Cerebral hemodynamic with intra-aortic balloon pump: business as usual?

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ABSTRACT

Intra-aortic balloon pump (IABP) is commonly used as mechanical support after cardiac surgery or cardiac shock. Although its benefits for cardiac function have been well documented, its effects on cerebral circulation are still controversial. We hypothesized that transfer function analysis (TFA) and continuous estimates of dynamic cerebral autoregulation (CA) provide consistent results in the assessment of cerebral autoregulation in patients with IABP.

Continuous recordings of blood pressure (BP, intra-arterial line), end-tidal CO_2, heart rate and cerebral blood flow velocity (CBFV, transcranial Doppler) were obtained i) 5 minutes with IABP ratio 1:3, ii) 5 minutes, starting 1 minute with the IABP-ON, and continuing for another 4 minutes without pump assistance (IABP-OFF). Autoregulation index (ARI) was estimated from the CBFV response to a step change in BP derived by TFA and as a function of time using an autoregressive moving-average model during removal of the device (ARI_t). Critical closing pressure and resistance area-product were also obtained.

ARI with IABP-ON (4.3 ± 1.2) were not different from corresponding values at IABP-OFF (4.7 ± 1.4, p=0.42). Removal of the balloon had no effect on ARI_t, CBFV, BP, cerebral critical closing pressure or resistance area-product.

IABP does not disturb cerebral hemodynamics. TFA and continuous estimates of dynamic CA can be used to assess cerebral hemodynamics in patients with IABP. These findings have important implications for the design of studies of critically ill patients requiring the use of different invasive support devices.

Keywords: autoregulation index, cerebral autoregulation, cerebral blood flow velocity, transcranial Doppler ultrasound, intra-aortic balloon pump

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Abbreviations list

ARI   Cerebral autoregulation index

ARI_t Cerebral autoregulation index estimated by function of time

BP   Blood pressure

CA   Cerebral autoregulation

CABG   Coronary artery bypass graft surgery

CBF   Cerebral blood flow

CBFV   Cerebral blood flow velocity

CO_2 Carbon dioxide

CPB   Cardiopulmonary bypass

CrCP   Critical closing pressure

$EtCO_2$ End-tidal CO2

HF   High frequency

HR   Heart rate

IABP   Intra-aortic balloon pump

ICC   Intraclass correlation coefficient

IQR   Inter-quartile range

LF   Low frequency

MBP   Mean blood pressure

MCA   Middle cerebral artery

RAP   Resistance-area product

SD   Standard deviation

TCD   Transcranial Doppler

TFA Transfer function analysis

VLF Very-low frequency

Introduction

Intra-aortic balloon pump (IABP) is commonly used as mechanical support after cardiac surgery or cardiac shock (Baskett *et al* 2002, Boning *et al* 2013, Jobs *et al* 2015). Although its benefits for improving cardiac function have been well documented, its effects on the cerebral circulation are still controversial (Yang *et al* 2014). Given on-going concerns about the effects of cardiac surgery on cognitive impairment and perioperative hypoperfusion stroke, the role of IABP on alterations of cerebral haemodynamic parameters is of considerable interest (Nadelson *et al* 2014, Saczynski *et al* 2012, Salazar *et al* 2001).

The main reason why IABP might disturb cerebral blood flow (CBF) and/or its regulatory mechanisms, is due to observed changes in CBF temporal patterns, including the occurrence of transient reversed diastolic (i.e. negative) values of CBF, or CBF velocity (CBFV) recorded with transcranial Doppler ultrasound (Fig. 1) (Brass 1990, Schachtrupp *et al* 2005, Schutt *et al* 2016). Chiefly amongst these regulatory mechanisms, is cerebral autoregulation (CA) that maintains cerebral perfusion within strict limits despite changes in mean arterial blood pressure (BP) in the range 60-150mmHg (Panerai 1998, Paulson *et al* 1990).

Disruption of CA has been associated with several cerebrovascular conditions such as stroke, head injury, pre-eclampsia, neonatal prematurity, ischemic heart disease, and autonomic nervous system failure (Beek *et al* 2008, Caldas *et al* 2017, Claassen *et al* 2016, Ma *et al* 2016, Panerai 2008, Panerai *et al* 1995, Salinet *et al* 2014, Veen *et al* 2015). Hypo- or hyper-perfusion, resulting from disturbances in CA are thought to be contributing factors in the neurological complications following cardiac surgery with cardiopulmonary bypass (CPB) (Hori *et al* 2014, Ono *et al* 2013) and the use of IABP could also play a part in the development of these complications.

