Spontaneous variability of arterial blood pressure, carbon dioxide and cerebral blood flow in critically ill patients.

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Submitted to Journal:
Frontiers in Medicine

Specialty Section:
Intensive Care Medicine and Anesthesiology

Article type:
Original Research Article

Manuscript ID:
333137

Received on:
22 Nov 2017

Frontiers website link:
www.frontiersin.org

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Author contribution statement

MS was responsible for study design, data acquisition, and initial analysis and data interpretation, as well manuscript first draft, revisions, and final approval. All other authors were responsible for study design, detailed analysis, final interpretation, manuscript revisions, and final approval of the manuscript. All authors accepts full responsibility for all aspects of the work presented in the manuscript.

Keywords

Carbon Dioxide, arterial pressure, cerebral blood flow, cerebral circulation, Cardiac arrest, Sepsis

Abstract

Word count: 195

Purpose: To measure the magnitude of spontaneous variations in arterial blood pressure, CO2 and cerebral blood flow (CBF) as a potential pathophysiologic mechanism contributing to delirium and long-term cognitive impairment in critically ill patients.

Methods: In this prospective observational study, we measured mean arterial blood pressure (MAP), end-tidal CO2, (PETCO2) and middle cerebral artery blood flow velocity (MCAv) as an indicator of global CBF continuously over eight hours in twelve mechanically ventilated patients with sepsis, septic shock or post cardiac arrest

Results: All three parameters varied significantly within and between patients. Within patients, interquartile range (IQR) for MAP varied from 3 to 16 (median 8) mmHg, for CO2 1 to 6 (median 2) mmHg and for MCAv 4 to 27 (median 14) percent relative to baseline, with some patients showing greater variability than others. Between patients, median MAP varied from 66 to 97 (median 78, IQR 12) mmHg, CO2 from 24 to 51 (median 36, IQR 15) mmHg, and MCAv from -24 to 46 (median 1, IQR 5) percent relative to baseline.

Conclusions: Arterial blood pressure, CO2 and CBF vary widely both within and between mechanically ventilated critically ill patients when observed over eight hours.

Funding statement

This study was funded by internal research fund for Program in Critical Care Medicine, Department of Medicine, University of Western Ontario.

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Conflict of Interest statement: we have no conflict of interest

Financial Disclosure statement: we have no financial conflicts to disclose

Financial support for study: This study was funded by internal research fund for Program in Critical Care Medicine, Department of Medicine, University of Western Ontario.

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Word count (main body): 1,912

Word count (abstract): 197

Abstract:

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Methods: In this prospective observational study, we measured mean arterial blood pressure (MAP), end-tidal CO_2, ($P_{ET}CO_2$) and middle cerebral artery blood flow velocity (MCAv) as an indicator of global CBF continuously over eight hours in twelve mechanically ventilated patients with sepsis, septic shock or post cardiac arrest

Results: All three parameters varied significantly within and between patients. Within patients, interquartile range (IQR) for MAP varied from 3 to 16 (median 8) mmHg, for CO_2 1 to 6 (median 2) mmHg and for MCAv 4 to 27 (median 14) percent relative to baseline, with some patients showing greater variability than others. Between patients, median MAP varied from 66 to 97 (median 78, IQR 12) mmHg, CO_2 from 24 to 51 (median 36, IQR 15) mmHg, and MCAv from -24 to 46 (median 1, IQR 5) percent relative to baseline.

Conclusions: Arterial blood pressure, CO_2 and CBF vary widely both within and between mechanically ventilated critically ill patients when observed over eight hours.

Keywords: carbon dioxide, arterial pressure, cerebral blood flow, cerebral circulation, cardiac arrest, sepsis

1 Introduction

Delirium (1) and long-term (2) cognitive impairment is a common problem in critically ill patients and survivors of critical illness. In acute settings, delirium is associated with increased mortality and cost of care (1), and often leads to long-term cognitive impairment that is severe (2), affects patients of all ages (2), and places a huge burden on caregivers, families and society (3).

