Arterial baroreceptors play a crucial role in the adjustment of the cardiovascular system to several surrounding conditions. In a simplified paradigm, baroreceptor stimulation results in arterial pressure changes that can modulate both sympathetic and vagal activity and, as a consequence, heart rate and myocardial electrophysiological properties, contractility and vascular resistance. Arterial baroreceptors are actively engaged at resting blood pressure values and are, therefore, 'loaded' at rest. Thus, a normal resting and otherwise 'stable' hemodynamic state reflects an ongoing, baseline level of baroreceptor reflex activity. Cardiovascular diseases are often accompanied by an impairment of baroreflex mechanisms, with a reduction of inhibitory activity and an imbalance in the physiological sympathetic–vagal outflow to the heart, thus resulting in a chronic adrenergic activation. Novel therapeutic strategies, exploring the use of electrical stimulation of the carotid sinus, have been evaluated recently in experimental and preliminary clinical studies to lower blood pressure and to reduce the level of baroreflex-mediated sympathoexcitation in heart failure. A recent study has also shown that the implementation of an artificial baroreflex system to regulate sympathetic vasomotor tone automatically is feasible.

Arterial Baroreflex Sensitivity Assessment

Research into human arterial baroreflex control mechanisms has taken advantage of a wide spectrum of techniques. The quantification of the baroreflex is difficult because it relies on the need to approximate an open-loop condition in the closed-loop control system that regulates arterial blood pressure.

In this respect, several methods are available to assess BRS by directly or indirectly stimulating arterial baroreceptors: Valsalva’s manoeuvre, neck suction, and vasoactive drug administration. Although the technique of directly stimulating baroreceptors with neck suction was described early, quantitative estimation of BRS did not gain acceptance until a bolus injection of a pressor agent was used to correlate RR interval lengthening with systolic pressure elevations. The original method—used intravenous injections of small boluses of angiotensin, which also causes a delayed central nervous sympathetic discharge, so phenylephrine was later used as a pressor agent.—The reflex RR interval lengthening results from an increase in vagal efferent activity, whereas a reduction in sympathetic vasoconstrictor tone develops with a few seconds delay. BRS is evaluated as the slope of the regression line fitting the relationship between changes in RR interval and the increase in systolic arterial pressure elicited by the drug.

The Valsalva’s manoeuvre is likely to be the most widely used test of human arterial baroreflex function; however, it is relatively non-selective because it affects the activity of several major receptor groups, including arterial baroreceptors. At variance with the previous methods, the estimates of BRS from spontaneous fluctuations of blood pressure and RR interval—the so-called ‘spontaneous BRS’—would partially reflect the gain of the baroreceptors in a closed-loop system. However, it has been shown that the buffering effect of RR fluctuations in the low-frequency range is negligible in supine resting individuals. Hence, in this condition, the open-loop approximation for the systolic arterial pressure–RR interval relationship can be considered adequate.

Abstract

The baroreflex mechanism has been recognised as a key part of cardiovascular regulation. Alterations in the baroreceptor-heart rate reflex (baroreflex sensitivity [BRS]) contribute to sympathetic–parasympathetic imbalance, playing a major role in the development and progression of many cardiovascular disorders. Therefore, the measurement of the baroreflex is a source of valuable information in the clinical management of cardiac disease patients. This article reviews the most relevant advances for the measurement of BRS and their clinical and prognostic implications. Novel therapeutic strategies, exploring the use of electrical stimulation of the carotid sinus, have been evaluated recently in experimental and preliminary clinical studies to lower blood pressure and to reduce the level of baroreflex-mediated sympathoexcitation in heart failure. A recent study has also shown that the implementation of an artificial baroreflex system to regulate sympathetic vasomotor tone automatically is feasible.

