Blood pressure analysis on time scales from seconds to days
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Appendix

Assessing arterial baroreflex control of heart rate: new perspectives

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Editorial commentary to Chapter 6

The arterial baroreflex is a key mechanism involved in blood pressure homeostasis (1) and its impairment is a characteristic feature of a number of cardiovascular diseases (1–6). There is evidence that a deranged baroreflex control of heart rate may carry an adverse prognosis in cardiac patients (7,8), while interventions that improve the sensitivity of the heart rate baroreflex (BRS), such as physical training (9–11) or β-adrenergic receptor blockade (12), may reduce the risk of cardiovascular events.

For several years, the conventional approach to BRS assessment has been based on the application of laboratory tests only (1,13). However, in the 1980s, innovative methods for the assessment of this parameter were described, based on the time or frequency domain analysis of spontaneous blood pressure fluctuations coupled with reflex changes in R–R interval (also termed heart interval) (13–19). Because all these newer techniques evaluate arterial baroreflex function by considering the reflex heart rate effects of blood pressure changes in the absence of external stimulations on the cardiovascular system, the estimates of BRS yielded were defined as ‘spontaneous’ (13,20).

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In this issue of the journal, a further contribution to this field is provided by Westerhof et al. (21), who propose a new approach to the assessment of spontaneous baroreflex function.

**Why assess spontaneous baroreflex function?**

The available methods for the assessment of spontaneous BRS all share a number of common features. First, these techniques do not require any external intervention on the cardiovascular system, thus preventing undesirable interferences with the autonomic function patterns explored. Second, they can be used not only to assess BRS in standardized laboratory conditions, but also to investigate the dynamic features of baroreflex modulation of heart rate over time in daily life (17,19,22–25). Third, arterial baroreflex control of heart rate is explored around the baroreflex 'set point', excluding the portions of the sigmoidal baroreceptor stimulus–response curve approaching threshold and saturation (14,20). The information on arterial baroreflex function obtained appears to be complementary to that provided by the application of conventional laboratory tests, based on either the injection of vasoactive drugs (26) or on the manipulation of carotid baroreceptors through a neck chamber device (27–30), which may explore arterial baroreflex function through a full-range, although artificial, stimulation of arterial baroreceptors. Following the first introduction of methods for spontaneous BRS assessment almost 20 years ago, a number of studies have supported the pathophysiological and clinical relevance of the information on baroreflex function that they provide (13,19,22,31–35), although the ability of ‘spontaneous’ BRS assessment to offer new insights into neural cardiovascular regulation over and above the solid evidence provided by classic laboratory tests has stimulated a lively debate (36–38).

**Available methods to explore spontaneous baroreflex function**

Each of the several methods proposed to estimate BRS from the spontaneous variability of blood pressure and heart rate is based on a specific physiological hypothesis and makes use of different techniques of signal analysis (Table 1). These differences may sometimes provide quantitatively different BRS estimates. The sequence method (15,18,19) can be seen as the natural extension of the traditional drug-injection technique applied to the analysis of spontaneous variability. It can be classified as a time-domain method because it is based on the identification of specific patterns in the time series of systolic pressure and heart interval. The technique scans the beat-to-beat series of
systolic pressure to identify a ‘sequence’ (i.e. a series of heart beats) in which a monotonic increase (or decrease) of systolic pressure is followed, after a delay of zero, one or two beats, by a monotonic increase (or decrease) of heart interval. The technique assumes that the progressive changes of heart interval following the monotonic changes of systolic pressure reflect the buffering action of the baroreflex. The slope of the regression line between heart interval and systolic pressure values within the sequence is taken as an estimate of BRS. The new xBRS estimator presented in this issue of the journal by Westerhof et al. (21) may be classified into the family of time-domain methods too. Similarly to the sequence method, BRS is obtained as the slope of the regression line between values of systolic pressure and heart interval. However, these values do not belong to a sequence, but to a 10-s window of data where the heart-interval values are delayed by applying a time-shift that maximizes the cross-correlation.

Table 1. Methods for spontaneous baroreflex sensitivity (BRS) assessment

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<thead>
<tr>
<th>Short Name</th>
<th>Type</th>
<th>References</th>
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<tbody>
<tr>
<td>Sequence technique</td>
<td>Time domain</td>
<td>(13, 18, 19)</td>
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<tr>
<td>xBRS</td>
<td>Time domain</td>
<td>(21)</td>
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<tr>
<td>$\alpha_{LF}$, $\alpha_{HF}$</td>
<td>Frequency domain</td>
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<td>$H_n$</td>
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<tr>
<td>XAR</td>
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<tr>
<td>ARXAR</td>
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<tr>
<td>Z-coefficient</td>
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BRS, baroreflex sensitivity; xBRS, cross-correlation BRS; $\alpha_{HF}$, alpha coefficient in the high frequency band (0.15–0.50 Hz); $\alpha_{LF}$, alpha coefficient in the low frequency band (0.04–0.14 Hz); $H_{LF}$, $H_{HF}$, modulus of the transfer function between changes in systolic blood pressure and changes in heart interval; $a_k$, BRS gain for mathematical models; $H_n$, gain of SBP-heart interval transfer function; ARMA, AutoRegressing Moving Average (model); XAR, eXogenous (model) with AutoRegressive input; ARXAR, bivariate AutoRegressive (model) with eXogenous input.

