Causal linear parametric model for baroreflex gain assessment in patients with recent myocardial infarction

GIANDOMENICO NOLLO,1 ALBERTO PORTA,2 LUCA FAES,1 MAURIZIO DEL GRECO,3 MARCELLO DISERTORI,3 AND FLAVIA RAVELLI1

1Dipartimento di Fisica, Università di Trento, and Istituto Trentino di Cultura-irst, 38050 Povo-Trento; 2Dipartimento di Scienze Precliniche, Laboratorio Interdisciplinare Tecnologie Avanzate di Vialba, Università di Milano, 20157 Milano; and 3Unità Operativa di Cardiologia, Ospedale Santa Chiara, 38100 Trento, Italy

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Nollo, Giandomenico, Alberto Porta, Luca Faes, Maurizio Del Greco, Marcello Disertori, and Flavia Ravelli. Causal linear parametric model for baroreflex gain assessment in patients with recent myocardial infarction. Am J Physiol Heart Circ Physiol 280: H1830–H1839, 2001.—Spectral and cross-spectral analysis of R-R interval and systolic arterial pressure (SAP) spontaneous fluctuations have been proposed for noninvasive evaluation of baroreflex sensitivity (BRS). However, results are not in good agreement with clinical measurements. In this study, a bivariate parametric autoregressive model with exogenous input (ARXAR model), able to divide the R-R variability into SAP-related and -unrelated parts, was used to quantify the gain (αARXAR) of the baroreflex regulatory mechanism. For performance assessing, two traditional noninvasive methods based on frequency domain analysis [spectral, baroreflex gain by autogressive model (αAR); cross-spectral, baroreflex gain by bivariate autoregressive model (αSEQ)] and one based on the time domain [baroreflex gain by sequence analysis (αSEQ)] were considered and compared with the baroreflex gain by phenylephrine test (αPHE). The BRS evaluation was performed on 30 patients (61 ± 10 yr) with recent (10 ± 3 days) myocardial infarction. The ARXAR model allowed dividing the R-R variability (950 ± 1,099 ms²) into SAP-related (256 ± 418 ms²) and SAP-unrelated (694 ± 728 ms²) parts. αAR (12.2 ± 6.1 ms/mmHg) and αSEQ (8.9 ± 5.6 ms/mmHg) as well as αSEQ (12.6 ± 7.1 ms/mmHg) overestimated BRS assessed by αPHE (6.4 ± 4.7 ms/mmHg), whereas the ARXAR index gave a comparable value (αARXAR = 5.4 ± 3.3 ms/mmHg). All noninvasive methods were significantly correlated to αPHE (αARXAR and αSEQ were more correlated than the other indexes). Thus the baroreflex gain obtained describing the causal dependence of R-R interval on SAP showed a good agreement with αPHE and may provide additional information regarding the gain estimation in the frequency domain.

baroreflex sensitivity; spectral analysis; phenylephrine; autoregressive models; R-R-SAP transfer function

EVALUATION OF BAROREFLEX SENSITIVITY (BRS) is considered an important clinical tool for diagnosis and prognosis in a variety of cardiac diseases (10, 14). In humans, two techniques based on provocative tests have been commonly used to measure the baroreflex gain. The first method estimates the baroreflex gain by evaluating the slope of the increase of heart period subsequent to the rise of arterial pressure induced by injection of a vasoconstrictive drug. The second one estimates BRS by measuring changes in heart rate and blood pressure after the external selective manipulation of carotid baroreceptors by a neck chamber device. Despite the encouraging results found by recent studies (13), the need for an intravenous line and pressure injection or neck chamber devices limits the use of this methodology to clinical settings for risk stratification protocols. Moreover, the induced large increase in blood pressure is a different stimulus compared with the small amplitude pressure changes occurring in physiological conditions. An episode of myocardial ischemia associated to phenylephrine injection has also been recently reported (9).

Recent studies have suggested that spontaneous fluctuations of arterial pressure and R-R intervals offer a noninvasive method for assessing BRS in natural circumstances. They were commonly based on spectral (21), cross-spectral (26), and baroreflex sequence (22) analyses of simultaneous R-R interval and systolic arterial pressure (SAP) variabilities. In most of these studies, the noninvasive measurements of BRS have been significantly correlated with pharmacologically derived estimates, even though the degree of correlation decreased moving from healthy subjects (26) to hypertensive (29) or post-myocardial infarction (MI) (24) patients. Methodological approach and physiological measuring conditions may be the main causes of disagreement between the phenylephrine estimates of the baroreflex gain and those obtained by noninvasive methods. In fact, the injection of the vasoactive drug forces the regulatory system to work in an open-loop condition, and the BRS slope is calculated by an open-loop linear model. On the other side, approaches based on spontaneous fluctuations of SAP and R-R interval are taken with all reflexes and control mechanisms fully active (i.e., in a closed loop) (8).

