Neth Heart J (2013) 21:61–63
DOI 10.1007/s12471-012-0349-8

SPECIAL ARTICLE

Clinical value of baroreflex sensitivity

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Published online: 27 November 2012

Abstract The arterial baroreflex is an important determinant of the neural regulation of the cardiovascular system. It has been recognised that baroreflex-mediated sympathoexcitation contributes to the development and progression of many cardiovascular disorders. Accordingly, the quantitative estimation of the arterial baroreceptor-heart rate reflex (baroreflex sensitivity, BRS), has been regarded as a synthetic index of neural regulation at the sinus atrial node. The evaluation of BRS has been shown to provide clinical and prognostic information in a variety of cardiovascular diseases, including myocardial infarction and heart failure that are reviewed in the present article.

Keywords Arterial baroreceptors · Baroreflex sensitivity · Autonomic nervous system · Prognosis · Myocardial infarction · Heart failure

Introduction

While it was known by the early 1970s that hypertensive and cardiac patients had subnormal vagal baroreflex sensitivity (BRS) [1, 2], the driving force for the clinical evaluation of BRS came from a series of experimental studies yielding important insights into the pathophysiological implications of baroreflex impairment related to heart disease. These studies showed a) that cardiac electrical stability can be affected by changes in autonomic flow [3, 4] and b) that baroreceptor reflexes can be modulated by cardiac afferent sympathetic activity activated by mechanical and chemical stimuli [5].

A major insight into the prognostic implication of BRS came from studies in an experimental preparation of sudden cardiac death [6]. In this model conscious dogs with a healed anterior myocardial infarction were submitted to a transient myocardial ischaemia produced during physiologically elevated sympathetic activity. It was found that the occurrence of ventricular fibrillation was much more frequent in the animals with depressed BRS and that the risk of developing ventricular fibrillation was inversely related to BRS. Importantly, the information provided by a depressed BRS was independent of left ventricular impairment [6]. Finally, it was also established that adequate baroreceptor activity was important for the response to the haemodynamic challenge of ventricular tachycardia [7].

Clinical value

A wealth of clinical studies validated the above experimental observations in patients with ischaemic heart disease. In the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study [8], which followed almost 1300 patients with recent (<1 month) myocardial infarction, abnormal BRS was highly predictive of both sudden and non-sudden death, primarily in patients with ejection fraction ≤35 % [8, 9]. In a series of patients admitted to the emergency room for sustained ventricular tachycardia, abnormal BRS was strongly related to the occurrence of haemodynamic collapse - independently of

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left ventricular ejection fraction or the cycle of the arrhythmia [10]. Recent data support the usefulness of the integrity of baroreceptor activity even in post-infarction patients with preserved left ventricular function [11].

The prognostic implication of BRS has also been addressed in patients with chronic heart failure. In a series of 282 patients, BRS was found to be an independent predictor of cardiac death or urgent transplantation after adjustment for known noninvasive risk factors such as New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), baseline RR interval and peak VO2 [12]. However, these data were mainly obtained at a time when the clinical use of β-blockade in heart failure was very uncommon and did not address the issue that the autonomic modification brought about by β-blockers might affect the predictive value of BRS. But recent data have also confirmed the predictive ability of a depressed BRS independently of known risk factors and β-blocker treatment [13].

While many of these data were obtained by the original method of testing BRS by correlating the RR interval response with the rise in blood pressure seen after vasoactive drug injection, more recently developed non-invasive techniques using spontaneous blood pressure fluctuations have now been shown to perform well in the clinical setting. The prognostic value of BRS obtained by the modified transfer function method has been assessed in a cohort of 317 mild-to-moderate clinically stable heart failure patients [14]. In the 228 subjects with a measurable index, a depressed BRS was significantly associated with a higher risk of cardiac death. But patients with a missing measurement due to severe ectopic activity also had a high event rate (36 %). Combining this information with the prognostic information of a measurable baroreflex, a new risk index could be obtained in almost all patients, which carried predictive information independent of most other common clinical and functional indicators. However, a direct comparison of the performance of the transfer function method with the vasoactive drug technique suggests that the transfer function method cannot replace the classical phenylephrine method either in physiopathological investigations or clinical applications dealing specifically with baroreceptor activity [15].

Several studies have provided further insights into the clinical role of BRS in heart failure by showing that cardiac resynchronisation therapy (CRT), through its mechanical and haemodynamic effects on the left ventricle, is able to reduce cardiac sympathetic afferent activity thus improving BRS [16, 17]. Furthermore, in a group of 32 patients studied 1 day after implantation and with the CRT device either on or off, CRT acutely increased BRS. The BRS changes correlated with changes in left ventricular ejection fraction caused by the acute mechanical response to CRT [18]. In a more recent study the hypothesis was tested that acute autonomic responses to CRT would be positively related to the clinical outcome [19].

However, in spite of the sound pathophysiological background and in spite of the large amount of clinical data suggesting that the quantitative estimation of BRS might also have a role in better refining risk stratification of candidates to implantable cardioverter defibrillator (ICD), the analysis of BRS has not yet gained wide acceptance in the routine clinical practice. Several reasons, besides the lack of randomised clinical trials, can be advocated including both practical and economical factors.

Future perspectives

The recently introduced analysis of heart rate turbulence (HRT), which is regarded as providing an indirect estimate of baroreflex function, more readily overcomes the practical and economic factors limiting the widespread use of invasive and non-invasive techniques providing an estimate of BRS. HRT can be obtained from 24-hour Holter recordings with the use of commercially available software [20]. HRT describes the average change in the R-R interval following an isolated ectopic beat. It has two components: turbulence onset (TO) and turbulence slope (TS). Although HRT was initially an empirical observation, later on it has been realised that it is strongly related to BRS, and perhaps TS is entirely dependent on the baroreflex [21, 22].

We have recently analysed the predictive value of Holter-derived autonomic variables in 388 patients with symptomatic chronic heart failure treated according to current recommendations and enrolled in a sub-study of the GISSI-HF trial [23]. The analysed variables included: 24-h time-domain (standard deviation, SDNN), frequency-domain (very low frequency and low frequency power, VLFP and LFP) and non-linear (detrended fluctuation analysis, DFA) heart rate variability indices, deceleration capacity (DC) and heart rate turbulence (HRT). The c-index and the integrated discrimination improvement (IDI) were used to assess the discrimination ability and the improvement in risk classification provided by each autonomic marker when added to clinical variables. In a median follow-up of 47 months, 57 patients died of cardiovascular causes and 47 experienced an arrhythmic event (combined sudden death + ICD discharge). It was found that while for cardiovascular mortality VLFP, LFP and TS improved both the c-index and the IDI when added to clinical variables (age ≥70 years, LVEF, NSVT, serum creatinine), for the occurrence of arrhythmic events — although the c-index increased in all three autonomic markers — the results of the IDI were statistically significant only for TS when added to NSVT, serum creatinine, and ischaemic aetiology. Moreover, depressed TS also provided a significant contribution to arrhythmic risk prediction among HF patients with LVEF >30 %, thus confirming the meaningful clinical value of baroreflex-related information and opening new perspectives that deserve to be further validated.

Disclosures The author has no conflict of interest to declare.

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