Comparing Models of Spontaneous Variations, Maneuvers and Indexes to Assess Dynamic Cerebral Autoregulation

Max Chacón, Sun-Ho Noh, Jean Landerretche, and José L. Jara

Abstract *Objective*: We analyzed the performance of linear and nonlinear models to assess dynamic cerebral autoregulation (dCA) from spontaneous variations in healthy subjects and compared it with the use of two known maneuvers to abruptly change arterial blood pressure (BP): thigh cuffs and sit-to-stand.

Materials and methods: Cerebral blood flow velocity and BP were measured simultaneously at rest and while the maneuvers were performed in 20 healthy subjects. To analyze the spontaneous variations, we implemented two types of models using support vector machine (SVM): linear and nonlinear finite impulse response models. The classic autoregulation index (ARI) and the more recently proposed model-free ARI (mfARI) were used as measures of dCA. An ANOVA analysis was applied to compare the different methods and the coefficient of variation was calculated to evaluate their variability.

Results: There are differences between indexes, but not between models and maneuvers. The mfARI index with the sit-to-stand maneuver shows the least variability.

Conclusions: Support vector machine modeling of spontaneous variation with the mfARI index could be used for the assessment of dCA as an alternative to maneuvers to introduce large BP fluctuations.

Keywords Dynamic cerebral autoregulation · Spontaneous variations · Thigh cuff maneuver · Sit-to-stand maneuver · Support vector regression · Linear and nonlinear models

Introduction

Dynamic cerebral autoregulation (dCA) is usually assessed by analyzing the cerebral blood flow velocity (CBFV) response signal to a change in arterial blood pressure (BP). There are several maneuvers for producing the BP stimulus, such as the sudden release of bilateral thigh cuffs [1, 2], varying the body posture [3, 4], the Valsalva maneuver, hand grip exercises and others that can induce significant transient changes in BP. However, these maneuvers are hard to implement in routine clinical practice, require patients' cooperation, cause discomfort, increase sympathetic activity or cannot be used in certain pathological conditions. Therefore, dCA should ideally be assessed from the spontaneous BP-CBFV fluctuations of subjects at rest (baseline). For this, it is usual to use a system identification method to capture the relationship between BP and CBFV, and manipulate a parameter or introduce changes in the inputs (i.e., BP) to obtain the response signal (i.e., CBFV), which can then be assess using, for example, the classic autoregulation index (ARI) [5]. Unfortunately, the signal-to-noise relationship in baseline signals has so far proved to be challenging for the adequate assessment of dCA.

The standard system identification method for evaluating dCA with baseline signals is transfer function analysis [6], whose potential has already been established, for example in Panerai et al. [7]. On the other hand, promising new methods that use nonlinear models of dCA have emerged [8, 9], but they have not been sufficiently compared with traditional BP maneuvers.

Materials and Methods

Subjects and Measurement

Twenty healthy subjects were recruited, aged between 21 and 41 years (27.6 ± 5.4), with no history of cardiovascular pathological conditions, hypertension, epilepsy, aneurysms

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or any other neurological disorder. The study was performed in the Biomedical Informatics Lab of the Departamento de Ingeniería Informática at the Universidad de Santiago de Chile. The study was approved by the university's ethics committee and all subjects gave written informed consent.

After a period of resting, 5-min-long beat-to-beat non-invasive baseline BP and CBFV signals were obtained using a Finometer MIDI Finapres, on the contra-lateral middle finger, and a DWL Doppler Box system with 2 MHz transducers, on the middle cerebral arteries respectively. Both signals were then recorded while the subjects were subjected to thigh cuff maneuvers (as in [10]) and sit-to-stand maneuvers (as in Sorond et al. [11], only the period moving from sitting to standing position was analyzed). Hereafter, these maneuvers for manipulating BP are referred to as the THC and the STAND methods respectively. Signals were directly recorded in a computer, via the analog/digital converter of the Doppler box, for off-line preprocessing that yielded mean BP and CBFV signals re-sampled at 5 Hz using spline interpolation.

