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Blood Pressure Trajectories Following Prehospital Adrenaline Infusion in Post-ROSC Out-of-Hospital Cardiac Arrest

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Abstract

Hypotension following the return of spontaneous circulation (ROSC) occurs frequently and correlates with poorer patient outcomes, yet the immediate circulatory reaction to prehospital adrenaline administration remains inadequately characterized. This study investigated minute-by-minute blood pressure pathways surrounding the recorded commencement of adrenaline infusions in patients with out-of-hospital cardiac arrest (OHCA) who attained stable ROSC and retained a palpable pulse upon emergency department arrival. We conducted a retrospective linked cohort investigation utilizing data from adult patients treated by emergency medical services for out-of-hospital cardiac arrest in Victoria, Australia, between 2019 and 2023. Eligible cases achieved stable ROSC, possessed linked ZOLL® monitor-defibrillator records, and presented with a pulse at hospital handover. The study sample was limited to individuals initiated on a prehospital adrenaline infusion within 60 min of achieving ROSC. Segmented mixed-effects models, controlled for initial pre-infusion values and pre-infusion trajectories, were applied to assess minute-level trends in mean arterial pressure (MAP) and systolic blood pressure (SBP) from 10 min before 20 min following infusion initiation. Among 3655 eligible adult ROSC cases with complete monitor integration and a pulse at hospital presentation, 1920 individuals received a prehospital adrenaline infusion within 60 min post-ROSC. Blood pressure values typically decreased during the 10 min preceding the infusion, reaching their lowest point concurrently with or immediately after infusion onset, then increased over the subsequent 20 min. In primary adjusted models, MAP decreased by 1.64 mmHg/min pre-infusion and increased by 1.15 mmHg/min post-infusion, representing a trajectory reversal of 2.79 mmHg/min (95% CI = 2.48–3.09). SBP decreased by 2.25 mmHg/min before infusion and increased by 1.71 mmHg/min afterward, demonstrating a trajectory change of 3.96 mmHg/min (95% CI = 3.55–4.38). These adjustments indicated a pronounced inversion in blood pressure trends at the onset of infusion. Descriptively, mean MAP rose from 81.2 mmHg at 5 min post-infusion to 95.4 mmHg at 20 min, whereas mean SBP climbed from 107.9 to 128.4 mmHg over the same period. The recorded initiation of an adrenaline infusion coincided with the termination of a declining blood pressure trend. It prompted a steady elevation in both MAP and SBP across the subsequent 20 min. These observations help characterize the arterial pressure responsiveness to adrenaline during prehospital post-ROSC care and provide data to inform future investigations regarding vasopressor timing, hemodynamic targets, and clinical trial methodologies.

Keywords: Cardiac arrest, Return of spontaneous circulation, Blood pressure, Prehospital, Out-of-hospital

Introduction

Post-cardiac arrest syndrome frequently manifests as an early phase characterized by myocardial dysfunction, vasoplegia, and cardiovascular instability following the return of spontaneous circulation (ROSC) [1, 2]. Consequently, preventing hypotension is a foundational objective of post-resuscitation management; current clinical guidelines advise maintaining the mean arterial pressure (MAP) at or above a minimum threshold of 65

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mmHg, though substantial ambiguity persists regarding ideal blood pressure targets and optimal vasopressor protocols [3, 4].

While vasopressor administration is regularly required, the expected hemodynamic benefits of catecholamines must be weighed against risks of elevated myocardial oxygen consumption and tachyarrhythmias, and data clarifying the optimal timing for implementing specific infusions post-cardiac arrest remain sparse [2-4]. Contemporary studies investigating post-ROSC blood pressure target related but distinct clinical questions. For instance, randomized controlled trials in intensive care units evaluate standardized hemodynamic algorithms after hospital admission. In contrast, the immediate prehospital phase involves unstable intervals shortly after ROSC, before the deployment of invasive monitoring lines and ICU-specific optimization protocols [3-5].

Nonetheless, observational data continually indicate that circulatory failure, lower absolute blood pressure, and greater cumulative exposure to hypotension correlate with unfavorable outcomes post-ROSC [6-8]. This underscores an unaddressed descriptive element: the precise timing, direction, and variation of arterial pressure adjustments directly surrounding the introduction of prehospital vasopressors. This specific phase is poorly captured in most current publications. A significant portion of post-ROSC hemodynamic literature relies upon an isolated blood pressure reading obtained during hospital handover or initial admission [6, 9].

Such static measurements condense a highly fluid management window and fail to differentiate unresolved early shock from physiological profiles already altered by intravenous fluids or vasoactive drugs. In contrast, recent minute-by-minute monitor-defibrillator data indicate that even transient periods of early hypotension and prolonged durations below standard SBP and MAP thresholds are associated with reduced post-ROSC survival, underscoring a highly vulnerable early window within the prehospital domain [7].

The core challenge is that routine observational registries cannot definitively determine whether a prehospital adrenaline infusion should be initiated. The decision to initiate an infusion is fundamentally influenced by shifting blood pressure values, recent directional trends, concurrent therapies, and individual clinician reasoning. Consequently, basic comparisons between patients receiving infusions and those who do not are highly susceptible to confounding by indication and time-dependent biases, including immortal-time and related resuscitation-time paradoxes [10]. Within integrated registry systems, electronic medical charts, and monitor captures, critical indicators of physiological instability are often incomplete. At the same time, distal endpoints such as survival or neurological status are influenced by numerous post-exposure variables long after the initial infusion decision.

In light of these observational limitations, focusing on a precise physiological inquiry is more viable and robust than conducting a broad causal efficacy evaluation: what specific arterial pressure trajectory occurs immediately surrounding the onset of a prehospital adrenaline infusion in patients who receive this intervention? This line of inquiry remains clinically meaningful because arterial pressure serves as an intermediate physiological metric linking post-ROSC circulatory shock to ultimate patient outcomes. Focusing on patients who received a prehospital adrenaline infusion following sustained ROSC, this investigation analyzed fluctuations in mean arterial pressure and systolic blood pressure directly flanking the point of infusion initiation.

