundamental limitation of this study is its retrospective nature and its lack of randomisation as to the induction drug regime. A number of patients were excluded due to incomplete haemodynamic data. This was often a consequence of the patient being transferred from ambulance service to HEMS team clinical monitoring equipment. Data from the former were not always entered into the HEMS database.

The post-induction haemodynamic instability of these medical post-cardiac arrest patients is clearly demonstrated. However, clinical team discretion regarding the induction drug and its dosing, even within an SOP, introduces considerable potential for bias, despite similar baseline characteristics and physiology between groups. Dosing was dictated by patient pathophysiology, convenience of administration and adjustment in obesity. Patient weights were estimated, a well-recognised source of error. Drug dosing regimes for ketamine could not reliably be delineated into 3:2:1 or 1:1:1 for further analysis as there were multiple dose permutations within these ranges.

It was not possible to eliminate the impact of pre-PHEA sedation, since doses were invariably administered shortly before induction and contributed to the onset of anaesthesia. A cumulative drug dose was therefore used in the analysis. The interval between sedation and PHEA is typically of the order of minutes but this will have been variable and may have had a confounding effect.

Doses of midazolam were more conservative than might be expected. In the midazolam group, the cumulative median midazolam dose administered was 0.03 mg/kg (IQR 0.02–0.04). However,midazolam was also used in 22.9% (11 of 48) of patients induced with ketamine at a median dose of 0.04 mg/kg (IQR 0.02–0.06). High rates of pretreatment with midazolam in the ketamine group may have obtunded the sympathetic response of ketamine and could potentially be a confounding factor for the lack of overall sympathetic stimulation response seen in the ketamine PHEA group. In a subgroup analysis, when patients in the ketamine group who received midazolam pre-PHEA sedation were excluded, there remained no significant difference in the primary outcome (p=0.51). The same was true in the midazolam PHEA group where only one patient received ketamine sedation prior to induction.

In contrast, drug doses for maintenance of anaesthesia were deliberately excluded. The service uses a wide variety of drugs for ongoing anaesthesia and analgesia and it was not possible to compare equivalent sedation doses between different drug classes due to population study size. Maintenance doses are not typically administered until haemodynamic stability has been achieved so their impact was felt to be modest.

In the absence of any randomised controlled trial data, however, this study supports maintaining a position of equipoise between these two induction agents. This is important. Ketamine is the default induction agent for most PHEA, particularly in trauma. Team familiarity with its pharmacodynamics and dosing is an important safety consideration. This study does not suggest a signal for inferiority or harm for ketamine in this patient cohort and supports its continued use.

CONCLUSION

PHEA delivered by a physician-paramedic team in patients with ROSC following a medical cardiac arrest is associated with potentially significant cardiovascular derangements when measured up to 30 min after induction of anaesthesia. There was no demonstrable difference in post-induction hypotension between ketamine-based or midazolam-based PHEA. Choice of induction agent alone is insufficient to mitigate haemodynamic disturbance. Attention should be directed to alternative strategies such as fluid resuscitation and inotropes.

Acknowledgements The authors are grateful for the charitable contributions from the people of Essex & Hertfordshire without which this clinical service could not be provided.

Contributors CKing—methodology, formal analysis, writing (original draft) and study submission. AL—methodology and writing (review and editing). CKeeliher—methodology and validation. SM—formal analysis and visualisation. JS—investigation. HK-C—investigation. PS—conceptualisation, formal analysis, writing (review and editing) and supervision.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval Local Research Ethics Committee approval was obtained from Anglia Ruskin University, East Anglia, meeting the National Institute of Health Research criteria for a service evaluation project (ref AHSREP-19-079). Permission for publication was obtained from the Caldicott guardian.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available on reasonable request from the corresponding author or from our patient liaison managers.