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The estimation of the baroreflex gain by means of the monovariate spectral analysis (21) and sequence analysis (7) is performed by assuming but not testing that the whole R-R variability is generated by SAP changes. On the other hand, cross-spectral approaches (26) explicitly consider the mutual interactions between R-R and SAP variabilities, but the causal dependencies are not taken into account when the baroreflex gain is calculated. Complex closed-loop models (3, 4) have been proposed to describe the causal relationship from SAP to R-R interval (the baroreflex pathway) and to separate it from the mechanical pathway (from R-R interval to SAP) in the estimation of baroreflex gain (23). In this study, a simpler approach based on an open-loop dynamic adjustment autoregressive model (ARXAR model) (25) was introduced. This model describes the causal relationship between R-R interval and SAP by dividing the R-R interval variability in SAP-related and -unrelated parts. Performance and reliability of this method were assessed compared with classical approaches based on frequency (i.e., spectral and cross-spectral methods) and time domain (baroreflex sequence method) analysis of R-R and SAP spontaneous variability and with the baroreflex slope computed by the phenylephrine method.

**METHODS**

Gain estimation by spectral and cross-spectral analysis. Monovariate spectral analysis allows estimating the baroreflex gain by a separate autoregressive (AR) description of R-R and SAP variabilities. The application of the AR model requires reducing R-R and SAP series to zero-mean processes (rr and sap series, respectively). According to Fig. 1A, AR analysis of the data considers the dependence of current rr and sap values on the samples of their own past (by A₁ and A₂ blocks) and on the current value of an input noise source (i.e., wₚ and wₛₚ). The parameter estimation of the AR model followed the Burg identification method (12, 19), and the model order was chosen inside the set {6, 8, 10, 12}, according to the minimum of the Akaike figure of merit (2). For the validation of the AR model, whiteness of the prediction error was verified by applying the Anderson test (15) on the residuals wₚ and wₛₚ. After the power contribution of each oscillatory component to the overall R-R and SAP variabilities (11) was calculated, two gain indexes were obtained as the square root of the ratio between the power content of the low-frequency (LF) [αₐR(AR)] and high-frequency (HF) [αₐR(AR)] bands as the square root of the ratio between the power content of the R-R and SAP spectra [Pₐ(AR)] and [Pₛₚ(AR)], respectively. A₁ and A₂, AR block coefficients; rr and sap, zero-mean of the R-R interval and SAP series, respectively; wₛₚ and wₛ, white noise input of the AR models and sap, respectively.

The intersections between R-R and SAP can be jointly considered for evaluating baroreflex gain by means of a bivariate autoregressive (2AR) model. In the diagram of Fig. 2A, A₁₁ and A₂₂ blocks contain the AR parameters of rr and sap signals, whereas A₁₂ and A₂₁ blocks pertain to the effects of SAP on R-R interval and vice versa. The model order P was chosen, in the set {6, 8, 10, 12}, minimizing the Akaike figure of merit (2) for the bivariate joint process |rr(n) or sap(n)|, where n is the current value of the rr or sap series. The same model order P was assigned to all the model blocks, thus avoiding advantaging one regulation mechanism with respect to the other. The model identification is based on the generalization of the Burg maximum entropy spectral estimation to the multichannel case (18). With the use of the 2AR model, we estimated a power spectral density (PSD) matrix whose elements were used to compute the gain function α₂AR(f) and the coherence function K²(f) as outlined in the Appendix. The coherence was used to estimate the strength of the coupling between R-R and SAP at each frequency. Thus the gain indexes at LF and HF [α₂AR(LF)] and [α₂AR(HF)] were obtained by sampling α₂AR(f) on the maximum of the coherence function inside the specific band (Fig. 2B).

Causal open-loop model for baroreflex gain estimation. The model considered in Fig. 3 belongs to the class of single-output ARXAR models (5, 25) and is defined by the equation

\[ \text{rr}(n) = -\sum_{k=1}^{P} a_{11}(k) \times \text{rr}(n-k) + \sum_{k=0}^{P} a_{12}(k) \times \text{sap}(n-k) + u(n) \]