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With potentially major changes in the temporal patterns of BP and CBF, the applicability of classical methods for assessment of CA during IABP cannot be taken for granted. CA can be assessed by either static or dynamic techniques (Tiecks *et al* 1995). Both approaches, either using steady-state values of BP (static) or the transient CBFV response to rapid changes in BP (dynamic), rely on linear models using BP as input and CBF as output. By far, the most common of these methods is transfer function analysis (TFA) of spontaneous fluctuations in BP and CBF that does not require any special maneuvers to obtain estimates of dynamic CA at rest (Claassen *et al* 2016). The assumption that TFA should also be applicable to patients with IABP though, cannot be accepted *a priori* as the altered CBF waveforms might indicate the occurrence of highly non-linear phenomena such as transient vessel collapse. The present study has benefited from an opportunistic sample of recordings obtained as part of a larger study on the effectiveness of IABP, containing continuous measurements of BP and CBFV during IABP removal. By examining the behavior of dynamic CA and other cerebrovascular parameters, we have been able to test the hypothesis that despite changes in CBFV waveforms, IABP does not disturb cerebral hemodynamics. The relevance of the study then, is to certify that TFA and continuous estimates of dynamic CA are acceptable methods to assess cerebral hemodynamics in patients with IABP, as a pre-condition to larger studies on the short- and long-term effects of this device on the cerebral circulation.

Methods

Subjects

This was an observational study, performed at the Heart Institute of the University of São Paulo from May 2014 to July 2015. Patients were considered eligible to participate in the study if they fulfilled the following criteria: (i) aged older than 18 years, (ii) submitted to

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elective coronary artery bypass graft surgery (CABG) with CPB and intra-operative prophylactic IABP, (iii) written informed consent. The study was approved by both the institutional review board of the hospital and the local research ethics committee (ref. 835.731).

Measurements

Following surgery, participants were at rest, lying in a supine position (30°) and clinically stable. Measurements were performed over 5 minutes with the IABP operating with a 1:3 ratio, that is one inflation every three cardiac cycles, triggered by the electrocardiogram (Schachtrupp *et al* 2005). A second measurement was performed for 5 minutes, starting one minute with IABP ON, continuing through removal of the IABP for another four minutes without pumping assistance (IABP OFF).

Data acquisition

Bilateral simultaneous TCD evaluation of the middle cerebral arteries (MCAs) was carried out using 2 MHz pulsed, range-gated probes (DWL, Dopplerbox, Germany), held in place using a head frame. If only one MCA could be found, that one side was used in the analysis. The insonation depths varied from 50 to 55 mm, with slight anterior angulation (15– 30°) of the probe through the temporal window. BP was continuously measured invasively with an intra- arterial line (Philips Monitor MP50, Germany).

End-tidal CO_2 (EtCO_2) was continuously measured with an infrared capnograph (Dixtal, dx 1265 ETCO2 Capnogard, Manaus, Brazil) via a closely fitting mask and was documented at 1 min intervals.

Data analysis

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Signals were sampled at a rate of 100 Hz and stored on a dedicated personal computer for offline analysis. Data editing and parameter extraction were performed as described previously (Salinet *et al* 2012). In brief, recordings were visually inspected, the BP signal was calibrated, and narrow spikes (<100 ms) and artefacts were removed by linear interpolation. Subsequently, all signals were filtered in the forward and reverse direction using an eighth-order Butterworth low-pass filter with a cut-off frequency of 20 Hz. The beginning and end of each cardiac cycle were detected from the BP signal, and mean values of BP, CBFV and heart rate were obtained for each heart beat. Critical closing pressure (CrCP) and resistance area-product (RAP) were obtained using the first harmonic method for each cardiac cycle (Panerai 2003). Beat-to-beat parameters were interpolated with a third-order polynomial and resampled at 5 Hz to generate signals with a uniform time base.

Dynamic CA was modelled with transfer function analysis (TFA), using spontaneous fluctuations of mean BP as input and corresponding changes in CBFV as output. Standard settings for TFA were adopted for the first 5 min segment of data (IABP ON). For the second segment of data (IABP OFF), the segment duration was reduced to 4 min (Claassen *et al* 2016; Salinet *et al* 2012). The Welch method was adopted for smoothing spectral estimates obtained with the fast Fourier transform (102.4 s segments, 50% superposition) leading to frequency dependent estimates of coherence, gain, and phase, which were then averaged for the very-low (VLF, 0.02-0.07 Hz), low (LF, 0.07-0.20 Hz) and high (HF, 0.20-0.50 Hz) frequency ranges. Using the inverse fast Fourier transform, the CBFV response to a step change in BP was also derived. The CBFV step response was compared with 10 template curves (Tiecks *et al* 1995) and the best fit curve corresponded to the autoregulation index (ARI) (Panerai *et al* 1998). Values of ARI = 0 indicate absence of CA whilst ARI = 9 corresponds to the most efficient CA that can be observed. A new statistical procedure was adopted to accept or reject values of ARI (Panerai *et al* 2016), based on the mean value of

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coherence in the 0.15-0.25 Hz frequency interval and the normalised mean square error of fitting Tiecks model (Tiecks *et al* 1995) to the CBFV step response.