The etiology of both delirium and long-term cognitive impairment is multifactorial, with impairment of cerebral blood flow (CBF) likely playing an important role given high prevalence of ischemic findings in both grey and white matter on neuroimaging studies (4,5), and on autopsy (6,7). Since CBF is exquisitely sensitive to changes in arterial blood pressure and CO_2, and given that cerebral autoregulation is often impaired in critically ill patients (8–10), we hypothesized that critically ill patients may sustain ischemic or hyperemic injury as a result of adverse CBF changes induced by spontaneous fluctuations in arterial blood pressure and CO_2.

Since both arterial blood pressure and CO_2 are closely monitored in intensive care units, the aim of this study was to test the biologic plausibility of this hypothesis, by quantifying intra and inter-patient variability in arterial blood pressure, CO_2 and CBF in a cohort of critically ill patients during a typical day in the intensive care unit.

2 Materials and methods

2.1 Study settings and patients

This study was carried out in the intensive care units at two tertiary care teaching hospitals in London, Canada. Institutional Health Science Research Ethics Board approved this study. Written informed consent was obtained from all patients or their substitute decision makers. We screened and enrolled adult (age $\geq$ 18 years) patients within 48 hours of admission to the intensive care unit with diagnosis of sepsis, septic shock or cardiac arrest. We excluded patients with prior craniotomy/craniectomy, or known cerebrovascular disease.

2.2 Study protocol

Following enrollment, we monitored middle cerebral artery blood flow velocity (MCAv) as an indicator of CBF, mean arterial pressure (MAP) and end-tidal CO_2 ($P_{ET}CO_2$) continuously for 8 hours while patients lay supine in their bed. Monitoring was only interrupted if the patient needed to be transported from the department (e.g. for imaging studies). Demographic and appropriate patient data were extracted from the medical chart using pre-defined case report forms. Arterial blood gases were drawn at the beginning and the end of the monitoring period.

2.3 CBF monitoring

MCAv was used as an indicator of global CBF. It was monitored in one/both middle cerebral arteries using 2-MHz transcranial Doppler probes (ST3, Spencer Technologies, USA). After adequate signals were attained using standard technique, Doppler probes were fixed in place using a commercially available head harness. Adequacy of MCAv signals was continuously monitored throughout the 8 hours of observation by study

investigators, and probes were readjusted as needed to ensure same angle of insonation and good signal power. Data were recorded continuously at 125 Hz using provided software.

2.4 MAP and $P_{ET}CO_2$ monitoring

Arterial pressure was monitored using an indwelling arterial catheter placed into radial, brachial or femoral arteries. CO_2 was monitored using continuous in-line capnography module integrated into the ventilator circuit (S/5, Datex-Ohmeda, GE Healthcare, USA). The transduced arterial pressure and expired CO_2 were displayed on clinical monitors (S/5, Datex-Ohmeda, GE Healthcare, USA) and continuous waveforms were recorded at 300 Hz on a laptop computer using provided software (S5 collect, Datex-Ohmeda, GE Healthcare, USA).

2.5 Data acquisition, processing and analysis

Continuous MCAv, arterial pressure and CO_2 signals were imported into specially developed software (LabView, National Instruments, USA) for offline analysis. Signals were aligned using established time stamps. The entire 8-hr recording was then processed to ensure adequacy of all signals and sections with poor signals (e.g. CO_2 and blood pressure calibration artifacts, coughing, movement resulting in poor signals) were excluded from analysis. The software then used custom algorithms to identify end-tidal CO_2 and systolic, diastolic and mean arterial pressures and MCAv, which were then checked by investigators to ensure appropriate identification of these values from continuous traces. Inappropriately picked values were manually readjusted or excluded from the analysis (e.g. double end-tidal picking due to ventilator asynchrony). Resulting MCAv, MAP and $P_{ET}CO_2$ signals were averaged over 5 second intervals and exported in ASCII format for statistical analysis.

2.6 Statistical analyses

Data were analyzed in Prism 7 (GraphPad, La Jolla, CA, USA). Descriptive statistics were used to report patient demographics and relevant clinical data. We used box plots and data distribution statistics to describe both within and between patient variation in MCAv, MAP and $P_{ET}CO_2$.

