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Using the relationship between brain tissue regional saturation of oxygen and mean arterial pressure to determine the optimal mean arterial pressure in patients following cardiac arrest: A pilot proof-of-concept study

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Keywords: cardiac arrest, cerebral autoregulation, cerebral oximetry

Abstract

Introduction: Prospectively assess cerebral autoregulation and optimal mean arterial pressure (MAP_{OPT}) using the dynamic relationship between MAP and regional saturation of oxygen (rSO2) using near-infrared spectroscopy.

Methods: Feasibility study of twenty patients admitted to the intensive care unit following a cardiac arrest. All patients underwent continuous rSO2 monitoring using the INVOS® cerebral oximeter. ICM+® brain monitoring software calculates the cerebral oximetry index (COx) in real-time which is a moving Pearson correlation coefficient between 30 consecutive, 10-sec averaged values of MAP and correspond rSO_2 signals. When rSO2 increases with increasing MAP (COx ≥0.3), cerebral autoregulation is dysfunctional. Conversely, when rSO2 remains constant or decreases with increasing MAP (COx <0.3), autoregulation is preserved. ICM+® fits a U-shaped curve through the COx values plotted versus MAP. The MAP_{OPT} is nadir of this curve.

Results: The median age was 59 years (IQR 54 - 67) and 7 of 20 were female. The cardiac arrest was caused by myocardial infarction in 12 (60%) patients. Nineteen arrests were witnessed and return of spontaneous circulation occurred in a median of 15.5 minutes (IQR 8 – 33). Patients underwent a median of 30 hours (IQR 23 – 46) of monitoring. COx curves and MAP_{OPT} were generated in all patients. The mean overall MAP and MAP_{OPT} were 76 mmHg (SD 10) and 76 mmHg (SD 7), respectively. MAP was outside of 5 mmHg from MAP_{OPT} in 50% (SD 15) of the time. Out of the 7672 5-minute averaged COx measurements, 1182 (15%) were at 0.3 or above, indicating absence of autoregulation. Multivariable polynomial fractional regression demonstrated an increase in COx with increasing temperature (P=0.008).

Conclusions: We demonstrated the feasibility to determine a MAP_{OPT} using cerebral oximetry in patients after cardiac arrest.

Introduction

Hypoxemic-ischemic brain injury (HIBI) is the major cause of death in patients following cardiac arrest[1]. Furthermore, approximately half of those who survive will be left with an unfavourable neurologic outcome[2]. HIBI is characterized by cerebral edema with elevated intracranial pressure (ICP) and dysfunctional cerebral autoregulation[3]. In healthy individuals, cerebral autoregulation attempts to maintain constant cerebral blood flow (CBF) over a wide range of mean arterial pressure (MAP). In HIBI, autoregulation is impaired, with the plateau becoming narrowed and right-shifted[4]. This may have consequences for targeting a specific MAP threshold in these patients. If the MAP is below the autoregulatory threshold, additional ischemia can result, leading to further brain injury. Conversely, if the MAP above the autoregulatory threshold, excessive perfusion may lead to increased cerebral edema and worsening brain injury.

The American Heart Association recommends keeping MAP at 65mmHg or above in all patients following cardiac arrest[5]. However this "one size fits all" philosophy clearly does not take into consideration intra-subject variability and, moreover, any possible disruption in a patient's cerebral autoregulation capacity. Recently, there has been interest in using the dynamic fluctuations in MAP on brain regional saturation of oxygen (rSO_2) using near-infrared spectroscopy (NIRS)[6,7]. If MAP and rSO_2 trend in the same direction (e.g. decreasing MAP leads to equal reductions in rSO_2), then effective cerebral autoregulation is likely severely compromised. Conversely, if rSO_2 remains constant during changes in MAP then autoregulation is likely intact. Over time, a moving correlation coefficient (a value between -1 and +1) between MAP and rSO_2 can be repeatedly calculated. This is termed the cerebral oximetry index (COx). A positive or negative COx indicates dysfunction or intact cerebral autoregulation, respectively[8]. The MAP_{OPT} can then be identified at the point with the lowest COx[7]. This approach has been applied to two studies in patients after cardiac arrest using differing definitions of intact autoregulation[6,9]. We thus conducted a single center proof-of-concept study to determine if we could prospectively determine MAP_{OPT} in a cohort of patients admitted after cardiac arrest. In addition, we wanted to determine additional feasibility outcomes: patient recruitment rates, duration of monitoring and adequacy of data capture. We also sought to assess the percentage of time of intact autoregulation and the ability to determine MAP_{OPT}.

Methods

This is a single-center feasibility proof-of-concept study. The Research Ethics Board at the University of British Columbia (H14-02405) approved the protocol and written informed consent was obtained from patients in a deferred manner.

Patient Inclusion

We included patients 16 years or older who were admitted following a cardiac arrest who had a post-resuscitation Glasgow Coma Score of 8 or less. Patients had to be enrolled within 36 hours of their cardiac arrest and had more than 20 consecutive minutes of spontaneous circulation following resuscitation. We excluded patients with a past history of cardiac arrest, traumatic brain injury, intracerebral hemorrhage or ischemic stroke. We also excluded patients where there was no commitment to ongoing support by the medical team.

