Can the Low-Frequency Component of the Maximal First Derivative of Arterial Pressure Waveform Indicate the Sympathetic Response to Isometric Exercise?

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Abstract

We propose using the low-frequency component (LF) of the maximal first derivative of arterial pressure waveform (AdP/dt_{max}) as a potential estimator of sympathetic activity ($LF_{AdP/dtmax}$). In 35 volunteers we assessed the effects of continuously and linearly increasing muscular force to the maximum (CLIMF) on the time courses of AdP/dt_{max}, systolic pressure (SBP), diastolic pressure (DBP), $LF_{AdP/dtmax}$, LF of SBP (LF_{SBP}) and DBP (LF_{DBP}). LF powers were computed using a time-frequency distribution. The continuous relations of the cardiovascular variables and spectral measures with the percentage of maximal muscular force ($\%MF_{max}$) showed that AdP/dt_{max}, SBP, and DBP increased gradually from the start of CLIMF to the maximum. The responses of $LF_{AdP/dtmax}$, LF_{SBP}, and LF_{DBP} displayed two phases: initially, they decreased, until around $65\%MF_{max}$, where they suddenly increased until the end of CLIMF. This pattern is considered a threshold phenomenon. In the post-threshold phase, the correlation and coherence of the continuous relations of $LF_{AdP/dtmax}$ with LF_{SBP} were 0.88±0.17 and 0.84±0.09, and with LF_{DBP} were 0.79±0.31 and 0.76±0.09, respectively. The strong correlations and high coherence support the proper performance of $LF_{AdP/dtmax}$ as a promising sympathetic activity measure.

1. Introduction

The maximal first derivative of the left ventricle pressure waveform ($LVdP/dt_{max}$) is used to assess the degree of deterioration of left ventricular (LV) function and the mortality risk of diseases such as hypertension and heart failure [1]. $LVdP/dt_{max}$ is either measured via invasive recordings or estimated by echocardiography, which makes its continuous monitoring non-feasible [1]. The maximal first derivative of the noninvasive recording of the arterial pressure waveform (AdP/dt_{max}) has been used as a surrogate of $LVdP/dt_{max}$ [1,2]. AdP/dt_{max} has the advantages that it can be recorded non-invasively and can be monitored for long periods in a beat-to-beat format [1]. The use of AdP/dt_{max} has contributed to document the overall increase of LV function in healthy subjects during either isometric (IE) or dynamic exercise [3,4].

The use of the low-frequency component (LF) of the systolic pressure time series (LF_{SBP}) as an adequate quantitative noninvasive measure of sympathetic activity has been widely documented [5,6,7], relevantly because it is strongly correlated with muscle sympathetic nerve activity (MSNA) [5]. There is also some evidence suggesting that the diastolic pressure LF (LF_{DBP}) can be considered a marker of sympathetic activity. The use of LF_{SBP} has enabled documenting the increased sympathetic activity in patients with atrial fibrillation [7], heart failure, and hypertension, and in subjects performing dynamic exercise [4]. No studies were found that have reported the spectral analysis of the AdP/dt_{max} time series variability.

IE is considered a provoking maneuver that stimulates sympathetic activity, as evidenced by the increase in MSNA it induces [8]. The IE test typically involves a single load set between 25 and 50% of the maximal voluntary contraction (MVC), lasting 2 to 4 minutes [3,8].

In this study, our goal was to provide evidence showing that the LF component of AdP/dtmax ($LF_{AdP/dtmax}$) can serve as a possible noninvasive quantitative measure of sympathetic activity, by comparing the performance of this novel spectral measure with those of the well-documented LF_{SBP} and LF_{DBP} during the execution of continuous and linearly increased IE to the maximal muscle force (CLIMF). Thus, we assessed the effects of CLIMF on the time courses of AdP/dt_{max}, systolic (SBP), and diastolic pressure (DBP) series, and their respective LF powers $LF_{AdP/dtmax}$, LF_{SBP}, and LF_{DBP}, estimated using the smoothed pseudo-Wigner-Villé time frequency distribution (TFD). Also, coherence and correlations between spectral indexes were obtained.

