Prognostic Value of Non Invasive Baroreflex Sensitivity in Chronic Heart Failure Patients

R Maestri [1], GD Pinna [1], E Robbi [2], M Gnemmi [2], MT La Rovere [2]

[1] Biomedical Engineering Unit, [2] Division of Cardiology,
S. Maugeri Foundation, IRCCS, Scientific Institute of Montescano, Italy

Abstract

Non invasive baroreflex sensitivity (BRS) by the classical transfer function (TF) method very often cannot be assessed in chronic heart failure (CHF) patients, due to a lack of coherence between heart period and systolic pressure. On the grounds of a previous investigation, we devised a new BRS index based on the average of the TF in the whole low frequency band (WBA-BRS), which does not require coherence check. In this study we assessed the clinical relevance of this index by testing its prognostic value in a population of 149 CHF patients.

During a 20 ± 12 months follow-up, 28 patients died or were urgently transplanted. Univariate relation of WBA-BRS with mortality was assessed by the Cox proportional hazards model and survival functions were estimated using the Kaplan-Meier method. We also investigated the independent effect of WBA-BRS, adjusting for NYHA class, LVEF, peak VO2, Na^+. WBA-BRS showed a significant univariate association with the risk of cardiac events. When its predictive value was assessed in multivariate analysis, WBA-BRS displayed independent prognostic information (risk ratio 3.0, 95%CI: 1.1-7.9, p=0.03). These preliminary data suggest that BRS assessed by a modified version of the classical TF method is a potential prognostic marker in CHF patients.

1. Introduction

The estimation of baroreflex sensitivity (BRS) according to the classical transfer function method, originally developed by Robbe *et al.* [1], has gained widespread diffusion due to its simplicity and to the substantial correlation shown with measurements obtained with the phenylephrine technique [1, 2]. According to this method, BRS is computed as the average value of the transfer function modulus (Gain), including only those points having a magnitude-squared coherence between systolic arterial pressure (SAP) and heart period (HP) ≥ 0.5 [1]. The threshold value of 0.5 for the coherence was arbitrarily chosen in order to guarantee reliable Gain estimates. Nevertheless, simple analytical considerations show that low or very low coherence values are an unavoidable consequence of low Gain and/or low arterial pressure variability. As a matter of fact, in patients with cardiovascular disease, characterised by an impaired baroreflex and/or a depressed pressure variability, it happens frequently that this criterion cannot be satisfied, leading to a large number of missing results just in those population of subjects at higher risk for cardiac death [3, 4, 5].

On the basis of a previous study in which we demonstrated that, choosing the analysis parameters appropriately, the behaviour of the "true" Gain can be well approximated by the estimated function even in conditions of low coherence [5], we devised a new BRS index based on the transfer function, not subjected to coherence restraints.

The aim of this study was to assess the clinical relevance of this index by testing its prognostic value in a population of chronic heart failure (CHF) patients.

2. Methods

We considered patients with dilated cardiomyopathy and in sinus rhythm consecutively referred to our Heart Failure Unit for evaluation and therapy of CHF, usually in conjunction with evaluation for heart transplantation. Inclusion criteria were absence of pulmonary or neurological disease, absence of acute myocardial infarction or cardiac surgery within the previous 6 months, absence of any other disease limiting survival, stable therapy for at least 2 weeks. All patients underwent several clinical and functional evaluations, including 2-D echocardiography, exercise testing, and blood tests.

Within one week from these evaluations, all patients underwent a 8 min resting recording of heart period (HP) and systolic arterial pressure (SAP, by Finapres) in our laboratory for the assessment of the autonomic nervous system. BRS assessment according to the phenylephrine test was also performed (Phe-BRS). Only patients with a

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good quality of heart period and systolic arterial pressure signals and with an ectopy rate < 5% were considered. The final study population consisted of 149 CHF patients. They all gave informed consent to participate in the study, which had been approved by the local Ethical Committee.