Patient Management

All patient care decisions were at the discretion of the treating team. As per institutional protocol, patients who have a cardiac arrest from a presumed cardiac cause undergo targeted temperature management to either 33°C or 36°C, at the discretion of the attending physician. This is undertaken with surface cooling using the Artic Sun® Temperature Management System (Bard Medical, Murray Hill, NJ, USA). During the time of the study, there was no institutional temperature management protocol for cardiac arrest from a presumed non-cardiac cause (e.g. hypoxemia).

Study site

Affiliated with the University of British Columbia, the intensive care unit (31 beds) and coronary care unit (14 beds) manage all of the post cardiac arrest patients at Vancouver General Hospital. The ICU and CCU are staffed by fellowship trained intensive care physicians and cardiologists, respectively.

Neurophysiologic Monitoring

We monitored brain regional saturation of oxygen (rSO2) bilaterally using the INVOS® cerebral oximeter (Covidien, Ireland) on the day of admission and continued for up to 48 hours

after the cardiac arrest. Invasive blood pressure and rSO2 data were captured in real-time using ICM+® brain monitoring software (Division of Neurosurgery, Cambridge University). Daily during the study, two investigators (DG, MS) measured MCA flow velocity using TCD.

Statistical methods

Categorical data are summarized as count (percent) and continuous data are summarized as mean (standard deviation) or median and interquartile range (25th - 75th percentile) if the data were skewed. We used Stata 10.0 (StataCorp, Texas, USA) for all analyses. All tests were two-sided and a p-value <0.05 was considered statistically significant. As this was a proof-of-concept study, no formal sample size calculation was performed. Twenty patients represented the maximum number of patients we could recruit with the available resources. TCD was used to estimate CPP using the following formula: CPP = MAP x FVd/FVm+14[10]. A non-invasive ICP was then estimated as ICP = MAP – CPP.

Determination of COx and MAP_{OPT}.

ICM+® brain monitoring software calculates both COx and MAP_{OPT}. COx is a moving Pearson correlation coefficient between 30 consecutive, 10-sec averaged values of MAP and corresponding rSO_2 signals (with 80% overlap of data)[11]. For the purposes of analysis, we averaged the rSO2, MAP and COx over a 5-minute time period[8]. To calculate MAP_{OPT}, ICM+® divides MAP into bins of 5mmHg and then discards the first and last MAP bins. MAP bins which contain <2% of data points are also discarded[12]. ICM+® then fits a U-shaped curve through the COx values plotted versus MAP[13]. The MAP_{OPT} is the nadir of this curve. MAP_{OPT} was calculated for each 6 hour time period. Figure 1 demonstrates data capture (MAP, rSO_2 and COx) and the generation of MAP_{OPT} in an individual patient. We then calculated the difference between the patients' actual average MAP (on an hourly basis) and the MAP_{OPT}. Presence of cerebral autoregulation was defined *a priori* as a COx <0.3[8,14].

Modeling of COx with MAP and temperature

The relationship was assessed visually by plotting COx vs. MAP and COx vs. temperature for each individual. For the relationship between COx and MAP, the median and IQR for COx was calculated for each 5mmHg bin of MAP of each individual. For the relationship between COx and temperature, we overlaid the scatterplot with a locally weighted

scatterplot smoothing function conditioned on the individual. In order to visually assess the relationship between COx and temperature across all patients, we used restricted cubic splines. This relationship was modeled using fractional polynomials.

Results

Between December 1st, 2014 and March 27th, 2015, 22 patients were screened and 20 enrolled. One patient refused and one patient could not be enrolled because the equipment was being used on another study patient. Recruitment rate was 5 patients per month. Overall, the median age was 59 years (IQR 54 – 67) and 6 of 20 (30%) were female. The majority of cardiac arrests were caused by myocardial infarctions (12 of 20, 60%) with 10 of 12 of these patients undergoing percutaneous coronary intervention. The arrest was witnessed in 19 of 20 (95%) of patients and ROSC occurred within a median of 15.5 minutes (8 – 33). The baseline characteristics are presented in table 1. The median time from ROSC until application of cerebral oximetry monitoring was 16.5 hours (9 – 19). Patients underwent a median of 30 hours (23 – 46) of monitoring, with one patient undergoing a total of 72 hours. The mean ONSD was 5.9mm (0.5) and three patients had an estimated ICP of greater than 20 mmHg using TCD. All three of these patients died. Overall, 11 of 20 patients (55%) died in hospital. ICU management characteristics are presented in table 2. During the first 24 hours, 13 of 20 (60%) of patients underwent targeted temperature management with a goal temperature of 33°C (3 patients) or 36°C (10 patients). For the twelve patients with a presumed cardiac cause of the cardiac arrest, the mean temperature for the first and second 24 hours were 35.4°C (1.4) and 36.1°C (1.7), respectively. For the 8 patients with a non-cardiac cause arrest, the mean temperature for the first and second 24 hours were 36.8°C (2.3) and 37.5°C (1.1), respectively. –

Relationship between COx and MAP

Examples of the relationship between COx and MAP for four individual patients over a 6-hour period are presented in figure 2. There were several patterns that emerged. The U-shaped relationship (figure 2A) identified a zone of autoregulation. Some patients maintained autoregulation throughout the range of observable MAP (figure 2B). Other patterns included up-sloping (figure 2C) and down-sloping (figure 2D) relationships which might indicate dysfunctional autoregulation with increasing and decreasing MAP, respectively, or may simply represent a portion of a U-shaped relationship.

