

# The Time Courses of the Spectral Components of Pulse Pressure and the Maximal First Derivative of Arterial Pressure are Similar in the Cold Face Test and May Indicate the Sympathovagal Coactivation it Elicits

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## Abstract

*This study aimed to assess how the cold face test (CFT) influences various cardiovascular parameters over time, including the maximum of the arterial pressure wave's first derivative ( $AdP/dt_{max}$ ), pulse pressure (PP), systolic pressure (SBP), diastolic pressure (DBP), and interbeat period (IP). It also aimed to verify the strong correlation observed between  $AdP/dt_{max}$  in patients, extend this correlation to their spectral index pairs, and determine if these indices can indicate sympathovagal coactivation induced by CFT. Results revealed that CFT produced similar, highly correlated responses in  $AdP/dt_{max}$ , PP, SBP, and DBP, characterized by rapid rises followed by slow increments until the end, then quick recovery. The high correlation between SBP,  $AdP/dt_{max}$ , and PP suggests a simple proportional mechanism:  $\uparrow AdP/dt_{max} \rightarrow \uparrow SBP \rightarrow \uparrow PP$ . Spectral analysis showed that  $LF_{AdP/dt_{max}}$  and  $LF_{PP}$  initially increased slightly, supported by high coherence levels.  $HF_{AdP/dt_{max}}$  and  $HF_{PP}$  gradually increased during the test, also with high coherence, and their power outdid that of the low-frequency components. Overall, these results confirm the covariation between  $AdP/dt_{max}$  and PP observed in patients, extend it to their spectral indices, and suggest that rises in  $LF_{AdP/dt_{max}}$ ,  $LF_{PP}$ ,  $HF_{AdP/dt_{max}}$ , and  $HF_{PP}$  reflect enlarged sympathetic and vagal activities: the former minor and early, the latter prominent and gradual.*

## 1. Introduction

The maximal value of the arterial pressure wave (APW) first derivative (APWFD), known  $AdP/dt_{max}$ , and the arterial pulse pressure (PP) have been used to evaluate the alteration of left ventricular (LV)-arterial coupling caused by diseases and as risk indices of cardiovascular morbidity and mortality [1,2]. Moreover, a strong correlation between PP and  $AdP/dt_{max}$  has been documented [3-5].

The robustness of  $AdP/dt_{max}$  as an index of overall LV-arterial function, specifically, of LV contractility, has been

widely documented. This index also shows the clinical advantage of continuous monitoring capability, to observe acute changes in the LV-arterial function, as has been documented in heart failure patients [3].

PP has been used in clinical practice specifically as an indicator of stroke volume, arterial stiffness and wave reflection [5]. Cardiovascular aging, specifically the vascular one, has been associated with systolic hypertension and increased PP as an index of increased arterial stiffness [1,2].

The proportional covariation between  $AdP/dt_{max}$  and PP was documented in 874 heart disease patients ( $r=0.91$ ) [3], and in studies that increased LV contractility by infusing norepinephrine and dobutamine in normotensive subjects ( $r=0.96$ ) [5], and in critically ill patients ( $r>0.92$ ) [4].

The cold face test (CFT) is a widely used intervention for its unique attributes of inducing a sympathetic-vagal coactivation that is expressed with a non-baroreflex and non-respiratory mediated cardiodeceleration and pressor response [6,7]. This response is increased in hypertensive patients [8] and blunted in familial dysautonomia [6].

We expect to corroborate the PP- $AdP/dt_{max}$  strong covariation found in patients, explore if their respective spectral components maintain this linked change in healthy subjects, and if the spectral measures of both variables can indicate the sympathovagal activation elicited by the CFT. To test these assumptions, we assessed and compared the effects of CFT on the time courses of  $AdP/dt_{max}$ , PP, systolic blood pressure (SBP), diastolic pressure (DBP), and interbeat period (IP) time series in healthy volunteers, including the low-frequency ( $LF_{AdP/dt_{max}}$ ,  $LF_{PP}$ ) and high-frequency ( $HF_{AdP/dt_{max}}$ ,  $HF_{PP}$ ) components of  $AdP/dt_{max}$  and PP, obtained by a time-frequency distribution (TFD).

## 2. Methods

### 2.1. Subjects

Twenty-four healthy, normotensive, non-addicted, and sedentary subjects, 13 men and 11 women, were studied.

Mean age, height, and weight were  $22.2 \pm 2.2$  years,  $167 \pm 8$  cm, and  $69.1 \pm 10.4$  kg, respectively. Their written informed consent was requested to participate. The ethics committee of our university approved this study.