Materials and Methods

This investigation is structured and reported in conformity with the STROBE guidelines for cohort studies [11].

Study design and setting

This retrospective observational investigation utilized integrated data from the registry, clinical charts, medication logs, and monitor-defibrillator captures of Ambulance Victoria, the provider of prehospital emergency medical care across Victoria, Australia. Ambulance Victoria operates a two-tiered prehospital model, staffed by Advanced Life Support paramedics and Mobile Intensive Care Ambulance paramedics. Clinicians lead Post-ROSC management according to standardized regional protocols that prioritize immediate transport while simultaneously correcting abnormalities in oxygenation, ventilation, and perfusion [12].

Post-ROSC hypotension is managed initially with conservative intravenous fluid boluses; total fluid volumes administered during resuscitation and post-ROSC management typically do not exceed 20 mL/kg unless addressing suspected hypovolemia, with smaller fluid volumes indicated for individuals vulnerable to fluid overload. The study protocol did not limit intravenous fluid administration during or following the start of the infusion; the continuation, addition, or cessation of fluid therapies was determined entirely by treating clinicians and analyzed only when recorded in the patient care chart. If hypotension persists despite initial fluid volume expansion, or if severe hypotension appears imminent, vasopressor management can be advanced at the clinician's discretion and in accordance with active guidelines, using vasopressor boluses and adrenaline infusions delivered via syringe pumps. The study protocol did not specify the timing of initiation and titration steps for the infusion. Accordingly, this study was structured as an intra-patient pharmacodynamic evaluation anchored to the moment of infusion commencement.

Data sources and participants

We combined data from the Victorian Ambulance Cardiac Arrest Registry, electronic patient care files, structured drug administration records, and ZOLL X Series® monitor-defibrillator printouts for OHCA incidents occurring during the study window spanning 11 February 2019 to 14 December 2023. The base cohort consisted of adult EMS-managed OHCA patients who experienced ROSC, possessed accessible ZOLL® data, and maintained a palpable pulse upon arrival at the receiving hospital. Individuals under 18 years of age and cases involving traumatic cardiac arrest were excluded from the analysis.

For this specific evaluation, the sample was further restricted to patients who were initiated on a prehospital adrenaline infusion within 60 min of achieving ROSC. The presence of a pulse at hospital arrival served as a functional indicator of the end of the prehospital care phase, rather than a strict duration-dependent classification of sustained ROSC. The point of infusion onset was defined by the initial non-zero documented adrenaline infusion rate timestamp when available, and by the first recorded infusion initiation timestamp otherwise. The interval to infusion onset was measured from the documented time of ROSC. The study did not dictate or standardize adrenaline infusion rates. Dosages were selected and recorded during routine clinical care, and a verified, minute-by-minute pump record capturing every rate modification was unavailable. Medication records offered patient-level summary metrics, including the median, mean, maximum, and total number of documented rate changes. Consequently, the primary exposure variable was the recorded minute of infusion onset, while infusion rate characteristics served strictly as descriptive background parameters.

Minute-level physiology and time-series construction

Timestamped monitor streams tracking systolic, diastolic, and mean arterial pressure were extracted directly from the raw ZOLL® files. The blood pressure metrics consisted predominantly of automated, non-invasive oscillometric cuff measurements captured by the ZOLL X Series® monitor-defibrillator. Because monitor-specific biomedical calibration logs, cuff-size documentation, and concurrent invasive arterial pressure verification records were unavailable, the accuracy of these readings was assumed to represent standard operational device performance rather than independently validated study parameters. Raw data points were aligned chronologically with ROSC and categorized into integer whole minutes relative to ROSC, with minute 0 corresponding to the interval from 0 to <1 min after ROSC. Outlying and physiologically implausible metrics were filtered out according to pre-established boundaries: non-positive values for SBP, DBP, and MAP; SpO_2 percentages less than 50% or greater than 100%; $ETCO_2$ values of 0; and respiratory rates less than 2 or greater than 100 breaths/min. No forward-fill or backward-fill imputation techniques were applied to missing data points.

Since non-invasive cuff measurements can be logged repeatedly by the monitoring device without executing a fresh inflation sequence, primary minute-level SBP and MAP data points were established as the mean of all unique SBP and MAP readings recorded within that specific patient-minute. A consecutive-hold suppression filter was then applied over successive minutes to clip extended sequences of unchanging SBP or MAP values that likely represented monitor-retained data. These processing constraints were designed to minimize the likelihood of counting repeated, stored cuff metrics as newly acquired blood pressure values. Nevertheless, the resulting dataset remains a collection of intermittent non-invasive cuff measurements rather than continuous, beat-to-beat arterial pressure waveforms. Monitor data extraction and minute-level categorization broadly mirrored our previously described ROSC-aligned framework, adjusted here so that the analytic baseline anchor was the start of the infusion rather than the moment of ROSC.7 Structured medication documentation was utilized to map out minute-by-minute post-ROSC adrenaline bolus exposure. Supplementary time-dependent covariates were generated from procedural and medication timestamps, including recent normal saline fluid challenges, recent endotracheal intubation, and recent delivery of sedatives or paralytic agents.

Around-infusion-start windows and derived measures

The primary modeling framework spanned 10 min before to 20 min after infusion initiation, with minute 0 designated as the exact time of infusion onset. The pre-infusion analytical window was restricted to the 10 min immediately preceding infusion start to target the cardiovascular trajectory closest to the clinical decision to initiate the intervention, while minimizing interference from early post-ROSC stabilization maneuvers and maximizing data retention for patients with short intervals to infusion start. Patient-specific pre-infusion mean pressure was determined across minutes −10 to −1, and individual pre-infusion and post-infusion trajectories were determined via simple linear regression of blood pressure against relative time within the pre- and post-intervention windows, respectively. To provide adequate data for baseline trajectory modeling, patients had to have at least 2 observed blood pressure entries within the pre-infusion interval and at least 2 within the post-infusion interval to be included in the respective MAP or SBP models. This served solely as a threshold for calculating individual slopes and did not limit the patient analysis to only four blood pressure readings; after data cleaning, all available patient-minutes within the designated assessment window were used in the mixed-effects trajectory models.