We were able to generate COx curves (e.g. figure 1) for at least one six-hour period in all twenty patients, including two patients who underwent veno-arterial extracorporeal life support. A MAP_{OPT} was generated for all 6 hour time periods in 10 patients. In six patients, there was 1

missing period and in 3 patients there were two missing periods. In one patient, 5 of 13 periods were missing. The mean overall MAP and MAP_{OPT} were 76 mmHg (10) and 76 mmHg (7), respectively. The mean percentage of time where the MAP was outside of 5 mmHg from MAP_{OPT} was 50% (15). The MAP was greater than 5 mmHg above MAP_{OPT} a mean of 22% (12) and greater than 5 mmHg below MAP_{OPT} a mean of 28% (15). The density distribution of the difference between actual MAP and MAP_{OPT} is presented in figure 3. The mean rSO2 was 61% (11) and mean COx was 0.066 (0.11). Out of the 7672 5-minute averaged COx measurements, 1182 (15%) were at 0.3 or above. On a per patient basis, this represents a median of 13% (6 – 19) of time when the prevailing MAP was outside the autoregulatory range. The median percentage of time with a COx of 0.3 or above was 18% (7 - 41) in those patients who died compared to 10% (6 - 13) for those who survived

Relationship between COx and temperature

Hourly temperature data was recorded in all 20 patients and the relationship between 5-minute COx and hourly temperature is displayed in figure 4. Multivariable fractional polynomial regression demonstrated an increase in COx with increasing temperature (P=0.008).

Discussion

In this single-centre proof-of-concept feasibility study we demonstrated the feasibility to use the dynamic relationship between MAP and rSO2 to assess cerebral autoregulation in real-time. We were able to calculate a MAP_{OPT} in all twenty patients and this was outside of 5 mmHg from the actual MAP for half of the monitoring time. Furthermore, using a cutoff of COx less than 0.3, autoregulation was present for the majority of time analyzed. Hyperthermia was associated with an increased COx and autoregulation was preserved with hypothermia.

There has been increasing interest in determining the optimal blood pressure targets following cardiac arrest. Although multiple observational studies demonstrating improved neurologic outcomes associated with higher MAP[15–19], these results are not consistent[20]. Furthermore, there is marked heterogeneity in these studies in terms of: patients included, definition of hypotension, and statistical modelling of blood pressure[21]. Given the lack of high-quality data[22], the American Heart Association recommends keeping MAP at 65mmHg or greater in all patients following cardiac arrest[5]. However, it may be that given the right-shifted and narrowed zone of autoregulation observed after cardiac arrest[3,23], we should be examining patient-specific blood pressure targets, rather than applying universal thresholds[24].

Patient-specific blood pressure thresholds have been used in patients with traumatic brain injury (TBI)[12], which shares similar pathophysiologic features with HIBI. Analogous to the methods used in our study, in patients with TBI, we can use the dynamic relationship between MAP and either intracranial pressure or brain tissue oxygen to assess autoregulation, and thus determine MAP_{OPT}[25]. Studies have consistently demonstrated that MAP_{OPT} is often greater than 80 or 90 mmHg in patients with TBI[12,26]. Furthermore, observational data indicate that patients who are maintained within 5 mmHg of their optimal MAP have decreased mortality and improved neurological outcomes[12]. However, the invasive methods used to determine MAP_{OPT} may not be routinely practical in patients after cardiac arrest.

In an attempt to characterize cerebral autoregulation and patient specific MAP targets, Ameloot and colleagues performed a historical cohort study of 51 cardiac arrest patients who underwent continuous MAP and cerebral oximetry monitoring for the first 24 hours of their ICU stay[6]. They demonstrated that 35% of patients had disturbed autoregulation as defined where the slope of a linear regression equation (rSO2%/mmHg) of > 0.05%/mmHg. In patients with

preserved autoregulation, MAP_{OPT} was 85 mmHg, similar to the results seen in our study. Finally, the time under the individual MAP_{OPT} was associated with a small effect on survival (OR 0.97, 95%CI: 0.96 to 0.99, P=0.02). In contrast to our study in which the ICM+ ® brain monitoring software is able to calculate COx in real-time, Ameloot and colleagues retrospectively calculated COx in order to determine the optimal MAP. The COx approach has also been used extensively and validated as a bedside measure of cerebral autoregulation in stroke[14], sepsis[27] and subarachnoid hemorrhage[28].