and the coherence function \( K²(f) \) as outlined in the Appendix. The coherence was used to estimate the strength of the coupling between R-R and SAP at each frequency. Thus the gain indexes at LF and HF \( [\alpha₂\text{AR}(LF)] \) and \( [\alpha₂\text{AR}(HF)] \) were obtained by sampling \( \alpha₂\text{AR}(f) \) on the maximum of the coherence function inside the specific band (Fig. 2B).
The R-R interval is affected by both $P$ values of the sap sequence [by $a_{12}(k)$ coefficients] and the current value of the noise source $u_{rr}$. Moreover, Eq. 1 takes the possible dependence of the R-R interval on $P$ samples of its own past into account [by $a_{11}(k)$ coefficients]. As outlined in Fig. 3, sap and $u_{rr}$ signals are described as AR processes with $w_{sap}$ and $w_{rr}$ zero-mean input white noises. The blocks $A_{22}$ and $D_1$ are formed by the AR parameters of sap and $u_{rr}$, respectively. In the open-loop ARXAR model, the variability of SAP around its mean value (i.e., the sap signal) is considered as an exogenous input, i.e., it may affect the R-R interval variability without being affected. The effects of other sources independent from SAP on R-R variability, considered as noise in this context, are accounted for in the model by means of the $u_{rr}$ signal.

The coefficient estimation follows an iterative identification task based on the generalized least-squares method (28). The model order $P$ was chosen, in the set {6, 8, 10, 12}, minimizing the Akaike figure of merit (2) for the bivariate joint process $[rr(n), sap(n)]$. The model validation required us to check the whiteness of the model inputs and the uncorrelation, even at zero lag, from $w_{sap}$ to $w_{rr}$.

The ARXAR model allows computing the PSD of R-R interval as a sum of two partial spectra (5), which represent the variability of R-R dependent and independent of SAP. In this way, the total R-R power, as well as its amount in the LF and HF bands, was decomposed in two parts, quantifying the SAP-related and -unrelated contribution to the R-R interval variability.

The gain of the R-R-SAP transfer function $[a_{ARXAR}(f)]$ was estimated in the frequency domain directly from the coefficients of $A_{12}$ and $A_{11}$ blocks (see APPENDIX for details). The function $a_{ARXAR}(f)$ was sampled in connection with the main oscillations of the driving signal sap inside the two major bands LF and HF, thus providing the corresponding gain indexes $a_{ARXAR}(LF)$ and $a_{ARXAR}(HF)$ (Fig. 4).

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Sequence analysis. The sequences (7) in which R-R and SAP values concurrently increased or decreased progressively over three variations (four beats) were extracted, and a linear regression analysis was performed on them. The sequences in which total R-R or SAP changes were smaller than 5 ms and 1 mmHg, respectively, and/or the correlation coefficients were smaller than 0.85 were excluded. The absolute values of the slopes of the regression lines were then averaged to accomplish a time domain-based estimation of BRS ($a_{SEQ}$).

Experimental protocol and data analysis. Thirty consecutive patients (25 men and 5 women; mean age 61 ± 10 yr)
were studied 10 ± 3 days after acute MI; the diagnosis of which was based on currently accepted criteria. The signal recordings and the BRS evaluation were executed in the electrophysiology laboratory between 9 AM and 12 AM, in comparably comfortable and quiet ambience conditions with patients in sinus rhythm and breathing spontaneously. After a period of 15 min (allowed for patient stabilization), the electrocardiogram, respiratory, and blood pressure signals were recorded in supine position for 10 min. Electrocardiograms were continuously traced by Siemens Mingograph 7 system. The respiratory activity was recorded in the nostril by using a differential pressure transducer. Arterial blood pressure was recorded at finger level (20) by a photoplethysmographic Finapres device (Ohmeda 2300, Finapres; Englewood, CO). All signals were digitized at the sampling frequency of 1 kHz by a 12-bit precision analog-to-digital converter.

Successively, patients underwent the phenylephrine test. A bolus of phenylephrine (2 μg/kg) was injected via peripheral vein to raise blood pressure from 15 to 40 mmHg. The test was repeated to obtain at least three recordings with sufficient pressure rise. Phenylephrine-induced beat-to-beat SAP increases were plotted against the corresponding R-R interval increases (Fig. 5). Linear least-squares fit was used to calculate the slope of the regression line. α_{PHE} was obtained by averaging the slopes of the successive recordings.

R-R intervals and SAP values were automatically measured on recorded electrocardiograms and arterial blood pressure signals. Variability series were then built up with the n-th SAP value inside the n-th R-R interval. From each series, mean values were subtracted to obtain zero-mean processes. Sequences of 300 samples that fulfilled the stationarity criterion were then analyzed by means of spectral methods. The PSD of respiratory activity was considered to locate the HF power content of SAP and R-R spectra in the AR model (Fig. 1B), sample the coherence function at HF in the 2AR model (Fig. 2B), and detect the respiratory-driven oscillation of SAP in the ARXAR model (Fig. 4). For each frequency domain approach, the mean of baroreflex gain was computed as the average of baroreflex gain estimated in the LF and HF bands \( \alpha_{AR} = [\alpha_{AR}(LF) + \alpha_{AR}(HF)]/2, \) \( \alpha_{2AR} = [\alpha_{2AR}(LF) + \alpha_{2AR}(HF)]/2, \) and \( \alpha_{ARXAR} = [\alpha_{ARXAR}(LF) + \alpha_{ARXAR}(HF)]/2 \) (16).