To assess the transition from the ON to the OFF stage during the withdrawal (or weaning) of IABP, the ARI index was estimated as a function of time (ARI_t) using an autoregressive moving-average (ARMA) model with orthogonal coefficient decomposition as described previously (Panerai *et al* 2010). This ARMA model had two coefficients for the autoregressive terms (CBFV), and three coefficients for the moving-average terms (BP), corresponding to order [2,3], to mimic the original second order differential equation proposed by Tiecks *et al* (1995) to define the classical ARI. In this case though, the model coefficients are assumed to be a function of time and are expressed as an orthogonal transform (similarly to the Fourier transform), using Walsh functions as the orthogonal basis. As demonstrated elsewhere (Panerai *et al* 2010), the ARMA coefficients and their Walsh decomposition coefficients can be estimated by least-squares. Once these are available, the CBFV step response can be calculated at each time interval along the recording, and at that point the ARI_t can be obtained with optimal fitting of one of the 10 template curves proposed by Tiecks *et al* (1995). The ARI_t and all other cerebral hemodynamic parameters were averaged for 10s before removal of IABP (T1), 1 minute after removal (T2) and 3 minutes after removal of the device (T3).

Statistical analysis

Following assessment of normality with the Kolmogorov-Smirnov (KS) one-sample test, parametric (Paired Student's t-test) or non-parametric (Wilcoxon) tests were used as appropriate. The intraclass correlation coefficient (ICC) was calculated to compare consistency of parameters with IABP ON and OFF. Fisher's exact text was used with categorical variables. Results are expressed as means ± SD or medians with interquartile

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ranges [IQRs]. Inter-hemispherical differences in parameters were tested with the paired Student's t-test or Wilcoxon non-parametric test. In the absence of differences, values for the right and left MCAs were averaged. Changes at T1, T2 and T3 were assessed with a 1-way repeated measures ANOVA (parametric) or Friedman test (non-parametric). Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL). A p-value < 0.05 was considered statistically significant.

Results

Good quality recordings were obtained for 14 patients (10 male) aged 63.9 ± 7.9 years. EuroSCORE was 5 [3-7] and echocardiogram LVEF was 40% [35-45]. All recordings showed acceptable TFA parameters, based on the average coherence in the 0.15-0.25 Hz frequency range, as well as the corresponding ARI values (Panerai *et al* 2016).

Cerebral hemodynamic parameters and dynamic CA during baseline

None of the bilateral parameters (CBFV, CrCP, RAP, and ARI) showed significant differences between the right and left MCAs and for this reason were averaged in further analyses. ARI_t is reported separately for each hemisphere.

Fig. 1 is illustrative of recordings with very low diastolic CBFV at the moment of IABP withdrawal showing abnormal BP and CBFV patterns with each inflation of the balloon with a 1:3 ratio. Similar patterns were observed in all subjects, but only 2 (out of 14) showed minimum values of CBFV approaching zero.

Table 1 presents the main cerebral hemodynamic parameters, averaged for 5 min segments of data with IABP ON and 4 minutes with IABP OFF showing that removal of the balloon changed systolic and diastolic blood pressure, and also diastolic cerebral blood flow velocity, but all other parameters were unaffected. For parameters with significant

differences, like systolic BP, ICC (Table 1) was correspondingly low, but in other cases it is in agreement with the literature as discussed below.

Despite the distorted waveforms (Fig. 1), CrCP and RAP estimated with the first harmonic method reflected velocity-pressure curves for IABP ON and OFF that were almost superimposed, as illustrated in Fig. 2.

Transfer function analysis parameters for the two assessment periods are given in Table 1 and Fig. 3. ARI values with IABP ON (4.3 ± 1.2) were not significantly different from corresponding values at IABP OFF (4.7 ± 1.4, p= 0.42) as suggested by the CBFV step response plots in Fig. 3D. None of the other TFA parameters showed statistically significant differences (Table 1, Fig. 3).

Cerebral hemodynamic and dynamic CA during weaning of IABP.

None of the cerebral and peripheral hemodynamic parameters assessed showed differences for the three time-points considered (T1-T3) during withdrawal of IABP (Table 2), despite the visual suggestion of potential trends in Fig. 4.

Dynamic CA during weaning of IABP showed a slight change between times, the ARI_t at T1 = 3.5 ± 2.1, T2 = 2.3 ± 1.6 and T3 = 2.8 ± 2.2 (p = 0.052). Following withdrawal of IABP at t=0 (Fig. 4), ARI_t showed a drop around t=100s and BP also dipped around t=60s, but like the other parameters shown in Fig. 4, there was a relatively stable transition from IABP ON to IABP OFF.

Discussion

We have demonstrated that use of TCD to assess cerebral hemodynamics in post-surgical patients with an IABP operating at a 1:3 ratio leads to CBFV values and other parameter estimates (ARI, CrCP, RAP) that are not different from baseline recordings obtained after removal of the balloon. Moreover, benefitting from a unique set of continuous recordings that include the period of IABP withdrawal, we have also observed that time-varying estimates of ARI, CBFV, CrCP, and RAP do not show any abrupt transitions that could suggest changes in the cerebral circulation associated with use of IABP. Taken together, these findings suggest that TCD-based assessment of cerebral hemodynamics with IABP operating at 1:3 mode, leads to reliable estimates that could be used in further studies of post-surgical patients using this device, mainly in the context of prospective studies of the effects of surgery, CPB, or the IABP itself, on the complications often associated with CABG, such as delirium, deterioration of cognitive function and stroke (Glick *et al* 1996, Bienvenuti *et al* 2012, Trabold and Metterlein 2014).

