MEASURABILITY AND CLINICAL CORRELATES OF THE TRANSFER FUNCTION METHOD IN THE ASSESSMENT OF BAROREFLEX SENSITIVITY IN HEART FAILURE PATIENTS: COMPARISON WITH THE PHARMACOLOGICAL APPROACH

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Abstract: The aim of this study was to assess the clinical applicability and relevance of the transfer function method in the measurement of baroreflex sensitivity (TF-BRS) in Chronic Heart Failure (CHF) patients, comparing the results with the classical phenylephrine method (PHE-BRS). In 317 stable CHF patients in sinus rhythm (age (median [interquartile range]): 54 years [48-59], NYHA class II-III: 88%, LVEF: 27% [22-33]) we measured TF-BRS during paced breathing and performed the phenylephrine test. Due to ectopic beats, TF-BRS could be computed in 72% of the patients and PHE-BRS in 93%. Correlation between the two methods was moderate (0.52, p<0.0001). Both BRS measurements were significantly associated with cardiac mortality (p=0.0003 and p<0.0001 respectively). Patients with a missing BRS had a higher event rate. Using this information, a new prognostic index computable in almost all patients was derived for each BRS method. Both indexes predicted the outcome even after adjustment for clinical and functional covariates (hazard ratio (95%CI): 2.6 (1.4–4.8), p=0.003 for TF-index, and 2.1 (1.2–3.7), p=0.01 for PHE-index). Although the measurability of TF-BRS in CHF patients is impaired by ectopic activity, its prognostic information can be extended to almost all patients, with a predictive power comparable to PHE-BRS.

Introduction

Abnormalities in arterial and cardiopulmonary reflexes play an important role in the development and progression of chronic heart failure (CHF) [1]. Therefore, the baroreceptor reflex function has been assessed in patients with heart failure in order to investigate the pathophysiology of their abnormal autonomic regulation and to obtain useful clinical information, particularly for prognostic evaluation [2]. Many efforts have been devoted to the development of non-invasive assessment methods that do not require the use of vasoactive drugs. We focused on the transfer function (TF) method for measuring the baroreceptor-heart rate reflex sensitivity (TF-BRS). This approach has sound mathematical foundations and allows a clear definition of the oscillatory components that contribute to BRS measurement. Major methodological issues related to the practical use of this technique have recently been investigated [3], and new application criteria developed [4].

This study was conceived to assess the applicability and clinical relevance of the TF-BRS method in the setting of moderate-to-severe CHF patients. Particularly, we wanted to determine i) the actual proportion of patients in whom this measurement can be performed (i.e., the measurability of TF-BRS), ii) the strength of the correlation with major clinical and functional indicators of heart failure, and iii) its prognostic value. All these facets of the TF-BRS method were compared with the classical phenylephrine approach based on the injection of this vasoactive drug. Special attention was paid to investigate the implications of failed measurements in relation to prognostic stratification, and to try to use profitably this information.

Materials and Methods

Study patients: We studied 317 patients with dilated cardiomyopathy and moderate-to-severe heart failure, who were referred to the Heart Failure Unit of the Institute of Montescano for evaluation and treatment of heart failure, including evaluation for heart transplantation. In order to be included in the study, all subjects had to be in sinus rhythm, stable clinical conditions (last 2 weeks) and optimized therapy.

All patients gave written informed consent and the study was approved by the local Ethics Committee.

Experimental protocol: The experimental protocol comprised: 1) instrumentation, patient's familiarization with paced breathing and signal stabilization (about 30 min), 2) 8 min supine resting recording of ECG, lung volume (inductance plethysmography, Respitrace Plus, Non-Invasive Monitoring Systems Inc.) and noninvasive arterial blood pressure at the finger (Finapres 2300, Ohmeda), 3) 8 min supine recording of

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the same signals during paced breathing at 0.25 Hz (15 breaths/min), 4) Phenylephrine test. To perform paced breathing, subjects were asked to follow a digitally recorded human voice inducing inspiratory and expiratory phases. The Phenylephrine test was carried out injecting an intravenous bolus of the drug (3 to 4 µg/kg) to rise systolic arterial pressure by 15-30 mmHg. If needed, the phenylephrine dose was increased by 50 µg in subsequent injections to reach the target blood pressure increase. The injection was repeated twice after a 10-minute interval.

Signal preprocessing: The ECG signal was manually edited to correct for wrong fiducial points in QRS complexes and classify ectopic beats. Beat-by-beat RR interval (resolution 1 ms) and systolic arterial pressure (SAP) time series were then automatically calculated.

Computation of TF-BRS: As the TF-BRS method requires the SAP and RR oscillations in the low frequency band (LF, 0.04 - 0.15 Hz) being of non-respiratory origin, keeping the breathing frequency out of this band is mandatory. Therefore, we computed TF-BRS on recordings carried out during paced breathing [5].

