# Cardiovascular control in women with fibromyalgia syndrome: do causal methods provide nonredundant information compared with more traditional approaches?

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[1]*Department of Physical Therapy, Federal University of São Carlos, São Carlos, Brazil;* [2]*Department of Biomedical Sciences for Health, University of Milan, Milan, Italy;* [3]*Istituti di Ricovero e Cura a Carattere Scientifico Galeazzi Orthopedic Institute, Milan, Italy;* [4]*Department of Electronics Information and Bioengineering, Politecnico di Milano, Milan, Italy; and* [5]*Internal Medicine, Humanitas Research Hospital, Rozzano, Biometra Department, University of Milan, Milan, Italy*

**Zamunér AR, Porta A, Andrade CP, Marchi A, Forti M, Furlan R, Barbic F, Catai AM, Silva E.** Cardiovascular control in women with fibromyalgia syndrome: do causal methods provide nonredundant information compared with more traditional approaches? *Am J Physiol Regul Integr Comp Physiol* 309: R79–R84, 2015. First published April 22, 2015; doi:10.1152/ajpregu.00012.2015.—The cardiovascular autonomic control and the baroreflex sensitivity (BRS) have been widely studied in fibromyalgia syndrome (FMS) patients through the computation of linear indices of spontaneous heart period (HP) and systolic arterial pressure (SAP) variabilities. However, there are many methodological difficulties regarding the quantification of BRS by the traditional indices especially in relation to the issue of causality. This difficulty has been directly tackled via a model-based approach describing the closed-loop HP-SAP interactions and the exogenous influences of respiration. Therefore, we aimed to assess whether the BRS assessed by the model-based causal closed-loop approach during supine and active standing in patients with FMS could provide complementary information to those obtained by traditional indices based on time and frequency domains. The findings of this study revealed that, at difference with the traditional methods to quantify BRS, the causality analysis applied to the HP, SAP, and respiratory series, through the model-based closed-loop approach, detected lower BRS in supine position, as well as a blunted response to the orthostatic stimulus in patients with FMS compared with healthy control subjects. Also, the strength of the causal relation from SAP to HP (i.e., along the cardiac baroreflex) increased during the active standing only in the control subjects. The model-based closed-loop approach proved to provide important complementary information about the cardiovascular autonomic control in patients with FMS.

fibromyalgia; baroreflex; autonomic nervous system; modeling; causality

FIBROMYALGIA SYNDROME (FMS) is a noninflammatory syndrome characterized by chronic diffuse musculoskeletal pain, stiffness, and pain hypersensitivity in 18 specific points located in muscles or tendon muscle insertion called tender points (27). Although the painful condition is the main characteristic of this syndrome, advancements regarding the etiology and pathophysiology of FMS have attributed an important role to dysautonomia (i.e., the autonomic nervous system dysfunction) (4, 7, 11, 12, 24, 25).

The dysautonomia has been widely demonstrated in patients with FMS. Thus, it is known that FMS patients present an alteration of the cardiac autonomic modulation characterized by a high cardiac sympathetic modulation and low cardiac parasympathetic modulation even at rest (4, 7, 11, 12, 24, 25). In addition, despite a normal baroreflex function, a lack of increased sympathetic discharge to vessels and decreased cardiac vagal activity has been reported during the orthostatic stimulus, which may account for the reduced orthostatic tolerance, commonly observed in these patients (7).

Traditionally, the baroreflex sensitivity (BRS) in FMS patients has been studied through the computation of indices derived from spontaneous heart period (HP) and systolic arterial pressure (SAP) variabilities (4, 7, 11, 12, 24, 25). However, these approaches to the quantification of BRS have many methodological drawbacks. The most relevant one is the inability to account for causality, thus merging the feedforward pathway from HP to SAP, which is related more to the mechanical properties of the heart and dynamical properties of circulatory system, to the feedback pathway, which is more related to cardiac baroreflex (18, 23).

In an attempt to overcome this issue, model-based causal closed-loop methods (1, 9, 13, 28), and more recently, a Granger causality approach have been proposed (18, 20, 22). These methods have been shown to provide complementary information to that obtained by traditional indices about the cardiovascular autonomic regulation. This capability has been attributed to their ability to account for both feedforward and feedback pathways, for the effects of respiration, and the issue of causality. Disregarding these factors usually hampers more traditional approaches to the description of the HP-SAP interactions.