3 Results

3.1 Patient details

After five patients were excluded due to poor MCAv signal or equipment malfunction, 12 patients were included in the analysis. The mean age of the participants was 61 ± 19 years, nine were male, three had documented history of hypertension and four of obstructive lung disease. Eight patients had sepsis with three of those having septic shock, and four were admitted post cardiac arrest. Median SOFA score on the day of testing was 10 (IQR 5). Mean arterial-endtidal PCO_2 difference was 11 ± 7.9 mmHg. Baseline characteristics are summarized in Table 1.

3.2 Variability in measured parameters

There was wide within and between patient variation in MAP, $P_{ET}CO_2$ and MCAv over the eight hours of recording (Figure 1). Within patients, IQR for MAP varied from 3 to

16 (median 8) mmHg with a range of 13 to 47 (median 30) mmHg. IQR for CO_2 varied from 1 to 6 (median 2) mmHg with a range of 4 to 15 (median 9) mmHg. IQR for MCAv varied from 4 to 27 (median 14) % related to baseline with a range of 21 to 104 (median 48) %. As shown in Figure 2, some patients showed greater variation in all measured parameters over eight hours than others. Some patients also showed wide variation in MCAv and MAP on the background of stable $P_{ET}CO_2$ (patient 11, Figure 3) suggesting impaired autoregulation, while others had minimal variation in MCAv despite wide variation in MAP and stable $P_{ET}CO_2$ (patient 8, Figure 3) suggesting intact autoregulation.

Between patients, median MAP varied from 66 to 97 (median 78, IQR 12) mmHg, minimum MAP from 51 to 87 (median 65, IQR 11) mmHg, and maximum MAP from 71 to 123 (median 95, IQR 18) mmHg. Median $P_{ET}CO_2$ varied from 24 to 51 (median 36, IQR 15) mmHg, minimum $P_{ET}CO_2$ from 17 to 49 (median 31, IQR 15) mmHg and maximum $P_{ET}CO_2$ from 26 to 60 (median 43, IQR 15) mmHg. Compared to baseline, median MCAv varied from -24 to 46 (median 1, IQR 5) %, minimum MCAv from -95 to -5 (median -24, IQR 37) %, maximum MCAv from 7 to 57 (median 17, IQR 14) %.

4 Discussion

Our results confirm wide *within* and *between* variation in arterial blood pressure, CO_2 and CBF in ventilated critically ill patients over eight hours of observation. This variability occurs despite close monitoring and control of arterial blood pressure and CO_2 in the intensive care unit. Some patients had wider range of *within*-patient variation in measured parameters than others (Figure 2), and in some patients the wide variation in arterial blood pressure was associated with wide perturbation in CBF suggesting impaired autoregulation (Figure 3).

This clinical significance of the observed CBF variation in ventilated critically ill patients is presently unknown. However, given high prevalence of ischemic findings in both grey and white matter on neuroimaging studies (4,5) and autopsy (6,7), coupled with commonly impaired cerebral autoregulation (8–10) in critically ill patients, the observed excursions of CBF due to spontaneous variations in arterial blood pressure and CO_2 provide a plausible biologic mechanism that may contribute to pathophysiology of delirium and long-term cognitive impairment in these patients.

The proposed mechanism is similar to that seen in chronic hemodialysis patients, who develop structural white matter brain injury with associated proportional cognitive impairment as a result of cumulative dialysis-induced hemodynamic stress within one year of starting dialysis (11). Interestingly, reduction of hemodynamic stress (via cooling of dialysate) exhibited complete protection against white matter injury (11), suggesting that interventions aimed at reducing hemodynamic instability may offer neuroprotection in the critically ill.

In view of hemodialysis studies, heterogeneity in the magnitude of arterial blood pressure, CO_2 and CBF variations *between* patients (Figure 2) is an important observation, since hemodynamic stress and consequent ischemic and/or hyperemic brain

injury may potentially be related to magnitude and cumulative duration of these variations. However, this requires further exploration with dedicated studies.

Another important observation from this study was the heterogeneity of CBF-MAP relationship between patients, with some showing large variations in MAP and CBF (suggesting impaired autoregulation), while others showing stable CBF despite large MAP changes (suggesting intact autoregulation, Figure 3). While our sample size was too small to determine any independent predictors of these differences based on patient characteristics, this observation may explain why some studies of critically ill show impaired cerebral autoregulation (8–10), while others show intact autoregulation (12,13), and highlights the need to consider autoregulation status in individual patients when prescribing MAP targets (14).