Keywords

Arterial baroreceptors, autonomic nervous system, phenylephrine, non-invasive assessment, carotid sinus stimulation
A variety of computational methods can be applied to the analysis of the interrelationship between RR and arterial pressure variabilities. There are two major approaches: one based on ‘time domain’ and the other on ‘frequency domain’ measurements. For spectral methods, different computational algorithms have been developed to calculate the gain of the baroreflex.\(^2\) The topic of methodologies, their advantages, and their limitations have recently been reviewed.\(^3\)

The recently introduced analysis of heart rate turbulence (HRT) can be regarded as providing an indirect estimate of baroreflex functioning. This term describes the average change in the RR interval following an isolated ectopic beat (in a subject in sinus rhythm)—generally over 24h, and requiring at least five ectopic beats. It has two components: turbulence onset (TO) and turbulence slope (TS). Initially, HRT was an empirical observation,\(^4\) but later it was realised that it was strongly related to BRS, and perhaps entirely dependent on the baroreflex.\(^5\)\(^,\)\(^6\) A recent consensus paper\(^7\) highlighted the technical aspects and the clinical use of HRT measures obtained from 24h electrocardiogram Holter recordings.

**Advances in Baroreflex Sensitivity Assessment**

The need for a drug injection has been regarded as a limitation on the widespread use of BRS estimation and, therefore, non-invasive methods providing information on baroreflex control have been welcomed as more suitable for large-scale use and have rapidly gained wide application. Accordingly, over the past 10–15 years, several methodological aspects, including their validation as estimates of the baroreflex, their measurability, and their reproducibility have been refined.

Both the sequence and the frequency domain technique have been compared with the phenylephrine method in small groups of normal and hypertensive subjects.\(^8\)\(^,\)\(^9\)\(^,\)\(^10\) Although high correlation coefficients between non-invasive and the phenylephrine estimates of BRS were found, careful assessment of the agreement between the two measurements revealed relevant random differences as large as the baroreflex gain itself.\(^11\)\(^,\)\(^12\)\(^,\)\(^13\)

The argument has been made that the two techniques—invasive and non-invasive—address two different facets of the dynamics of the baroreflex: spectral methods focus on the response to small oscillatory perturbations of arterial blood pressure around the set point, whereas the phenylephrine method focuses on the strength of the response to a larger and unidirectional ramp increase in arterial pressure. However, it remains unclear whether non-invasive indices broadly represent the arterial baroreflex function. The issue has been addressed in a large population of volunteers with (30%) and without coronary artery disease in whom the relation to carotid distensibility and respiratory sinus arrhythmia was also examined.\(^14\) It was found that all spontaneous indices and the invasive phenylephrine measurement were related to respiratory sinus arrhythmia, but only the latter was related to carotid distensibility, suggesting that spontaneous indices are inconsistent with arterial baroreflex function and more likely reflect vagally mediated heart rate variability. By contrast, it has been shown recently in a computer model that BRS computed as the average transfer function in the low-frequency band is linear with and depends almost exclusively on, the vagal BRS gain to the heart.\(^15\)\(^,\)\(^16\) Despite this controversy, recent studies have demonstrated the prognostic utility of spontaneous indices.\(^17\)\(^,\)\(^18\)

Several limitations affect the measurability of spectral techniques. A major one is their reduced measurability in patients with severe ectopic activity.\(^19\) This is because of the need to have a sufficiently long stationary record (≥3 min) in order to obtain baroreflex estimates with acceptable accuracy.\(^20\) Another potential problem may arise with the use of the coherence criteria (>0.5 usually required) to assess the strength of the association between blood pressure and RR interval oscillations. Pathological subjects, such as heart failure patients, often present profound abnormalities in baroreflex control and depressed blood pressure variability. Both factors lead to a reduced coherence that in turn translates into a reduction in the reliability of the measurements.\(^21\) As a result of these criticisms, new criteria for the computation of baroreflex sensitivity aimed at overcoming the limitations of the coherence criterion have been evaluated recently.\(^22\)

The reproducibility of the measures provided by spontaneous indexes is relevant to allow their applicability for clinical and research purposes. Recently, this has been addressed in 44 healthy volunteers and 57 patients with a previous myocardial infarction who underwent blood pressure and heart rate recording on two consecutive days.\(^23\) In this study the intra-class coefficient ranged from 0.70 and 0.83, both in normal subjects and in post-myocardial infarction patients, indicating that only a small portion of measurement variability of BRS across individuals is due to random variations in the physiological characteristics being measured.