Whether patients with FMS present a dysfunction in the baroreflex function is not clear. Reyes del Paso et al. (24) reported an overall reduction in the spontaneous cardiac baroreflex function in patients with FMS assessed by the sequence analysis based on continuous blood pressure and HP series recordings. On the other hand, Furlan et al. (7) did not find any significant differences between patients with FMS and healthy control subjects, thus making controversial the issue of the quantification of BRS in FMS.

Thus, the aim of this study was to assess whether the BRS assessed by the model-based causal closed-loop approach based on spontaneous HP and SAP variabilities during supine and active standing in patients with FMS could provide com-

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plementary information to those obtained by traditional indices based on time and frequency domains and shed light on the baroreflex control in FMS.

## MATERIALS AND METHODS

*Participants.* Twenty six women with a clinical diagnosis of FMS and 20 healthy women took part in the study. The diagnosis was made by a board-certified rheumatologist, according to criteria established by the American College of Rheumatology (27). The subjects with FMS were recruited from the local community after they responded to flyers posted in university buildings or orthopedic and rheumatologic clinics, or were chosen from our database of FMS patients who had been enrolled in other studies. The control group (CG) was recruited from the local community and through personal contacts of the investigators. Age and clinical characteristics of both groups are presented in Table 1.

To fulfill the inclusion criteria, subjects were not allowed to have a history of cardiovascular, respiratory, or metabolic disease of any kind; inflammation as a cause of pain; neurological disorders; or cognitive deficits that would prevent understanding and conduct of the evaluations; also, they could not be smokers, engaged in regular physical activity, or continuously use drugs or alcohol. The study was approved by the Ethics in Research Committee, and all participants gave written informed consent.

*Experimental procedure.* All experiments were carried out in the afternoon to minimize circadian changes. Room temperature was maintained at 22°C, and relative air humidity was maintained between 40% and 60%. Participants were acquainted with the experimental protocol and were instructed to abstain from stimulants (e.g., coffee, tea, or soft drinks) and alcoholic beverages 24 h before the examination and to have a light meal at least 2 h before the test. To avoid any residual fatigue, subjects were asked to refrain from strenuous physical activity at least 2 days before the tests. Participants had not taken any psychotropic or other medications known to alter autonomic activity for at least 4 wk before the study, including antihypertensive drugs, tranquilizers, or antidepressants. The participants with regular menstrual cycles (28 ± 2 days) were assessed during the follicular phase, i.e., 7–10 days after the start of menses.

In every subject, we recorded the ECG (modified lead I) (BioAmp FE132; ADInstruments, Bella Vista, NSW, Australia), noninvasive blood pressure (Finometer Pro; Finapres Medical Systems Ohmeda, Amsterdam, The Netherlands), and respiratory activity by a piezo-electric respiratory belt (Thoracic Belt, Marazza, Monza, Italy). The arterial pressure signal was cross-calibrated in each session by regularly measuring the blood pressure with a sphygmomanometer. Sig-

nals were digitalized using a commercial device (BioAmp Power Lab; AD Instruments) and were sampled at 1,000 Hz.

Data acquisition was performed during 15 min in supine resting position and during 15 min in an orthostatic position reached by active standing. Before the beginning of data acquisition, we allowed about 20 min for stabilization.

*Extraction of the beat-to-beat variability series.* The R-wave peaks were detected over the recorded ECG using parabolic interpolation. The temporal distance between two consecutive R-wave peaks was estimated as HP. The maximum of arterial pressure inside an HP was defined as SAP, and the *i*th SAP [i.e., SAP($i$)] was taken inside the *i*th HP [i.e., HP($i$)], where $i$ is the cardiac beat counter. Respiratory (RESP) series was obtained by sampling the respiratory signal in correspondence with the R-wave peak. The *i*th RESP [RESP($i$)] was taken at the first R-wave peak delimiting HP($i$).

The occurrences of QRS and SAP peaks were carefully checked to avoid erroneous detections or missed beats. HP = {HP($i$), $i$ = 1, . . ., $N$}, SAP = {SAP($i$), $i$ = 1, . . ., $N$} and RESP = {RESP($i$), $i$ = 1, . . ., $N$} were extracted on a beat-to-beat basis, where $N$ is the series length. Sequences with $N$ = 256 consecutive measures were selected inside supine and standing periods. According to the test proposed in Magagnin et al. (10), synchronous stationary sequences of HP, SAP, and RESP values could always be found.