## 2.2. Protocol

In a first visit to the laboratory, the volunteers' health status and anthropometric variables were evaluated, and in a second visit volunteers underwent 1-min control, 1-min maneuver and 2-min recovery stages. CFT was performed by applying a bag filled with iced-water at  $0^\circ\text{C}$  on the face, excluding the eyes, with the subject in supine position and breathing spontaneously. ECG, APW, and forehead temperature were recorded.

## 2.3. Signal recording and acquisition

ECG was detected at the thoracic bipolar lead CM5 using a bioelectric amplifier (Biopac Systems). Noninvasive APW was measured by Finapres (Ohmeda). A thermistor measured forehead temperature. All signals were digitized at a sampling rate of 1 kHz via an acquisition and display system (Biopac Systems).

## 2.4. Data processing

From the APW, the APWFD signal was obtained. Zero crossings, maxima, and minima of APWFD were detected to extract  $\text{AdP}/\text{dt}_{\text{max}}$ , SBP, DBP, and PP as the SBP-DBP difference. Time series of SBP, DBP,  $\text{AdP}/\text{dt}_{\text{max}}$ , and PP were formed, cubic-spline interpolated, resampled at 4 Hz, and detrended by the *smoothness priors* method.

Auto and cross time-frequency spectra of  $\text{AdP}/\text{dt}_{\text{max}}$  and PP were estimated with the smoothed pseudo-Wigner-Ville TFD. We extracted the instantaneous  $\text{LF}_{\text{AdP}/\text{dt}_{\text{max}}}$ ,  $\text{LF}_{\text{PP}}$ ,  $\text{HF}_{\text{AdP}/\text{dt}_{\text{max}}}$ , and  $\text{HF}_{\text{PP}}$  from the first two-order moments of their TFD in the standard HRV bands, and their respective coherences by cross-time-frequency analysis. The ensemble averages of the time courses of all variables were computed to highlight any patterned responses, and their similarities and differences were analyzed by correlations and coherence. Indexes dynamics were divided into 20-s epochs for statistical purposes.

## 2.5. Statistical analysis

Data are expressed as mean  $\pm$  SD. Differences between control and 20-s epoch values of each variable were tested by ANOVA for repeated measures. Post-hoc pairwise comparisons were performed by the Tukey test. Indexes dynamics were used to compute linear regressions and correlations subject by subject. Statistical significance was accepted at  $p < 0.05$ .

## 3. Results

The mean values of the 20-s epochs of all variables were different ( $p < 0.01$ ) in relation to their mean baseline, except for those at 40 and 60 s of  $\text{LF}_{\text{PP}}$  and  $\text{LF}_{\text{AdP}/\text{dt}_{\text{max}}}$ .

The APW-derived variables SBP, DBP, PP, and  $\text{AdP}/\text{dt}_{\text{max}}$  showed a similar time course response pattern to CFT, consisting of, relative to the control, an initial rapid increase followed by a slow and progressive increase until term, and a fast return to their baseline in early recovery, to be below it in late recovery (Fig. 1 A-C).

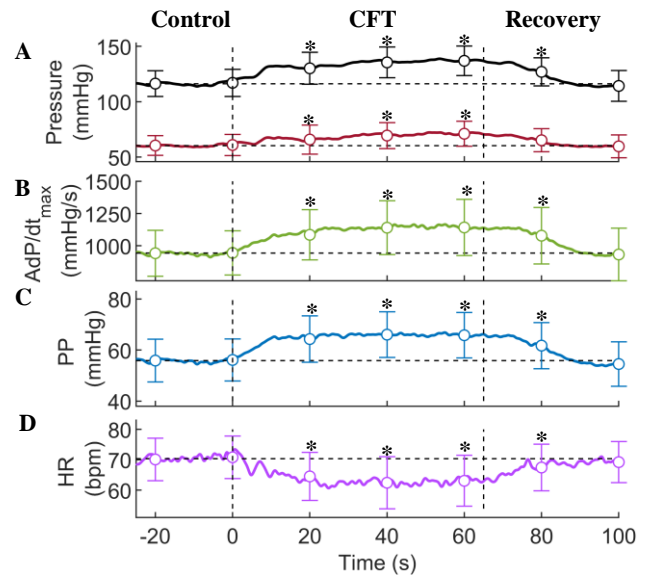


Fig. 1. Ensemble average and 20-s epoch mean values of the time courses of: A) SBP (black) and DBP (red); B)  $\text{AdP}/\text{dt}_{\text{max}}$ ; C) PP; D) HR. \* $p < 0.01$  vs. baseline.