We demonstrated a lower proportion of time of dysfunctional autoregulation than reported by Ameloot and colleagues[6]. In their study, the authors defined autoregulation as present when the slope of the linear regression prediction was <0.05%/mmHg, and absent when the slope was higher than this threshold. Under their definition, patients with up-sloping (figure 2c) or down-sloping (figure 2d) relationships between COx and MAP would have been labeled as disturbed autoregulation. This may not be correct as patients do maintain the ability to autoregulate, but the range of observable MAP spans the autoregulatory thresholds. Furthermore, using linear regression may introduce model misspecification when the true relationship may in fact be non-linear. These concerns highlight the limitations of many studies examining autoregulation, including our own: the definition of adequate or dysfunctional cerebral autoregulation. These studies all have the underlying assumption of a fixed autoregulatory curve. Autoregulation is more likely dynamic with regional and temporal heterogeneity[3]. In addition, studies use varying definitions of what constitutes dysfunctional autoregulation: near zero slope of the relationship between COx and MAP[6], specific COx thresholds[8,14], or the inability to calculate MAP_{OPT}[29]. We chose a COx threshold of 0.3 or above to indicated dysfunctional autoregulation. This approach allows for a time-dependent change in the autoregulatory curve, which may not be seen with the other methods listed. This also allowed us to examine non-linear relationships between COx and MAP, and thus addressing the constraints placed by linear regression.

Much like our study, Pham and colleagues prospectively assessed COx (termed tissue oxygenation index – TO_X) in 23 patients following cardiac arrest[9]. They defined dysfunctional autoregulation as a COx greater than 0, a lower threshold than used in our study. We chose 0.3 as this represents the threshold used in previously published studies[8,30,31]. However, it is likely that there is no specific threshold for dysfunctional autoregulation, rather it is a continuum. This

is suggested in patients with TBI where an autoregulatory threshold for favorable outcome (0.05) was lower than for survival (0.25)[32]. Further work is needed to delineate the definition of dysfunctional autoregulation as it relates to clinical outcomes.

In patients with traumatic brain injury, rapid rewarming above 37°C results in dysfunction autoregulation[33]. Likewise, there is evidence that hyperthermia may be detrimental following cardiac arrest[34,35]. Although the specific target temperature remains unclear, temperature control, with strict avoidance of hyperthermia, remains an important management priority following cardiac arrest[2,36]. Our results suggest that hyperthermia may result in dysfunctional autoregulation in this population. However this interpretation may be skewed by the few patients with marked hyperthermia. The important relationship between temperature and cerebral autoregulation deserves further investigation.

Because this was a proof-of-concept study, this study was not designed to rigorously examine for clinically important outcomes. Thus, any inference regarding the relationship between COx and either MAP or temperature should be interpreted with caution. Finally, we do not have granular data on arterial carbon dioxide, an important potential modifier of cerebral autoregulation.

Conclusion

In our single-centre proof-of-concept study, we demonstrated the ability to assess cerebral autoregulation and determine a MAP_{OPT} using cerebral oximetry in patients after cardiac arrest. This study justifies further observational work to examine the relationship between COx and time-within MAP_{OPT} ranges and neurologic outcomes.

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Conflicts of interest

ICM+ software is licensed by Cambridge Enterprise Ltd, UK. PS and MC have financial interest in a part of licensing fee. None of the other authors have any other conflicts of interest to declare.

Ethical standards

All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Authors' Contribution

Dr. Donald Griesdale and Dr. Mypinder Sekhon were the co-principal investigators and responsible for the concept and design of the study. They collected all of the data for the study. They had access to all of the data and takes full responsibility for the integrity of the data and the accuracy of the data analysis. They were also involved in interpretation of the data and drafting of the manuscript. They have no conflicts of interest and approves of the final submitted version of the manuscript.

Dr. Penny Brasher performed part of the primary statistical analysis for the study. She was involved in data interpretation and drafting the manuscript. She has no conflicts of interest and approves of the final version of the manuscript.

Dr. Peter Smielewski was involved in the study design and interpretation of the study. He also wrote the configuration files to ensure that our bedside monitors would communicate with ICM+®. He help prepare and critically review the manuscript. He has no conflicts of interest and approves of the final version of the manuscript.

Dr. Tahara D Bhate collected data and was involved in data interpretation and manuscript preparation. She has no conflicts of interest and approve of the final version of the manuscript.

Ms. Denise Foster was involved with the study design. She collected data and was involved in interpreting and preparing the manuscript. She has no conflicts of interest and approve of the final version of the manuscript.

Drs. David Menon, Arun Gupta, Marek Czosnyka, William Henderson, Kenneth Gin and Graham Wong were all involved with the study design. They also contributed in writing the final version of the manuscript. They all approve of the final version of the manuscript.

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Figure Legends

Figure 1: Clinical recording from ICM+ ® brain monitoring software of a patient in order to generate the optimal mean arterial pressure (MAP_{OPT}) over an 8-hour period. The first three planes are the MAP, regional saturation of oxygen (rSO_2), and COx. The COx is a moving Pearson correlation coefficient between 30 consecutive, 10-sec averaged values of MAP and the corresponding rSO_2 signals. The bottom panel is the COx plotted against the intervals of MAP in 5 mmHg. A U-shaped curve is plotted with the nadir of the curve being MAP_{OPT}.