*Frequency domain BRS assessment.* The power spectrum was estimated according to an univariate parametric approach fitting the series with an autoregressive (AR) model (17). AR spectral density was factored into components, each of them characterized by a central frequency. If the central frequency of the component belonged to the low-frequency band (LF, from 0.04 to 0.15 Hz), it was labeled as LF. The LF power was defined as the sum of the powers of all LF components.

The BRS estimated via spectral analysis was computed as the square root of the ratio of the LF power of HP on the LF power of SAP (17) and indicated as $\alpha_{LF}$ in the following. As prerequisites for the reliable estimation of BRS, two parameters were considered (17): *1*) the HP-SAP correlation must be significant in the LF band; i.e., the squared coherence function $K^2_{HP-SAP}$ (LF) should be higher than 0.5; and *2*) HP changes must lag behind SAP variations in the LF band, i.e., the phase of the cross-spectrum $Ph_{HP-SAP}$ (LF) should be lower than 0 with the adopted convention for the calculation of the HP-SAP cross spectrum. The calculation of the BRS in the high-frequency band (from 0.15 to 0.5 Hz) was not performed because the prerequisites for its calculation are only fulfilled in a small percentage of subjects.

*Time domain BRS assessment.* Time domain assessment of the BRS was based on the detection of spontaneous sequences of three or more SAP and HP values that simultaneously increase (positive sequences) or decrease (negative sequences) (2). The lag between HP and SAP values was set to 0 to pick up the fast vagal arm of the baroreflex. Sequences were considered to reflect baroreceptor activity if the following criteria had been matched: *1*) HP variations were >5 ms; *2*) SAP changes were >1 mmHg; and *3*) sequences were longer than 4 beats. For each sequence, a linear regression of HP on SAP was computed, and the slope of the regression line was calculated. In each subject, all of the slopes with a correlation coefficient >0.85 were averaged, and the final value was taken as the gain of arterial baroreflex control of heart rate and indicated as $\alpha_{SEQ}$ in the following.

*Closed-loop model-based estimate of the BRS and feedforward mechanical pathway gain.* The BRS and the gain of the feedforward mechanical pathway were estimated by the methodology reported by Porta and colleagues (1, 9, 18). Briefly, after identification of the coefficients of the *M*-variate autoregressive model with $M$ = 3 in $\Omega$ = {HP, SAP, RESP}, the baroreflex feedback arm, from SAP to HP, was described by the regression of HP on past SAP values, whereas the regression of SAP on past HP values described the mechanical feedforward arm, from HP to SAP. The two regressions accounted for

Table 1. *Age and clinical characteristics of the control and the fibromyalgia syndrome groups*

| | CG ($n$ = 20) | FMS ($n$ = 26) | $P$ Value |
|---|---|---|---|
| Age, yr | 46 ± 7 | 48 ± 7 | 0.33 |
| BMI, kg/m² | 24.7 ± 3.0 | 26.1 ± 2.5 | 0.18 |
| Number of postmenopausal women, $n$ | 4 | 6 | 0.91 |
| Disease duration, yr | | 8.0 ± 5.1 | |
| FIQ score | | 62.7 ± 15.5 | |
| BDI score | 6.2 ± 5.5 | 18.2 ± 7.4 | <0.0001 |
| BAI score | 4.5 ± 3.9 | 20.6 ± 11.9 | <0.0001 |
| VAS pain, mm | 1.4 ± 1.3 | 46.9 ± 24.0 | <0.0001 |
| Tender points | 8.7 ± 3.2 | 17.2 ± 1.4 | <0.0001 |
| Pain pressure threshold, kg/cm² | 3.6 ± 0.9 | 1.9 ± 0.5 | <0.0001 |

Values are expressed as means ± SD. BMI, body mass index; FIQ, fibromyalgia impact questionnaire; BDI, Beck depression inventory; BAI, Beck anxiety inventory; CG, control group; FMS, fibromyalgia syndrome group; VAS, visual analogue scale.

the possible common influences of RESP and memory effects of HP and SAP on their own past values as well.