A completely different approach is followed by the frequency domain methods. Spectral analysis shows that spontaneous fluctuations of systolic pressure and heart interval tend to be linearly correlated at the respiratory frequency (high frequency, HF, band) and around 0.1 Hz (low frequency, LF, band). The alpha method (17) assumes that this
correlation is due to baroreflex cardiovascular control. Estimates of BRS are obtained by computing the root-squared ratio between heart-interval and systolic pressure powers calculated in the LF band ($\alpha_{LF}$) or in the HF band ($\alpha_{HF}$), provided that the coherence between systolic pressure and heart interval (an index of their linear correlation) is sufficiently high. The transfer function method (16) assumes that the heart interval is the noisy output of a linear system in which systolic pressure is the input. BRS is then estimated as the modulus of the transfer function, $H$, of this system. This is achieved by computing the modulus of the cross-spectrum between systolic pressure and heart interval, divided by the systolic pressure spectrum. The transfer function is usually evaluated separately in the LF and HF frequency bands, obtaining two distinct estimates of BRS: $H_{LF}$ and $H_{HF}$. Also the recently proposed trigonometric method (39) belongs to the class of frequency domain methods, because it estimates BRS by means of a decomposition of blood pressure and heart-rate variabilities in periodic components.

Another approach for estimating BRS is based on the description of spontaneous blood pressure and heart rate variability by means of a mathematical model of circulation. The model coefficients are tuned to fit the experimental data (13). The proposed models differ in terms of their complexity and modelling strategies, including, as possible examples, dynamic adjustment models (40), autoregressive-moving average (ARMA) models (41), exogenous models with autoregressive input, XAR (42), and bivariate autoregressive models with two exogenous inputs ARXAR (43). Once the model has been identified, BRS is derived from the model parameters.

Mathematical models for BRS assessment have been proposed to take into account the complex relationship between blood pressure and heart interval. An increase or decrease in blood pressure may result in an increase or decrease in heart interval. This process, known as negative feedback, is an attempt to return blood pressure to its original value. The other arm of this negative feedback control system, which closes the loop, is the transmission of the heart interval change into a change in blood pressure, which can be thought of as feedforward. For the baroreflex, the feedback gain which is the estimated BRS, has been generally termed $\alpha$-gain, while the feedforward has been termed $\beta$-gain by some investigators (44). However, most baroreflex quantification techniques are based on the assumption that the feedforward response is inconsequential, quantifying only the feedback relation between blood pressure and heart interval. Models that account for only the effect of blood pressure on heart interval are bivariate open loop and unidirectional, while those that also consider the effect of heart interval on blood pressure are bivariate closed loop and bidirectional. Finally, closed loop models that
account for other variables in addition to blood pressure and heart interval can be considered multivariate. The inclusion of respiration in the baroreflex model is the most common application of a multivariate model.

A multivariate closed-loop bidirectional model that includes as many parameters as possible will clearly be the most accurate, because it is able to reduce the variance of the BRS estimates due to factors other than blood pressure and heart interval. However, such models are also limited by their complexity and the necessity of measuring multiple parameters during spontaneous operation. Thus, most models focus on the use of only blood pressure and heart interval. Finally, the issue of causality in computing the BRS must be addressed. Causal models take into account the physiological timing relationships between the parameters in the model, assuming that current values of a parameter are dependent on past values of both itself and of the other parameters that influence it. Non-causal models do not impose such timing relationships, effectively assuming causality does not exist or is unimportant. Most spectral methods do not include causality, but a variety of methods do include feedback causality, including the sequence method, the xBRS proposed by Westerhof et al. (21) and most bivariate autoregressive techniques (44–47).

Finally, an alternative way to quantify BRS is to statistically assess the probability to find an association between values of systolic blood pressure and heart interval. The statistical level of coupling is quantified by the Z-index, which is a function of two variables: systolic pressure and heart interval. Z may range between –1 and +1: negative values indicate exclusion, positive values indicate a link between the two variables. BRS is derived from the shape of the Z-surface on the systolic pressure–heart interval plane (48) (Table 1).