2. Methods

2.1. Subjects

Thirty-five young, healthy, nonsmoking, and sedentary volunteers participated, 25 men and 10 women. Their age, height, and weight were 22.4±2.7 years, 167±8 cm, and 66.2±11.0 kg respectively. Their written informed consent was requested to participate. This study was approved by the ethics committee of our university.

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2.2. Protocol

During the first visit to the laboratory, the subjects' health status was evaluated and they were trained to execute CLIMF correctly. In the second visit, subjects performed static knee extension (KE) while sitting. Each session consisted of three successive stages: 1 minute of control, incremental isometric right KE at a rate of 0.21 $kg \cdot s^{-1}$ until exhaustion, where the maximum muscular force (MF) is attained, and a 2-minute recovery period. The subjects' MF signal was displayed on a screen so that they could follow the linear pattern shown on the screen.

2.3. Signal recording and acquisition

ECG was detected at the thoracic bipolar lead CM5 using a bioelectric amplifier (Biopac Systems). Arterial pressure (AP) was recorded by Finapres (Ohmeda). Respiratory movements were recorded with a pneumograph (Nihon Kohden). MF signal was recorded from a handgrip dynamometer (Stoelting) mechanically adapted to a chair to measure MF during isometric KE. All signals were digitized at a sampling rate of 1 kHz via an acquisition and display system (Biopac Systems).

2.4. Data processing

R-wave peaks, SBP, and DBP were detected beat-to-beat to generate R-R intervals (RR), its inverse, heart rate (HR), SBP, and DBP time series. The beat-to-beat dAP/dt_{max} series was computed as the difference between the peak value of the first derivative of the AP waveform and the immediate previous zero crossing. The resulting series were cubic-spline interpolated, resampled at 4 Hz, and detrended by the smoothness priors method. Time-frequency spectra of the oscillations of the series were estimated with the smoothed pseudo-Wigner-Ville TFD and integrated over the standard LF band to compute the instantaneous dynamics of $LF_{AdP/dtmax}$, LF_{SBP}, and LF_{DBP} powers. The time-frequency coherences of the relationships between the LF powers were computed as the cross-spectrum divided by the square root of the product of the auto-spectra. Indexes dynamics of each subject were expressed as changes from their mean baseline and ensemble-averaged for visualization. MF was normalized for the individual maximal force and expressed as a percentage ($\%MF_{max}$). The continuous relations of the LF powers vs. $\%MF_{max}$ showed an inflection point that we considered a threshold effect. The threshold $\%MF_{max}$ was detected, subject by subject, by the V-slope method, thus dividing the response into the before (BT) and after threshold (AT) phases.

2.5. Statistical analysis

Data is expressed as mean±SD. Linear regressions and correlations were calculated for each subject's indexes dynamics during CLIMF, for both BT and AT when applicable. Student's paired *t*-test was employed to compare the coherences and correlations between phases. Statistical significance was accepted at $p<0.05$.

3. Results

The MF developed by the subjects was continuously and linearly increased to its maximum (Fig. 1).

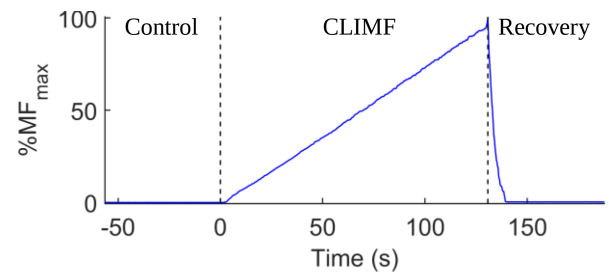

Fig. 1. Ensemble averages of the time courses of $\%MF_{max}$, during control, CLIMF, and recovery stages.

Fig. 2 shows a representative TFD of AdP/dt_{max}, SBP, and DBP series during CLIMF. The similarity between the spectra of the three variables is remarkable.