The goodness of fit of the model in fitting HP and SAP in $\Omega = \{HP, SAP, RESP\}$, indicated as $\rho^2_{HP}$ and $\rho^2_{SAP}$ in the following, was calculated after normalizing the series to have unit variance as the complement to 1 of the mean square prediction error. The model-based closed-loop estimate of the BRS was obtained by observing the response of the relation from SAP to HP induced by an artificial increase of SAP with unit slope (1, 9, 18). The corresponding slope of the HP increase was taken as an estimate of the BRS and indicated as $\alpha_{CL}$ (1, 9, 18). Values larger than 0 were obtained when the HP variation had the same sign of the SAP variation, as expected from a working baroreflex. On the other hand, values lower than 0 might occur only in the case of activation of nonbaroreflex mechanisms. The value of the first coefficient of the regression from HP to SAP was taken as an index quantifying the gain of the feedforward mechanical pathway from HP to SAP and was indicated as $K_{CL}$.

*Granger causality indices.* A Granger causality approach (18, 20, 22) is utilized to assess, through the calculation of the causality ratio (CR), the strength of the causal relation from SAP to HP ($CR_{SAP \to HP}$) and from HP to SAP ($CR_{HP \to SAP}$) variability series in $\Omega$. In this context, SAP is said to Granger-cause HP if the HP dynamics can be better predicted in $\Omega$ than in $\Omega = \{HP, SAP, RESP\}$ after exclusion of SAP (i.e., $\Omega \backslash SAP = \{HP, RESP\}$) (8). By simply reversing the role of HP and SAP, it is possible to define the causality from HP to SAP. The inclusion of RESP in the minimal set of series is necessary to evaluate the HP-SAP causal relations, because RESP affects both HP and SAP (1, 19). The Granger approach to the evaluation of causality from SAP to HP was described in detail elsewhere (18, 20). Briefly, after computing the prediction error as the difference between the current HP value and its prediction based on the model, $CR_{SAP \to HP}$ is defined as the fractional decrement of the mean square prediction error of HP over the entire series due to the introduction of SAP in $\Omega \backslash SAP$. Thus, the more negative the $CR_{SAP \to HP}$, the higher the strength of the causal link from SAP to HP. The significance of $CR_{SAP \to HP}$ was checked by comparing the mean square prediction error of HP in $\Omega$ and in $\Omega \backslash SAP$ via the $F$ test carried out over the absolute values of CR (26). If the $CR_{SAP \to HP}$ adjusted for the degrees of freedom (19, 26) was larger than the critical value of the $F$ distribution for a significance level of 0.01, the null hypothesis that SAP did not Granger-cause HP was rejected, and the alternative hypothesis of unidirectional causality from SAP to HP, indicated as SAP→HP in the following, was accepted (i.e., cardiac baroreflex is working). Reversing the role of SAP and HP allowed the calculation of $CR_{HP \to SAP}$ and the test of the null hypothesis that HP did not Granger-cause SAP. If the null hypothesis was rejected, the unidirectional causality from HP to SAP, indicated as HP→SAP in the following, was accepted.

*Statistical analysis.* Normal data distribution was verified by the Shapiro-Wilk test. The Student's independent *t*-test was used to perform between-group comparisons for age and clinical data. A two-way mixed-design ANOVA was used to test for differences between groups in the hemodynamic, respiratory, and baroreflex and closed-loop variables over the two postures (group × posture). When a significant group × posture interaction was observed, the interpretation of the main effects was not considered, and pairwise comparisons were performed with Bonferroni adjustment. Effect size was reported using partial η2 ($\eta_\rho^2$). The nonparametric Pearson $\chi^2$-test with Yates's correction for 2 × 2 contingency tables was used to assess the statistical significance of differences between groups regarding the percentages of subjects showing a given HP-SAP causal relation. Moreover, the McNemar $\chi^2$-test was applied to verify the difference between supine and standing postures on the percentage of subjects exhibiting a given HP-SAP causal relation. Statistical significance was set at 5% for all tests. SPSS 20.0 (SPSS, Chicago, IL) was used for all analysis.

