Correlation between Baroreflex Sensitivity and Cerebral Autoregulation Index in Healthy Subjects

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Abstract

Despite the acknowledged interaction between baroreflex and cerebral autoregulation (CA), their functional relationship remains controversial. The study investigates this relationship in a healthy population undergoing an orthostatic challenge. Thirteen healthy subjects (age: 27 ± 8 yrs; 5 males) underwent electrocardiogram, arterial pressure (AP) and cerebral blood flow velocity (CBFV) recordings at supine resting (REST) and during 60° head-up tilt (TILT). CA was assessed via the autoregulation index (ARI) from spontaneous variations of mean AP and mean CBFV. The cardiac control and baroreflex were evaluated via frequency domain and transfer function analyses applied to systolic AP and heart period variability. We found at REST a borderline positive correlation between ARI and indexes of sympathetic modulation and a stronger negative correlation with markers of vagal modulation and baroreflex sensitivity. Correlations were lost during TILT. Our data support the hypothesis that, when sympathetic drive is limited, vagal control and cardiac baroreflex have a compensatory effect on CA and sympathetic control could play a favorable role on CA.

1. Introduction

Cerebral autoregulation (CA), in combination with cerebral vasoreactivity to arterial gases and neurovascular coupling, maintains an adequate cerebral blood perfusion. CA ensures that cerebral blood flow (CBF) stays relatively constant by adjusting the cerebral arteriolar caliber in response to swings in arterial pressure (AP). This behavior occurs continuously over time within the physiological interval of AP between 60 and 140 mmHg. Concurrently, the autonomic nervous system and baroreflex operate to keep AP within this range [1].

Despite the acknowledgement of the vital integration between baroreflex and CA during physiological challenges, the functional relationship between the two mechanisms is unclear [2]. While Tzeng et al. [3] have found an association between baroreflex sensitivity (BRS) and CA markers, animal studies have failed to prove any alteration in CBF following baroreceptor stimulation nor denervation [4,5]. The difficulties in typifying this relation is likely due to the controversial role of sympathetic nerve activity on cerebral vasculature [2]. Conversely, its negative impact on cardiac baroreflex control in limiting heart period (HP) changes in response to systolic AP (SAP) variations is well known [6,7].

The study evaluates concomitantly spectral markers of vagal and sympathetic modulations [7,8], baroreflex control indexes derived from transfer function analysis [6], and the autoregulatory index (ARI) [9] describing the dynamic component of CA. This analysis, carried out in healthy subjects, could provide a preliminary characterization of the interactions between cardiac regulation, baroreflex and CA mechanisms.

2. Methods

2.1. ARI

ARI was evaluated from mean AP (MAP) and mean CBF velocity (MCBFV) variations via the time domain approach as described in [10,11]. Briefly, the beat-to-beat series of MAP was resampled at f=10 Hz and normalized according to [11] with critical closing pressure set to 12 mmHg. The Tiecks' differential equations [9] were fed by the normalized MAP. Ten different sets of parameters (i.e. time constant, damping factor, and autoregulatory

Table 1. ARI, cardiac control, baroreflex markers at REST and during TILT.

Index	REST	TILT
ARI	6.46±2.44	4.84±2.23
HFa_{HP} [ms^2]	710 ± 1020	208 ± 252 *
LFa_{HP}/HFa_{HP}	1.97 ± 1.48	5.21 ± 3.68 *
LFa_{SAP} [$mmHg^2$]	4.27 ± 4.81	25.11 ± 31.15 *
BRS(LF) [$ms \cdot mmHg^{-1}$]	14.45 ± 17.77	7.66 ± 5.80 *
BRS(HF) [$ms \cdot mmHg^{-1}$]	15.61 ± 18.71	5.11 ± 2.56
Ph_{HP-SAP}(LF) [rad]	-1.07 ± 0.60	-1.00 ± 0.33
Ph_{HP-SAP}(HF) [rad]	-0.06 ± 1.07	-0.39 ± 1.18
K^2_{HP-SAP}(LF)	0.71 ± 0.19	0.88 ± 0.11 *
K^2_{HP-SAP}(HF)	0.75 ± 0.25	0.83 ± 0.11

