Causal and Non-Causal Frequency Domain Assessment of Spontaneous Baroreflex Sensitivity after Myocardial Infarction*

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***Abstract*— Acute myocardial infarction (AMI) is thought to alter the baroreflex control of arterial pressure. We tested this hypothesis investigating the changes of the cardiovascular response after AMI in comparison with young and old healthy controls studied at rest and during head-up tilt, using causal and non-causal frequency domain measures of the baroreflex sensitivity. Our results indicate: (i) the importance of using a causal approach that takes into account not only feedback but also feedforward effects in the study of interactions between the heart period and the arterial pressure; (ii) the compromised capacity of baroreceptors to control SAP fluctuations in post-AMI patients, both at rest and during postural stress.**

I. Introduction

The arterial baroreflex is often represented as a control system with negative feedback, and plays a major role in controlling the joint variability of the heart period (measured as the RR interval of the ECG) and the systolic arterial pressure (SAP) [1]. The baroreflex sensitivity (BRS) is often evaluated from the spontaneous beat-to-beat fluctuations of RR and SAP as the magnitude of the reflex change in RR corresponding to a unitary change in SAP. Such an approach is of particular interest for the identification of cardiovascular symptoms of orthostatic intolerance and acute myocardial infarction (AMI), as postural circulatory stress and cardiovascular diseases elicit baroreceptor unloading [2].

Frequency domain approaches to the estimation of the spontaneous BRS [3] are widely used as they allow to focus on specific RR and SAP oscillatory components such as the low-frequency rhythm (LF: 0.04–0.15 Hz), in order to avoid the confounding effects of other variables operating at different frequencies (e.g., respiration). The main limitation of the traditional methods for spectral evaluation of BRS [4,5] is that they do not impose causality and, as such, they cannot reveal whether joint changes in SAP and RR result from feedback mechanisms from SAP to RR (i.e., the baroreflex pathway) or from feedforward effects from RR to SAP (mainly of mechanical nature). For this reason, closed-loop approaches implementing causality have been proposed for BRS estimation [6,7]. In this study, we aim at testing the relevance of implementing a causal method [7], in comparison with traditional non-causal methods [4,5], for the spectral evaluation of the spontaneous BRS in AMI monitored at rest and during orthostatic stress, and in control groups formed by young and old healthy subjects.

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II. Methods

The study included 35 post-AMI patients (58.5 ± 10.2 yrs), examined 10 ± 3 days after AMI, and two groups of healthy subjects: 20 young (25.0 ± 2.6 yrs) and 12 old (63.1 ± 8.3 yrs) [2]. Subjects were monitored in the resting supine position and in the 70° upright position reached after passive head-up tilt. From the ECG and finger arterial pressure signals, the variability series of RR interval and SAP were measured on a beat-by-beat basis, and two stationary and artifact-free windows, each of 300 beats, were selected in correspondence with the two epochs of the test.

Each pair of observed RR interval and SAP series, denoted as $r(n)$ and $s(n)$ in the following, was taken as a realization of a bivariate autoregressive (AR) process $Y(n)=[y_1(n)\ y_2(n)]^T=[s(n)\ r(n)]^T$, described as:

$$Y(n) = \sum_{k=0}^{p} \mathbf{A}(k)Y(n-k) + U(n) \tag{1}$$

where $U(n)=[u_1(n)\ u_2(n)]^T$ is a vector of uncorrelated white noises with 2×2 covariance matrix $\mathbf{\Sigma}$, and $\mathbf{A}(k)$ is a 2×2 coefficient matrix. Model identification was performed via the vector least-squares approach, setting the model order p according to the multivariate version of the Akaike criterion. Then, the estimated model coefficients were represented in the frequency domain to get the coefficient matrix $\mathbf{A}(f)$, and the variability and interactions were described through the transfer matrix $\mathbf{H}(f)=[\mathbf{I}-\mathbf{A}(f)]^{-1}$ and the spectral density matrix $\mathbf{S}(f)=\mathbf{H}(f)\cdot\mathbf{\Sigma}\cdot\mathbf{H}(f)^*$. These two matrices were then exploited to compute frequency domain measures of coupling and causality via the definition of the squared coherence, $|\Gamma_{12}(f)|^2=|S_{12}(f)|^2/(S_{11}(f)\ S_{22}(f))$, and causal coherence, $|\gamma_{12}(f)|^2=\Sigma_{11}|H_{21}(f)|^2/S_{22}(f)$. Details about the computation of these frequency measures can be found in [7].