## RESULTS

No significant differences were observed between CG and FMS group regarding age, body mass index, and number of postmenopausal subjects. FMS group presented higher values for Beck depression inventory, Beck anxiety inventory, visual analog scale scores, and number of tender points (Table 1).

Table 2 summarizes the hemodynamic and respiratory variables of both groups. There was neither significant interaction between posture and group, nor significant main effect of group for any of these variables ($P > 0.05$). A main effect of posture was found for heart rate ($F = 74.3$, $P = 0.0001$, $\eta_\rho^2 = 0.63$) and HP ($F = 85.6$, $P = 0.0001$, $\eta_\rho^2 = 0.66$).

Table 3 summarizes the baroreflex indices for both groups studied. Only a significant main effect of posture was found on $\alpha_{SEQ}$ ($F = 74.3$, $P = 0.0001$, $\eta_\rho^2 = 0.63$) and $\alpha_{LF}$ ($F = 74.3$, $P = 0.0001$, $\eta_\rho^2 = 0.63$). A significant posture × group interaction was found for $\alpha_{CL}$ ($F = 19.5$, $P = 0.0001$, $\eta_\rho^2 = 0.37$). Pairwise comparisons revealed that in supine posture, the CG presented higher values of $\alpha_{CL}$ compared with the FMS group ($P < 0.05$). Regarding the comparisons between supine and standing postures, the CG presented a significant decrease of $\alpha_{CL}$ ($P < 0.05$), which was not observed in the FMS group.

The goodness of fit of the models fitting HP and SAP is reported in Table 4. There was neither a significant interaction between posture and group, nor a significant main effect of group for $\rho^2_{HP}$ and $\rho^2_{SAP}$ ($P > 0.05$). However, a main effect of posture was found for $\rho^2_{HP}$ ($F = 5.84$, $P = 0.02$, $\eta_\rho^2 = 0.12$). The results indicate the ability of the models in describing the HP and SAP dynamics in any group and in any condition. The increase in the $\rho^2_{HP}$ during the standing posture might be due to the increase of the regularity of the HP series.

Figure 1 displays the results relevant to the strength of the causal relation from SAP to HP and vice versa. A significant posture × group interaction was found for $CR_{SAP \to HP}$ ($F = 4.97$, $P = 0.03$, $\eta_\rho^2 = 0.11$). During active standing, the CG

**Table 2.** *Hemodynamic and respiratory measures of the control and the fibromyalgia syndrome groups*

| | Supine | | Standing | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | CG | FMS | CG | FMS | P | G | I |
| HR, bpm | 66 ± 8 | 67 ± 7 | 76 ± 8 | 73 ± 9 | < 0.05 | ns | ns |
| HP, ms | 913 ± 111 | 912 ± 98 | 806 ± 113 | 828 ± 100 | < 0.05 | ns | ns |
| SAP, mmHg | 117 ± 12 | 122 ± 25 | 125 ± 17 | 122 ± 25 | ns | ns | ns |
| DAP, mmHg | 66 ± 7 | 66 ± 8 | 74 ± 9 | 70 ± 8 | ns | ns | ns |
| Respiration, cycles/min | 17 ± 2 | 17 ± 2 | 17 ± 2 | 16 ± 2 | ns | ns | ns |

Values are expressed as means ± SD. P, posture main effect; G, group main effect; I, interaction; HR, heart rate; HP, heart period; SAP, systolic arterial pressure; DAP, diastolic arterial pressure.

Table 3. *Closed loop indices of the control and the fibromyalgia syndrome groups in supine and standing positions*

| | Supine | | Standing | | | | |
|---|---|---|---|---|---|---|---|
| | CG | FMS | CG | FMS | P | G | I |
| $\alpha_{SEQ}$, ms/mmHg | $13.5 \pm 1.8$ | $11.0 \pm 1.2$ | $8.0 \pm 0.9$ | $8.0 \pm 0.8$ | $<0.05$ | ns | ns |
| $\alpha_{LF}$, ms/mmHg | $10.3 \pm 1.7$ | $8.0 \pm 1.5$ | $7.8 \pm 0.8$ | $5.6 \pm 0.7$ | $<0.05$ | ns | ns |
| $\alpha_{CL}$, ms/mmHg | $5.0 \pm 0.5$* | $2.1 \pm 0.4$ | $2.0 \pm 0.6$# | $2.2 \pm 0.5$ | $<0.05$ | $<0.05$ | $<0.05$ |
| $K_{CL}$, mmHg/s | $-22.6 \pm 2.5$ | $-16.4 \pm 2.2$ | $-20.0 \pm 2.5$ | $-14.9 \pm 3.4$ | ns | ns | ns |