REST: at rest in supine position; TILT: head-up tilt at 60°; ARI: autoregulation index; HF: high frequency; LF: low frequency, HP: heart period; SAP: systolic arterial pressure; LFa_{HP}: LF power of the HP series expressed in absolute units; HFa_{HP}: HF power of the HP series expressed in absolute units; LFa_{HP}/HFa_{HP}: the ratio of the LFa_{HP} to HFa_{HP} powers; LFa_{SAP}: LF power of the SAP series expressed in absolute units. BRS(LF): baroreflex sensitivity in the LF band; BRS(HF): baroreflex sensitivity in the HF band; Ph_{HP-SAP}(LF): phase between SAP and HP in the LF band; Ph_{HP-SAP}(HF): phase between SAP and HP in the HF band; K^2_{HP-SAP}(LF): square coherence function between SAP and HP in the LF band; K^2_{HP-SAP}(HF): square coherence function between SAP and HP in the HF band; rad: radians. Results are presented as mean±standard deviation. The symbol * indicates $p<0.05$ versus REST.

dynamic gain [9]), corresponding to ARI graded from 0 to 9 according to the efficiency in performing CA, with 5 being the limit between impaired and intact CA [9], allowed the computation of ten predicted MCBFVs. The matching between the original and predicted MCBFV series was calculated using the normalized mean square prediction error and the selected ARI corresponded to the curve providing the best matching.

2.2. Autonomic nervous system indexes

Power spectral density was computed via a parametric approach using the autoregressive (AR) model [12]. the Akaike figure of merit was utilized to optimize the model order in the range from 10 to 16. A spectral component was labelled as low frequency (LF) or high frequency (HF) if its central frequency was, respectively, between 0.04 and 0.15 Hz or between 0.15 and 0.4 Hz [8]. The LF power was computed over HP and SAP series (LFa_{HP} and LFa_{SAP}) and expressed in absolute units (i.e. ms^2 and $mmHg^2$). HF power was computed over HP series (HFa_{HP}) and expressed in absolute units (i.e. ms^2). The HFa_{HP} power series was taken as a marker of vagal modulation [8]. The ratio of the LFa_{HP} to the HFa_{HP} (LFa_{HP}/HFa_{HP}) was used to monitor sympathovagal balance [8]. The LFa_{SAP} power was taken as an index of sympathetic modulation [7].

2.3. Cardiac baroreflex indexes

We applied a traditional parametric cross-spectral method to typify cardiac baroreflex control in the frequency domain [12]. The cross-spectrum was computed from the coefficients of the bivariate AR model and from the variance of the white noises. The model order was fixed at 10. The transfer function was estimated as the ratio of the cross-spectrum from SAP to HP to the power spectrum of HP. The transfer function modulus, expressed in $ms \cdot mmHg^{-1}$, represents the magnitude of HP change per unit variation of SAP, thus being a traditional metric for the assessment of baroreflex sensitivity (BRS). The phase (Ph_{HP-SAP}) was expressed in radians (rad) and ranged between $-\pi$ and $+\pi$, with negative value indicating that the HP changes lagged behind SAP variations. We estimated the squared coherence function (K^2_{HP-SAP}) as the ratio of the squared cross-spectrum modulus to the product of the power spectra of HP and SAP series. The K^2_{HP-SAP} was dimensionless and ranged between 0 and 1, where 0 indicated full uncoupling and 1 perfect association between HP and SAP. The BRS, Ph_{HP-SAP} and K^2_{HP-SAP} were sampled at the frequency where the K^2_{HP-SAP} peaked the maximum value within LF and HF bands and denoted as BRS(LF), BRS(HF), Ph_{HP-SAP}(LF), Ph_{HP-SAP}(HF), K^2_{HP-SAP}(LF) and K^2_{HP-SAP}(HF).