The rapid and slow increases in PP during the maneuver are due to the greater increase in SBP than DBP. The return of PP to its baseline is caused by the greater decrease in DBP than in SBP. The time course of SBP was moderately correlated with  $\text{AdP}/\text{dt}_{\text{max}}$  (Fig. 4B) and PP (Fig. 4C).

The time course response pattern of HR was in the opposite direction to the one shown by the APW variables: an initial fast decrease, a reduction that is sustained until the end, followed by a rapid return to the baseline in recovery (Fig. 1D).

The TFD of  $\text{AdP}/\text{dt}_{\text{max}}$  and PP were strikingly similar during CFT. The time courses of  $\text{LF}_{\text{AdP}/\text{dt}_{\text{max}}}$  and  $\text{LF}_{\text{PP}}$  exhibited a slight and rapid increment at the onset of CFT. In contrast, the time courses of  $\text{HF}_{\text{AdP}/\text{dt}_{\text{max}}}$  and  $\text{HF}_{\text{PP}}$  increased gradually and prominently through CFT (Fig. 2).

The time course of  $\text{LF}_{\text{AdP}/\text{dt}_{\text{max}}}$  was similar and strongly correlated to that of  $\text{LF}_{\text{PP}}$  (Fig. 4D); both indices initially rose quickly but then dropped toward their baseline (Fig. 3 A&B). The mean value of the time coherence between these indices was  $0.87 \pm 0.02$  (Fig. 3C).

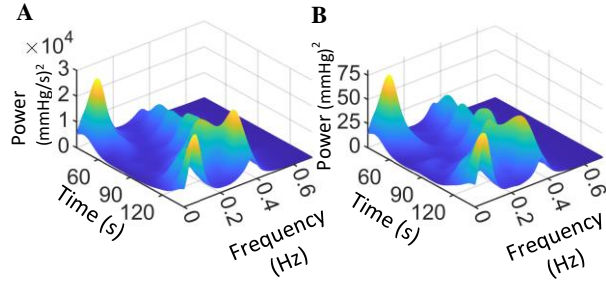


Fig. 2. Representative example during CFT of the time-frequency spectra of: A)  $\text{AdP/dt}_{\text{max}}$  and B) PP series.

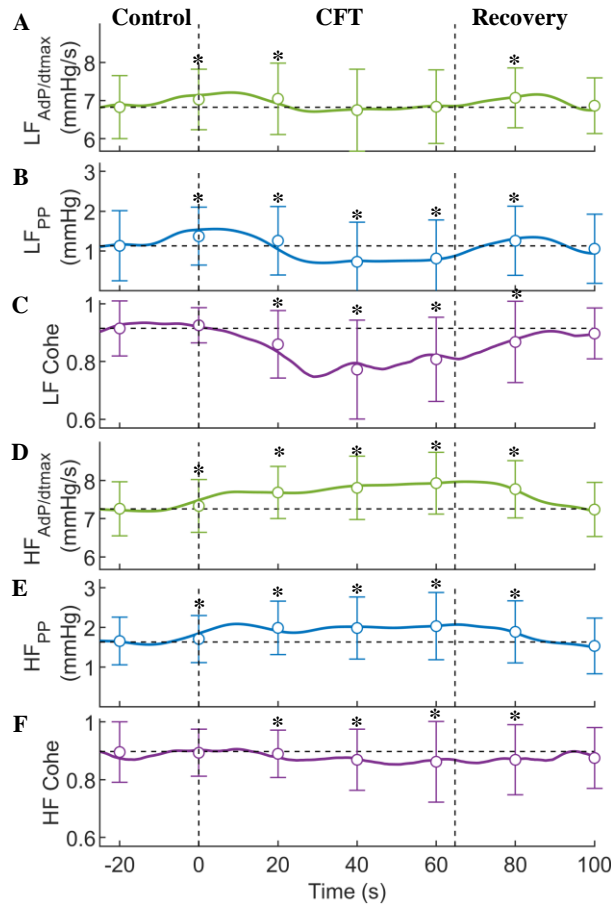


Fig. 3. Ensemble average and 20-s epoch mean values of the time courses of: A)  $\text{LF}_{\text{AdP/dt}_{\text{max}}}$ , B)  $\text{LF}_{\text{PP}}$ , C) coherence of  $\text{LF}_{\text{AdP/dt}_{\text{max}}}$  with  $\text{LF}_{\text{PP}}$ , D)  $\text{HF}_{\text{AdP/dt}_{\text{max}}}$ , E)  $\text{HF}_{\text{PP}}$ , F) coherence of  $\text{HF}_{\text{AdP/dt}_{\text{max}}}$  with  $\text{HF}_{\text{PP}}$ . \*  $p < 0.01$  vs. baseline.