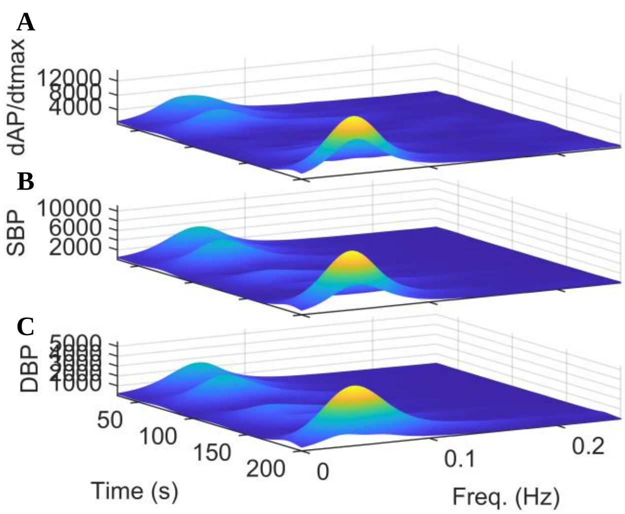

Fig. 2. Representative time-frequency spectra of A) AdP/dt_{max}, B) SBP, and C) DBP series during control, CLIMF (from 60 to 200 s), and recovery.

The correlations of the relationships of AdP/dt_{max} vs. SBP and DBP were 0.65±0.32 and 0.53±0.32, respectively. The relationships of the cardiovascular variables vs. $\%MF_{max}$ showed strong mean correlations (Fig. 3). The ensemble averages of the continuous relations between the time courses of cardiovascular variables and $\%MF_{max}$ showed that: AdP/dt_{max} increased gradually from the beginning to 53.5±11.2 %MF_{max}, reached a plateau up to 73.1±9.7 %MF_{max}, from which it rose progressively until the end of CLIMF. HR, SBP, and DBP increased gradually from the onset of CLIMF to the maximum MF (Fig. 3).

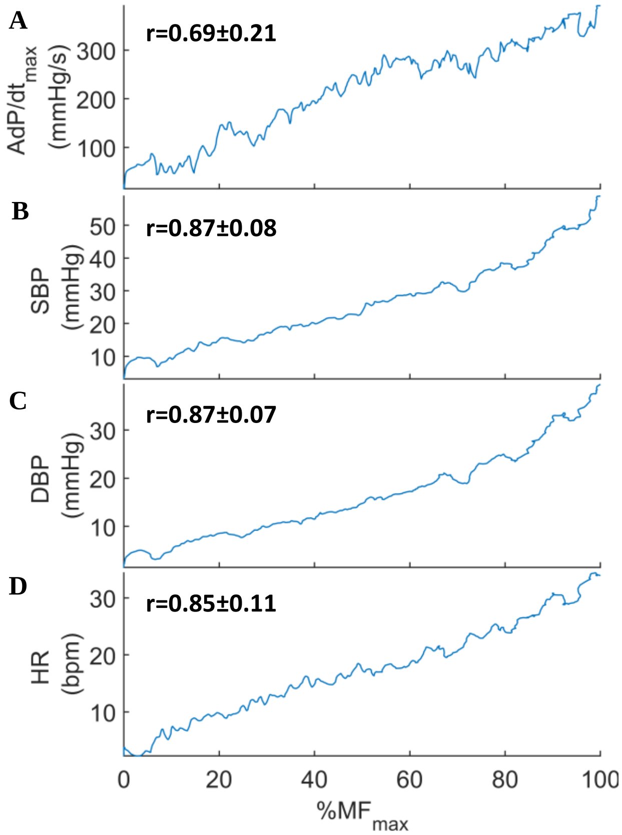

Fig. 3. Ensemble averages of the continuous relations of %MF_{max} with A) AdP/dt_{max}, B) SBP, C) DBP, D) HR, expressed as change from baseline.

Table 1. Means ± SD of correlations and coherence of the relations between studied indexes. N=35.