The values of ICC we estimated, comparing recordings with IABP ON and OFF (Table 1), are in good agreement with the literature. For the ARI, Brodie *et al* (2009) obtained values of ICC ranging from 0.43 to 0.51, which compare favourably with the value 0.61 we obtained. For TFA parameters like gain and phase, the results in Table 1 are also in good agreement with what was reported by Gommer *et al* (2010). With spontaneous breathing they reported ICC for gain ranging from 0.32-0.68 and for phase ranging from 0.43-0.60. Although the values of ICC that we obtained, as well as those of Brodie *et al* (2009) and Gommer *et al* (2010) would be regarded as indicating low to average reliability, in the context of the present study, it confirms that measurements with IABP ON are not different to what is normally obtained without an intra-aortic balloon pump, from the perspective of the ICC.

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With few exceptions, previous studies of the effects of IABP on the cerebral circulation have been confined to reporting changes in CBF, usually assessed with transcranial Doppler. In agreement with our findings, two studies reported unaltered CBFV with weaning from IABP, as long as systemic hemodynamics remained unchanged (Cheung *et al* 1998, Schachtrupp *et al* 2005) On the other hand, either reduction (Oster *et al* 1974,Gee *et al* 1986) or increase in CBFV (Pfluecke *et al* 2014, Yang *et al* 2014) have also been reported. Unfortunately, none of these studies have reported CA, that jointly with simultaneous changes in BP, could have helped to explain the directional changes in CBFV observed. Likewise, inclusion of data on CrCP and RAP would have helped to clarify whether IABP operation had any effects on the instantaneous flow (or velocity)-pressure curves of the cerebral circulation. As exemplified by Fig. 2, the constancy of CrCP and RAP (Table 3) indicates that although balloon inflation leads to distorted waveforms (Fig. 1), there is almost perfect superposition of the instantaneous flow-pressure relationships, except for the narrow 'trough' induced by balloon inflation which leads to noticeably low values of CBFV, that can often be negative (Schachtrupp *et al* 2005).

A previous study of dynamic CA with IABP was based on the time-delay between fluctuations in CBFV and BP, estimated using a cross-correlation technique, under the assumption that absence of a time-delay reflects impairment of CA (Bellapart *et al* 2010). Of interest, recordings were obtained for IABP pulsation ratios ranging from 1:1 to 1:3, in all cases with time-delays significantly greater than zero. Unfortunately, the use of cross-correlation for assessment of dynamic CA is not taken up as much as TFA (Claassen *et al* 2016), with very limited information available to allow interpretation of time-delay data, including ranges of normality. Nevertheless, the study by Bellapart *et al* suggests that dynamic CA is operational with IABP ON, independently of different inflation ratios.

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Our study had some limitations. First, TCD cannot provide absolute measurements of CBF, the use of CBFV as a surrogate relies on the assumption that the MCA diameter remains approximately constant. This is likely to be the case during 5-minute baseline measurements obtained at rest, without large fluctuations in $PaCO_2$ as was the case of our study (Coverdale *et al* 2014). Secondly, the fact that we have only studied patients with IABP inflation ratios of 1:3 means that our conclusions cannot be automatically extended to other operating modes, such as 1:1 and 1:2 ratios. Nonetheless, it is known that the waveform pattern of cerebral blood flow is similar in all three ratios (Cheung *et al* 1998). Thirdly, Fig. 4 gives visual indication of a drop in BP around 60s after removal of IABP and in ARI_t around 100s post-withdrawal. Careful inspection of all individual recordings though, shows that these drops only occurred in a minority of individuals, but their magnitude was sufficient to influence the population average, from only 14 patients, albeit somewhat amplified by the limited range of values displayed in Fig. 4. Finally, we estimated the ARI index based on spontaneous fluctuations in BP and CBFV. This index was originally proposed to quantify the dynamic CA response to the thigh cuff maneuver (Aaslid *et al* 1989, Tiecks *et al* 1995), but following the demonstration that it can also be estimated from spontaneous fluctuations (Panerai *et al* 1998), it has been extensively adopted in physiological and clinical studies of dynamic CA (Panerai 2008, Panerai *et al* 2010, Salinet *et al* 2012, Salinet *et al* 2014, Veen *et al* 2015, Claassen *et al* 2016, Caldas *et al* 2017).

Conclusion

The current study has demonstrated the feasibility of TFA to analyse changes in the pattern of CBFV response and ARI during the removal of the IABP device. Our findings have important implications for the design of studies of critically ill patients requiring the use of different invasive support devices. In particular, confirming the ability to undertake cerebral hemodynamic assessment and to investigate the potential contribution of peripheral and cerebral hemodynamic perturbations to short- and long-term neurological consequences of cardiac surgery.