$\text{HF}_{\text{AdP/dt}_{\text{max}}}$  time course was similar to that of  $\text{HF}_{\text{PP}}$  (Fig. 3 D&E), and they were strongly correlated (Fig. 4E). Both indices steadily grew throughout CFT. The mean value of their time coherence was  $0.85 \pm 0.03$  (Fig. 3F). The pooled mean values of  $\text{HF}_{\text{PP}}$  ( $10.5 \pm 8.3 \text{ mmHg}^2$ ) and  $\text{HF}_{\text{AdP/dt}_{\text{max}}}$  ( $3287 \pm 2586 \text{ (mmHg/s)}^2$ ) were greater ( $p < 0.001$ ) than  $\text{LF}_{\text{PP}}$  ( $5.3 \pm 4.8 \text{ mmHg}^2$ ) and  $\text{LF}_{\text{AdP/dt}_{\text{max}}}$  ( $1928 \pm 1971 \text{ (mmHg/s)}^2$ ).

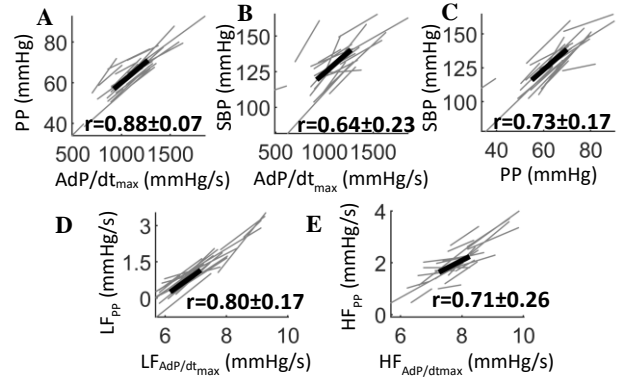


Fig. 4. Individual (thin grey lines) and mean (thick black line) linear regressions and correlations of: A)  $\text{AdP/dt}_{\text{max}}$  vs. PP; B)  $\text{AdP/dt}_{\text{max}}$  vs. SBP; C) PP vs. SBP; D)  $\text{LF}_{\text{AdP/dt}_{\text{max}}}$  vs.  $\text{LF}_{\text{PP}}$ ; E)  $\text{HF}_{\text{AdP/dt}_{\text{max}}}$  vs.  $\text{HF}_{\text{PP}}$ .

## 4. Discussion

The main findings of this study are that CFT provokes characteristic and similar time course responses in  $\text{AdP/dt}_{\text{max}}$ ,  $\text{LF}_{\text{AdP/dt}_{\text{max}}}$ ,  $\text{HF}_{\text{AdP/dt}_{\text{max}}}$ , PP,  $\text{LF}_{\text{PP}}$ , and  $\text{HF}_{\text{PP}}$ , and that the responses of  $\text{AdP/dt}_{\text{max}}$  and its spectral indexes are very similar to those of PP and its spectral indexes. Similarity supported by the strong correlations and coherences they present. These findings corroborate, in healthy subjects, the similarity in the time domain of the variation of  $\text{AdP/dt}_{\text{max}}$  and PP found in patients with cardiovascular disease, and extend it to the frequency domain. In addition, they contribute relevant knowledge to the physiology of CFT and the field of study of cardiovascular variability.

Part of our methodological strategy is the use of the time series of the APW variables and their spectral indexes, obtained by a TFD, to characterize/track the non-stationary beat-to-beat response of each one of them to CFT, to assess the similarities and differences of their respective time courses, and to obtain the correlations between them.

Relevant attributes of AWP-derived variables and spectral indices documented by the findings of the present study in a beat-to-beat format are:

- Similarity of the characteristic time course responses of SBP and DBP of rapid increase followed by slow increase to CFT term and fast recovery (Fig. 1A), and rapid decrease in HR that is sustained until CFT term (Fig. 1D). These responses corroborate the conventional pressor and cardio-deceleration effect reported [6], complements it by adding the increases in  $\text{AdP/dt}_{\text{max}}$  (Fig. 1C) and PP (Fig. 1D) not previously reported, and refines it by the similarity of the response of all pressures, including those of PP and  $\text{AdP/dt}_{\text{max}}$ . The increase response of  $\text{AdP/dt}_{\text{max}}$ , PP, SBP and DBP results from the coupling between the characteristic increases of LV function made mainly by increases in contractility, since the stroke volume does not

change significantly [7], and afterload due to increases in peripheral vascular resistance [8] and wave reflection.