4.1 Study limitations

We used transcranial Doppler to measure MCAv as an estimate of global CBF. MCAv is proportional to CBF as long as the diameter of the insonated vessel remains constant. Previous research (15,16) indicates that MCAv is a reliable and valid index of global CBF when compared against MRI (17), although recent studies suggest that this assumption may be violated at the extremes of hypercapnia (18). Furthermore, transcranial Doppler only measures global CBF and provides no information about regional changes in CBF that can be gained from advanced imaging modalities such as MRI. However, it does have the advantage of that it can be used at the bedside in the ICU avoiding transport of unstable critically ill patients to the MRI, which is both risky and cumbersome.

We used $P_{ET}CO_2$ for continuous estimate of arterial PCO_2, and compared $P_{ET}CO_2$ values with arterial PCO_2 at the start and at the end of the experiment to estimate arterial-end tidal PCO_2 difference. In our cohort the mean arterial-endtidal PCO_2 difference (11 ± 7.9 mmHg) was larger than that observed in previous cohort studies of critically ill patients (4.0 ± 0.97 mm Hg) (19). $P_{ET}CO_2$ is known to deviate from $PaCO_2$, especially in patients with lung disease (20). Five of our patients had documented history of lung disease (4 obstructive, 1 restrictive). The advantage of using $P_{ET}CO_2$ is that it can be recorded continuously, but it should always be compared to corresponding arterial PCO_2 values as was done in this study. Our study sample size was too small to explore potential association between observed variability in CBF, MAP and $P_{ET}CO_2$ and clinical outcomes.

4.2 Future directions

Future properly powered studies should determine whether the observed variability in CBF due to spontaneous variation in arterial blood pressure and CO_2, when accumulated over time, leads to structural brain injury, delirium or long-term cognitive impairment in critically ill patients. Additional studies can then explore whether interventions aimed at reducing this CBF variability abrogate structural brain injury and improve cognitive outcomes.

5 Conclusions

CBF, arterial blood pressure and CO2 vary significantly within and between mechanically ventilated critically ill patients. Detailed study of these variations is an important and novel entity that may uncover mechanism responsible for ICU-associate brain injury, and provide previously unconsidered therapeutic targets for improvement of long-term cognitive outcomes in critical illness survivors.

Acknowledgements: The authors would like to thank, Fran Priestap for helping with statistical analysis. Dr Marat Slessarev would like to acknowledge the Resident Research Career Development Fund award (Schulich School of Medicine & Dentistry), Ontario Graduate Scholarship and Vanier Canada Graduate Scholarships for supporting his PhD graduate studies.

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Figure captions:

Figure 1: Box-plot graphs showing variability of mean MCAv (expressed in % changes is signal from baseline), MAP and $P_{ET}CO_2$ in individual patients over 8 hours of observation. Cardiac arrest patients (01-04) are represented in red and sepsis/septic shock patients (05-12) are shown in blue. Note significant *within* and *between* patient variability in all measured parameters. Small dots represent outlier values

Figure 2: Continuous and respective box-plot graphs of mean MCAv, MAP and $P_{ET}CO_2$ variation over eight hours from two patients illustrating low (Patient 01) and high (Patient 06) *within* patient variability in measured parameters

Figure 3: Continuous and respective box-plot graphs of mean MCAv, MAP and $P_{ET}CO_2$ variability over eight hours from two patients illustrating presumably *intact* (Patient 08 - significant variability in MAP with minimal MCAv variability) and *impaired* (Patient 11 – significant corresponding variability in MAP and MCAv) autoregulation

Table 1: Baseline Patient Characteristics

Baseline characteristics	
Number of patients	12
Age (years)	61 ± 19
Sex (M:F)	9 : 3
MODS score (ICU admission)	6 (IQR 3)
NEMS score (study day)	39 (IQR 11)
SOFA score (study day)	10 (IQR 5)
Arterial-end-tidal PCO_2 difference (mmHg)	11 ± 7.9
Admission Diagnosis	
Sepsis	5
Septic shock	3
Cardiac arrest	4
Ventilation mode	
Spontaneous	4
Controlled	8
Comorbidities	
Hypertension	3
Coronary artery disease	3
Congestive heart failure	3
Atrial fibrillation	2
Diabetes	2
Dyslipidemia	2
COPD or Asthma	4
Interstitial lung disease	1

Data are reported as absolute numbers, mean ± SD, or median (interquartile range).