Models were built from the baseline signals re-sampled at 2 Hz (see details below) and their step responses were obtained. dCA effectiveness was measured on the CBFV responses in all experimental conditions using classic ARI. In addition, we used a newer autoregulation index that does not make assumptions of linearity, as the classic ARI does [5], namely the model-free ARI (mfARI) [12]. Both indexes range between 0 (no autoregulation) and 9 (most effective autoregulation).

Modeling

Models were built using support vector regression (SVR) [13] with BP as input and CBFV as output. Input time delays were introduced to obtain finite impulse response (FIR) dynamic models. Specifically, we procured linear (LFIR) and nonlinear models (NFIR) using the usual linear kernel and radial basis function kernel respectively. The number of time delays and the model's hyper-parameters (ν, C, and, in the case of NFIR, σ) were set empirically by grid search. Twofold cross-validation was applied to select the models with the best test correlations. A smoothed inverted BP step was introduced to each model and the resulting step response was evaluated by an algorithm on how physiologically plausible it looked and scored accordingly. The model with highest test correlation coefficient and highest plausibility score was chosen from each set of baseline signals.

Statistics

Data normality was confirmed using the Shapiro–Wilk statistic. Paired comparisons between LFIR and NFIR models were made using the Student's t test. Intra-subject variability of the four dCA assessment methods (THC, STAND, LFIR, and NFIR) were compared in terms of their standard deviation normalized as a percentage of the mean, that is, their unbiased coefficient of variation (CoV). A global comparison of the four methods and the two autoregulation indexes was obtained with a two-way repeated-measures ANOVA. Tukey's method was used for post-hoc analysis. In all tests, a value $p < 0.05$ was considered significant.

Results

Good baseline recordings were procured for 19 out of the 20 subjects, which allowed valid LFIR and NFIR models to be obtained. Mean ± SD values of the training parameters and goodness-of-fit are shown in Table 1. NFIR models achieved borderline-significantly higher test correlation coefficients ($p = 0.051$).

Figure 1 presents the ANOVA plot of means. No significant interaction was observed ($p = 0.080$[1]) and the factors were then analyzed individually, finding relevant differences between indexes ($p < 0.001$), but not between methods ($p = 0.084$[1]). Post-hoc analysis revealed that only a few combinations of method/index are dissimilar: THC/mfARI vs STAND/ARI, LFIR/ARI and NFIR/ARI ($p = 0.003$, $p = 0.036$, and $p < 0.001$ respectively) and STAND/mfARI vs STAND/ARI and NFIR/ARI ($p = 0.020$ and $p < 0.005$ respectively).

Mean ± SD values of both autoregulation index and CoV are detailed in Table 2. mfARI consistently exhibited the best

Table 1 Statistics for the training hyper-parameters and correlations of selected LFIR and NFIR models

Models	*np*	*C*	σ	ν	Test CC
LFIR	10 [2–10]	28.5 ± 56.9	–	0.4 ± 0.3	0.67 ± 0.16
NFIR	10 [2–19]	3455.4 ± 4457.2	17.6 ± 13.8	0.5 ± 0.3	0.70 ± 0.13

Mode and range is reported for the number of input time delays (*np*). Mean ± SD for the other values
CC Pearson's correlation coefficient

[1] Corrected using the Greenhouse–Geisser procedure.