Figure 2. Scatter plot between COx and the corresponding MAP over a 6-hour period for four individual patients. The light grey dots are corresponding COx and MAP measurements. The black boxes and lines represent median and IQR for COx values within 5mmHg width bins of MAP. The dashed line is at a COx of 0.3 which is the threshold for autoregulation. Values above that line indicated lack of autoregulation. The demonstrated relationships include: U-shaped (2A), flat (2B), upsloping (2C) and down-sloping (2D).

Figure 3: Density plot of the difference between the actual MAP and the MAP_{OPT} (as determined using COx) for each hour over the entire study period. Each bin is a width of 5 mmHg.

Figure 4. Scatter plot between COx and temperature. The light grey solid lines are a locally weighted scatterplot smooth for each patient. The solid black line is a predicted curve generated using a restricted cubic splines model. Using multivariable polynomial fractional regression, there was a non-linear relationship between COx and temperature with increasing COx with hyperthermia (P=0. 008).

Abbreviations

AHA	American Heart Association
CCU	coronary care unit
COx	Correlational coefficient between MAP and rSO2
CPP	cerebral perfusion pressure
FVd / FVm	Flow Velocity diastolic / mean
HIBI	hypoxemic ischemic brain injury
ICP	intracranial pressure
ICU	intensive care unit
IQR	Interquartile range
MAP	mean arterial pressure
MAP_{OPT}	optimal mean arterial pressure
ONSD	optic nerve sheath diameter
ROSC	return of spontaneous circulation
rSO2	regional saturation of oxygen
SD	standard deviation
TBI	traumatic brain injury
TCD	transcranial Doppler

Table 1. Baseline characteristics of cohort

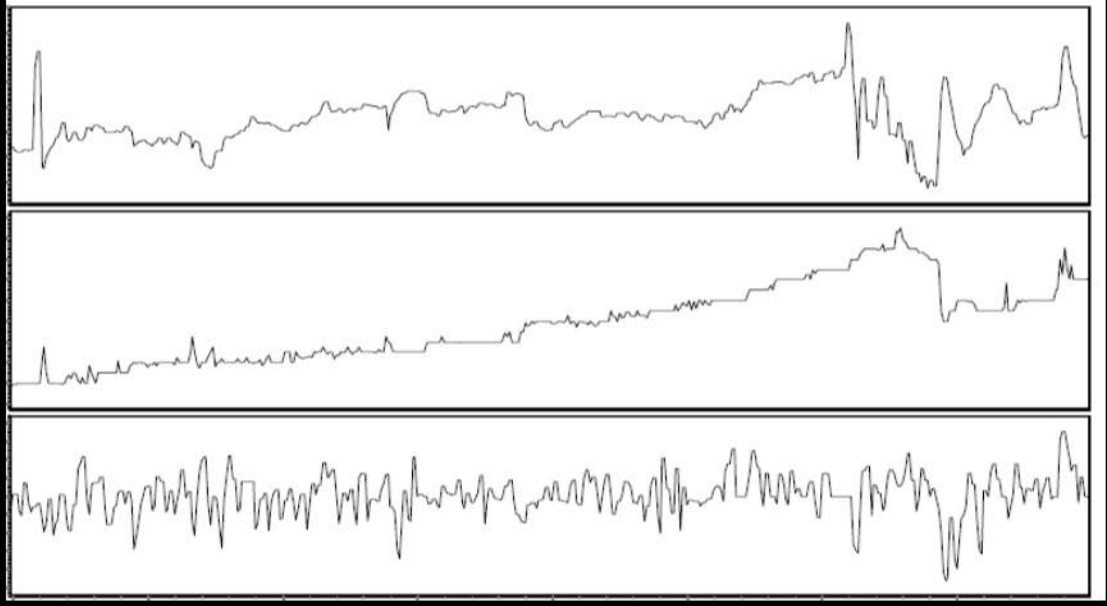
	Cohort (n=20)	Survivors (n=9)	Non-survivors (n=11)
Age in years, median (IQR)	59 (54 – 67)	55 (48 – 66)	65 (57 – 67)
Female sex, n (%)	6 (30)	4 (44)	2 (18)
Etiology of arrest, n(%)			
Myocardial ischemia / infarction	12 (60)	8 (89)	4 (36)
Hypoxemia	4 (20)	0	4 (36)
Other	4 (20)	1 (11)	3 (28)
Out of hospital arrest, n(%)	17 (85)	9 (100)	8 (73)
Witnessed arrest, n(%)	19 (95)	9 (100)	10 (91)
Shockable rhythm, n(%)	6 (30)	4 (44)	2 (18)
Epinephrine dose in miligrams, median (IQR)	2 (1 – 6)	5 (1 – 10)	1.5 (1 – 3)
Minutes prior to CPR, median (IQR)	0 (0 – 0)	0 (0 – 0)	0 (0 – 10)
Minutes prior to ROSC, median (IQR)	15 (5 – 33)	5 (4 – 16)	24 (11 – 33)
Percutaneous intervention, n(%)	10 (50)	8 (89)	2 (18)