Relation	Correlation		Coherence	
	BT	AT	BT	AT
$LF_{AdP/dtmax}$ -LF_{SBP}	0.61±0.26	0.91±0.13*	0.79±0.10	0.84±0.09*
$LF_{AdP/dtmax}$- LF_{DBP}	0.54±0.27	0.89±0.13*	0.76±0.09	0.71±0.11*
LF_{SBP} - LF_{DBP}	0.88±0.11	0.94±0.14*	0.95±0.034	0.90±0.08*

*p<0.01 BT vs. AT phases

The ensemble averages of the continuous relations between the spectral measures and %MF_{max} showed that $LF_{AdP/dtmax}$, LF_{SBP}, and LF_{DBP} responses exhibited two phases: initially, they decreased gradually until 64.7±13.1 %MF_{max} for $LF_{AdP/dtmax}$, 65.3±11.3 %MF_{max} for LF_{SBP} and 66.2±10.3 %MF_{max} for LF_{DBP}, followed by an abrupt increase that continued until the end of CLIMF. This behavior is considered a threshold phenomenon. The mean inflection %MF_{max} of $LF_{AdP/dtmax}$, LF_{SBP}, and LF_{DBP} were similar.

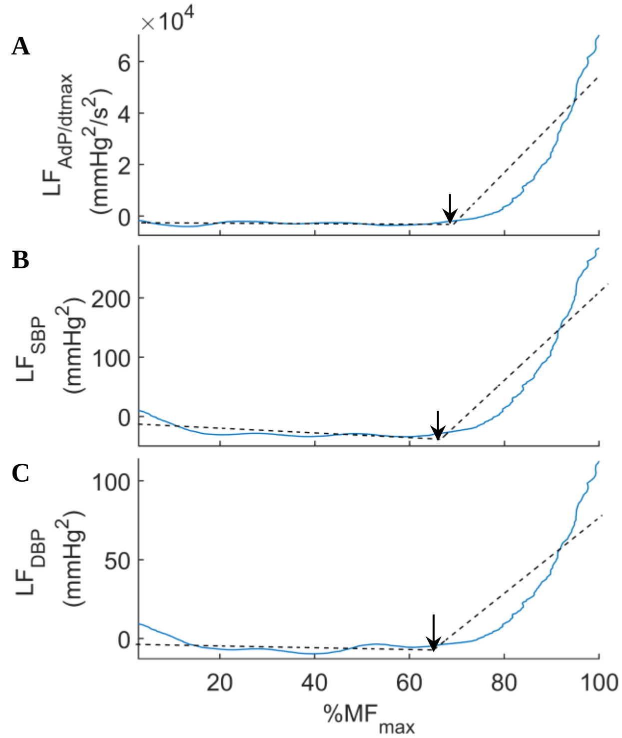

Fig. 4. Ensemble averages (solid lines) and mean regressions (broken lines) of the continuous relations of %MF_{max} with: A) $LF_{AdP/dtmax}$, B) LF_{SBP}, C) LF_{DBP}, expressed as change from baseline. Arrows (↓) mark the mean slope inflection points in %MF_{max}.

Table 1 shows the mean correlations and coherence of the relations between indexes in the BT and AT phases.

4. Discussion

The current study provides original knowledge to the fields of cardiovascular variability and IE, by documenting that using a TFD on the AdP/dt_{max} time series reveals that the $LF_{AdP/dtmax}$ time course shows a slight depression followed by an important increase in response to the maneuver CLIMF. Our main findings indicate that during CLIMF, AdP/dt_{max}, SBP, and DBP show similar patterns over time. These variables gradually increase and are strongly correlated with each other and with %MF_{max}. The time courses of $LF_{AdP/dtmax}$, LF_{SBP}, and LF_{DBP} also exhibit similar patterns, with strong correlations and high coherence throughout CLIMF. These variables initially decline during BT and then progressively increase during the AT phase. The continuous relationships, obtained over a wide operating range, of $LF_{AdP/dtmax}$, LF_{DBP}, LF_{SBP} vs. %MF_{max}, reveal an inflection point followed by a sudden increase in the second half of CLIMF.