Descriptive summaries of blood pressure variation were also calculated at approximately +5, +10, +15, and +20 min by averaging recorded blood pressure entries within a ± 2-min interval centered on each target minute. Secondary exact-time metrics were calculated from raw, irregularly spaced blood pressure tracking entries via trapezoidal integration; these included time-weighted average pressures and the cumulative pressure-deficit burden beneath pre-established targets [13]. The pre-specified boundaries for hypotension were MAP < 65 mmHg and SBP < 90 mmHg.

The primary pharmacodynamic outcome under evaluation was the variation in blood pressure trajectory following the start of the infusion. For descriptive evaluations, we also pre-specified two binary indicators of blood pressure elevation: a minimum increase in MAP of 5 mmHg at approximately 10 min post-infusion start, and a minimum increase in SBP of 10 mmHg at approximately 15 min post-infusion start. Additionally, we tabulated whether individual patient MAP slopes transitioned in a positive direction. These elevation summaries were descriptive and not meant to categorize patients definitively as clinical pharmacological responders or non-responders.

Statistical analysis

Continuous variables are presented as means with standard deviations or as medians with interquartile ranges, depending on the data distribution, while categorical variables are reported as absolute counts with percentages. The primary analyses used segmented mixed-effects linear models with patient-specific random intercepts to map minute-level trends in MAP and SBP around the start of the infusion. Fixed effects comprised relative time, a binary marker for the post-initiation phase, and a post-initiation time parameter, enabling the estimation of the pre-infusion trajectory, any instantaneous step change at infusion onset, the post-infusion trajectory, and the net directional shift in slope following infusion initiation. The primary pharmacodynamic parameter of interest was post-initiation trajectory variation, as a continuously adjusted infusion is conceptually expected to gradually alter blood pressure trends over the subsequent several minutes rather than producing an immediate stepwise jump.

The baseline model adjusted for each individual's pre-infusion mean pressure and pre-infusion trajectory, meaning that the post-initiation response was evaluated conditional on the baseline value and direction of cardiovascular performance immediately before the infusion, because post-initiation co-interventions can occur directly along the physiological pathway through which an infusion functions. The primary model did not control for clinical care administered after the infusion started. A pre-planned sensitivity model incorporated one-minute-lagged, time-varying markers for recent adrenaline boluses, recent normal saline administration, recent intubation, and recent sedation or paralysis. This lagged approach prevented the incorporation of future temporal data at any analyzed minute. Still, it was treated as a secondary sensitivity check rather than the primary estimate because these clinical variables can be directly influenced by the acute deterioration that originally prompted the infusion. As an additional test of robustness, the primary MAP and SBP segmented mixed-effects models were refitted utilizing a first-order autoregressive residual correlation structure, mapped to the true observed minute intervals within each patient, to account for serial dependence across consecutive blood pressure recordings. This evaluation checked whether the main slope-change estimates surrounding the infusion start were substantially biased by within-patient residual autocorrelation.

Pre-specified falsification and sensitivity models separately evaluated early and late pre-infusion trajectories, introduced a sham intervention point at 5 min before the actual infusion onset, and replicated the segmented models across alternative analytical intervals of −5 to +15, −10 to +15, and −10 to +30 min. Additionally, fake-start evaluations were performed by shifting the mathematical intervention point 3 and 5 min before the true recorded infusion-start minute. These validation checks were deployed to confirm whether any observed post-initiation trajectory pivot could be explained by an underlying physiological rebound or by arbitrary selections of the mathematical breakpoint. Each model was restricted to complete cases containing the specific variables required for that individual analysis; consequently, total sample sizes fluctuated between the MAP and SBP models and across various derived summaries.

Supplementary exploratory models evaluated whether blood pressure responses varied according to pre-infusion hemodynamic baseline, recent clinical management, time elapsed from ROSC to infusion onset, and recorded infusion dosage groups. Occurrences of implausible blood pressure values were also tabulated. These sub-analyses were interpreted purely descriptively, given that the underlying patient subgroups, interventions, timing, and documented dosages were driven by active clinical decision-making rather than randomized allocation.

All statistical procedures were carried out using Stata® version 19 (StataCorp, College Station, TX, USA). Statistical estimates are presented alongside their corresponding 95% confidence intervals.

Ethics

Approval for this research was granted by the Monash University Human Research Ethics Committee (ID 41476). The study protocol was also approved by the Ambulance Victoria Research Committee (R24-001).

Results and Discussion

Cohort

Out of 3655 adult patients presenting with ROSC, integrated ZOLL® monitor records, and a palpable pulse at hospital handover, 1920 individuals had a prehospital adrenaline infusion initiated within 60 min of ROSC, establishing the infusion-starter study cohort **(Figure 1)**. The median age of the cohort was 65 years, 66.3% of the sample were male, the median downtime (combining low-flow and no-flow intervals) was 30 min, and VF/VT represented the initial arrest rhythm in 41.0% of cases. Infusions were initiated at a median interval of 11 min following ROSC. Before infusion onset, 67.9% of patients were administered at least one post-ROSC adrenaline bolus. At the exact minute of infusion commencement, the total cumulative recorded bolus administration reached a median of 60 µg (IQR = 0–400). The median recorded baseline infusion rate was 20 µg/min (IQR = 10–50). Because the vast majority of patients had only a single numeric infusion-rate entry logged in their records (median = 1, IQR = 1–3), these infusion-rate evaluations remained purely descriptive and were not modeled as minute-by-minute dose–response trends.