A novel approach based on a novel mathematical algorithm capable of detecting periodic patterns in complex biological signals has been described recently and awaits clinical validation.\(^24\)

**Baroreflex Sensitivity and Heart Disease**

Although the use of a quantitative estimation of baroreflex gain was initially focused on the study of physiological aspects of baroreflex control in humans, by the early 1970s it became apparent from a study of a disparate group of patients with heart disease that cardiac patients had subnormal vagal baroreflex sensitivity.\(^25\)

In the same years, some experimental studies yielded important insights into the pathophysiological implications of heart disease-related baroreflex impairment. Indeed, it was recognised not only that cardiac electrical stability can be affected by changes in autonomic flow,\(^26\)\(^,\)\(^27\) but also that baroreceptor reflexes can be modulated by cardiac afferent sympathetic activity activated by mechanical and chemical stimuli.\(^28\)

The development of an animal model was crucial to appreciate that baroreflex impairment has major adverse prognostic implications and adds to that of other cardiovascular risk factors, including left ventricular impairment.\(^29\) Finally, the importance of adequate baroreceptor activity to respond to the hemodynamic challenge of ventricular tachycardia was also established.\(^30\)

A wealth of clinical studies validated the experimental observations in patients with ischemic heart disease. In the Autonomic tone and
reflexes after myocardial infarction (ATRAMI) study, which followed almost 1,300 patients with recent (<1 month) myocardial infarction, abnormal BRS was highly predictive of both sudden and non-sudden death, primarily in patients with an ejection fraction of ≤35%. 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 the left ventricular ejection fraction and the cycle of the arrhythmia. Recent data support the usefulness of the integrity of baroreceptor activity even in post-infarction patients with preserved left ventricular function. Indeed, in a long-term follow-up of five years, cardiovascular mortality was dramatically low in patients with a preserved BRS (2.4%) compared with those with an abnormal BRS (26%).

In spite of the sound pathophysiological background and in spite of further data showing that the quantitative estimation of BRS might have a role in better defining risk stratification of candidates for implantable cardioverter-defibrillator (ICD) implantation, the analysis of BRS has not yet gained wide acceptance in routine clinical practice. The National Institutes of Health-sponsored 4,500 patient study (VEST/PREDICTS), which aims to refine selection of patients for ICD implantation, is likely to define the contemporary place for BRS assessment in risk evaluation.

An impairment in baroreflex control is a prominent characteristic of the heart failure syndrome and plays a central role in sustaining sympathetic activity. Along with the rise in angiotensin II levels in the medulla, an increased cardiac sympathetic afferent reflex has been recognised to be pivotal in reducing the gain of the baroreflex. A recent study tested the hypothesis that cardiac resynchronisation therapy (CRT), by its mechanical and hemodynamic effects on the left ventricle, would be able to reduce cardiac sympathetic afferent activity, thus improving BRS. BRS was measured in a group of 32 patients one day after CRT implantation, both when the device was switched on and when it was switched off. It was found that CRT acutely increased BRS and that BRS changes were correlated with changes in the left ventricular ejection fraction taken as a measure of acute mechanical response to CRT.

Although the predictive ability of BRS in patients with heart failure was well established in an early study, one relevant question in the modern era of widespread use of beta-blocker treatment is whether the autonomic modulation brought about by beta-blockers might affect the predictive value of BRS. This has been addressed in a recent study that showed that a depressed BRS was significantly associated with higher mortality, independently of known risk factors and beta-blocker treatment.

It has long been thought that baroreceptors account for short-term blood pressure control only. This assumption was based on experimental observations in animal models showing that baroreceptors rapidly reset to the prevailing level of mean arterial pressure and that total baroreceptor denervation has no lasting effect on the daily mean arterial pressure. However, more recent studies have cast doubt on the accuracy of the original experimental models and have indicated that the baroreflex has a more complex and long-term role in hypertension. More specifically, there is clear evidence that baroreceptors control sympathetic output on a more long-term basis and participate in fluid volume regulation by the kidney, and thus have the potential to adjust blood pressure chronically. These findings, which are also consistent with studies and observations in humans, have led to a re-appreciation of the role of arterial baroreceptors in arterial hypertension.