### Statistical analysis.

All results are expressed as means ± SD. The ANOVA test was used for comparison of BRS measures. Regression analysis was used to assess the BRS slope and compare different measures of baroreflex gain.

The agreement between the invasive and noninvasive tests was further assessed by sensitivity and specificity analysis. Data were divided into true positive and true negative on the basis of a threshold, set at 4 mmHg for \( \alpha_{PHE}. \) For each noninvasive test, the corresponding cutoff was defined by the equation found by linear regression analysis between \( \alpha_{PHE} \) and the noninvasive gain index.

### RESULTS

**Model validation.** To verify the whiteness of the inputs of the parametric models, the Anderson test was performed over 40 lags of the normalized autocorrelation functions of \( w_{rr} \) and \( w_{sap}. \) The autocorrelation functions of \( w_{sap} \) and \( w_{rr} \) were zero for each lag > 0 with 5% confidence (=2 points out of the confidence intervals) in all 30 patients. In addition, the causal structure of the ARXAR model required verification of the uncorrelation from \( w_{sap} \) to \( w_{rr} \) even at zero lag. The normalized cross-correlation was zero for each lag ≥ 0 with 5% confidence in all patients.

In the sequence analysis, regression slopes were carried out on the 2.5% of the total number of se-
quences on average. Moreover, it could not be performed on 3 of 30 subjects due to the absence of valid sequences in the variability series.

Spectral decomposition. According to the causal ARXAR open-loop model, R-R spectrum was the sum of the R-R interval variability driven by SAP changes (due to baroreflex mechanisms) and that independent of SAP changes. An example of R-R interval spectrum decomposition accomplished by the ARXAR model is plotted in Fig. 6 along with the PSDs of SAP and the respiratory series. Both the SAP-driven R-R variability (Fig. 6, top; dotted line) and that owing to different inputs (Fig. 6, top; dashed line) showed two main components in LF and HF bands well synchronized with those of SAP and respiratory spectra. On the whole population, the mean variance of R-R series (950 ± 1,099 ms²) was divided by the model in 256 ms² as induced by SAP changes and in 694 ms² as owing to unpredictable inputs. As shown in Table 1, the LF rhythms were present both in SAP-related and -unrelated R-R variabilities and were larger than the HF rhythms.

Gain assessment. Mean values of BRS estimates are shown in Table 2. The central tendency and variability of the different methods used for baroreflex gain assessment are reported in Fig. 7. The box and whisker plots display the mean of the baroreflex gains (α_PHE, α_SEQ, α_AR, α_2AR, and α_ARXAR) and the dispersion by means ± SE (box) and means ± SD (whisker). Only the gain index obtained by the ARXAR model resulted comparable with α_PHE, whereas α_SEQ, α_AR, and α_2AR overestimated the invasive BRS gain.

The reliability of noninvasive methods for BRS estimation was assessed by performing linear regression analysis between each index and α_PHE. Although the correlation coefficients were relatively low, all the non-

Table 1. Decomposition of R-R interval spectrum

<table>
<thead>
<tr>
<th>Spectrum Type</th>
<th>SAP-Related Power, ms²</th>
<th>SAP-Unrelated Power, ms²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total spectrum</td>
<td>256 ± 418</td>
<td>694 ± 728</td>
</tr>
<tr>
<td>LF band</td>
<td>124 ± 340</td>
<td>282 ± 476</td>
</tr>
<tr>
<td>HF band</td>
<td>40 ± 55</td>
<td>119 ± 137</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 30 patients. SAP, systolic arterial pressure; HF, high frequency; LF, low frequency.