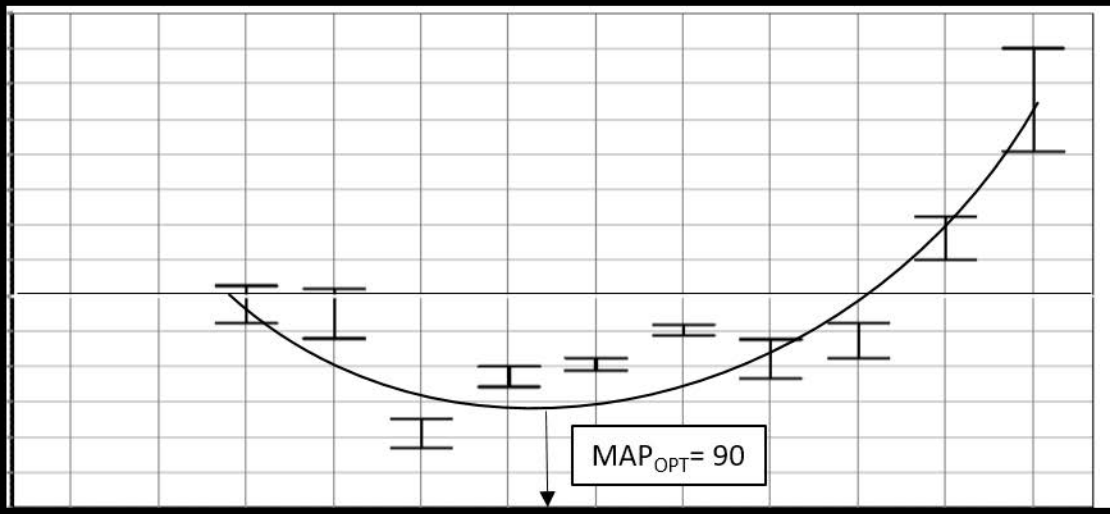
IQR = interquartile range; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation;

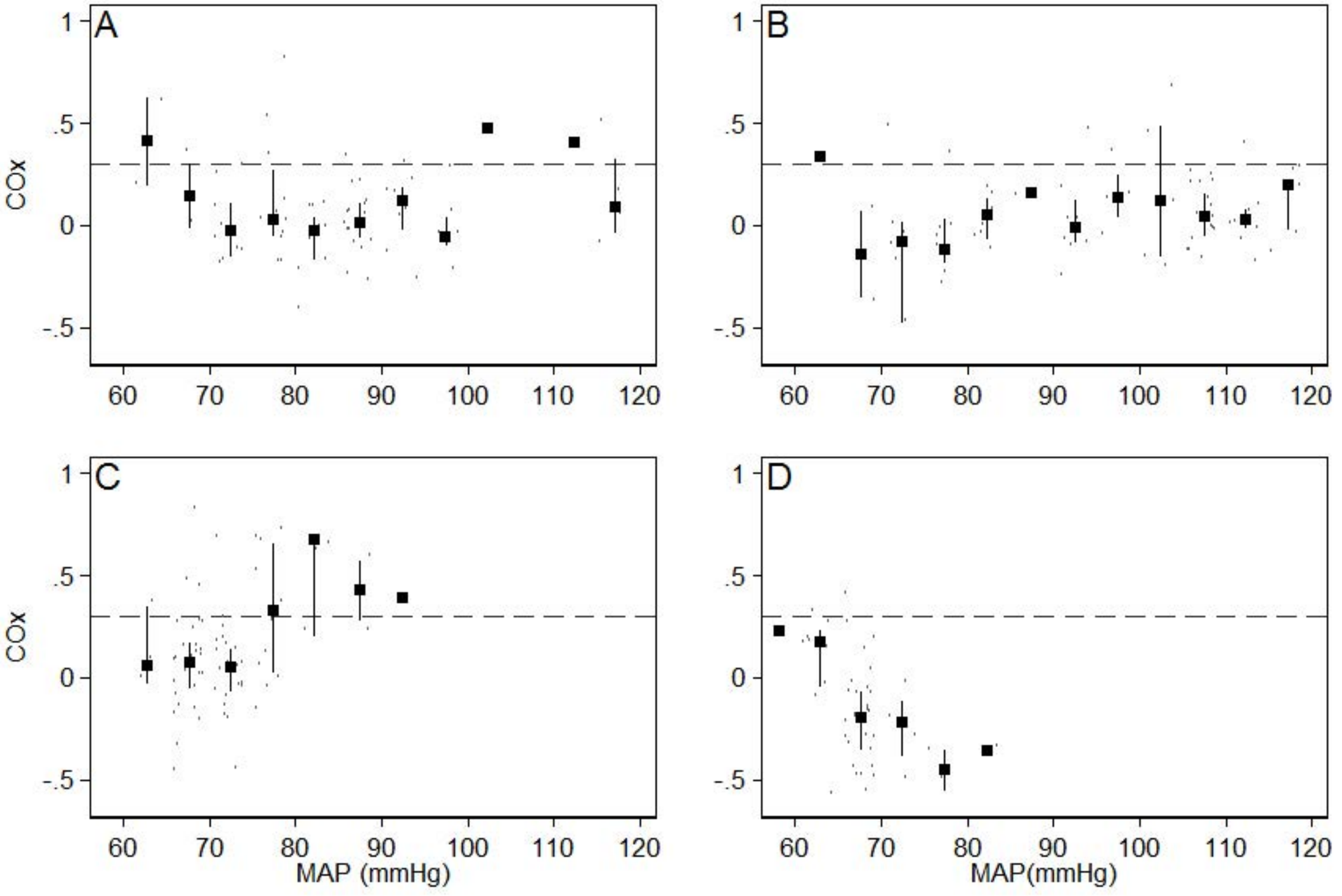
Table 2: Management characteristics of cohort