Crystalloid fluids had been delivered to 50.5% of patients, and 79.1% of the cohort had undergone endotracheal intubation. The primary segmented models incorporated 1391 patients for the MAP analysis and 1397 patients for the SBP analysis. Exact-time trapezoidal metrics were calculated for 1884 patients, and paired exact-time pre-versus-post comparative profiles included 1381 MAP and 1387 SBP observations. Expanded characteristics of the study cohort and associated procedural treatments are outlined in **Table 1**.

The presence of non-positive blood pressure parameters in the integrated ZOLL® database was negligible, with 0 SBP, 0 MAP, and 10 DBP values across 553,177 logs (0.002%).

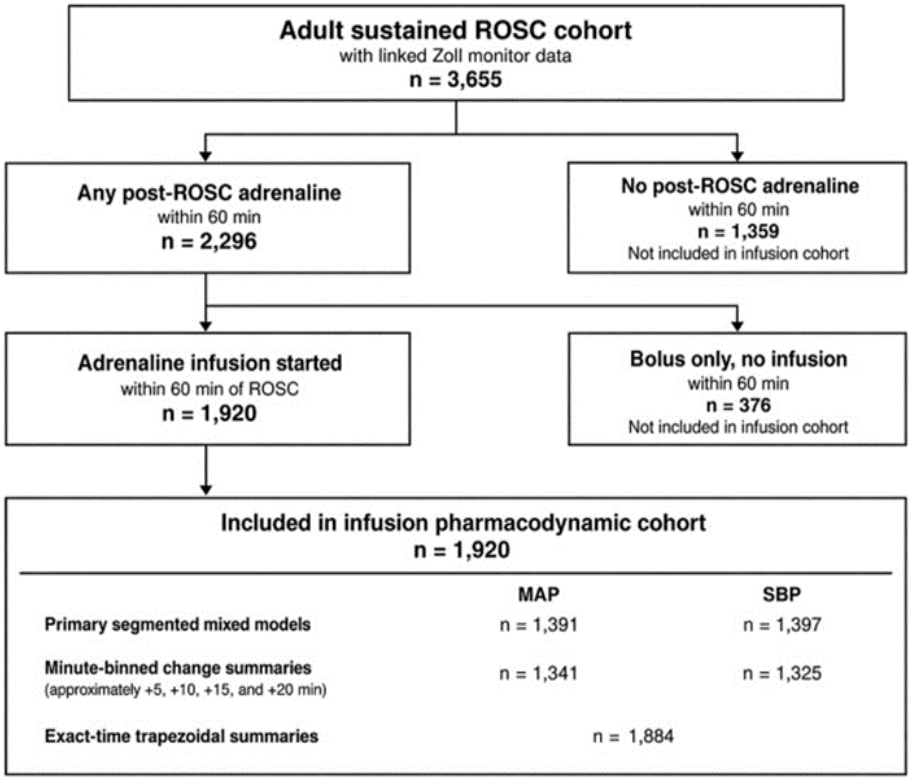


Figure 1. Patient selection and analytic cohorts.

The baseline sample comprised mature OHCA individuals who achieved ROSC, had accessible data logs from a ZOLL monitoring unit, and maintained a palpable pulse upon arrival at the emergency department. The core analytical group was restricted to individuals who began receiving an intra-resuscitation prehospital adrenaline infusion within one hour of initial ROSC. To calculate exact-time paired adjustments, subjects needed valid circulatory records captured both before and after drug initiation.

Table 1. Characteristics of the infusion-starter cohort and treatment context at infusion start.

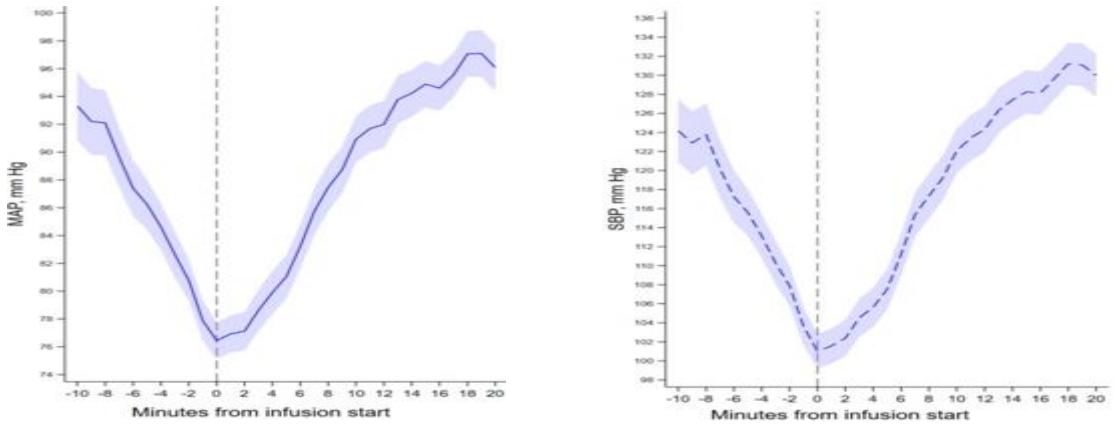
Parameter	Adrenaline infusion initiation group (n = 1920)
Demographic and cardiac arrest characteristics	
Age (years)	65 (53–76)
Male participants, n (%)	1273 (66.3)
Arrest downtime (min)	30 (23–40)