Values are expressed as means $\pm$ SE. $\alpha_{SEQ}$, baroreflex sensitivity estimate via sequence method; $\alpha_{LF}$, baroreflex sensitivity estimate via spectral method in the low frequency band; $\alpha_{CL}$, baroreflex sensitivity estimate via model-based closed-loop approach; $K_{CL}$, gain of the mechanical feedforward arm of the HP-SAP closed-loop; P, posture main effect posture; G, group main effect; I, interaction. #$P < 0.05$ vs. supine. *$P < 0.05$ vs. FMS group.

presented lower values of $CR_{SAP \to HP}$ compared with the FMS group ($P < 0.05$), indicating that CG is characterized by a stronger strength of the relation from SAP to HP. In the comparisons between supine and standing postures, the CG presented a significant decrease of $CR_{SAP \to HP}$ ($P < 0.05$), indicating an augmented strength of the relation from SAP to HP, which was not observed in the FMS group.

When $K_{CL}$ and $CR_{HP \to SAP}$ were considered, there was neither a significant interaction between group and posture nor significant main effects of group and posture (Table 3 and Fig. 1).

Figure 2 depicts the results of causality analysis displaying the percentage of subjects presenting a significant causal relationship from SAP to HP along the cardiac baroreflex pathway in supine and standing positions in both groups. In supine position, 50% of the CG and 59% of the FMS group presented causal link from SAP to HP series along the cardiac baroreflex. During standing posture, the percentage of subjects presenting a causal link from SAP to HP series significantly increased in the CG (75%) and was higher compared with the FMS group (50%).

## DISCUSSION

The main finding of this study is that, although the traditional methods to quantify the spontaneous baroreflex based on a time- and frequency-domain approach did not show any significant differences between groups, the model-based closed-loop causality analysis applied to the HP, SAP, and RESP series detected in supine position lower BRS and weaker strength of the baroreflex control. The blunted response to the orthostatic stimulus in patients with FMS compared with the CG was suggested by the decrease of BRS and the augmented strength of the causal relation from SAP to HP along the cardiac baroreflex observable only in the CG.

Considering the results of the BRS obtained by the traditional methods, our findings are in accordance with Furlan et al. (7), who reported no significant differences between patients with FMS and healthy controls, while they are in disagreement with those reported by Reyes del Paso et al. (25),

who reported an overall reduced BRS in FMS patients. A possible reason to explain this divergence may rely on the difference between the prerequisites required for BRS calculation regarding the sequence method. In the present study, we used the parameter setup for sequence analysis proposed by Bertinieri et al. (2), which was the same setup used by Furlan et al. (7). This method requires, as prerequisites, consideration of sequences to reflect baroreceptor response to HP variation $>5$ ms, SAP changes $>1$ mmHg, sequences longer than 4 beats, and correlation coefficient $>0.85$. Conversely, in the method used by Reyes del Paso et al. (24), they considered 2 ms as the minimal criterion for changes in HP, and no minimal value for correlation coefficient was required, since they stated that the mean slope of all detected SBP ramps was included in the analysis.

Regarding the results provided by the methods addressing causality and accounting for respiration, the findings are different from those obtained by the traditional methods. The strength of the causal relation from SAP to HP series increased in the CG during the active standing, indicating an increase in

Table 4. *Goodness of fit $\rho^2$ of the causal models explaining the series HP and SAP in $\Omega = \{HP, SAP, RESP\}$*

| | Supine | | Standing | | | | |
|---|---|---|---|---|---|---|---|
| | CG | FMS | CG | FMS | P | G | I |
| $\rho^2_{HP}$ | $0.76 \pm 0.12$ | $0.75 \pm 0.09$ | $0.84 \pm 0.08$ | $0.78 \pm 0.20$ | 0.02 | ns | ns |
| $\rho^2_{SAP}$ | $0.91 \pm 0.07$ | $0.92 \pm 0.04$ | $0.91 \pm 0.06$ | $0.87 \pm 0.12$ | ns | ns | ns |