ORCID iD

Christopher King http://orcid.org/0000-0002-2127-0902

REFERENCES

1 Neumar RW, Nolan JP, Adrie C, *et al*. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. a consensus statement from the International liaison committee on resuscitation (American heart association, Australian and New Zealand Council on resuscitation, European resuscitation Council, heart and stroke foundation of Canada, InterAmerican heart Foundation, resuscitation Council of Asia, and the resuscitation council of southern Africa); the American heart association emergency cardiovascular care committee; the council on cardiovascular surgery and anesthesia; the council on cardiopulmonary, perioperative, and critical care; the council on clinical cardiology; and the stroke council. *Circulation* 2008;118:2452–83.

2 Heffner AC, Swords D, Kline JA, *et al*. The frequency and significance of postintubation hypotension during emergency airway management. *J Crit Care* 2012;27:e9-13:417.e9–417.e13.

3 Trzeciak S, Jones AE, Kilgannon JH, *et al*. Significance of arterial hypotension after resuscitation from cardiac arrest. *Crit Care Med* 2009;37:2895–903.

4 Gelissen HP, Epema AH, Henning RH, *et al*. Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle. *Anesthesiology* 1996;84:397–403.

5 Medicines.org.uk. Ketalar 10 mg/ml injection - summary of product characteristics (SmPC) - (emc), 2020. Available: https://www.medicines.org.uk/emc/product/2231/smpc [Accessed 06 Aug 2020].

6 White PF. Comparative evaluation of intravenous agents for rapid sequence induction--thiopental, ketamine, and midazolam. *Anesthesiology* 1982;57:279–84.

7 Waxman K, Shoemaker WC, Lippmann M. Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg* 1980;59:355???358–8.

8 Miller M, Kruit N, Heldreich C, *et al*. hemodynamic response after rapid sequence induction with ketamine in out-of-hospital patients at risk of shock as defined by the shock index. *Ann Emerg Med* 2016;68:181–8.

9 Egan TD, Kuramkote S, Gong G, *et al*. Fentanyl pharmacokinetics in hemorrhagic shock: a porcine model. *Anesthesiology* 1999;91:156–66.

10 Greenblatt DJ, von Moltke LL, Ehrenberg BL, *et al*. Kinetics and dynamics of lorazepam during and after continuous intravenous infusion. *Crit Care Med* 2000;28:2750–7.

11 Ishimaru T, Goto T, Takahashi J, *et al*. Association of ketamine use with lower risks of post-intubation hypotension in hemodynamically-unstable patients in the emergency department. *Sci Rep* 2019;9:17230.

12 Zuin M, Rigatelli G, Dell'Avvocata F, *et al*. Ketamine and midazolam differently impact post-intubation hemodynamic profile when used as induction agents during emergency airway management in hemodynamically stable patients with ST elevation myocardial infarction. *Heart Vessels* 2018;33:213–25.

13 Miller M, Groombridge CJ, Lyon R. Haemodynamic changes to a midazolam-fentanyl-rocuronium protocol for pre-hospital anaesthesia following return of spontaneous circulation after cardiac arrest. *Anaesthesia* 2017;72:585–91.
14 Libungan B, Lindqvist J, Strömsöe A, *et al*. Out-of-hospital cardiac arrest in the elderly: a large-scale population-based study. *Resuscitation* 2015;94:28–32.
15 Sasson C, Rogers MAM, Dahl J, *et al*. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2010;3:63–81.
16 Althunayyan SM. Shock index as a predictor of post-intubation hypotension and cardiac arrest; a review of the current evidence. *Bull Emerg Trauma* 2019;7:21–7.
17 Newton A, Ratchford A, Khan I. Incidence of adverse events during prehospital rapid sequence intubation: a review of one year on the London helicopter emergency medical service. *J Trauma* 2008;64:487–92.
18 Chalkias A, Pavlopoulos F, Papageorgiou E, *et al*. Development and testing of a novel anaesthesia induction/ventilation protocol for patients with cardiogenic shock complicating acute myocardial infarction. *Can J Cardiol* 2018;34:1048–58.
19 Petersen JW, Felker GM. Inotropes in the management of acute heart failure. *Crit Care Med* 2008;36:S106–11.
20 Webb JG, Lowe AM, Sanborn TA, *et al*. Percutaneous coronary intervention for cardiogenic shock in the shock trial. *J Am Coll Cardiol* 2003;42:1380–6.