We plotted acquired signals on the PC screen and selected the widest sub-record free from ectopic beats, artifacts, large transients or marked changes in the fluctuation pattern [6, 7]. In case of isolated ectopic beats, they were linearly interpolated provided i) they were preceded or followed by at least 3 minutes of ectopy-free recording, and ii) inclusion or exclusion of the corrected beat in the analysis window did not change TF-BRS by more than 15%. Recordings shorter than 3 min were excluded from subsequent analysis as the reliability of TF estimates would become intolerably low [3].

We performed bivariate spectral analysis on selected sub-records of SAP and RR interval time series (Blackman-Tukey method - 0.03 Hz-bandwidth Parzen window), and computed the coherence and the transfer function modulus (gain) between them [3]. TF-BRS was finally computed by averaging the gain function across the LF band [8].

Computation of Phe-BRS: In order to assess BRS from the phenylephrine test, RR intervals were plotted against the preceding SAP value and the analysis window was interactively defined as the interval between the beginning and the end of the first significant (> 15 mmHg) increase in systolic arterial pressure following drug injection. The strength of the reflex was measured by the slope of the regression line fitting the points within this window, and was expressed in ms/mmHg. Ectopic beats were automatically discarded before regression analysis. If the number of remaining beats in the analysis window was too low (<10), the record was discarded. The analysis procedure was repeated for the three drug injections and baroreflex sensitivity was finally computed as mean value of the three regression slopes. We will refer this measurement in the text as phenylephrine BRS (PHE-BRS).

Clinical evaluation, laboratory testing and follow-up: Within 1 week of autonomic evaluation, we performed standard clinical and laboratory examinations, including assessment of symptoms severity, 2D echo-cardiography, cardiopulmonary exercise testing, 24-hour Holter recording (with arrhythmia and heart rate variability analysis), and routine blood test.

Statistical analysis: Comparisons between groups were performed by the ANOVA, Mann-Whitney U test or Chi-square test when appropriate. The linear association between continuous variables was assessed by regression and correlation analysis. The bias and limits of agreement between spectral and phenylephrine BRS measurements were assessed by computing the median and the 2.5^{th} and 97.5^{th} percentiles of their paired differences.

End point of survival analysis was total cardiac death, including appropriate and documented ICD discharge for fast ventricular tachycardia or ventricular fibrillation and urgent transplantation.

The association between BRS and the risk of death was assessed by the Cox proportional hazards regression model after dichotomization of BRS values according to the optimal cut-off point between the 20^{th} and 50^{th} percentiles.

As failure to have a measurable BRS was associated with an increased risk of event, this information was used as surrogate prognostic information in place of the missed measurement. Accordingly, two risk indexes (one for each BRS method) were obtained in all patients, regardless of having or not a measurable BRS.

Due to the marked skewness in the distribution of some variables (including BRS), descriptive statistics are given as median, lower and upper quartile, unless otherwise stated..

Results

Demographic and clinical characteristics of the patients are given in table 1.

Table 1: Demographic and clinical characteristics of studied patients

Age (years)	54 (48-59)
Sex (% male)	84
NYHA Class (%)	
-I	10
-II	51
-III	37
-IV	2
Cause of CHF (%):	
-Ischemic	48
-Idiopathic	40
-Other	12
LVEF (%)	27 (22-33)
VPCs (N/hour)	16 (3-71)
NSVT (%)	39

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Measurability of TF-BRS: Eighty-one (26%) out of the 317 recordings carried out for the computation of TF-BRS could not be analyzed due to a high number of ectopic events (113 (75-234) events/hour). Six recordings were excluded due to artifacts or large signal transients, while other 2 were excluded due to poor execution of paced breathing. Isolated ectopic beats were corrected in 45 recordings. Thus, the analysis of TF-BRS was carried out on 228 (72%) of available recordings.

Seven (2%) phenylephrine tests could not be carried out for technical reasons. Fourteen (4%) out of the 310 feasible tests could not be analyzed due to the presence of a high number of premature ventricular complexes within the analysis window. In other 12 patients the test was not executed or could not be analyzed due to, among others, low arterial pressure increase, high baseline arterial pressure, poor patient compliance, repeated cough during the test etc. Hence PHE-BRS could be measured on 284 (93%) of feasible tests.

Relationship between BRS measurements: The correlation coefficient between TF-BRS and PHE-BRS in the common dataset of 214 patients was 0.52 ($p<0.0001$). Descriptive statistics of the two measurements are given in table 2. The median difference between TF-BRS and PHE-BRS was 0.2 ms/mmHg. The limits of agreement were –9.3 ms/mmHg and 8.2 ms/mmHg.