Cardiac arrest occurring in a public setting, n (%)	359 (18.7)
Witness classification	
Witnessed by EMS personnel, n (%)	289 (15.1)
Unwitnessed arrest, n (%)	466 (24.3)
Witnessed by a member of the public, n (%)	1159 (60.6)
Receipt of bystander CPR, n (%)	1294 (67.4)
Initial cardiac rhythm	
Ventricular fibrillation/ventricular tachycardia (VF/VT), n (%)	785 (41.0)
Pulseless electrical activity (PEA), n (%)	539 (28.1)
Asystole, n (%)	519 (27.1)
Other or non-shockable rhythms, n (%)	72 (3.8)
Suspected cardiac etiology, n (%)	1431 (74.5)
Number of defibrillation shocks delivered	1 (0–3)
Clinical status at the time of infusion commencement	
Interval from ROSC to infusion initiation (min)	11 (6–20)
Prior adrenaline bolus administration before infusion start, n (%)	1303 (67.9)
Total adrenaline bolus dose administered before infusion initiation (mg)	0.06 (0.00–0.40)
Any crystalloid fluid given before infusion start, n (%)	969 (50.5)
Endotracheal intubation completed before infusion start, n (%)	1519 (79.1)
Administration of rocuronium, midazolam, ketamine, or fentanyl bolus before infusion initiation, n (%)	527 (27.4)
Hemodynamic measurements before infusion	
Average pre-infusion MAP (mmHg)	84.0 (70.3–99.6)
Lowest pre-infusion MAP (mmHg)	73.0 (59.0–89.0)
Mean pre-infusion SBP (mmHg)	111.8 (92.0–133.7)
Minimum pre-infusion SBP (mmHg)	95.0 (76.0–118.0)
Rate of change in MAP before infusion (mmHg/min)	−1.15 (−4.16–0.00)
Rate of change in SBP before infusion (mmHg/min)	−1.67 (−5.97–0.00)

Values are median (IQR) or n (%). Percentages are column percentages. “Start” refers to the documented infusion-start minute. Available denominators differed from the header N for downtime (1919), witness status (1914), initial rhythm (1915), pre-window MAP summaries (1505), pre-window SBP summaries (1512), pre-infusion MAP slope (1391), and pre-infusion SBP slope (1397).

Haemodynamic trajectories

Circulatory pressure lines were predominantly decreasing before pharmacotherapy. These recorded metrics demonstrated a clear directional turnaround flanking the drug introduction **(Figure 2)**: MAP and SBP values continuously deteriorated during the 10 min preceding the event, reached their lowest physiological thresholds at or near minute 0, and progressively rebounded over the next 20 min. According to the primary segmented mixed-effects linear framework, the introduction of the infusion was linked to a directional shift in the MAP slope of 2.79 mmHg/min (95% CI = 2.48–3.09; P < 0.001) and a shift in the SBP slope of 3.96 mmHg/min (95% CI = 3.55–4.38; P < 0.001) **(Table 2)**. Pre-infusion trend lines were negative (−1.64 mmHg/min for MAP and −2.25 mmHg/min for SBP), whereas post-infusion trend lines shifted to positive values (1.15 and 1.71 mmHg/min, respectively). No sharp, instantaneous vertical jump was observed at the precise timestamp of drug deployment: calculated immediate shifts were −0.68 mmHg for MAP (95% CI = −2.20 to 0.83; P = 0.374) and −1.75 mmHg for SBP (95% CI = −3.86 to 0.37; P = 0.106).



a) b)

Figure 2. Observed blood pressure trajectories around prehospital adrenaline infusion start. (a) Mean arterial pressure. (b) Systolic blood pressure. Lines show observed minute-level means; shaded bands show 95% confidence intervals for the observed means. Minute 0 (dashed line) denotes infusion start. Values are based on cleaned intermittent non-invasive blood pressure observations and should not be interpreted as continuous beat-to-beat arterial pressure.

Table 2. Segmented mixed-model estimates for MAP and SBP trajectories around prehospital adrenaline infusion start.

Outcome measure and statistical model	P-value	Effect estimate (95% CI)
Mean arterial pressure (MAP) analyses		
Main analysis model		
Change in pressure trajectory following infusion initiation	< 0.001	2.79 (2.48–3.09)
Rate of MAP change before infusion commencement	< 0.001	−1.64 (−1.91 to −1.37)
Rate of MAP change after infusion commencement	< 0.001	1.15 (1.05–1.25)
Instantaneous MAP shift at the time of infusion initiation	0.374	−0.68 (−2.20 to 0.83)
Sensitivity analysis model		
Change in pressure trajectory following infusion initiation	< 0.001	2.50 (2.19–2.81)
Rate of MAP change before infusion commencement	< 0.001	−1.52 (−1.79 to −1.24)
Rate of MAP change after infusion commencement	< 0.001	0.99 (0.89–1.09)
Instantaneous MAP shift at the time of infusion initiation	0.705	−0.29 (−1.81 to 1.22)
Systolic blood pressure (SBP) analyses		
Main analysis model		
Change in pressure trajectory following infusion initiation	< 0.001	3.96 (3.55–4.38)
Rate of SBP change before infusion commencement	< 0.001	−2.25 (−2.63 to −1.88)
Rate of SBP change after infusion commencement	< 0.001	1.71 (1.58–1.85)
Instantaneous SBP shift at the time of infusion initiation	0.106	−1.75 (−3.86 to 0.37)
Sensitivity analysis model		
Change in pressure trajectory following infusion initiation	< 0.001	3.57 (3.14–4.00)
Rate of SBP change before infusion commencement	< 0.001	−2.09 (−2.46 to −1.71)
Rate of SBP change after infusion commencement	< 0.001	1.49 (1.35–1.63)
Instantaneous SBP shift at the time of infusion initiation	0.273	−1.19 (−3.32 to 0.94)

Coefficients are in mmHg or mmHg/min—primary models adjusted for the patient-specific pre-infusion slope and pre-window mean pressure. Lagged sensitivity models additionally adjusted for 1-min lagged recent bolus adrenaline, crystalloid proxy, intubation, and sedative/paralytic exposure. MAP models used 25,874 patient-minutes from 1391 patients; SBP models used 26,078 patient-minutes from 1397 patients.

The primary MAP model integrated 25,874 patient-minutes from 1391 individuals, while the primary SBP model integrated 26,078 patient-minutes from 1397 individuals. Typifying the sample, subjects contributed a median of 5 valid pressure entries during the 10-min pre-infusion interval and 13 entries during the 20-min post-infusion interval for both monitored parameters. Within the lagged sensitivity frameworks, the calculated slope adjustment remained stable at 2.50 mmHg/min for MAP and 3.57 mmHg/min for SBP. From a purely descriptive perspective, the mean MAP climbed from 81.2 mmHg at roughly 5 min following drug deployment to 95.4 mmHg at the 20-min mark, while the mean SBP rose from 107.9 to 128.4 mmHg over this identical timeframe. These findings were unaltered during AR(1) sensitivity calibrations, yielding trend-line modifications of 2.83 mmHg/min for

MAP and 4.09 mmHg/min for SBP, without demonstrating an abrupt baseline step-change; consecutive measurements displayed high serial dependency for both outcomes (rho 0.87 and 0.88).