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Tables

Table 1 Peripheral and cerebral hemodynamic and parameters obtained from transfer function analysis for baseline recordings and with IABP

	IABP ON N= 14	IAPB OFF N = 14	ICC	*P* (Paired T-Test)
$EtCO_2$ (mmHg)	32.2 ± 2.6	32.9 ± 2.8	0.75	0.520
Mean BP (mmHg)	79.5 ± 15.9	74.8 ± 13.3	0.77	0.360
Systolic BP (mmHg)	133.3 ± 20.3	117.4 ± 21.1	0.12	0.030
Diastolic BP (mmHg)	45.6 ± 11.7	53.1 ± 9.0	0.46	0.013
HR (bpm)	104.3 ± 14.8	105.7 ± 20.0	0.82	0.177
Mean CBFV (cm/s)	80.5 ± 16.5	81.9 ± 17.1	0.95	0.371
Systolic CBFV (cm/s)	116.6 ± 19.8	118.5 ± 23.4	0.88	0.504
Diastolic CBFV (cm/s)	51.4 ± 12.9	58.5 ± 13.2	0.80	0.001
CrCP (mmHg)	5.3 ± 9.0	7.1 ± 10.5	0.35	0.245
RAP (mmHg.s.cm^{-1})	0.91 ± 0.4	0.86 ± 0.17	0.46	0.543
Transient reversed CBFV (n)	2	-		-
ARI	4.3± 1.2	4.7 ± 1.4	0.61	0.316
COH VLF	0.46 ± 0.20	0.47 ± 0.19	0.62	0.837
COH LF	0.70 ± 0.16	0.63 ± 0.17	0.67	0.111
COH HF	0.78 ± 0.16	0.76 ± 0.15	0.69	0.523
Gain VLF cm.mmHg^{-1}s^{-1}	0.96 ± 0.40	0.92 ± 0.28	0.34	0.523
Gain LF cm.mmHg^{-1}s^{-1}	1.02 ± 0.40	1.01 ± 0.25	0.37	0.942
Gain HF cm.mmHg^{-1}s^{-1}	0.91 ± 0.34	0.97 ± 0.25	0.59	0.345
Phase VLF (rad)	0.66 ± 0.34	0.62 ± 0.30	0.25	0.629
Phase LF (rad)	0.30 ± 0.16	0.29 ± 0.19	0.59	0.245
Phase HF (rad)	0.16 ± 0.14	0.12 ± 0.13	0.42	0.251

Values are population mean ± SD. IABP, intra-aortic balloon pump; IABP ON, intra-aortic

balloon pump (ratio 1:3); IABP OFF, without intra-aortic balloon pump; $EtCO_2$, end- tidal

CO_2; BP blood pressure; HR, Heart rate; CBFV, cerebral blood flow velocity; CrCP, critical

closing pressure; RAP, resistance area product; ARI, autoregulation index; COH, coherence

function; VLF, very low frequency; LF, low frequency; HF, high frequency band, ICC, intra-

class correlation coefficient.

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Table 2 Cerebral hemodynamic and peripheral parameters during weaning of IABP.

VARIABLES	T1	T2	T3	P- value
$ETCO_2$ (mmHg)	32.6 ± 2.8	32.1 ± 2.7	32.1 ± 2.6	0.375
MAP (mmHg)	77.0 ± 14.7	74.5 ± 14.5	74.4 ± 14.8	0.417
HR (bpm)	103.3 ± 18.4	104.1 ± 24.0	106.2 ± 20.7	0.257
CBFV (cm/s)	81.9 ± 16.9	82.1 ± 18.1	81.7 ± 18.0	0.871
RAP ($mmHg.s.cm^{-1}$)	0.91 ± 021	0.86 ± 0.19	0.82 ± 0.19	0.595
CrCP (mmHg)	5.3 ± 6.4	7.0 ± 10.7	9.81 ± 15.3	0.257
ARI_t	3.5 ± 2.1	$2.3 \pm 1.6*$	2.8 ± 2.2	0.052

Values are population mean $\pm$ SD. $EtCO_2$, end- tidal CO_2; MAP, mean arterial pressure; HR,

heart rate; CBFV, cerebral blood flow velocity; CrCP, critical closing pressure; RAP,

resistance area-product; T1, baseline; T2, 1 minute after removal of IABP; T3, 3 minutes

after removal of the device.

Figures Legends

Figure 1. Continuous recording of BP and CBFV from a 63 year-old male patient with IABP ratio 1:3 showing the moment of balloon withdrawal (vertical dashed line). ABP, arterial blood pressure; CBFV, cerebral blood flow velocity; IABP, intra-aortic balloon pump.

Figure 2 – Instantaneous velocity-pressure curves for cardiac cycles labelled in Fig. 1 (*, #), before (open circles) and after (filled triangles) removal of IABP.

Figure 3. Population averaged transfer function analysis results during baseline recordings for IABP ON (dashed line) and IABP OFF (continuous line). (A) coherence function, (B) gain, (C) phase and (D) normalized CBFV response to a step change in BP. Largest ± 1 standard error is represented at the point of occurrence.