From the measures defined above, we followed different approaches to derive frequency domain estimates of the spontaneous BRS [7]. According to the alpha-BRS method (αBRS) proposed by Pagani et al. [5], BRS was estimated as the ratio of the RR spectral power to the SAP spectral power:

$$G_\alpha(f) \equiv \sqrt{\frac{S_{22}(f)}{S_{11}(f)}} \tag{2}$$

According to the transfer function BRS method (tfBRS) proposed by Robbe et al. [4], a second BRS estimate was taken as the gain of the transfer function from SAP to RR:

$$G_{TF}(f) \equiv \sqrt{\frac{S_{22}(f)|\Gamma_{12}(f)|^2}{S_{11}(f)}} \tag{3}$$

As a third estimate of the BRS in the frequency domain we implemented the gamma BRS method (γBRS) proposed

by Faes et al. [7], whereby the gain function is computed as:

$$G_\gamma(f) \equiv \sqrt{\frac{S_{22}(f)|\gamma_{21}(f)|^2}{S_{11}(f)}} \quad (4)$$

The three measures in (2-4) rely on different assumptions for the estimation of BRS: in the αBRS measure, the main assumption is that the whole variability of RR is driven by SAP; the tfBRS measure weights the power ratio through the squared coherence, thereby considering that part of the measured RR variability can be originated by sources other than SAP variability; the γBRS measure weights the power ratio through the causal coherence from $y_1=s$ to $y_2=r$, thereby considering only the portion of the RR spectrum causally driven by SAP variability.

After their computation, the estimated gain functions were averaged to give overall values within the LF band (0.04–0.15 Hz) of the frequency spectrum. Then, for each gain measure (G_α, G_{TF}, G_γ), the statistical significance of the changes across groups (Young, Old, AMI) and conditions (rest, tilt) was tested using a two-way ANOVA with post-hoc pairwise comparisons implemented using the Student t-test for paired data (between conditions) and the two sample t-test (between groups), with 5% significance level.

III. Results

Fig.1 shows the distributions of the three gain measures obtained for the three groups in the rest and tilt conditions. In all groups and conditions, the values of median and quartiles of the gain distribution were lower for tfBRS than for αBRS, and for γBRS than for αBRS. For all three measures, the statistical analysis documented a significantly lower gain in Old compared to Young in both rest and tilt conditions. Moreover, the γBRS method detected a statistically significant decrease of the gain in the AMI patients compared with the Young subjects. The comparison between the two experimental conditions reveals that the gain index decreased significantly moving from rest to tilt in all three groups if computed using the αBRS method, in Young and AMI using the tfBRS method, and only in AMI patients using the causal approach (γBRS method).

IV. Discussion and Conclusion

Our results confirm the importance of employing a causal approach for the frequency domain evaluation of BRS [7]. Indeed, while the decrease of the baroreflex gain with age was documented by all measures, only the γBRS measure decreased significantly in the AMI patients compared to the young healthy controls. Moreover, although all methods detected in the AMI patients a decreased gain during postural stress, the αBRS and tfBRS measures detected a decrease also in the young subjects. This latter finding, which was documented also previously [8], is of difficult physiological interpretation and can be rather ascribed to the fact that non-causal gain measures do not reflect exclusively the BRS as they mix feedback and feedforward RR-SAP interactions. Also the lack of significant differences between AMI and the other groups in non-causal measures could be ascribed to altered non-baroreflex effects which confuse BRS estimates.

Since no statistically significant differences were observed between AMI patients and age-matched healthy subjects, the deterioration of the baroreflex response documented by lower values of γBRS is likely more related to aging than to the infarction. Nevertheless, the significant decrease of γBRS in the upright position compared with the supine, observed in the AMI patients but not in the Old subjects, seems to indicate the symptoms of an impaired response to postural stress which may be indicative of orthostatic intolerance associated with AMI.

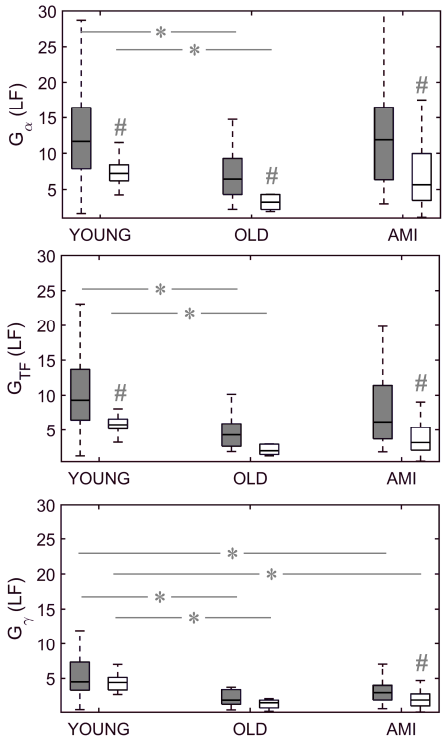

Fig. 1. Distributions over subjects of the BRS computed in the LF band with the three different approaches (top: αBRS; middle: tfBRS; bottom: γBRS;), in the rest (grey) and tilt (white) phases of the testing protocol. Statistically significant differences: *, YOUNG vs. OLD or YOUNG vs. AMI; #, rest vs. tilt.

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