3. Protocol and data analysis

3.1. Experimental protocol

We analyzed 13 young healthy individuals (age: 27 ± 8 yrs; 5 males) undergoing the simultaneous monitoring of cardiovascular and cerebrovascular controls [13,14]. The subjects were enrolled at the Neurology Division of Sacro Cuore Hospital, Negrar, Italy. They gave written informed consent before performing the experimental session. The

Table 2. Correlation analysis of cardiac control and baroreflex markers to ARI.

Correlation analysis versus ARI	REST		TILT	
	r	*p*	*r*	*p*
HFa_{HP}	-0.797	1.90×10^{-3} #	-0.121	7.07×10^{-1}
LFa_{HP}/HFa_{HP}	0.334	2.89×10^{-1}	0.138	6.85×10^{-1}
LFa_{SAP}	0.578	4.90×10^{-2} #	0.201	5.32×10^{-1}
BRS(LF)	-0.897	7.76×10^{-5} #	-0.174	5.89×10^{-1}
BRS(HF)	-0.821	1.05×10^{-3} #	-0.005	9.88×10^{-1}
$Ph_{HP\text{-}SAP}$(LF)	-0.478	1.16×10^{-1}	-0.338	2.82×10^{-1}
$Ph_{HP\text{-}SAP}$(HF)	0.024	9.42×10^{-1}	-0.255	4.42×10^{-1}
$K^2_{HP\text{-}SAP}$(LF)	-0.364	2.45×10^{-1}	0.112	7.29×10^{-1}
$K^2_{HP\text{-}SAP}$(HF)	-0.330	2.95×10^{-1}	0.072	8.25×10^{-1}

REST: at rest in supine position; TILT: head-up tilt at 60°; ARI: autoregulation index; HF: high frequency; LF: low frequency, HP: heart period; SAP: systolic arterial pressure; LFa_{HP}: LF power of the HP series expressed in absolute units; HFa_{HP}: HF power of the HP series expressed in absolute units; LFa_{HP}/HFa_{HP}: the ratio of the LFa_{HP} to HFa_{HP} powers; LFa_{SAP}: LF power of the SAP series expressed in absolute units. BRS(LF): baroreflex sensitivity in the LF band; BRS(HF): baroreflex sensitivity in the HF band; $Ph_{HP\text{-}SAP}$(LF): phase between SAP and HP in the LF band; $Ph_{HP\text{-}SAP}$(HF): phase between SAP and HP in the HF band; $K^2_{HP\text{-}SAP}$(LF): square coherence function between SAP and HP in the LF band; $K^2_{HP\text{-}SAP}$(HF): square coherence function between SAP and HP in the HF band; *r*: Pearson correlation coefficient; *p*: type I error probability. The symbol # indicates a significant association with $p<0.05$.

study adhered to the principles of the Declaration of Helsinki. The local ethical committee approved the study. Detailed protocol description and preprocessing steps were reported in [13]. Briefly, we recorded electrocardiogram (lead II), AP (Finapres Medical Systems, Enschede, The Netherlands), and CBFV (Multi-Dop T, DWL, 2MHz, Compumedics, San Juan Capistrano, CA, USA). Signals were acquired at 1000 Hz for 10 minutes at supine resting (REST) followed by 10 minutes of head-up tilt (TILT) with table inclination at 60°.

3.2 Beat-to-beat series extraction

HP was computed as the time distance between two consecutive R-wave peaks. The *k*th SAP was defined as the maximum AP value within the *k*th HP. Diastolic arterial pressure (DAP) was detected as the minimum AP value after the *k*th SAP. The *k*th MAP was computed as the ratio of the definite integral of AP between the (*k*–1)th and *k*th DAP occurrences to the interdiastolic interval [14]. The same procedure was applied to compute MCBFV from CBFV [14]. The series were manually inspected and corrected in case of misdetection or isolated arrhythmic events through linear interpolation. Sequences of 250 consecutive beats were selected during REST and TILT.