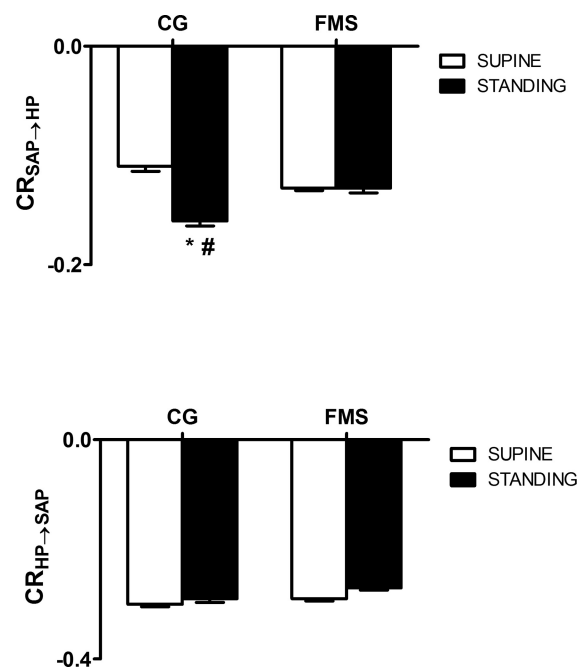Values are expressed as means $\pm$ SE.



Fig. 1. Bar graph of the causal ratio (CR) from systolic arterial pressure (SAP) to heart period (HP) series and from HP to SAP in the control group (CG) and fibromyalgia syndrome group (FMS) during supine and standing phases. Error bars indicate the standard deviation. *$P < 0.05$ vs. Supine CG; #$P < 0.05$ vs Standing FMS.
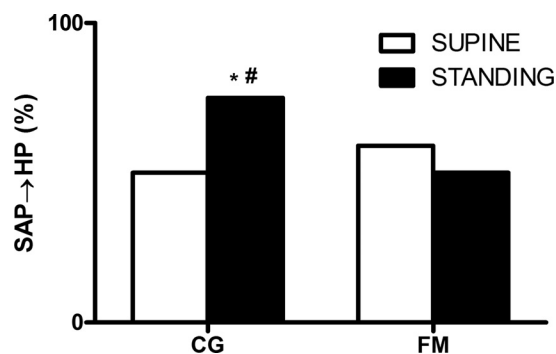
Fig. 2. Bar graph of the percentage of subjects of the CG and FMS presenting a significant causal interaction from SAP to HP (i.e., SAP → HP) during supine and standing phases.*$P < 0.05$ vs. Supine CG; #$P < 0.05$ vs. Standing FMS.

involvement of the baroreflex in governing HP-SAP variability interactions during the orthostatic stimulus, which was not observed in the FMS group. Previous studies have shown that gravitational stimulus increases the involvement of baroreflex pathway in the control of heart rate (14, 21). A possible explanation relies on the unloading of cardiopulmonary baroreceptors consequent to the decrease of the central blood volume, leading to an activation of the cardiac baroreflex. Another possible factor that could play a role is the reduction of the venous return, making the effect of respiration on arterial pressure more pronounced and resulting in a stronger activation of the cardiac baroreflex in the absence of significant changes of the mean SAP. Anyway, the results showed that a higher percentage of subjects with FMS did not elicit the baroreflex during active standing. Remarkably, this finding is already observable in the resting condition. Moreover, the spontaneous baroreflex gain estimated by the closed-loop approach revealed higher values in CG subjects compared with FMS patients in supine posture. During the active standing, the CG presented a reduction in the BRS gain, which was not observed in FMS patients, since their baroreflex gain was already low in supine posture.

The reason to use the $\alpha_{CL}$ and the $CR_{SAP \to HP}$ indices in the present study is due to the fact that they measure different aspects of a relation between variables (18, 22). Whereas the $CR_{SAP \to HP}$ estimates the strength of the causal link from SAP to HP, thus quantifying the degree of involvement of the baroreflex (22), $\alpha_{CL}$ estimates the gain of relation from SAP to HP, i.e., the magnitude of the HP variation in response to a unit SAP change. As a general rule, BRS indexes should be considered reliably assessed only when the baroreflex is active, i.e., when the strength of the relation from SAP to HP is significant. An active baroreflex, characterized by a significant $CR_{SAP \to HP}$, might be working, in principle, with either high or low BRS. Therefore, the two indexes convey complementary information.