Figure 4. Population averages of mean arterial blood pressure (A), heart rate (B), cerebral blood flow velocity (C), autoregulation index (D), critical closing pressure (E), and resistance area product (F) synchronised by the moment of IABP withdrawal (t=0).   Averages from the right (continuous line) and left (dashed line) MCA are distinguished in C, D, E and F. Largest ± 1 standard error is represented at the point of occurrence
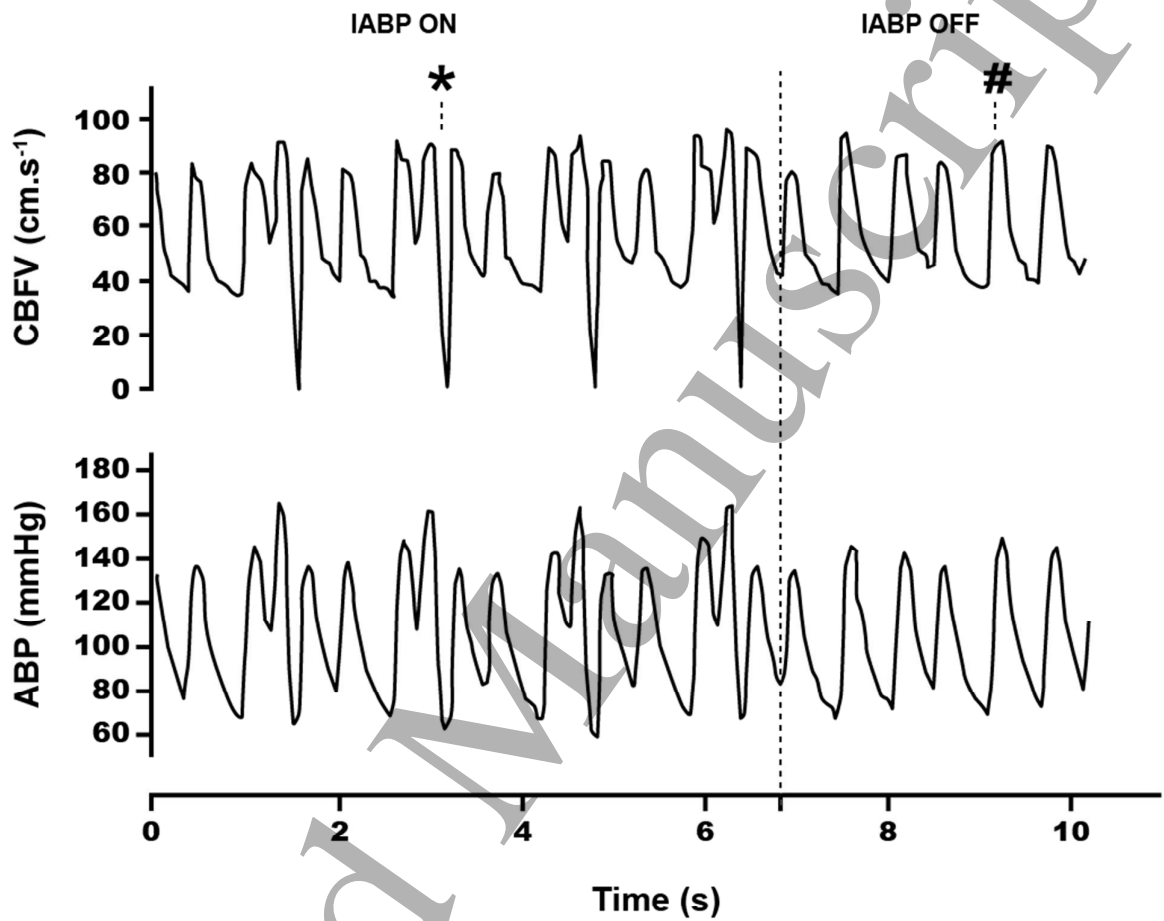
Figures