3.3. Statistical analysis

Paired t test, or Wilcoxon signed rank test when appropriate, was performed to check the effect of TILT. The Pearson correlation analysis was used to assess the association between ARI and all remaining indexes. Pearson product moment correlation coefficient *r* and type I error probability *p* were calculated. Statistical analysis was carried out using the statistical program Sigmaplot (Sigmaplot, v.14.0, Systat Software, Inc., Chicago, IL, USA). A $p<0.05$ was considered as significant.

4. Results

Table 1 reports ARI, cardiac control and baroreflex at REST and during TILT. ARI remained unvaried during TILT. All cardiac control indexes, namely HFa_{HP}, LFa_{HP}/HFa_{HP} and LFa_{SAP}, were significantly affected by TILT. More specifically, HFa_{HP} decreased during TILT, while LFa_{HP}/HFa_{HP} and LFa_{SAP} increased. Among baroreflex control indexes, namely BRS(LF), BRS(HF), $Ph_{HP\text{-}SAP}$(LF), $Ph_{HP\text{-}SAP}$(HF), $K^2_{HP\text{-}SAP}$(LF) and $K^2_{HP\text{-}SAP}$(HF), only BRS(LF) and $K^2_{HP\text{-}SAP}$(LF) varied with TILT. More specifically, BRS(LF) decreased and $K^2_{HP\text{-}SAP}$(LF) increased with TILT.

Table 2 reports the results of correlation analysis between cardiac control, or baroreflex, markers and ARI at REST and during TILT. Among cardiac control indexes, at REST HFa_{HP} and LFa_{SAP} were significantly associated to ARI and the sign of the correlation was negative and positive respectively. Among baroreflex indexes, solely BRS(LF) and BRS(HF) at REST were significantly and negatively associated to ARI.

5. Discussion

The main findings of the study can be summarized as follows: i) ARI did not vary with postural challenge, while

HFa_{HP} and BRS decreased and LFa_{SAP} increased; ii) at REST ARI was correlated to HFa_{HP}, LFa_{SAP} and BRS; iii) the associations with ARI were lost during TILT.

In spite of the role played by the sympathetic drive in governing the modification of the vessels diameter to counteract MAP changes [15], we did not find any variation of ARI during the sympathetic activation induced by TILT. This result confirmed results based on markers of CA different from ARI [16]. However, a certain link between CA and sympathetic drive was detected at REST as stressed by the positive association of ARI and a marker of sympathetic modulation, such as LFa_{SAP}.

It is known that ARI and BRS are negatively associated [3]. However, this relation was found using an interventional protocol based on thigh cuff deflation to induce a significant AP drop and stimulate CA response. In the present study the negative correlation between ARI and BRS was confirmed using spontaneous variability and without imposing an artificial, and sizable, AP change that might expose the subject to risky situations. We hypothesize that at REST CA has a compensatory effect on BRS. Individuals with a lower BRS can compensate with an augmented dynamic CA their inefficiency in buffering rapid SAP variations [3]. Given the more vagal nature of cardiac arm of the baroreflex [6,7], the inverse relationship between ARI and BRS might indicate a dependence of CA on sympathetic control [15]. Indeed, at REST ARI was found to be positively correlated with LFa_{SAP}. Future studies should check the correlation of CA markers with indexes describing the sympathetic arm of baroreflex [7].

Remarkably, correlations with ARI were lost during TILT. It can be hypothesized that the compensatory action of BRS on CA, and even any beneficial effect of the sympathetic control, could be reduced in situations of sympathetic hyperactivity, thus tending to exacerbate conditions of unpaired CA because baroreflex control cannot be of help.

6. Conclusion

The inverse relation between the efficiency of CA and baroreflex at REST and its loss during TILT indicates that, in presence of a limited sympathetic drive, when one of the mechanisms is lacking or impaired, the other tends to make up for. The relationship of CA with sympathetic control is more limited and favorable again solely in situations of low sympathetic activity. Future studies should confirm these findings by analyzing subjects with different baroreflex gains and/or with diverse tonic levels of sympathetic activity, by correlating ARI with markers derived from the sympathetic branch of the baroreflex, and by performing the analysis with CA markers different from ARI.

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