During follow-up, patients were periodically re-evaluated and readmitted to hospital if they became clinically unstable. For those patients who died, the date and modality of death were recorded. Time-event information for each subject were saved in a dedicated database together with the demographic, clinical, functional and BRS parameters recorded at baseline. For the estimation of noninvasive BRS, the signals were visually inspected and the widest sub-record with all signals free from artifacts, large transients or marked changes in the fluctuating behavior of the signals was interactively selected. After quadratic detrending, bivariate spectral analysis between SAP and HP time series was performed using the weighted covariance method with a 0.03 Hz bandwidth Parzen window [6, 7]. BRS was estimated averaging the transfer function modulus in the low frequency band (LF, from 0.04 to 0.15 Hz) according to the classical criterion (i.e. taking only those points having a corresponding coherence $\geq$ 0.5) and taking all points without any restriction (whole band average, WBA-BRS). An example of WBA-BRS computation is given in Figure 1.

End-point of survival analysis was total cardiac death or urgent transplantation. Patients who underwent an elective heart transplantation, as well as those who died of non cardiac causes, were considered censored observations.

The association of WBA-BRS with mortality was assessed by univariate Cox proportional hazards model. Kaplan-Meier survival curves were used to describe the survival of patients stratified according to the median value of WBA-BRS. The same analysis was also performed on Phe-BRS. Multivariate Cox proportional hazards model was used to assess the independent association of WBA-BRS with survival, after adjustment for other known predictors of mortality in CHF patients, namely NYHA class, Na^+, peak VO_2 consumption and LVEF. Results are presented as relative risk (RR) and corresponding 95% confidence intervals.

3. Results

The clinical characteristics of the population are reported in Table 1. During a follow-up period of 20±12 months, twenty-eight patients died or were urgently transplanted.

BRS measured using the classical coherence-based TF method could be determined only in 62 (42%) patients.

The 36 months survival curves according to WBA-BRS are displayed in Figure 2. Mortality was significantly higher in patients with WBA-BRS $\leq$ 3.2 ms/mmHg (median value). Univariate results of Cox analysis for WBA-BRS and Phe-BRS are summarized in Table 2.

The results of the multivariate Cox proportional hazards model are given in Table 3.

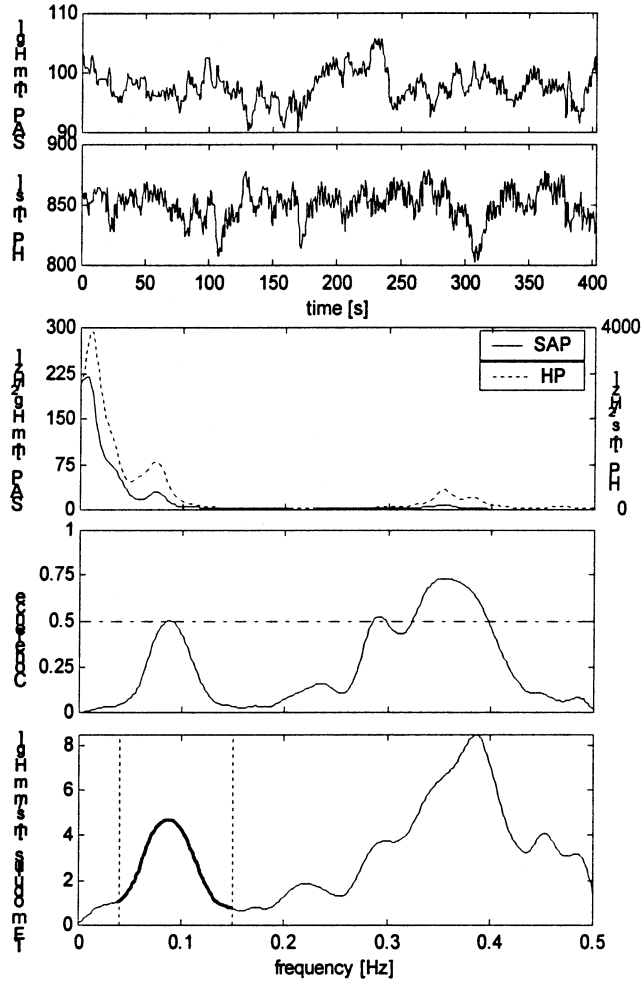

Figure 1. Representative example of the calculation of WBA-BRS index. From top to bottom: SAP time series, HP time series, power spectral density of the SAP and HP signals, the Coherence function and 0.5 threshold, transfer function modulus (Gain). Vertical dashed lines show the limits of LF band (0.04 – 0.15 Hz), over which the Gain is averaged to compute WBA-BRS.
Note that in this example, BRS according to the classical TF method cannot be computed, since in the LF band the coherence is always < 0.5.