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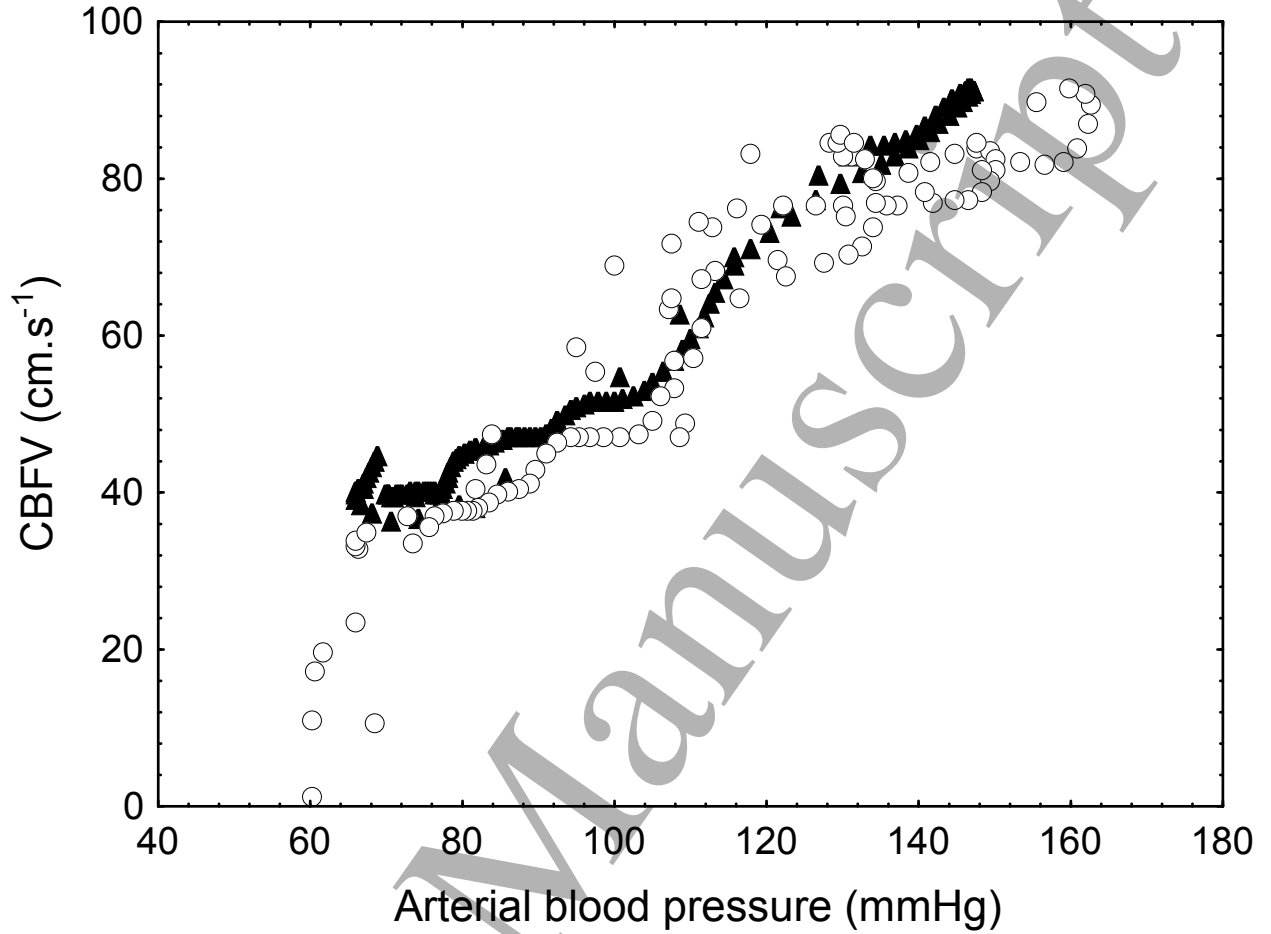
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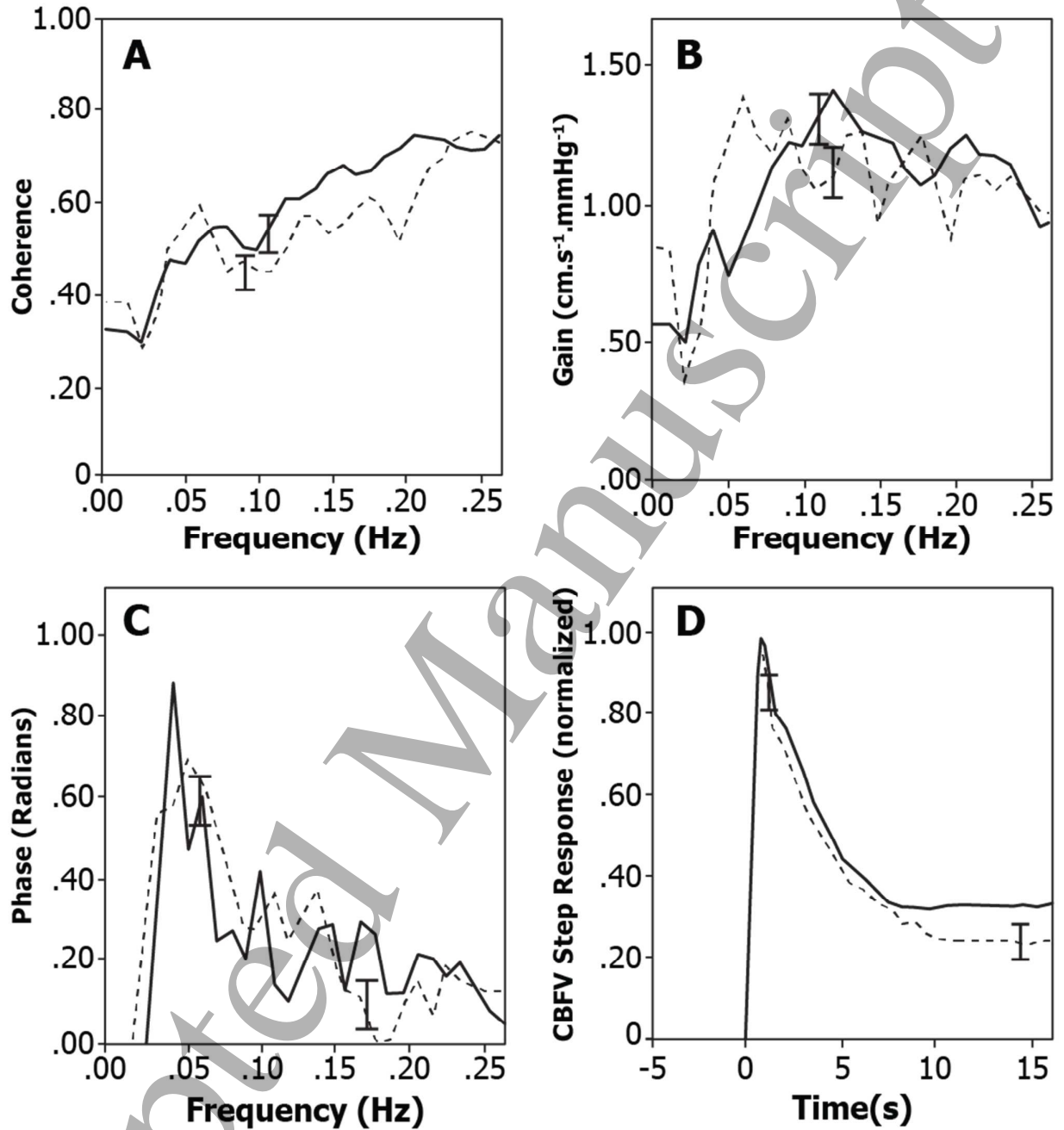