Table 2. Estimates of baroreflex sensitivity by phenylephrine test and noninvasive gain indexes

<table>
<thead>
<tr>
<th>Index</th>
<th>Gain Value, ms/mmHg</th>
<th>P vs. α_PHE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenylephrine estimate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α_PHE</td>
<td>6.43 ± 4.73</td>
<td></td>
</tr>
<tr>
<td><strong>Sequence analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α_SEQ</td>
<td>12.56 ± 7.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>α_AR(LF)</td>
<td>12.54 ± 8.35</td>
<td>0.003</td>
</tr>
<tr>
<td>α_AR(HF)</td>
<td>11.73 ± 6.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>α_AR</td>
<td>12.19 ± 6.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>2AR model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α_2AR(LF)</td>
<td>8.30 ± 6.51</td>
<td>0.122</td>
</tr>
<tr>
<td>α_2AR(HF)</td>
<td>9.58 ± 6.42</td>
<td>0.010</td>
</tr>
<tr>
<td>α_2AR</td>
<td>8.94 ± 5.56</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>ARXAR model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α_ARXAR(LF)</td>
<td>4.38 ± 3.54</td>
<td>0.024</td>
</tr>
<tr>
<td>α_ARXAR(HF)</td>
<td>6.34 ± 4.10</td>
<td>0.798</td>
</tr>
<tr>
<td>α_ARXAR</td>
<td>5.37 ± 3.28</td>
<td>0.164</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 30 patients, n = 27 patients for sequence analysis. α_PHE, gain evaluated by phenylephrine test; α_SEQ, α_AR, α_2AR, and α_ARXAR gain indexes evaluated by spectral analysis; α_2AR, gain indexes evaluated by cross-spectral analysis [bivariate autoregressive (2AR) model]; α_ARXAR gain indexes evaluated by the bivariate parametric autoregressive (AR) model with exogenous input (ARXAR) model.
invasive indexes were significantly correlated ($P < 0.05$) with the reference. The low correlation may be explained by considering that the relationship between a PHE and noninvasive indexes may change for different levels of BRS. In fact, a PHE distribution showed a skew for high values. Therefore, to limit the spread of a PHE values, the distribution was cut at the 90th percentile. The results of linear regression analysis after exclusion of the upper tail from the a PHE distribution (3 patients) are reported in Table 3. The baroreflex gain provided by the sequence analysis showed the best linear correlation coefficient ($r = 0.80$). The gain obtained by the ARXAR model was better correlated with a PHE ($r = 0.76$; Fig. 8) than those obtained by the AR and 2AR models. Furthermore, the slope of the regression line for the ARXAR model was closer to one than the slope for all other approaches.

**DISCUSSION**

Regression analysis demonstrates that all noninvasive gain indexes were significantly correlated with a PHE. The correlations found by this study were smaller than those previously reported in healthy subjects (26), thus reflecting the characteristics of the considered sample of post-MI patients showing a huge range of a PHE values ($1.7 \pm 22.2 \text{ ms/mmHg}$). This result is not surprising because baroreceptor response caused by phenylephrine injection can be affected in a different way in post-MI patients than in healthy subjects. The degree of correlation found in our study was

![Fig. 7. Box and whisker diagram of the central tendency and variability of the different methods used for BRS assessment. The index obtained by the sequence analysis ($\alpha_{SEQ}$) as well as AR and 2AR gain indexes ($\alpha_{AR}$ and $\alpha_{2AR}$, respectively) overestimated values assessed by $\alpha_{PHE}$, whereas the ARXAR index $\alpha_{ARXAR}$ gave comparable values. Indexes provided by parametric models are the average of the gain in the two major bands (LF and HF). *$P < 0.02$ and **$P < 0.01$ vs. $\alpha_{PHE}$.

![Fig. 8. Correlation between estimates of baroreflex gain by the ARXAR model ($\alpha_{ARXAR} = [\alpha_{ARXAR}(\text{LF}) + \alpha_{ARXAR}(\text{HF})]/2$) and the phenylephrine method ($\alpha_{PHE}$) in postmyocardial infarction patients ($n = 27$). Equation for solid line is $\alpha_{ARXAR} = 0.86 \times \alpha_{PHE} + 0.86 (r = 0.76, P < 0.001)$.](http://ajpheart.physiology.org/)

Data of sensitivity and specificity carried out for the four noninvasive tests are also shown in Table 3. Better agreement was found between $\alpha_{PHE}$ and $\alpha_{2AR}$ or $\alpha_{ARXAR}$ then between $\alpha_{PHE}$ and $\alpha_{AR}$. The sequence analysis demonstrated a higher specificity but a lower sensibility than the ARXAR model.