Figure 1.TIFF

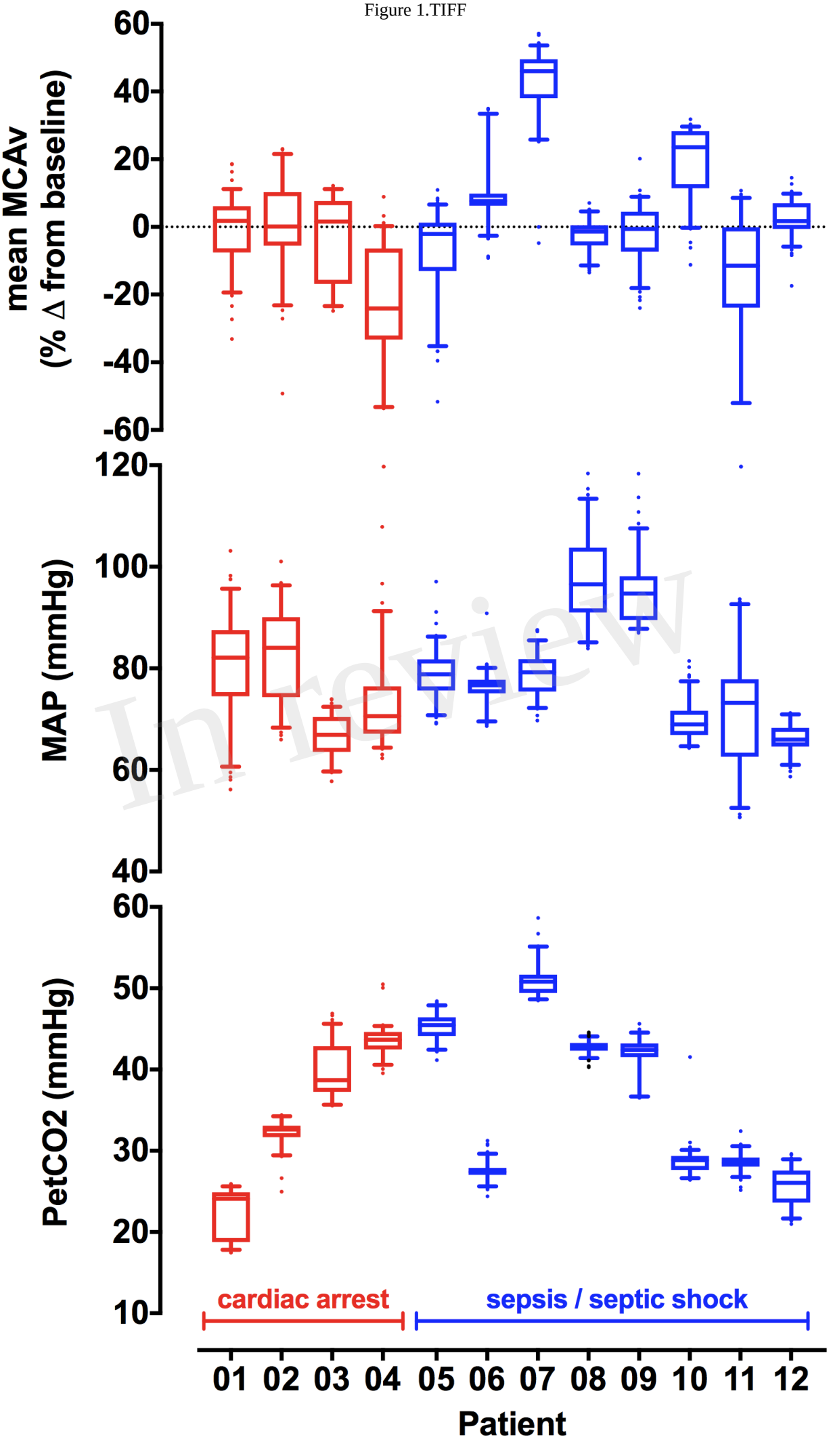