Clinical correlates of TF-BRS: No significant change in TF-BRS was observed between patients with ischemic and idiopathic cardiomyopathy ($p=0.44$), while a significant increase in the latter group was observed for PHE-BRS. Both methods consistently showed a significant decrease of BRS in patients with more severe symptoms and mitral regurgitation, but no change was observed between patients with and without non-sustained ventricular tachycardia ($p> 0.4$). Correlation of TF-BRS with LVEF and SDNN was fair ($r=0.18$, $p=0.01$; $r=0.32$, $p<0.0001$ respectively) and was slightly lower than that of PHE-BRS ($r=0.34$, $p<0.0001$; $r=0.42$, $p<0.0001$).

Table 2: Descriptive statistics of BRS measurements

	TF-BRS (ms/mmHg)	PHE-BRS (ms/mmHg)
Median	3.4	3.0
25th - 75th Pctl	1.7 - 6.5	1 - 6.8
2.5th - 97.5th Pctl	0.5 - 15.7	-1.1 - 18

Prognostic value of TF-BRS in the common dataset: During a median follow-up of 28 months (min – max: 0.2 – 36 months), 73 (23%) out of the overall cohort of 317 patients experienced a cardiac event, including 6 urgent transplantations and 8 appropriate ICD discharges.

In the common dataset of 214 patients (median follow-up: 30 months (min-max: 1.2–36 months), event rate: 19%), both TF-BRS and PHE-BRS were significantly lower in the patients with a poor outcome (3.9 (1.9 – 6.6) ms/mmHg vs 2.2 (1.0 – 5.7) ms/mmHg, $p=0.02$; 4.0 (1.4 - 7.5) ms/mmHg vs 1.5 (0.1 - 2.7) ms/mmHg, $p<0.0001$, respectively).

Using Cox analysis we found that optimal dichotomization values were 3.1 ms/mmHg and 2.9 ms/mmHg for respectively the spectral and the pharmacological technique. Hazard ratios (95% CI) were respectively 3.3 (1.7 – 6.2) ($p=0.0003$) and 5.5 (2.6 – 11.6) ($p<0.0001$). Sensitivity, specificity, negative and positive predictive values were respectively 66%, 61%, 28% and 88% for TF-BRS and 78%, 60%, 31% and 92% for PHE-BRS. Corresponding survival curves are shown in fig 1.

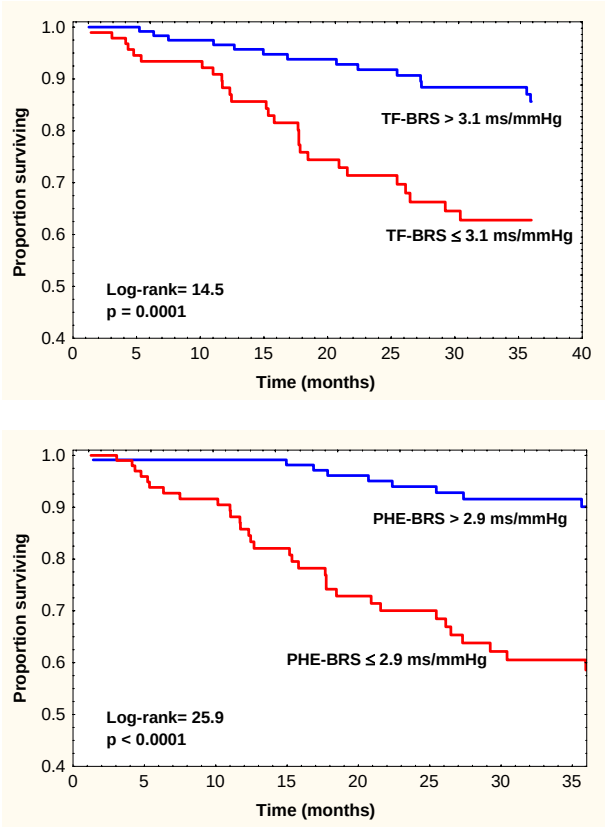

Figure 1: Kaplan-Meier survival curves for dichotomized TF-BRS and PHE-BRS

Relationship between missing measurements and survival: In the 81 patients in whom TF-BRS could not be analyzed due to a high number of ectopic beats, the event rate was much higher than in the remaining subjects (36% vs 19%, $p=0.002$). The same was found in the 14 subjects with missing PHE-BRS (event rate: 43% vs 23%, $p=0.035$). In the patients in whom either BRS measurement could not be performed for other causes, mortality was lower or comparable to patients with a measured BRS. Accordingly, two new prognostic indexes, one for each BRS method, were derived. Briefly, a patient was considered at high risk according to TF-BRS if the latter was depressed (i.e. ≤ cut-off point) or if failure to measure was due to high ectopic activity; on the contrary, he/she was considered at low risk if BRS was more preserved (i.e. > cut-off point). The same criterion was applied to PHE-BRS. This

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allowed to extend the prognostic classification to 309 and 298 patients using the TF- and PHE-index respectively, with a common dataset of 292 subjects. Survival analysis was then carried out on this dataset.