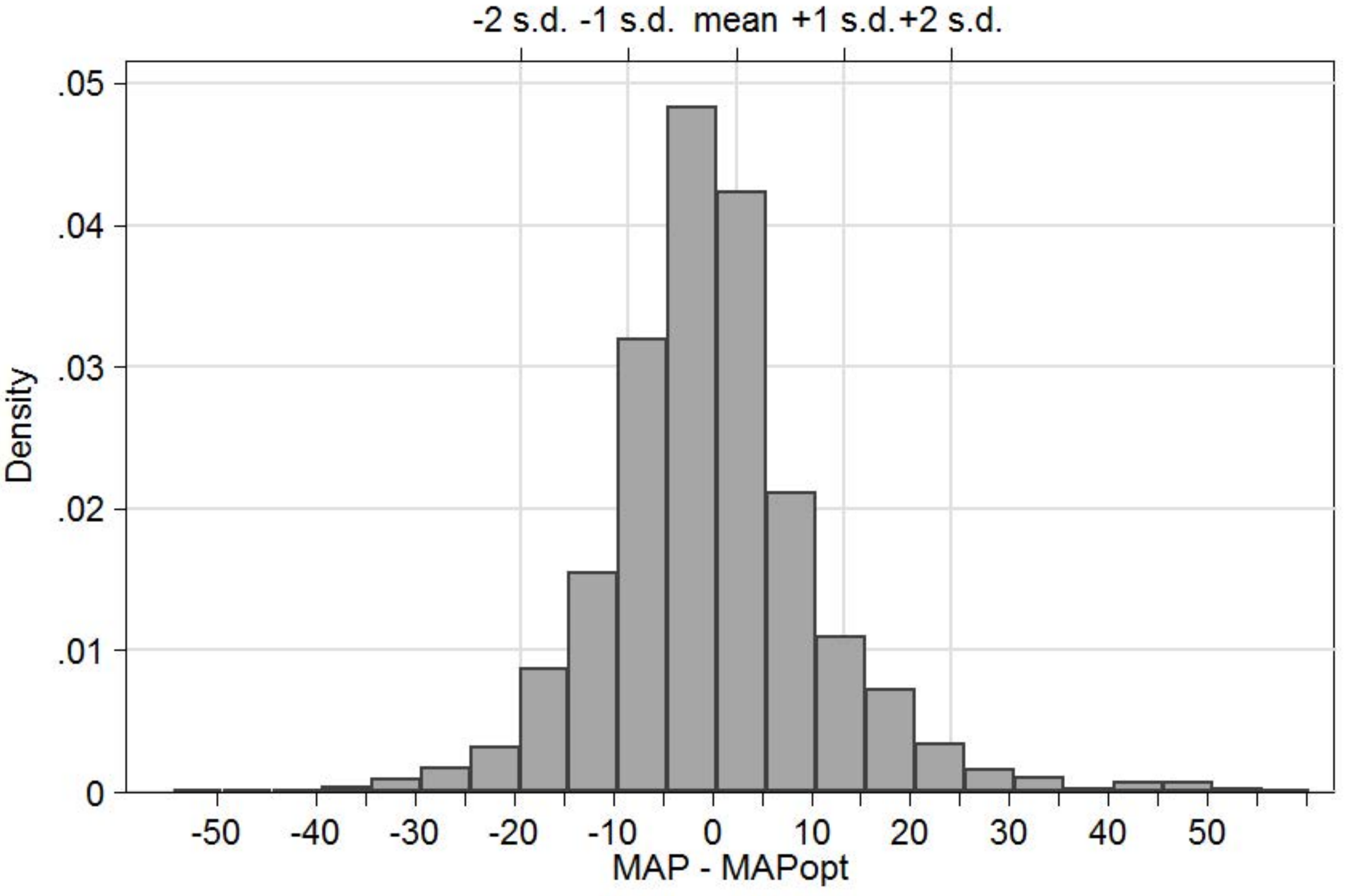
	Cohort (n=20)	**Survivors (n=9)**	**Non-survivors (n=11)**
Temperature in ^{o}C, mean (SD)	36.4 (1.8)	36.5 (1.6)	36.2 (1.9)
PaCO2 in mmHg, mean (SD)	37 (9)	38 (9)	36 (10)
Hemoglobin in g/L, mean (SD)	121 (20)	115 (24)	126 (16)
MAP in mmHg, mean (SD)	76 (10)	79 (8)	74 (11)
MAP_{OPT} in mmHg, mean (SD)	76 (7)	77 (7)	75 (8)
rSO2 %, mean (SD)	59 (11)	57 (5)	65 (14)
COx, mean (SD)	0.066 (0.11)	0.034 (0.047)	0.099 (0.14)
Percent of time with COx ≥ 0.3, median (IQR)	13 (6 – 19)	10 (6 – 13)	18 (7 - 41)
Norepinephrine use, n(%)	19 (95)	8 (89)	11 (100)
Norepinerphrine dose in mcg/min, mean (SD)	12 (13)	11 (13)	12 (13)
Dobutamine use, n(%)	3 (15)	2 (22)	1 (9)
Dobutamine dose in mcg/kg/min, mean (SD)	5.3 (1)	6 (1)	4.5 (4)
Propofol dose in mcg/kg/min, mean (SD)	40 (15)	44 (19)	36 (12)