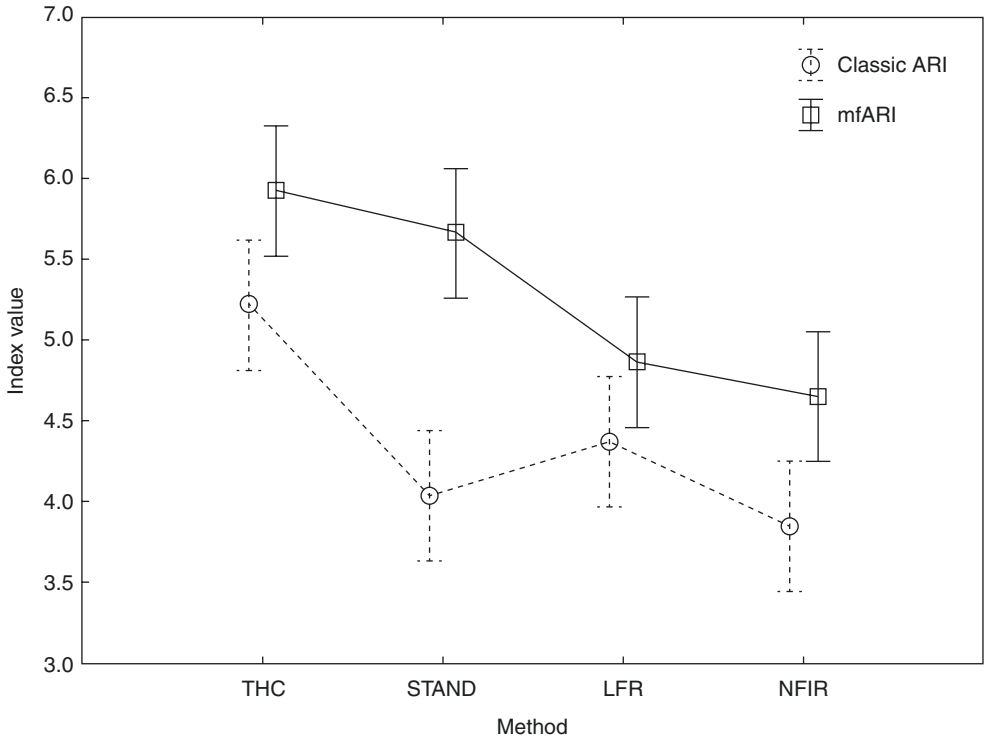

Fig. 1 Two-way ANOVA. Mean autoregulation index values for each method of assessing dynamic cerebral autoregulation (dCA; THC, STAND, LFIR, and NFIR) as measured with the classic ARI (*dashed line*) and mfARI (*solid line*)

Table 2 Autoregulation index mean ± SD values and coefficients of variation (CoV) for each combination of method–index

		Method			
Autoregulation Index		THC	STAND	FIR	NFIR
mfARI	Means ± SD	5.8 ± 1.4	5.7 ± 1.1	4.9 ± 1.5	4.7 ± 2.0
	CoV	23.73%	19.30%	30.61%	42.55%
ARI	Means ± SD	5.2 ± 1.4	4.0 ± 1.4	4.4 ± 2.2	3.8 ± 2.2
	CoV	26.92%	35.00%	50.00%	57.90%

intra-subject variability in every method. STAND/mfARI and NFIR/ARI are the combinations with the lowest and higher variations respectively.

Discussion

Models were successfully acquired with high correlation levels, of around 0.7, between the real CBFV signal and the models' output. It should be noted that multi-step-ahead prediction was applied in the evaluation; thus, the 2.5-min test signal was reproduced using exclusively the input BP signal.

The analysis of variance showed that significant differences were due to the autoregulation index utilized. mfARI achieved significantly higher values than the classic ARI in every method. High index values, on the upper half of the scale 0–9, were expected for the group of subjects studied, as none of them had neurological or cardiovascular problems, confirming the findings in Chacón et al. [12].

Considering measures with mfARI only, although models showed lower values, there was no significant difference between assessment methods ($p > 0.164$). Therefore, using mfARI, the efficiency of the dCA can be equivalently evaluated with signals from two of the most frequently used maneuvers to perturb BP or from spontaneous variations at rest, with the clear advantage of being simpler to perform and applicable to a wider range of patients.

mfARI also exhibited the least variability. Nonetheless, the BP maneuvers obtained lower CoV values than the models, indicating that even though mfARI improved the discriminatory ability of the models, the index could not completely eliminate the intra-subject variability of the latter.

Future studies are necessary. For instance, the age range should be broadened to include older subjects. Also, pathological cases should be considered, to investigate the perfor-

mance of the proposed method–index pairs so as to recognize impaired dCA. Finally, a reliability study may be of great relevance, but this would require repeated measurements in both baseline and BP maneuver conditions [12].

Conclusion

We have shown that SVR models built from spontaneous BP-CBFV fluctuations of healthy subjects at rest can measure dCA efficiency in a way that is statistically equivalent to two of the most commonly used methods based on maneuvers to produce large BP perturbations. We believe that conducting a reproducibility analysis of the proposed methods is necessary.

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Conflicts of interest statement We declare that we have no conflicts of interest.

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