Net Synergy/Redundancy Balance of Cardiovascular Interactions Allows the Stratification of the Risk in Patients with Asymptomatic Carotid Stenosis

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Abstract

The net balance between redundancy and synergy can be exploited to characterize cardiovascular control from spontaneous variability of systolic arterial pressure (SAP) and heart period (HP) in patients with asymptomatic carotid stenosis (ACS), whose impairment could be graded according to features of the carotid plaque. A predictive information decomposition approach based on bivariate autoregressive model of HP with an exogenous SAP input was applied in 67 patients with ACS scheduled for carotid endarterectomy (age 74.9±7.6 yrs, 44 males). Patients were divided in two groups according to the presence of a plaque fibrous cap thicker than 200 μm (CAP>200, n=40) or not (CAP<200, n=27) as detected from postoperative histological analysis. HP and SAP time series were acquired preoperatively in supine position and during active standing (STAND). Redundancy was prevalent over synergy in both populations and conditions. During STAND, a more negative net synergy\redundancy balance, indicating a more prevalent redundancy, was observed in CAP>200. Findings suggest that in patients with thicker fibrous cap the shared contribution of baroreflex and non-baroreflex regulatory mechanisms to cardiac control is more important, thus indicating a greater fault tolerance. Advanced information domain markers can thus be exploited for risk stratification in ACS patients.

1. Introduction

Carotid artery stenosis is observed in presence of a narrowing of the carotid lumen due to a carotid plaque. Vulnerability of the carotid plaque, being a determinant factor to the occurrence of the stroke [1], depends on mechanical and histological characteristics of the plaque with patients with thicker a fibrous cap classified as those at less risk of carotid plaque rupture [2]. The early prediction of plaque vulnerability becomes thus important especially in patients with asymptomatic carotid stenosis (CAS), for whom there is still a debate whether to proceed with surgery or with pharmacological treatment only [3].

Previous works have shown how different markers related to the mechanical properties of the plaque, noninvasively derived via elastography, or related to autonomic function and cardiovascular control can be associated to plaque vulnerability [2], [4]. Cardiovascular control can be studied inferring the spontaneous variability of heart period (HP) and systolic arterial pressure (SAP) time series. Among the different approaches, predictive information decomposition (PID) allows one to assess the net balance of the past of SAP and HP to reduce the uncertainty about the current state of HP [5]. In particular, cardiac and vascular systems should interact via baroreflex and non-baroreflex components in such a way that their interaction should generate more information that their action taken separately [6]. These methods were proven helpful to characterize changes with age and pathological conditions [5], [7] and we hypothesize they can help in improving risk stratification in CAS patients.

The aim of this study was to assess the net synergy/redundancy balance of HP and SAP in patients with CAS as related to the histological characteristics of the carotid plaque during an active standing (STAND) test.

2. Methods

2.1. Experimental Protocol and Data Acquisition

Sixty-seven consecutive patients (age: 74.2+7.7 yrs, 27 females) with ACS scheduled for carotid endarterectomy were enrolled at the operative unit of vascular surgery of IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy. San Raffaele Hospital ethical committee approved the study on 20 June 2019 (110/int/2019) and it was registered on ClinicalTrial.gov (NCT05566080). Patients respecting the inclusion criteria signed an informed consent prior to participating. Lead II electrocardiogram (ECG, BioAmp, ADInstruments, Australia) and photoplethysmographic arterial pressure (AP) via volume clamp technique (CNAP, CNSytems, Graz, Austria) were acquired from patients while resting in supine position (REST) and during STAND. Every phase lasted 10 minutes. Beat-to-beat time series of HP and SAP were extracted starting from ECG and AP signals. HP was computed from the ECG as the time distance between two consecutive R-wave peaks and SAP as the maximum of AP inside the HP. Series of 256 beats were extracted for each experimental condition after manually checking and correction of ectopic bats via linear interpolation. After surgery, the removed carotid plaque underwent histological analysis, and the thickness of the carotid plaque was taken as the outcome [2]. Patients were then divided in two groups according to the presence of a fibrous cap thicker than 200 μm (CAP>200, n=40) or not (CAP<200, n=27). The two groups did not differ for age and sex composition.