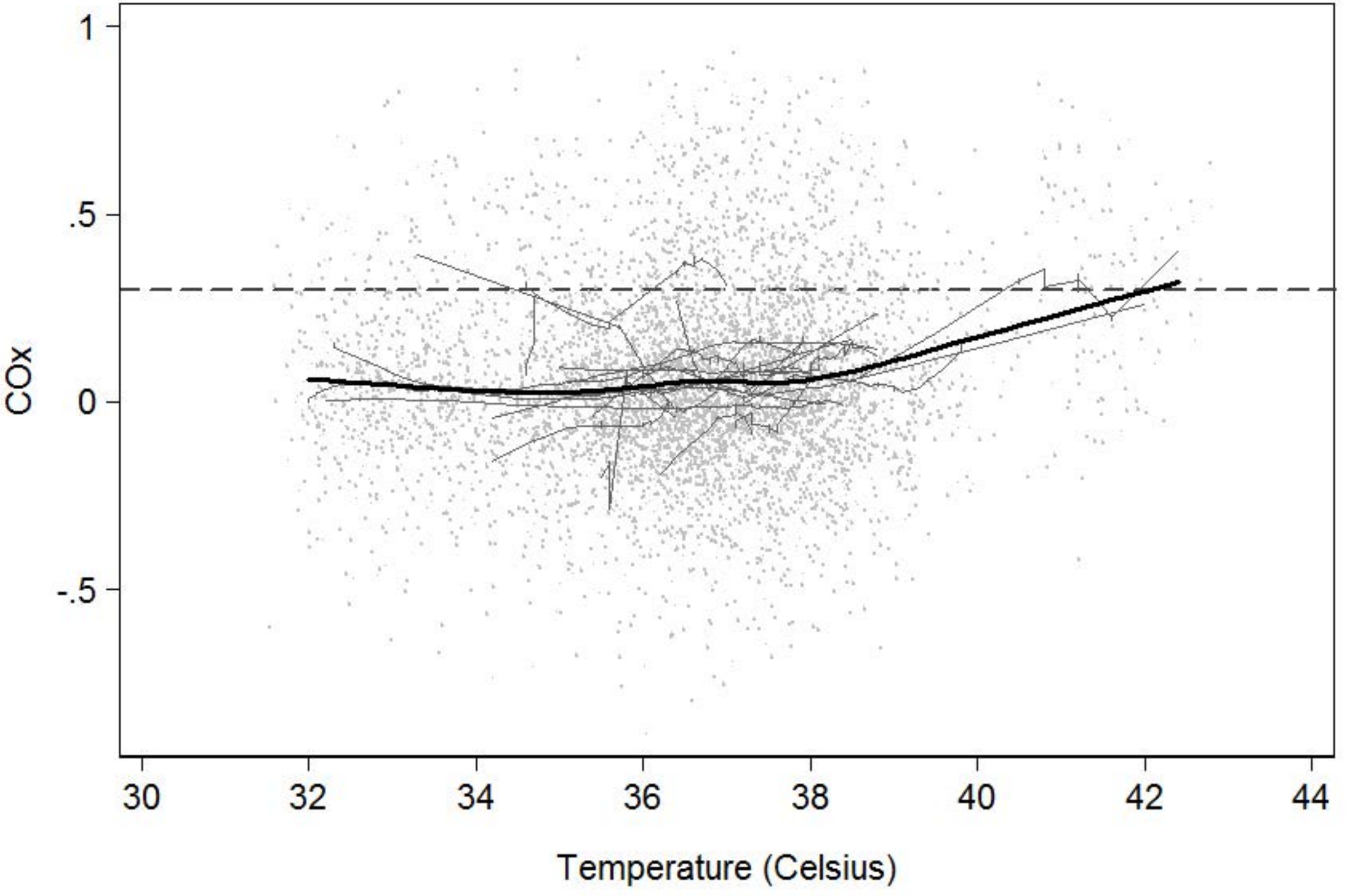
MAP = mean arterial pressure; rSO2 = regional saturation of oxygen; PaCO2 = arterial carbon dioxide tension; IQR = interquartile range; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation;




MAP$_{OPT}$= 90


A
B
C
D
COx
1
.5
0
-.5
60
70
80
90
100
110
120
MAP (mmHg)
MAP(mmHg)


-2 s.d. -1 s.d. mean +1 s.d. +2 s.d.
.05
.04
.03
.02
.01
0
Density
-50
-40
-30
-20
-10
0
10
20
30
40
50
MAP - MAPopt


1
.5
0
-.5
COx
30
32
34
36
38
40
42
44
Temperature (Celsius)