Figure 2.TIFF

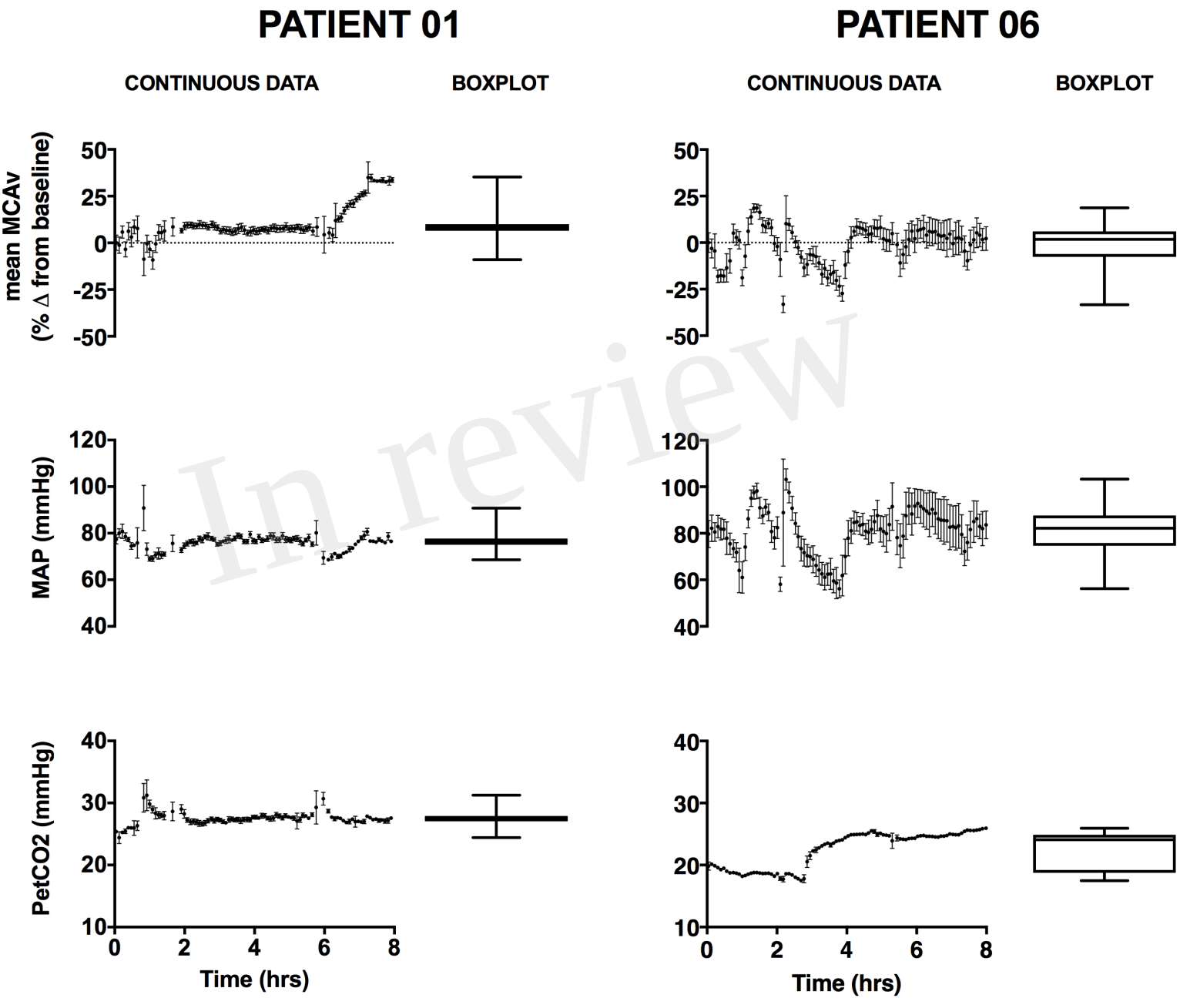

Figure 3.TIFF