Table 1. Clinical characteristics of the studied population (N=149).

Age [years]	52±10
NYHA	2.3±0.7
VO_2 [ml/kg/min]	14.8±4.1
Na^+ [mEq/l]	140±3
LVEF [%]	26±7
PCP [mmHg]	19±10
CI [l/min/m^2]	2.2±0.5
Phe-BRS [ms/mmHg]	3.7±4.5
Mean RR [ms]	820±151

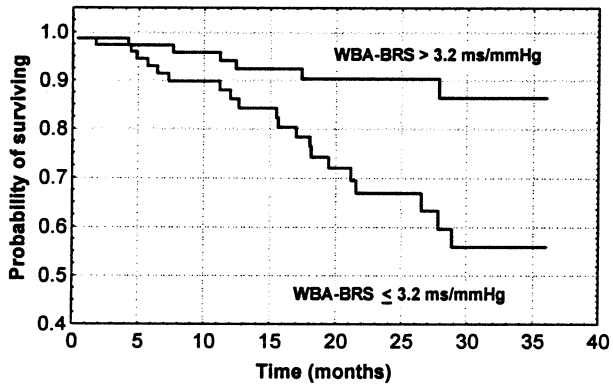

Figure 2. Kaplan-Meier survival curves for WBA-BRS in relation to the end-point of total cardiac death and urgent transplantation. Patients with an Average Gain ≤ 3.2 ms/mmHg were at increased risk of mortality.

Table 2. Univariate association of risk variables with total cardiac mortality, including urgent transplantation.

Variable (cutoff value)	RR (95% CI)	P
WBA-BRS (≤ 3.2 ms/mmHg)	3.5 (1.47 - 8.13)	0.004
Phe-BRS (≤ 2.6 ms/mmHg)	1.7 (0.78 – 3.56)	0.186

Table 3. Relative risks assessed by multivariate Cox regression.

Variable (cutoff value)	RR (95% CI)	P
WBA-BRS (≤ 3.2 ms/mmHg)	3.0 (1.11 – 7.93)	0.03
NYHA (≥ 3)	1.3 (0.54 – 3.27)	0.54
VO_2 (≤ 11.7 ml/kg/min)	0.9 (0.36 – 2.48)	0.91
Na^+ (≤ 137 mEq/l)	0.7 (0.27 – 2.14)	0.59
LVEF (≤ 24 %)	1.9 (0.83 – 4.55)	0.13

4. Discussion

This study highlights a potential important role played by noninvasive baroreflex sensitivity in the prognostic stratification of moderate-to-severe CHF patient. Our results from a sample of 149 CHF patients indicate that the new BRS index WBA-BRS, computed as simple average of the Gain function in the low frequency band, is a significant prognostic marker, of total cardiac death independent of several known prognostic factors in CHF patients.

The better performance of noninvasive spectral BRS than BRS measured by the phenylephrine method was not surprising. In fact, from a physiological point of view, the phenylephrine baroreflex gain, which is the result of the complex interplay of multiple receptors and the hemodynamic burden produced by the afterload increase, yields information on the whole capability of the system to evoke an increase in vagal activity, whereas the spectral baroreflex gain yields information on the tonic level of autonomic modulation [8]. Particularly in patients with CHF, the afterload increase induced by the phenylephrine might be the cause of some uncompensated hemodynamic burden (e.g. in presence of mitral regurgitation), biasing the assessment of BRS [3].

Further studies are needed to confirm our preliminary data, challenging the predictive value of this index in a larger population against the whole set of clinical variables commonly used in the risk assessment of these patients.

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Address for correspondence:

Ing. Roberto Maestri,
Fondazione S. Maugeri, Centro Medico di Montescano,
I-27040, Montescano (PV), ITALY
rmaestri@fsm.it