Predictive value of BRS risk indexes: The hazard ratios (95% CI) of the 2 risk indexes were respectively 3.5 (2.0 – 6.4) ($p<0.0001$) and 3.3 (2.0 – 5.6) ($p<0.0001$). Among the clinical and functional parameters, NYHA class, systolic arterial pressure, LVEF, mitral regurgitation, LVESD, LVEDD, deceleration time, sodium, potassium, bilirubine, creatinine, BUN and PVC/h were significantly associated with the outcome and were used as adjusting factors in multivariate analysis. Both BRS indexes remained independent predictors after adjustment. Significant covariates in the two final models were potassium, bilirubine and PVCs/hour, with $p< 0.01$ in all of them. Adjusted hazard ratios were 2.6 (CI: 1.4 – 4.8, $p=0.003$) for the TF-index, and 2.1 (CI: 1.2 – 3.7, $p=0.01$) for the PHE-index.

Discussion

This study shows that i) the measurability of TF-BRS is much lower than that of PHE-BRS, being mostly affected by the high prevalence of severe ectopic activity, ii) although the agreement with PHE-BRS is poor, clinical correlates are similar, iii) a depressed TF-BRS is associated with a worse prognosis and iv) combining the information on measured BRS with the information on the reasons for failed measurement, a new risk index can be obtained, with a prognostic power equal to that achievable through the phenylephrine test.

The agreement between the pharmacological and spectral method was poor, confirming previous findings using different spectral algorithms and/or different populations of subjects.

TF-BRS was significantly lower in patients with more severe symptoms. A poor, albeit statistically significant, correlation was found with both LVEF and SDNN. Overall, clinical correlates of TF-BRS showed a trend similar to PHE-BRS, yet the strength of the association, if any, was lower, indicating that PHE-BRS better reflects the clinical and functional status of the patients.

Both a reduced TF-BRS and a reduced PHE-BRS were significantly associated with a poorer outcome. These results clearly indicate that an impaired baroreflex plays an important role in the progression of the disease and event occurrence.

An interesting finding of this study was the strong association between failure in TF-BRS measurement due to high ectopic activity and the outcome. A new risk index was derived grouping together the patients with missing TF-BRS due to ectopic beats with those with depressed TF-BRS. In this way, risk classification could be extended to 97% of the sample. This strategy proved to be successful, as not only the risk index was strongly related to the outcome, but the prediction power was substantially maintained adjusting for all significant clinical and functional predictors.

The predictive stratification power and accuracy of the TF-index were substantially superimposable to those similarly obtained using phenylephrine measurements and rejection information, making the former a potential competitor of the latter.

References

[1] GRASSI G, SERAVALLE G, CATTANEO BM, ET AL. (1995): Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. *Circulation*, **92** (11), pp. 3206-11

[2] MORTARA A, LA ROVERE MT, PINNA GD, ET AL. (1997): Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. *Circulation*, **96** (10), pp. 3450-8

[3] PINNA GD, MAESTRI R. (2001): Reliability of transfer function estimates in cardiovascular variability analysis. *Med Biol Eng Comput*, **39** (3), pp. 338-47

[4] PINNA GD, MAESTRI R. (2002): New criteria for estimating baroreflex sensitivity using the transfer function method. *Med Biol Eng Comput*, **40**, pp. 79-8

[5] PINNA GD, R MAESTRI, E ROBBI, M GNEMMI, MT LA ROVERE. (2001): Effect of controlled breathing on short-term cardiovascular variability: an investigation in chronic heart failure patients. *IEEE Computers in Cardiology*, **28**, pp. 217-9.

[6] PINNA GD, MAESTRI R, DI CESARE A.(1996): Application of time series spectral analysis theory: analysis of cardiovascular variability signals. *Med Biol Eng Comput.*, **34** (2), pp. 142-8.

[7] MAESTRI R, PINNA GD. (1998): Polyan: a computer program for polyparametric analysis of cardio-respiratory variability signals. *Comput Methods Programs Biomed.*, **56** (1), pp. 37-48.

[8] PINNA GD, MAESTRI R, RACZAK G, LA ROVERE MT. (2002): Measuring baroreflex sensitivity from the gain function between arterial pressure and heart period. *Clin Sci (Lond,.* **103** (1), pp. 81-88.

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