How to select the proper method for spontaneous BRS assessment

Given such a wide variety of different BRS estimators, there is a need to define the criteria for the selection of the most appropriate method in a given experimental or clinical setting. Indeed, the choice of the most appropriate technique depends on the nature of the experiment, and it is often determined by stationarity level and length of the signals, by the experimental protocol and by the characteristics of the subjects under evaluation.
**Stationarity**

Most frequency domain methods and methods based on black-box modelling require the stationarity of blood pressure and heart rate time series (i.e. they require the probability distributions of the time series values to be independent of time translations). By contrast, this is not a prerequisite for the Z-analysis or for the sequence technique, the latter estimating BRS at the time of a clear non-stationarity of the recorded signals, such as a blood pressure ramp.

**Length of the signals**

Theoretically, the method that requires the shortest segment of data to provide a single BRS estimation is the sequence technique. An estimate can be obtained by only four heart beats if they are characterized by a sequence-like progressive change in blood pressure and heart interval. However, in practice, baroreflex sequences occur randomly in blood-pressure and heart-rate time series, and signal lengths of the order of minutes are therefore required to obtain reliable BRS estimates. The xBRS method described in this issue of the journal (21) is characterized by very good performances in terms of the minimal signal length required to obtain BRS estimates. Compared to the sequence technique, the shortest segment of data needed to compute a BRS estimate is slightly longer (15 s). However, the probability to obtain a BRS quantification from this short segment is much higher compared to the sequence technique, and reliable BRS estimates can be derived from shorter recordings. Frequency domain methods and black-box models require longer segments of data to compute power spectra with the required frequency resolution, or to reliably identify the model parameters. Z-analysis, which implies the need to calculate conditional probabilities of events, also requires much longer recordings.

**Differentiation of BRS estimates**

If there is an interest in assessing the BRS separately during a rise and a fall in blood pressure, then the obvious method is the sequence technique, which can provide separate estimates for increasing and decreasing blood pressure ramps, corresponding to arterial baroreceptor stimulation and deactivation, respectively. By contrast, if a separate estimation of the ‘vagal’ and ‘sympathetic’ contribution to BRS values is desired, frequency-domain methods appear to be preferable.
Estimation of very low BRS

Generally, the various techniques make use of thresholds to limit the interference of noise, and to ensure sufficiently reliable estimates. For example, with the sequence technique, estimates of BRS can be obtained only from sequences of beats in which the absolute changes between consecutive systolic pressure values or heart-interval values are greater than a given threshold. Similarly, \( \alpha \) and transfer function techniques estimate BRS only if the squared coherence modulus between systolic pressure and heart interval is greater than a pre-defined threshold. However, this means that, because of these thresholds, a given technique may be unable to provide estimates in subjects with very low BRS (e.g. in patients with autonomic failure). In this regard, the xBRS technique presented by Westerhof et al. (21) appears to score sufficiently well because it is able to provide reliable BRS estimates even in subjects with very low BRS values.

Improving the assessment of BRS: the contribution of the method by Westerhof et al.

When quantifying the short-term relationship between arterial pressure and inter-beat interval, it is important to consider that this relationship may not invariably represent the physiology of the heart rate baroreflex because there are many systems other than the baroreflex (e.g. respiration) that influence both blood pressure and heart interval on a beat-to-beat basis. Theoretically, unless all of these systems are accounted for, or controlled, the quantified baroreflex relationship is likely to be biased, and to have reduced accuracy, regardless of the technique used for its quantification. Other limitations of the available methods for spontaneous BRS assessment include within subject variance of the BRS values, restriction to a fixed time delay from blood pressure to heart interval changes, inability to detect low BRS values due to threshold issues, and the availability of only a small number of BRS values in many instances. The xBRS model described by Westerhof et al. (21) is aimed at addressing some of the above problems. Conceptually, the xBRS model is simply a more complicated version of a sequence model, using a variety of computation rules to address some of the limitations of previous sequence and spectral methods. The authors do demonstrate that their model addresses these limitations by reducing BRS estimate variance, providing more BRS values and more accurately including timing effects. However, even this bivariate method of blood pressure and heart interval interaction cannot be regarded as using a complete model that is closed loop and causal, such as the autoregressive techniques that have been previously described (39–47).
Finally, it has to be acknowledged that the new method proposed by Westerhof et al. (21) has not yet been validated in studies making use of experimentally-induced baroreflex dysfunction (e.g. through surgical baroreceptor denervation or pharmacological blockade). However, it has been tested on the systolic blood pressure and heart interval time series of a European dataset collected in the frame of the activities of the Working Group on Blood Pressure and Heart Rate Variability of the European Society of Hypertension. This dataset represents the first step of a ‘EuroBAVAR’ (European BAroreflex VARiability) Project that originally focused on the technical comparison between different methods for assessing spontaneous BRS (49), and which is now also used to tune and validate new approaches proposed for this analysis, as in the case of the xBRS model by Westerhof et al. (21).

However, besides its technical validation, the actual clinical relevance of this new index, with respect to the other available BRS estimates, now needs to be assessed in longitudinal outcome studies.
References