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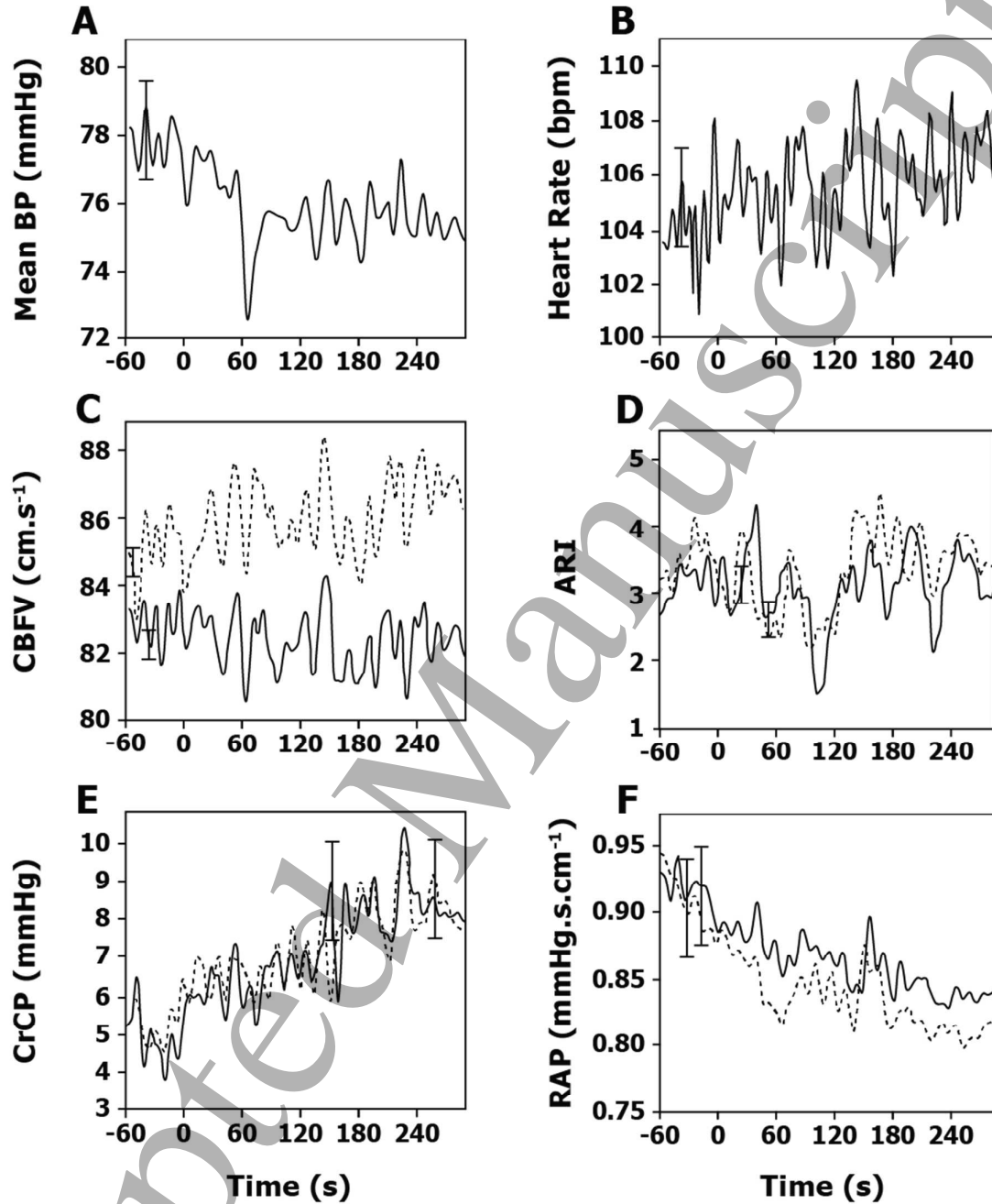
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