**Table 3. Summary of linear regression analysis versus $\alpha_{PHE}$ and of specificity and sensitivity analysis for each noninvasive gain index**

<table>
<thead>
<tr>
<th>Index</th>
<th>$r$</th>
<th>$P$</th>
<th>Intercept of Regression Line</th>
<th>Slope of Regression Line</th>
<th>Specificity, %</th>
<th>Sensitivity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_{SEQ}$</td>
<td>0.80</td>
<td>$&lt;0.001$</td>
<td>1.89</td>
<td>2.19</td>
<td>81.2</td>
<td>83.3</td>
</tr>
<tr>
<td>$\alpha_{AR}(\text{LF})$</td>
<td>0.49</td>
<td>0.036</td>
<td>5.40</td>
<td>1.29</td>
<td>53.8</td>
<td>75.0</td>
</tr>
<tr>
<td>$\alpha_{AR}(\text{HF})$</td>
<td>0.66</td>
<td>$&lt;0.001$</td>
<td>3.72</td>
<td>1.48</td>
<td>82.4</td>
<td>69.2</td>
</tr>
<tr>
<td>$\alpha_{AR}$</td>
<td>0.70</td>
<td>0.001</td>
<td>4.71</td>
<td>1.31</td>
<td>76.9</td>
<td>75.0</td>
</tr>
<tr>
<td>$\alpha_{2AR}(\text{LF})$</td>
<td>0.65</td>
<td>$&lt;0.001$</td>
<td>0.55</td>
<td>1.48</td>
<td>64.7</td>
<td>92.3</td>
</tr>
<tr>
<td>$\alpha_{2AR}(\text{HF})$</td>
<td>0.57</td>
<td>0.002</td>
<td>2.93</td>
<td>1.25</td>
<td>70.6</td>
<td>84.6</td>
</tr>
<tr>
<td>$\alpha_{2AR}$</td>
<td>0.71</td>
<td>$&lt;0.001$</td>
<td>1.74</td>
<td>1.36</td>
<td>76.5</td>
<td>92.3</td>
</tr>
<tr>
<td>$\alpha_{ARXAR}(\text{LF})$</td>
<td>0.63</td>
<td>$&lt;0.001$</td>
<td>0.31</td>
<td>0.78</td>
<td>68.8</td>
<td>92.9</td>
</tr>
<tr>
<td>$\alpha_{ARXAR}(\text{HF})$</td>
<td>0.68</td>
<td>$&lt;0.001$</td>
<td>1.41</td>
<td>0.94</td>
<td>75.0</td>
<td>78.6</td>
</tr>
<tr>
<td>$\alpha_{ARXAR}$</td>
<td>0.76</td>
<td>$&lt;0.001$</td>
<td>0.86</td>
<td>0.86</td>
<td>75.0</td>
<td>92.9</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 27$ patients, $n = 24$ patients for sequence analysis. $r$, Correlation coefficient.
indeed comparable to the one reported in other works analyzing patients with hypertension (29) or coronary artery disease (1, 24). Furthermore, the correlation turned out to be higher by cutting the distribution of $\alpha_{\text{HE}}$ to the 90th percentile. Indeed, it is unlikely that the linear relation between invasive and noninvasive methods is held throughout the whole range of BRS values. To explain the low degree of correlation found between the pharmacological test and noninvasive methods, the methodological differences in BRS measurement also have to be considered. Indeed, the phenylephrine test and noninvasive methods for BRS estimation explore different physiological conditions. Because of phenylephrine infusion, the reflex changes in peripheral vasoconstriction and the heart rate-SAP mechanism are basically overridden, thus approximating an open-loop condition. On the other hand, measurements based on the analysis of spontaneous fluctuations of SAP and heart rate consider all reflexes and control mechanisms fully active; consequently, they are carried out in closed-loop condition. Thus, according to other authors (1, 23, 24), invasive and noninvasive approaches seem to provide reliable but not identical information.

Spectral approaches. The computation of the baroreflex gain based on separate spectral analysis of R-R and SAP variabilities (21) assumes that all R-R changes are caused by SAP variations. This approach does not explicitly consider the closed-loop interactions between R-R and SAP. In the bivariate analysis, the causal dependencies between R-R and SAP are not taken into account even if the strength of the link is assured by the coherence function (17, 26). This means that the effect of SAP on the R-R interval cannot be disentangled from the effect of the R-R interval on SAP. On the contrary, in the present study, the causality relationships are accounted for by utilizing an ARXAR model designed to separate the contribution of a driving signal to the variance of a driven process from the effects of independent unpredictable inputs (25). Thus the proposed open-loop model makes it possible to estimate the R-R-SAP transfer function on a specific path. In this way, only the amount of R-R variability that can be ascribed to SAP variations is exploited for gain computation. For these reasons, the spectral estimation of BRS seemed to be improved by introducing causality. Indeed, better agreement with the phenylephrine method was shown by the ARXAR model with respect to the AR and 2AR models. Moreover, because in our post-MI population the SAP-unrelated R-R power is about three times greater than the SAP-related one, the spectral decomposition of R-R interval variability is mandatory to reliably evaluate the baroreflex gain based on the analysis of SAP and R-R spontaneous fluctuations. Otherwise, the baroreflex gain is overestimated as a result of considering the overall R-R variability as completely driven by SAP changes.