2.2. Autonomic Function Assessment

Time domain markers were extracted from the series in terms of mean and variance of HP and SAP, labelled as μ_{HP}, σ^2_{HP}, μ_{SAP}, σ^2_{SAP} and expressed in ms, ms^2, mmHg, mmHg^2. A parametric approach exploiting autoregressive (AR) modeling of the series was used to compute power spectral density after linear detrending. Coefficients of the model were identified via Levinson-Durbin recursion and optimized via Akaike information criterion (AIC) in the range 10-14. HP power in high frequency (HF) band (0.15-0.4 Hz), was taken as an index of vagal modulation directed to the heart and was labeled as HF_{HP} and expressed in ms^2 [8]. SAP power in low frequency (LF) band (0.04-0.15 Hz), labeled as LF_{SAP} and expressed in mmHg^2, was taken as a marker of sympathetic modulation directed to the vessels [9].

2.3. PID Assessment

After normalizing the series to have zero mean and unit variance, the net balance synergy/redundancy was assessed as interaction transfer entropy (ITE) between HP and SAP.

Briefly, we defined as Y_n and X_n the stochastic variables defining the present of the process Y and X, where Y=HP and X=SAP, and with $\boldsymbol{Y}_n^-$ and $\boldsymbol{X}_n^-$ the discrete vector describing their past. Synergy is detected when the information jointly transferred to Y_n by its past $\boldsymbol{Y}_n^-$ and by $\mathbf{X}_n$, formed by concatenating X_n and $\boldsymbol{X}_n^-$, is larger than the sum of the two contributions taken separately [7]. If the opposite is found, redundancy is prevalent [7]. The relationship from X to Y was computed via an AR model with exogenous (X) input (ARX). The coefficients of the model were estimated via traditional least squares and Cholesky decomposition approach, estimating the model order in the range 4-16 and optimizing it via AIC. ITE was defined [7] as

$$\mathrm{ITE} = \frac{1}{2}\log\frac{\lambda_x^2 \cdot \lambda_{AR}^2}{\lambda^2 \cdot \lambda_{ARX}^2}$$

where λ_{ARX}^2, λ_{AR}^2, and λ_x^2 were the variance of the prediction error of the ARX, of the reduced AR and X models respectively, and λ^2 is the variance of the process Y. According to [6], if ITE<0, redundancy is prevalent over synergy and *vice versa*.

2.4. Statistical Analysis

Autonomic control and synergy/redundancy markers were compared between CAP>200 and CAP<200 patients during REST and STAND via a two-way repeated measures analysis of variance with one factor repetition and using Holm-Sidak test for multiple comparisons. A $p<0.05$ was taken as significant.

3. Results

Table 1 shows markers of autonomic control as derived from HP and SAP time series. As expected, μ_{HP} decreased during STAND in both groups. σ^2_{HP} and HF_{HP} decreased as well during STAND with respect to REST only in CAP>200 patients. SAP variability markers did not change in response to the orthostatic challenge. Remarkably, no index was different between groups.

The grouped error bar graphs in Fig.1 show results of ITE as a function of the experimental conditions in CAP<200 and CAP>200 patients. During STAND ITE was more negative in CAP>200 than CAP<200. In both populations we did not observe differences between REST and STAND. Remarkably, ITE was always negative showing a prevalence of redundancy over synergy in all groups and conditions.

4. Discussion

The main findings of this work can be summarized as follows: i) ACS patients with a thicker fibrous cap exhibited a preserved autonomic control in response to STAND, while in patients with a thinner fibrous cap the

Table 1. Time and frequency domain indexes in ACS patients at REST and during STAND.

Index	CAP<200		CAP>200	
	REST	STAND	REST	STAND
μ_{HP} [ms]	868.873±153.785	808.357±157.483*	916.545±157.241	838.926±154.485*
σ^2_{HP} [ms^2]	581.066±523.138	605.697±597.539	1003.76±1563.479	552.225±580.833*
HF_{HP} [ms^2]	168.388±204.7	160.939±215.243	247.001±570.811	88.166±104.731*
μ_{SAP} [mmHg]	143.172±22.54	146.801±21.577	145.916±16.039	147.975±20.746
σ^2_{SAP} [mmHg^2]	31.096±33.374	27.997±15.727	37.493±34.038	38.14±22.186
LF_{SAP} [mmHg^2]	3.955±5.119	3.656±5.768	4.279±4.436	5.432±9.427

REST = at supine resting; STAND = during active standing; CAP<200 = patients fibrous cap less thick than 200 μm; CAP>200 = patients fibrous cap thicker than 200 μm; HP = heart period; SAP = systolic arterial pressure; μ = mean; σ^2 = variance; LF = low frequency; HF = high frequency. The symbol * indicates $p<0.05$ with respect to REST.

response was blunted; ii) in both groups we showed a prevalence of redundancy over synergy; iii) the net synergy/redundancy balance allowed the separation of ACS patients according to fibrous cap thickness.