Patient-level change summaries and heterogeneity of early pressure rise

Despite the comprehensive turnaround in collective blood pressure patterns at drug deployment, individual patient pathways proved highly diverse. At the 10-min mark, MAP shifted by an average of 4.03 mmHg (SD = 30.16). At the 15-min mark, SBP shifted by an average of 11.67 mmHg (SD = 42.86). The mean post-minus-pre slope modifications were 2.93 mmHg/min for MAP and 4.33 mmHg/min for SBP.

Simplified intra-patient pre-versus-post datasets exposed an identical overarching phenomenon, though the average shifts were more constrained. The mean modification in time-weighted average pressure was 1.96 mmHg (SD = 23.92) for MAP and 2.74 mmHg (SD = 33.72) for SBP. Furthermore, subjects exhibited reduced cumulative exposure to acute circulatory deficits after the infusion began, as shown by drops in time-standardized hypotension burdens of −0.58 for MAP and −1.01 for SBP **(Table 3)**.

Table 3. Time-weighted haemodynamic change summaries and pre-specified rise-definition frequencies around infusion start.

Measurement	Median (IQR)	Mean (SD) or n/N (%)	N
Paired analyses using exact-time measurements			
Difference in time-weighted mean MAP (mmHg)	0.57 (−12.60–17.30)	1.96 (23.92)	1381
Difference in time-weighted mean SBP (mmHg)	1.82 (−18.39–24.56)	2.74 (33.72)	1387
Variation in time-normalized MAP deficit burden	0.00 (0.00–0.63)	−0.58 (5.57)	1381
Variation in time-normalized SBP deficit burden	0.00 (−0.65–1.31)	−1.01 (8.56)	1387
Predefined blood pressure increase criteria			
MAP increase of at least 5 mmHg at approximately +10 min	–	627/1341 (46.8)	1341
SBP increase of at least 10 mmHg at approximately +15 min	–	684/1325 (51.6)	1325
Improvement in MAP slope following infusion initiation	–	1018/1367 (74.5)	1367

Exact-time paired summaries were based on trapezoidal integration of irregular blood pressure observations. Time-standardised deficit burden represents the average amount by which blood pressure was below the pre-specified hypotension thresholds across the analysis window, standardised for window length; thresholds were MAP < 65 mmHg and SBP < 90 mmHg. Pre-specified rise definitions were MAP increase ≥ 5 mmHg at approximately +10 min, SBP increase ≥ 10 mmHg at approximately +15 min, and positive MAP slope change. Negative change values indicate less overall hypotension exposure after infusion initiation.

Using these predetermined criteria for pressure elevation, 46.8% of subjects displayed a MAP increase of 5 mmHg or greater, roughly 10 min after the start of the infusion. The matching proportion was 51.6% for an SBP increase of at least 10 mmHg at roughly 15 min post-initiation, and 74.5% for an upward shift in the MAP slope, which highlights a favorable change in direction even when the absolute pressure gain was minimal **(Table 3)**. These distributions prove that while an early rebound in pressure occurred frequently, it was not universal. Individuals who met the criteria for MAP elevation had baseline pressures that were significantly lower than those of individuals who failed to meet the threshold. This variation was also evident in the exact-time paired data, where subjects meeting the elevation metrics demonstrated positive time-weighted average changes in both MAP and SBP, whereas non-meeting subjects experienced average declines.

The variance between a positive trend inversion and an absolute elevation in MAP demonstrates that these response criteria serve as descriptive indicators rather than authentic, distinct clinical phenotypes. Exploratory evaluations of clinical subsets revealed immense diversity in early MAP adaptations. Subjects presenting with a pre-infusion MAP < 65 mmHg demonstrated the most striking absolute elevation: 85.6% achieved a MAP increase of at least 5 mmHg, showing a mean ΔMAP of 29.1 mmHg at roughly +10 min. Conversely, among those starting with a pre-infusion MAP ≥ 85 mmHg, a mere 25.6% experienced a MAP increase of 5 mmHg or more, although 76.3% still demonstrated a positive pivot in their MAP slope. These data underscore the variable nature of early arterial responsiveness and must be interpreted descriptively rather than as definitive, causal subgroup phenomena **(Figure 3)**.