### Advances in Treatment Strategies

Based on advances in device technology that allow chronic carotid nerve stimulation, novel aspects in treatment strategies have recently emerged aimed at ‘reversing’ baroreceptor abnormalities in heart rate or blood pressure control, which are involved in several pathological conditions.

The possibility of manipulating baroreceptor activity through electrical stimulation of the carotid sinus was first explored almost 50 years ago in hypertensive and angina patients. However, efforts to use the reflex therapeutically were not successful because of technical problems and an inability to fine-tune the stimulation to produce the desired effect on blood pressure without producing symptomatic hypotension or symptoms of local tissue or nerve stimulation. Modern devices consist of an implanted pulse generator with leads that tunnel subcutaneously and bilaterally attach to the carotid sinuses. Moreover, they are fully programmable after implantation to allow adjustment of stimulation parameters.

Consistent data have now been provided showing that device-based chronic baroreceptor activation may be a useful addition for the treatment of drug-resistant hypertension and heart failure. Recent results from the European multicenter feasibility study involving 45 subjects with a mean baseline blood pressure of 179/105 and a median of five anti-hypertensive drugs found that subjects receiving therapy from the implanted device showed substantial reductions in mean blood pressure at three months and at two years, and that the device had a favourable safety profile. The depressor response to electric stimulation of carotid sinus baroreflex afferents seems to be mediated mainly through sympathetic inhibition, without negative effects on physiological baroreflex regulation.

In dogs with pacing-induced heart failure, carotid sinus stimulation led to a general decrease in sympathetic activation, nearly doubling their survival time in spite of little change in ventricular function, suggesting that the beneficial effects might be more attributable to peripheral vascular and/or neurohumoral inhibition than to cardiac benefits. At variance, in a model of microembolisation-induced heart failure, long-term baroreflex stimulation improved global left ventricular function, decreased plasma norepinephrine and partially reversed left ventricular remodelling at cellular and molecular levels, supporting the initiation of clinical trials.

Finally, artificial neural interfaces should make bionic cardiovascular treatments possible. In an animal model of central baroreflex failure, an artificial feedback control system has been developed for automatic regulation of sympathetic vasomotor tone. The bionic baroreflex system consists of a pressure sensor, computer, electrical stimulator, and epidural catheter with sympathetic nerve stimulation electrodes, and has been tested in a clinical model of orthostatic hypotension during knee-joint surgery.
Baroreflex Sensitivity Assessment—Latest Advances and Strategies

Conclusions

The arterial baroreflex is an important determinant of the neural regulation of the cardiovascular system. A quantitative description of baroreflex gain, i.e. baroreflex sensitivity, may provide a useful synthetic index of neural regulation at the sinus atrial node. This information has clinical and prognostic value in a variety of cardiovascular diseases, including myocardial infarction and heart failure. Many different methods have been devised to examine arterial baroreceptor responses. Although the largest body of evidence supporting the prognostic value of BRS is from studies using the phrenylephrine method, ‘non-invasive’ quantification of BRS might become highly relevant in the clinical setting, being applicable to wide populations. Over the past decade, evidence has been accumulating to support the suggestion that arterial baroreflex could be a target of treatment to reduce the negative impact of baroreflex-mediated sympathoexcitation.

