Baroreflex sensitivity: mechanisms and measurement

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Abstract This article is a brief review of baroreflex physiology, the definition and functional meaning of baroreflex sensitivity, and the methods used to measure baroreflex sensitivity. The arterial baroreflex is important for haemodynamic stability and for cardioprotection, and it has convincingly been demonstrated that baroreflex sensitivity, even when assessed with different methods, has a strong prognostic value. Development of new baroreflex assessing procedures is still ongoing, with a focus on increased reliability in difficult measuring circumstances, e.g., in patients with a weak baroreflex and in patients with frequent arrhythmias.

Keywords Baroreflex sensitivity · Blood pressure variability · Heart rate variability · Noninvasive · Prognostic value

Introduction

The arterial baroreflex exerts a pervasive influence throughout the body. Sensed by aortic and carotid baroreceptors, the afferent vagal and glossopharyngeal pathways convey burst-like information regarding every blood pressure (BP) pulsation to the brain stem. Efferent pathways also carry heart beat related nerve traffic: the parasympathetic, vagal limb of the reflex transports burst-like patterns, while the sympathetic limb shows inhibitory responses upon each BP pulsation [1]. Importantly, the heart is permanently under combined parasympathetic and sympathetic influence, which means that the electrophysiological properties of the entire heart, ventricular myocytes, conduction system, but also the atrium and sinus node, are modulated by these two antagonistic influences. The baroreflex elicits reciprocal responses of the autonomic

nervous system: when afferent baroreflex nerve traffic intensifies (this happens when BP increases), the efferent sympathetic traffic decreases, while the efferent parasympathetic traffic increases. The inverse response occurs when BP lowers. Moreover, the sympathetic outflow to the whole body is likewise modulated by the baroreflex, thus constantly adjusting vascular resistance [2].

By adjusting systemic vascular resistance, the arterial baroreflex buffers BP. When BP rises or falls, a few seconds are needed to accomplish the counteracting resistance adjustments (fall or rise, respectively). Like all negative feedback control systems with a time lag, the baroreflex BP buffering mechanism shows resonance behaviour: the resonance period is around 10 s (Mayer waves). This BP buffering mechanism effectively reduces hypotensive and hypertensive excursions; the buffering action may well be considered the primary function of the arterial baroreflex. However, the effects of the baroreflex on the heart are also particularly relevant. For example, in stressful conditions, when the BP increases, the baroreflex reduces sympathetic outflow and increases parasympathetic tone, which protects the heart, e.g., against arrhythmias. In conclusion, both BP buffering and cardioprotection are major effects of the arterial baroreflex.

Quantification of the arterial baroreflex

In order to determine the role of the arterial baroreflex in health and disease, its quantification is a *sine qua non*. The scientific community has almost univocally agreed that baroreflex sensitivity (BRS) would be the measure in which baroreflex vigour is expressed. BRS is defined as the change in interbeat interval (IBI) in milliseconds per unit change in BP. For example, when the BP rises by 10 mmHg and IBI increases by 100 ms, BRS would be $100/10=10$ ms/mmHg. Two remarks should be made here: first, it is obvious that this index has no direct relation to the BP buffering capacity

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of the baroreflex, but rather focuses on the reflex effect on the sinus node [3]; second, this measure does not take into account the way in which the effect (IBI increase/decrease upon BP increase/decrease) is attained. For instance, the 100 ms increase of IBI in the example above could be the result of a decrease in sympathetic tone, an increase of parasympathetic tone, or a combination thereof.

Baroreflex sensitivity assessment

Initially, BRS was measured by injecting a vasoconstrictive agent (phenylephrine) to increase BP, thus reflexly decreasing heart rate (HR) and, hence, increasing IBI [4]. Soon thereafter, attempts started to assess BRS noninvasively, most frequently from spontaneous heart rate variability (HRV) and BP variability (BPV) obtained from a continuous noninvasive finger arterial pressure measured by the Finapres method. The underlying idea is that there is always spontaneous BPV, due to respiration (that beat-to-beat modulates cardiac filling, stroke volume, and, thus, the BP pulsations) and due to the above-mentioned resonance phenomenon (Mayer waves) [5]. Normal respiration rates are often faster (≈ 0.25 Hz) than Mayer waves (≈ 0.1 Hz), hence spontaneous BPV is often a mix of slower and faster fluctuations. Usually, variability around 0.1 Hz (sometimes precisely defined, like 0.04–0.15 Hz) is termed low frequency (LF) and variability around 0.25 (sometimes precisely defined, like 0.15–0.40 Hz) is termed high frequency (HF).

The baroreflex efferents to the heart, more specifically, to the sinoatrial node, ‘translate’ BPV into HRV. HF respiration-related BPV results in corresponding fast changes in parasympathetic and sympathetic outflow. However, the response of pacemaker cells in the sinoatrial node to an alteration in norepinephrine concentration is too slow to follow these fast changes. Thus, only the changes in parasympathetic firing lead to HRV. Moreover, respiration modulates transmural atrial pressure, and this variable wall stress modulates the sinoatrial pacemaker rate. Thus, respiration does not only induce HRV by mediation of the arterial baroreflex, but it also induces HRV by direct mechanical modulation of the sinus node pacemaking properties.

Algorithms in the time and frequency domain

A multitude of algorithms for noninvasive BRS assessment have been proposed during the past decades [6], and new variants are still being introduced [7, 8]. Implicitly, this means that there remain unresolved issues. BRS algorithms fall apart in two major groups: time domain methods, and frequency domain methods [9]. Most time domain methods consider sequences of beats during which IBI and BP

monotonously increase or decrease, measure IBI-BP slopes in these sequences, and average the slopes, eventually separating positive and negative slopes. Due to its nature, this method might miss part of the sympathetic component of the baroreflex. Selection of (relatively short) beat sequences is a form of high-pass filtering, while the sympathetic limb of the baroreflex manifests itself rather in the low-frequency Mayer waves. Also, and especially in patients with a weak baroreflex, the direct mechanical influences of respiration (that are not filtered out because they are HF) might suggest the presence of a baroreflex even while it would completely dysfunction.

Algorithms in the frequency domain compute a spectral BP to IBI transfer function. The amplitude of the transfer function is analogous to the slope of the IBI-BP relationship; however, that slope is now computed over the frequency spectrum, which makes it possible to focus on a specific frequency band. Some researchers compute the transfer function in the LF band alone, some compute the transfer function in the LF as well as in the HF band (α -LF and α -HF). Measuring the transfer function in the LF band would imply that false mechanical influences of respiration would be discarded, provided that respiration was not in the LF band. Spontaneous respiration is not always regular, and to ensure that respiration is in the HF band, it is useful to instruct the subjects to breathe in a fixed rate, e.g., at 0.25 Hz and guided by a respiration metronome computer screen [10].

Challenges and future

It is a major challenge to develop analysis methods that yield reliable BRS values even in patients with a low BRS value. In such patients, BRS assessment is usually corrupted by even small amounts of noise, and by frequent arrhythmias (BRS assessment requires sinus rhythm) [11].

Various studies have demonstrated that a low BRS implies a less favourable prognosis, e.g. after myocardial infarction and in heart failure [12]. Also, BRS measurement may be clinically useful to assess the efficacy of interventions that are meant to increase BRS (e.g., exercise training of heart failure patients). Given this considerable clinical potential, BRS measurement methodology deserves continued attention.

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