Although disagreement exists concerning the nature of the LF and HF rhythms of R-R variability (6, 27), in humans, a contribution of the baroreflex mechanism to the genesis of both of these oscillations cannot be excluded. Therefore, to provide a global measure of the baroreflex-mediated adjustments of the heart rate, the average of LF and HF gain indexes was introduced. Independently of the kind of model, a closer correlation and an improved agreement with $\alpha_{\text{HE}}$ were found using this average index. However, averaging LF and HF gain indexes has to be done very cautiously, because one needs to consider the possibly different autonomic contribution of LF and HF coupling between R-R and SAP. Indeed, experimental evidence (17) has recently suggested the baroreflex nature of HF gain, whereas in the HF frequency band the coupling between R-R and SAP does not seem to exclusively depend on the baroreflex mechanism. Our results confirm these findings because a greater power content in the SAP-related R-R spectrum was observed in the LF (124 ms$^2$) than HF (40 ms$^2$) band. Again, introduction of causality seems to make more reliable the spectral estimates of BRS in the HF band.

Time domain approaches. The sequence analysis (7) has been previously applied in a variety (22, 24) of clinical conditions with promising results. Also in our study, the estimates of BRS accomplished with this technique gave good results in terms of correlation with the phenylephrine test. This good correlation can be explained by considering that sequence analysis, calculating the slope of regression line between changes of R-R and SAP values, attempted to spontaneously reproduce the procedure of the drug test.

Nevertheless, some limitations are implicitly present in this approach. First, in case of low amplitude and/or fast changes of R-R and SAP values, as could happen in elderly and post-MI subjects, the sequence technique could fail due to the low number of sequences (<3% in our study) useful for the analysis. Second, the comparison of gain values and slopes of the regression line documented an overestimate of the BRS values. This result can be considered as due to independent inputs (as respiration or enhanced sympathetic tone) acting on the cardiac rhythm, but not on the systolic pressure, and erroneously ascribed by the sequence technique to the baroreflexes. Indeed, even though the baroreflex nature of this technique has been demonstrated on an experimental animal preparation (7), it does not provide information on causality.

Closed-loop parametric models should be introduced to overcome these limitations. In these models, the whole dynamics of the investigated series is exploited, and the causal feedback effects of SAP on R-R are separated from the feedforward influences of R-R on SAP (3, 4). In a recent study (23), these approaches were followed to accomplish a time domain estimation of the baroreflex gain. In the study, causality was accounted for by measuring the open-loop baroreflex gain under closed-loop global conditions. Differently, the ARXAR model utilized in this work is simpler and specifically addressed to describe the baroreflex pathway; thus the causal dependence of R-R from SAP is imposed by its open-loop structure. In the proposed model, the influences of respiration impinging directly on R-R interval are not directly taken into account and...
are treated as an unmeasurable input uncorrelated with SAP (described by \( u_r \) in Fig. 3). On the contrary, the effects of respiration on R-R interval mediated by SAP are accounted for both in LF and HF bands by the R-R-SAP block (\( A_{12} \) block). The lack of evaluation of respiration independently of SAP is a limitation for the model, but these influences are not accounted for by any traditional noninvasive method based on spectral, cross-spectral, and sequence analyses. In Ref. 23, the respiratory influences were explicitly modeled and utilized to explore the baroreflex modulation during controlled random interval breathing, thus making possible the investigation of the broadband dynamic effect of SAP on R-R. However, in our study, patients were allowed to spontaneously breathe. This choice was considered useful to disclose the performance of the ARXAR model for evaluating BRS in post-MI patients and also for future applications in a clinical setting.

Clinical implications. With traditional noncausal approaches, noninvasive evaluation of BRS is difficult due to the presence of the feedforward effects of R-R interval on arterial pressure and more specifically of other inputs directly affecting the sinus node. Thus the introduction of dynamic causal models should be suggested to avoid spurious effects in the calculation of baroreflex gain. This becomes mandatory in post-MI patients, characterized by low amplitude of R-R and SAP variability and enhanced sympathetic tone.