- The strongly correlated similarity in the characteristic time-course responses of  $\text{AdP/dt}_{\text{max}}$  and PP (Fig. 1 B&C), which have not been reported, corroborates the proportional covariation of these variables found in patients [3-5]. A possible explanation for this similarity, supported by the moderate correlation of SBP with  $\text{AdP/dt}_{\text{max}}$  and PP (Fig. 4 B&C) could be the following simple mechanism: the increase in the LV function, modulated by the increase in afterload, increases the  $\text{AdP/dt}_{\text{max}}$  that induces a proportional increase in the SBP (Fig. 4B) greater than the increase in DBP, and therefore, necessarily and proportionally, an increase in PP (Fig. 4C). There are no available studies that have characterized the beat-to-beat  $\text{AdP/dt}_{\text{max}}$  responses to CFT.

CFT has been reported to induce an increase in sympathetic activity, indicated by increases in APW [7] and muscular sympathetic nerve activity [8], and in vagal activity shown by the rise in the high frequency component of HR [6,7]. This autonomic activity is centrally generated, independently of baroreflex and respiration [6], and its firing is dependent on distinctive temperature thresholds of the device used to cool the face, 7°C for the increase of sympathetic activity with attenuation of the vagal one, and 0°C for the increase of vagal outflow, with attenuated sympathetic activity [7].

- Similarity of the time course responses of  $\text{LF}_{\text{AdP/dtmax}}$  and  $\text{LF}_{\text{PP}}$  (Fig. 3A&B) which show, at the beginning of the maneuver, a rapid and slight increase that quickly returns to baseline, and of  $\text{HF}_{\text{AdP/dtmax}}$  and  $\text{HF}_{\text{PP}}$  (Fig. 3D&E) that present a prominent gradual increase until the term, of greater power than the previous ones. Similarity of both pairs of indices supported by the high coherences (Fig. 3C&F) and correlations presented by their respective relationships (Fig. 4D&E). Findings that extend the proportional covariation found between  $\text{AdP/dt}_{\text{max}}$  and PP to their respective spectral indices. The characteristic and similar time course responses of  $\text{LF}_{\text{AdP/dtmax}}$  and  $\text{LF}_{\text{PP}}$  and  $\text{HF}_{\text{AdP/dtmax}}$  and  $\text{HF}_{\text{PP}}$  to CFT are possibly induced by the increase in sympathetic and vagal modulations, indirectly mediated, with similar effects on  $\text{AdP/dt}_{\text{max}}$  and PP time series. These time courses responses would indicate an initial and slight increase in sympathetic activity and a prominent and gradual rise of the vagal outflow until the end of CFT, characteristic autonomic response in accordance with the temperature-dependent threshold [8], since the APW recording in the present study was performed at a face cooling device temperature of 0°C, in which sympathetic activity is attenuated and vagal activity is increased. The finding that both  $\text{AdP/dt}_{\text{max}}$  and PP series present spectral components in standard HRV low and high frequency bands, which distinctively increase their power during CFT, expands the knowledge in the field of cardiovascular variability analysis by documenting that the time series of other features extracted from the APW are

modulated by sympathetic and vagal activities. Further studies are required to corroborate the potential usefulness of the spectral components of  $\text{AdP/dt}_{\text{max}}$  and PP series as indices of autonomic activity. We found no available studies that have used time-variant spectral variability analysis of PP and  $\text{AdP/dt}_{\text{max}}$  time series in CFT.

In conclusion, the proportional covariation that CFT induces in the characteristic time course responses of the pairs of indices  $\text{AdP/dt}_{\text{max}}$ -PP,  $\text{LF}_{\text{AdP/dtmax}}$ - $\text{LF}_{\text{PP}}$ , and  $\text{HF}_{\text{AdP/dtmax}}$ - $\text{HF}_{\text{PP}}$ , supported by their strong correlations and coherences, corroborate the one reported in cardiac patients, possibly due to the covariation that these two variables present with each other and with the SBP in the time domain, and extend it to the frequency domain. Also, these findings suggest, according to the respective characteristic increment in their time-course response, that  $\text{LF}_{\text{AdP/dtmax}}$  and  $\text{LF}_{\text{PP}}$  would indicate an initial slight increase in sympathetic activity and  $\text{HF}_{\text{AdP/dtmax}}$  and  $\text{HF}_{\text{PP}}$  a prominent and gradual increase until the end of the vagal.

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