1. Eckberg DL, Sleight P (eds), Human Baroreflexes in Health and Disease, Oxford: Clarendon Press, 1992.
2. Ernsting J, Perry DJ. Some observations on the effects of stimulating the stretch receptors in the carotid arteri of man, J Physiol, 1967;192:409–414.
3. Smith JH, Sleight P, Pickering GW. Regulatory arterial pressure during sleep in man. A quantitative method for assessing baroreflex control, Circ Res, 1969;24:104–109.
4. Bristow JD, Honnor AJ, Pickering TG, Sleight P. Cardiovascular and respiratory changes during sleep in normal and hypertensive subjects, Cardiovasc Res, 1969;3:476–486.
5. Palermo HA, Carleo TO, Iosi DA, Bus I. Baroreceptor reflex sensitivity index derived from phase 4 of the Valsalva manoeuvre, Human Physiol, 1981;8:193–197.
6. Smith SA, Stalard TL, Salih MM, Litter WA. Can sinoaortic baroreceptor heart rate reflex sensitivity be determined from phase 4 of the Valsalva manoeuvre? Cardiovasc Res, 1987;21:422–427.
7. Taylor JA, Eckberg DL. Fundamental relationships between short-term HR interval and arterial pressure oscillations in humans, Circulation, 1994;90:1527–32.
8. Pisanò D, Di Renzo M, Bertinié D, et al. Evaluation of the baroreceptor heart rate reflex by 24-hour intra-arterial blood pressure monitoring in humans, Hypertension, 1988;12:514–522.
9. Pagani M, Somers V, Furlan R, et al., Changes in autonomic baroreflex sensitivity, blood pressure buffering and reactivity: what are the limits? Computer simulation of healthy subjects and heart failure patients, J Appl Physiol, 2007;102:1348–56.
10. Pisanò D, Assessing baroreflex sensitivity by the transfer function: what are we really measuring? J Appl Physiol, 2007;101:1210–1215.
11. Isaraka N, Semrad B, Fiser B, Labrova R. Baroreflex sensitivity determined by spectral method, and heart rate variability, and two years mortality in patients after myocardial infarction, Hypertension, 1998;12:604–610.
12. Robie HW, Muller LM, Rudolf H, et al., Assessment of baroreceptor reflex sensitivity by means of spectral analysis, Hypertension, 1997;30:38–43.
13. Pisanò D, Maestri R, Capodanno S, et al., Applicability and clinical relevance of the transfer function method in the assessment of baroreflex sensitivity in heart failure patients, J Am Coll Cardiol, 2006;48:1341–1347.
14. Pisanò D, Maestri R, Reliability of transfer function estimates in cardiovascular variability analysis, Med Biol Eng Comput, 2001;39:338–47.
15. Pisanò D, Raczak G, La Rovere MT. Measuring baroreflex sensitivity from the gain function between arterial pressure and heart period, Clin Sci (Lond), 2002;103:259–267.
16. Baur A, Makki M, Schmidt G, et al., Heart rate turbulence parameters correlate with post-PCI changes in muscle sympathetic nerve activity, Heart Rhythm, 2007;4:248–249.
17. Baur A, Makki M, Schmidt G, et al., Heart rate turbulence: standard of measurements, physiological interpretation, and clinical use: International Society for Heart and Noninvasive Electrophysiology Consensus, J Am Coll Cardiol, 2009;53:1533–40.
18. Pagani M, Somers V, Furlan R, et al., Changes in autonomic regulation induced by physical training in mild hypertension, Med Biol Eng Comput, 1996;34:293–299.
19. Parlow J, Viale JP, Annat G, et al., Spontaneous cardiac baroreflex baroreceptor-heart rate reflex by 24-hour intra-arterial blood pressure monitoring in hypertensive patients, J Am Coll Cardiol, 2003;42:481–487.
20. van de Vooren H, Gademan MG, Swenne CA, et al., Baroreflex sensitivity, blood pressure buffering and resistance: what are the limits? Computer simulation of healthy subjects and heart failure patients, J Appl Physiol, 2007;102:1348–56.
21. Pisanò D, Assessing baroreflex sensitivity by the transfer function: what are we really measuring? J Appl Physiol, 2007;101:1210–1215.
22. Honzikova N, Semrad B, Fiser B, Labrova R. Baroreflex sensitivity determined by spectral method, and heart rate variability, and two years mortality in patients after myocardial infarction, Hypertension, 2008;42:649–653.
23. Colombo R, Mazzuero G, Spinatondo G, et al., Comparison between spectral analysis and the phrenylephrine method for the assessment of baroreflex sensitivity in chronic heart failure, Clin Sci (Lond), 1999;97:523–533.
24. Liptzan RO, Salisbury JK, Taylor JA. Spontaneous indices are inconsistent with arterial baroreflex gain, Hypertension, 2003;42:481–487.
25. van de Vooren H, Gademan MG, Swenne CA, et al., Baroreflex sensitivity, blood pressure buffering and resistance: what are the limits? Computer simulation of healthy subjects and heart failure patients, J Appl Physiol, 2007;102:1348–56.
26. Pisanò D, Assessing baroreflex sensitivity by the transfer function: what are we really measuring? J Appl Physiol, 2007;101:1210–1215.