It has been reported that performing IE increases sympathetic outflow, as recorded by electroneurography. Furthermore, the increase in MSNA depends on the IE intensity [8]. This association justifies using IE in physiological and clinical settings to elicit an increase in sympathetic output [3,4,8]. Our CLIMF protocol considers the maximum operating range of the variables and, in combination with the use of TFD, enables the construction of continuous relationships between the autonomic-cardiovascular variables and $\%MF_{max}$. The highly correlated continuous relationship between AdP/dt_{max} and $\%MF_{max}$ (Fig. 3A), indicates the progressive increase of overall LV function during CLIMF. This finding is consistent with the reported rise of AdP/dt_{max} in response to a 2-minute-long load of IE at 30% of MVC [3]. Moreover, the significant correlations between the time courses of AdP/dt_{max} and those of SBP and DBP, suggest the association of this variable with LV function and with arterial factors, such as arterial stiffness and peripheral vascular resistance. This association is supported by the fact that AdP/dt_{max} is measured in a peripheral artery.

The available evidence documents that LF_{SBP} is a reliable marker of sympathetic activity [4,5,6,7]. This is supported by the strong correlation between LF_{SBP} and MSNA, observed in healthy subjects during head-up tilt both before and after bed rest [5]. Unlike LF_{RR}, there have been no opposing evidence challenging the usefulness of LF_{SBP} as a sympathetic activity marker. This favorable situation allows us to consider LF_{SBP} as a suitable reference for evaluating the performance of $LF_{AdP/dtmax}$ as a sympathetic index. This evaluation can be done by analyzing the similarity between them, through the assessment of their correlation and coherence.

The very strong correlation and high coherence between LF_{DBP} and LF_{SBP} we found (Table 1) align with the limited but existing use of LF_{DBP} as a sympathetic marker. LF_{DBP} is a relevant index due to its association with vasomotor sympathetic activity.

Our main findings show that the changes of $LF_{AdP/dtmax}$ elicited by the maneuver CLIMF, exhibit high coherence and strong correlations with LF_{SBP} and LF_{DBP} in the BT and the AT phases (Fig. 4, Table 1). These results provide evidence that indicates that $LF_{AdP/dtmax}$ can be a suitable noninvasive quantitative measure of sympathetic activity. Even more, $LF_{AdP/dtmax}$ could be a useful supplementary index to LF_{SBP}, as they are based on different physiological substrates. $LF_{AdP/dtmax}$ represents the variation in the maximum rate of pressure increase during the LV ejection phase, while LF_{SBP} and LF_{DBP} indicate the variability of the maximum and minimum arterial pressure, respectively. The higher correlation of $LF_{Adp/dtmax}$ with LF_{SBP} than with LF_{DBP} indicates its stronger association with cardiac events than with arterial events. Cardiovascular diseases that decrease LV function and increase sympathetic activity may have distinct effects on these indicators. Furthermore, the continuous relationships between $LF_{AdP/dtmax}$, LF_{SBP}, and LF_{DBP} with $\%MF_{max}$ depict a sudden shift from decreasing to increasing amplitude that we interpret as a threshold phenomenon. This shift may be linked to the metaboreflex activation, which, as $\%MF_{max}$ increases, induces a growing sympathoexcitation (Fig. 4).

It is noteworthy that the time series of the variables derived from the contour of AP waveform, AdP/dt_{max}, SBP, and DBP show variability in LF, which is associated with sympathetic activity, and also exhibit high coherences and correlations between them. This similarity supports the proper performance of our novel index $LF_{AdP/dtmax}$ as a promising measure of cardiac sympathetic activity. This indicator would complement others due to their different functional bases. Furthermore, tracking the time courses of $LF_{AdP/dtmax}$, $LF_{SBP,}$ and LF_{DBP} during CLIMF enabled us to show a slight decrease in sympathetic outflow in the BT and a sudden increase in the AT phase, the latter possibly associated with the metaboreflex activation threshold.

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