Thus, the FMS patients in the present study showed not only a diminished baroreflex gain, but also a reduced intensity of the causal relation from SAP to HP during standing, suggesting a reduction of the efficiency of the cardiac baroreflex control.

Another important aspect of the model-based method (1, 9, 13, 28) is the possibility to identify nonbaroreflex mechanisms quantifying the gain of the feedforward mechanical pathway from HP to SAP series. On the basis of modeling approaches,

a prevalence of nonbaroreflex interactions during supine position was demonstrated (14, 21, 23). The present study confirms this observation. Indeed, regardless of the posture (supine or standing) or groups studied, the feedforward path is active in most subjects. These findings may explain the divergence in the results obtained by the $\alpha_{SEQ}$ and $\alpha_{LF}$ analyses, since they may have overestimated the involvement of the baroreflex mechanism in governing HP-SAP interactions, especially during supine posture, thus stressing the importance of accounting for causality in studies aiming to quantify the spontaneous baroreflex gain. As to the between-group comparison, indexes related to the mechanical feedforward did not show significant differences.

This study shed further light on the issue of autonomic nervous system in FMS. The sympathetic hyperactivity in FMS, which is well established in the literature (4, 7, 12), was attributed to a primary increase of central sympathetic drive, since it was unlikely to be due to a failure of the inhibitory modulation exerted by arterial baroreceptors. However, on the basis of the present results, a deficient afferent baroreceptor feedback restraining the sympathetic activity may take place in these patients. On the other hand, it must be taken into account that the relationship between baroreceptor activity and sympathetic activity is bidirectional: an increase of sympathetic activity might be an effect of a baroreflex unloading, as well as a direct effect of a central sympathetic drive restraining, as a consequence, baroreflex activity (16), thus supporting that the reduced baroreceptor function observed in the fibromyalgia patients might result from a central primary sympathetic hyperactivity previously hypothesized (7).

Even though it was not possible to clarify whether the reduced BRS leads to the sympathetic hyperactivity in FMS, this study has an important clinical implication regarding the risk of hypertension in this population. Some studies have found that chronic pain might be associated with increased prevalence of hypertension (3, 15). Moreover, Ducher et al. (6) found that a lower BRS was a consistent predictor for an increase in SAP at 5 years of follow-up. In addition, Dauphinot et al. (5) found that increased BRS reduces the risk of day-time hypertension and suggested that BRS may represent an intermediate goal to be considered by clinicians aiming to prevent hypertension. Thus, the findings of the present study has drawn attention to the risk of hypertension in subjects with FMS, which should be addressed in future investigations.

In conclusion, a Granger causality linear model-based approach that assesses the variabilities of spontaneous HP and SAP interactions provides nonredundant information compared with more traditional indices, based on time- and frequency-domain approaches, by revealing a reduced BRS in FMS patients, a reduced strength of the baroreflex control, as well as a blunted response to the orthostatic stimulus.

*Perspectives and Significance*

Advanced signal processing techniques were found helpful in typifying the impaired cardiac baroreflex control in subjects affected by fibromyalgia syndrome and in detecting their reduced response to an orthostatic stimulus above and beyond more traditional indexes. These findings suggest the possible role of depressed baroreflex control in the deteriorating condition of FMS patients and suggest that the use of countermea-

sures or therapies to improve baroreflex control might have beneficial effects.

## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

Author contributions: A.R.Z., C.P.A., and E.S. conception and design of research; A.R.Z., C.P.A., M.F., and A.M.C. performed experiments; A.R.Z., A.P., C.P.A., A.M., and M.F. analyzed data; A.R.Z., A.P., C.P.A., A.M., R.F., F.B., A.M.C., and E.S. interpreted results of experiments; A.R.Z. and A.P. prepared figures; A.R.Z., A.P., A.M., R.F., and F.B. drafted manuscript; A.R.Z., A.P., C.P.A., A.M., M.F., R.F., F.B., A.M.C., and E.S. edited and revised manuscript; A.R.Z., A.P., C.P.A., A.M., M.F., R.F., F.B., A.M.C., and E.S. approved final version of manuscript.

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