4.1. CAP<200 and CAP>200 Patients Exhibit Different Autonomic Control

Both populations showed the expected tachycardic response to STAND, but the vagal withdrawal, usually observed after the orthostatic challenge, was detected only in CAP>200 patients, as shown by the reduction in HP variance and HF power [10], [11]. This result suggests that, despite the thicker fibrous cap, the CAP>200 group features a more physiological response to STAND. Remarkably, none of the two groups showed the expected increase of sympathetic modulation, suggesting an impairment of sympathetic control [12]. In a previous study of our group, ACS patients were classified according to the vulnerability of the plaque observing that patients with a less stiff plaque had a more preserved autonomic response [4]. Present findings would suggest that the thickness of the fibrous cap and vulnerability of the plaque [4], could be differently linked to autonomic control. While the vulnerability was found related to mechanical properties of the plaque [2], [13], the presence of a thick fibrous cap was found less correlated to vulnerability [2]. As a matter of fact, fibrous cap thickness and Young's modulus were not similarly associated to vulnerability in our cohort [2], thus confirming that histological features of the plaque lead to a different dichotomization compared to that based on that assessed in [4]. Remarkably, none of the traditional variability markers allowed the separation of the groups.

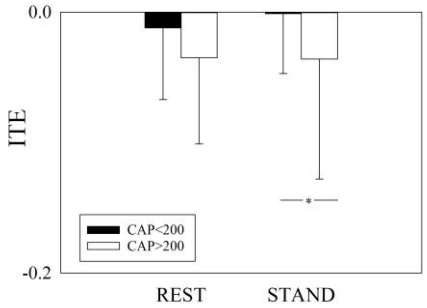

Figure 1. The grouped error bar graphs show ITE as a function of the experimental condition in CAP<200 (black bars) and CAP>200 (white bars) patients. The symbol * means $p<0.05$.

4.2. Net Synergy/Redundancy Balance Differentiates Patients with a Thicker Fibrous Cap

Advanced methods derived from information theory exploiting PID were here applied to HP and SAP variability permitting to determine the influence of the past of both SAP and HP to the presence state of HP. The negative net balance observed in both populations and conditions confirmed the prevalence of redundancy over synergy already observed in healthy subjects [6]. In this work, the net synergy/redundancy balance expressed as ITE was originally found able to separate groups in relation to their fibrous cap thickness, with a higher prevalence toward redundancy in subjects with thicker fibrous cap, being indicative of a more stable plaque [2], [14]. Remarkably, none of the traditional indexes was able to separate populations, suggesting the complementarity of information theory markers with respect to traditional analyses, similarly to what was already observed when they have been applied on cardiorespiratory coupling [7]. This finding suggests that in CAP<200 patients the common contributions of baroreflex and non-baroreflex mechanisms to cardiac control are less relevant compared to CAP>200 cohort, thus suggesting a more important impairment of cardiac control [5], [6] that is especially visible during STAND. This finding can be compatible with a reduction of the importance of baroreflex within the set of mechanisms responsible for cardiac control and with less reactive autonomic regulation in CAP<200 patients. Present findings would thus suggest that PID markers could be exploited for risk stratification in ACS patients.

5. Conclusions

We proposed the assessment of the net synergy/redundancy balance, as derived via PID in patients with ACS divided according to fibrous cap thickness. Findings show that patients with a thick fibrous cap have a preserved response to STAND with respect to those with a less thick cap. The net synergy/redundancy balance allowed the separation of the two populations (*i.e.* CAP<200 and CAP>200) and suggests that in presence of a thicker fibrotic cap, the common action of baroreflex and non-baroreflex mechanisms in controlling HP was more important than in CAP<200 group. This result is compatible with a more important impairment of the cardiac control in CAP<200 cohort compared to patients with a thicker fibrous cap.

In the future, it would be important to verify our conclusions over a larger population, to provide a comparison with a control group, and to test separately the contribution of synergy and redundancy, to check the contribution of confounding factors such as respiration and to differentiate the contribution of different frequency bands [15], [16]. While confirmed, advanced information theory metrics could be used to stratify the risk in ACS patients.

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