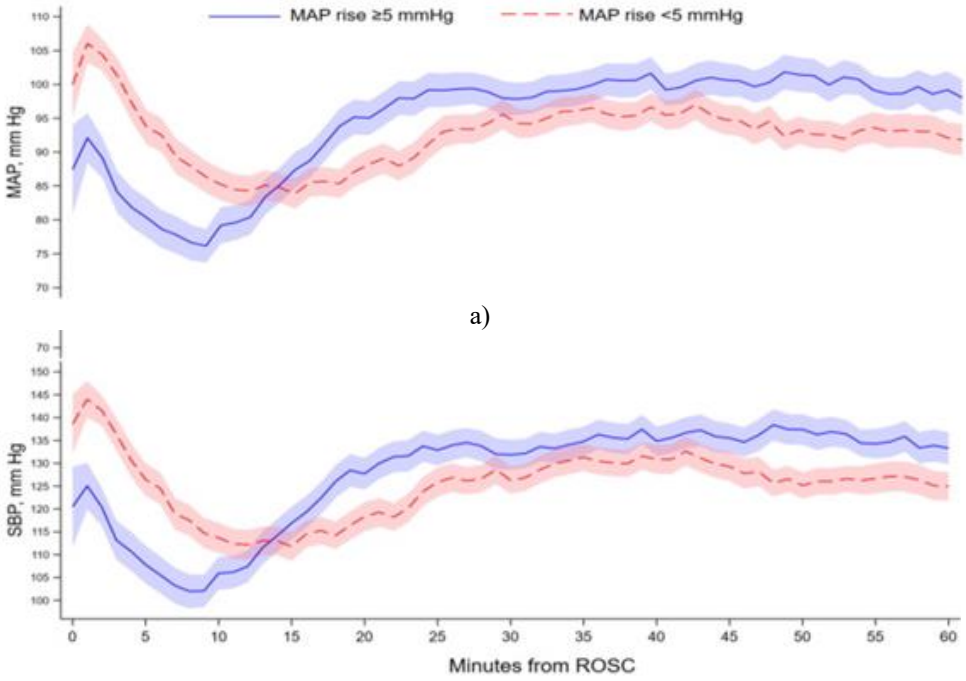


Figure 3. ROSC-anchored blood pressure trajectories by MAP-rise category: (a) Mean arterial pressure, and (b) Systolic blood pressure. Patients were grouped according to whether MAP increased by at least 5 mmHg at approximately +10 min after the start of the infusion. Curves show observed minute-level means with 95% confidence intervals.

This post-start grouping is descriptive and should not be interpreted as a baseline predictor analysis.

Robustness analyses

Sensitivity models confirmed a broad, around-start trend inversion, while also showing that this physiological signal was not locked to a single, specific logged minute. Pre-infusion slopes remained negative across both the earlier and later pre-start intervals, sham-breakpoint frameworks positioned at −5 min failed to show a false turnaround, and positive slope-change configurations remained stable across alternative analytic windows and mock-initiation tests. The reduction in effect size when the analytical breakpoint was mathematically advanced aligns with a genuine physiological pivot occurring close to the recorded start time, accommodating minor errors in real-world clinical timekeeping.

This intra-patient evaluation of drug dynamics determined that among prehospital patients achieving ROSC, MAP, and SBP typically exhibited downward trends before starting an adrenaline infusion, followed by progressive elevation once the intervention was initiated. Within the primary segmented models, the start of the infusion was associated with MAP trajectory changes of 2.79 mmHg/min and SBP trajectory changes of 3.96 mmHg/min. Pre-intervention trajectories were uniformly negative, post-intervention trajectories were positive, and no immediate vertical step-change occurred at minute zero.

The lack of a sharp, immediate vertical shift, combined with negative pre-infusion and positive post-infusion trajectories, indicates that the primary phenomenon observed was a gradual reversal in blood pressure direction rather than an instantaneous spike at the baseline. This configuration aligns more closely with a steady, multi-minute cardiovascular adjustment than with an immediate bolus-driven reaction, which is logical for a low-dose titration. Even so, this pattern represents an observed physiological sequence flanking the onset of therapy rather than definitive confirmation that the infusion directly caused the entire subsequent pressure rise. An elevation in blood pressure in this clinical environment is meaningful, but it does not, in itself, confirm improvements in survival rates or long-term neurological recovery. Furthermore, a rising pressure trend does not clarify whether tissue perfusion improved; this analysis did not evaluate parameters such as cardiac output, systemic vascular resistance, or cardiac workload.

This analysis corresponds with the current consensus on post-resuscitation circulatory failure. Following ROSC, cardiovascular stability is highly volatile due to the simultaneous evolution of myocardial impairment, vasoplegia, relative intravascular volume deficits, and disrupted autoregulation over minutes and hours [1, 2]. Consequently, contemporary management strategies focus heavily on preventing hypotension, while recognizing that the most appropriate endpoints and ideal timing for prehospital vasopressor initiation remain poorly defined [3, 4]. Epidemiological investigations have repeatedly linked diminished post-ROSC blood pressure,

cardiogenic/vasoplegic shock, and extended durations of hypotension to lower survival rates [6-9]. Our prior work evaluating minute-level post-ROSC trajectories noted a related point from the core registry: early post-ROSC hemodynamics fluctuate rapidly, and even transient hypotension during the initial minutes following resuscitation can have clinical consequences [7]. The current study builds on those insights by realigning the timeline to the start of the infusion, revealing that vasoactive therapy was typically introduced during an active downward trend rather than a stable or self-correcting physiological phase.

We have intentionally avoided drawing direct comparisons to randomized trials evaluating MAP endpoints within intensive care units. Those investigations evaluate distinct clinical algorithms within a delayed, highly structured environment, whereas this study characterizes the acute prehospital window surrounding a paramedic-initiated intervention. The primary utility of these data is not to justify elevated MAP targets or to prove that adrenaline infusions improve clinical endpoints, but rather to provide detailed, high-resolution insights into arterial pressure patterns that future prehospital vasopressor trials must account for in their study design.

Subsequently, it is necessary to consider the degree of uniformity exhibited by this cohort-wide pattern across individual subjects. The predetermined benchmark of an elevated MAP was achieved by merely 46.8% of the cohort, and the observed variations in individual pressure shifts were extensive. Even though 74.5% of the individuals demonstrated an upward adjustment in their MAP trend line, fewer than half achieved an absolute MAP elevation of 5 mmHg or greater by the 10-min mark. This indicates that, while the MAP direction inverted for a portion of the sample, it did not result in a substantial immediate increase in pressure. Subjects who ultimately achieved the defined MAP elevation typically initiated therapy at lower baseline pressures and subsequently experienced a more abrupt upward trajectory after the infusion was initiated.

This degree of heterogeneity is pathophysiologically expected within the context of post-resuscitation circulatory failure, an unstable state driven by shifting, variable interactions between myocardial impairment, vasoplegia, relative intravascular volume deficits, and fluctuating shock progression, all of which are further altered by localized treatment choices and concurrent medical procedures [1, 2, 6]. Because these clinical subcategory reviews are strictly descriptive, they cannot establish causal relationships. Nevertheless, documenting this individual variance is critical for the design of future prospective trials, as it directly impacts patient selection algorithms, projected clinical response parameters, and the temporal alignment of clinical endpoints. These exploratory subset data corroborate this perspective but remain purely descriptive. While individuals grouped into higher documented initial dosage brackets experienced more pronounced blood pressure elevations, this must be evaluated as a descriptive therapeutic context rather than as proof of a direct, dose-dependent causal relationship, given that the underlying infusion rates were guided by real-world clinical choices and recorded as patient-level averages rather than continuous, verified minute-by-minute pump output data.