At present, the phenylephrine test still remains the only accepted technique for risk stratification by BRS assessment in postinfarction (13). Specificity and sensitivity values obtained by comparing invasive and noninvasive tests for BRS evaluation were generally high. Particularly, a high correspondence with the clinical classification was found when the gain index was computed after assessing the strength of the link between R-R and SAP variabilities, as was done by checking the correlation coefficient in the sequence analysis, the coherence function in the 2AR model, and the tests of the modeling hypotheses in the ARXAR model. The agreement found between the phenylephrine test and noninvasive tests supports the feasibility of the noninvasive measures of baroreflex gain. However, because of the different aspects of the baroreflex regulation investigated by invasive and noninvasive approaches, the clinical information provided by the phenylephrine test cannot be fully extrapolated by the “spontaneous” methods. Therefore, further studies are needed to facilitate the introduction of approaches describing the causal interactions between R-R and SAP for baroreflex gain quantification into clinical practice, for instance, addressing the correlation analysis of the results directly to the prognosis instead of to the invasive method. Finally, the results provided by the proposed causal model should be validated in conditions of normal and impaired baroreflex modulation (e.g., in an experimental animal preparation before and after sinoaortic denervation).

In conclusion, this study provides evidence that the ARXAR model, specifically designed to describe the causal influences of SAP on R-R interval, is able to quantify baroreflex gain in humans without altering blood pressure through pharmacological interference. Thanks to the model structure and to the estimation in the frequency domain, reliable measures of baroreflex gain in both the LF and HF bands can be obtained by the ARXAR method. Moreover, the model allows us to quantify the amount of R-R variability imputable to arterial pressure changes.

Our results confirm the correlation between the baroreflex gain estimated by noninvasive measurements and by the phenylephrine method, but this agreement was dependent on the structure of the model and the methodology used. The findings of this study suggest that the introduction of dynamic causal models could provide additional information on the estimation of baroreflex gain by noninvasive approaches. In any case, further investigation will be necessary to delineate the stratification of patients at increased risk of mortality associated with cardiovascular disease.

APPENDIX

Computation of baroreflex gain by linear parametric models. The autoregressive (AR) description of the zero-mean series of the R-R interval and systolic arterial pressure (SAP) (rr and sap series, respectively) is given by the equations

\[
rr(n) = - \sum_{k=1}^{P} a_r(k) rr(n-k) + w_r(n) \quad (A1)
\]

\[
sap(n) = - \sum_{k=1}^{Q} a_s(k) sap(n-k) + w_sap(n) \quad (A2)
\]

where the coefficients \( a_r(k) \) and \( a_s(k) \) represent the regression of rr and sap (respectively) on \( P \) and \( Q \) samples of their own past (respectively), \( k \) is the delay of the rr or sap sample series, \( n \) is the current value of the rr or sap sample series, and \( w_r \) and \( w_sap \) are set to be zero-mean white noise inputs with variance \( \sigma^2_{w_r} \) and \( \sigma^2_{w_sap} \). The power spectral density (PSD) of R-R interval and systolic arterial pressure variabilities are computed as follows

\[
P_{rr}(f) = P_{rr}(z) \Big|_{z=e^{j2\pi fT}} = \frac{\sigma^2_{w_r}}{|1 + \sum_{k=1}^{P} a_r(k)e^{-2\pi k f T}|^2} \quad (A3)
\]

\[
P_{sap}(f) = P_{sap}(z) \Big|_{z=e^{j2\pi fT}} = \frac{\sigma^2_{w_sap}}{|1 + \sum_{k=1}^{Q} a_s(k)e^{-2\pi k f T}|^2} \quad (A4)
\]

where \( z \) is the complex frequency, \( f \) is frequency, and \( T \) is the sampling period. The AR spectral decomposition method (11) can be used to calculate the power contribution of the poles of the Z-transform of the rr and sap series \( [P_{rr}(z) \text{ and } P_{sap}(z)] \) and, consequently, the percentage of rr and sap variance inside a specific frequency band.

In the bivariate AR model, the interactions between rr and sap series are considered by accounting for the dependence of a series on the samples of the other by \( a_{12} \) and \( a_{21} \) coefficients.
It is worth pointing out that a SAP transfer function directly from the coefficients of R-R variability that cannot be explained by SAP changes.

The AR model. It is worth pointing out that a SAP transfer function directly from the coefficients of R-R variability that cannot be explained by SAP changes.

The colored noise (\( u_r(n) \)) sequence, being described by the coefficients of \( D_1 \) block in Fig. 3, represents the fraction of R-R variability that cannot be explained by SAP changes. The ARXAR model is used to estimate the gain of the R-R-SAP transfer function directly from the coefficients of \( a_{11}(k) \) and \( a_{12}(k) \)

\[
\alpha_{\text{ARXAR}}(f) = \left| \frac{A_{12}(f)}{1 - A_{11}(f)} \right| = \left| \frac{\sum_{k=0}^{P} a_{12}(k)e^{-j2\pi ft}}{1 + \sum_{k=0}^{P} a_{11}(k)e^{-j2\pi ft}} \right| \quad (A11)
\]

REFERENCES