These inherent analytical limits explain why this investigation was intentionally structured as an intra-patient, around-initiation pharmacodynamic assessment rather than a comparative trial matching infused versus non-infused populations. The decision to introduce the infusion was dictated by a fluid constellation of shifting arterial pressures, recent directional trend lines, prior bolus administration, fluid volume delivery, advanced airway management, and subjective clinical assessment. Under such conditions, standard inter-group comparative models would be severely vulnerable to confounding by indication, time-varying bias, immortal-time paradoxes, and the absence of a methodologically viable untreated control cohort within specific physiological severity tiers [10, 14]. Resolving a true causal inquiry into infusion deployment versus non-deployment—or secondary questions about immediate versus delayed initiation—would require an alternative investigative design. Such a design would have to strictly define patient eligibility criteria, anchor a true time-zero baseline, pre-specify comparative therapeutic strategies, map out longitudinal risk sets, and mathematically manage blood pressure simultaneously as a trigger for intervention and as an outcome modified by past care.

Furthermore, such an approach would require a far more comprehensive quantification of acute post-ROSC shock severity than is traditionally recorded within emergency medical service registries and electronic patient charts, including continuous biomarkers of metabolic acidosis, vasoplegia metrics, direct indicators of myocardial performance, true volume status, and real-time co-interventions [14]. The current study was not designed to address those causal questions; instead, its explicit purpose was to characterize the acute physiological variations surrounding the documented point of infusion onset exclusively among patients who received the drug.

The practical value of this study lies in its focus on physiology and trial methodology. It offers a detailed, minute-level map of the prehospital post-ROSC interval, demonstrating that the introduction of an adrenaline infusion typically occurred during an active downswing in blood pressure, which subsequently turned upward over the ensuing 20 min. For practicing clinicians and clinical trialists, the primary insight is that the typical physiological response did not manifest as an instantaneous vertical jump at minute zero, but rather as a progressive directional pivot over several minutes. Crucially, the initiation of therapy frequently occurred while absolute pressures were still tracking near or above standard diagnostic limits for hypotension. This pattern is clinically logical; paramedics likely intervene in response to an active downward trend, a frequent requirement for repeat fluid or drug boluses, or an overarching protocol target (such as maintaining an SBP of approximately 100 mmHg), rather than delaying therapy until a single physiological threshold is crossed. Combined, these observations introduce high-resolution

prehospital data to a body of medical literature that has predominantly relied on static handover metrics or delayed readings captured after intensive care admission [3, 7-9]. This trajectory-focused framework also helps establish realistic physiological expectations for clinicians tracking the minutes immediately following the start of an infusion. Ultimately, whether advancing the timing of initiation, modifying target endpoints, or utilizing alternate vasopressor protocols can improve objective, patient-centered survival remains unproven.

This investigation is subject to several significant limitations. First, it cannot establish a direct causal impact of adrenaline administration. Because the initiation of the infusion was fundamentally linked to the evolving severity of the patient's illness, recent hemodynamic trends, and individual clinical decision-making, a notable risk of confounding by indication remains despite the utilization of an intra-patient study design. Second, the recorded timestamps for the start of the infusion were likely subject to real-world imprecision; this is supported by the positive findings in our mock-initiation tests, which demonstrate that the observed directional turnaround was not isolated to a single documented minute. Consequently, the statistical signal may be partially driven by regression to the mean or a broader, multi-factorial stabilization pattern surrounding the initiation period. Third, blood pressure data collection relied primarily on automated, intermittent, non-invasive monitoring devices rather than continuous, gold-standard invasive arterial lines, thereby limiting the temporal precision of the measurements.

Automated non-invasive cuff readings are prone to reduced reliability in the setting of profound hypotension, impaired peripheral perfusion, patient movement, or active ambulance transport, and this dataset lacked biomedical calibration logs or paired invasive measurements for validation. Additionally, we lacked high-resolution data regarding precise pump mechanics, continuous minute-by-minute titration adjustments, post-initiation fluid volumes, real-time cardiac output, myocardial oxygen consumption, and subsequent inpatient hemodynamic tracking. As a result, this study cannot determine whether the subsequent rise in pressure was driven by enhanced volumetric blood flow, systemic vasoconstriction, elevated cardiac workload, concurrent clinical interventions, or spontaneous physiological stabilization. Furthermore, sample sizes fluctuated across individual sub-analyses due to varying data completeness requirements, and the final cohort was strictly confined to patients with complete integrated monitor files, a documented infusion start within 60 minutes of ROSC, and a palpable pulse upon emergency department delivery. Collectively, these boundaries indicate that the data support a highly consistent turnaround in the blood pressure pathway at the start of therapy. Still, they cannot be interpreted as an unconfounded causal evaluation of adrenaline delivery.

Conclusion

Within this specific cohort of prehospital patients achieving ROSC and initiated on an adrenaline infusion, MAP and SBP pathways regularly transitioned from an active decline to a subsequent progressive elevation directly surrounding the recorded start of therapy. While the average cohort-wide arterial pressure signal remained consistent, individual physiological responses were highly variable, and the underlying impacts on dose titration, true systemic flow, and myocardial workload could not be directly measured. These observations refine our understanding of dynamic, prehospital post-ROSC arterial pressure responsiveness to adrenaline. Still, they do not confirm that starting an adrenaline infusion improves absolute survival or long-term neurological status. Future protocolized clinical trials or explicit causal designs are required to evaluate whether variations in vasopressor timing, physiological targets, dosage ranges, or specific pharmaceutical agents can optimize meaningful, patient-centered outcomes.

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