The Effect of Baroreceptor Activity on Cardiovascular Regulation

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The hypothesis that the cardiovascular system can be regulated by nerve reflexes originating from the heart and the great vessels was first formulated in 1866 by Cyon and Ludwig[1], who showed that electrical stimulation of the aortic depressor nerve caused deceleration of the heart rhythm and of the arterial pressure (AP) in rabbits. The origin of this reflex was initially attributed to the myocardium; however, in 1902, Koester and Tschermak indicated that this was wrong. They discovered the correct distribution of the aortic depressor nerve and introduced the concept that the arterial system contains pressure sensitive areas[2]. Despite all that, in 1923 Hering was the first to discover the carotid sinus reflex and showed that the responsible nerve fibres are in the carotid sinus and in the common carotid artery bifurcation. He also showed that the afferent stimulation is located in a branch of the glossopharyngeal nerve (Hering's nerve) and that stimulation of the specific nerve causes deceleration of the heart function and hypotension that are independent of the accompanying bradycardia[3].

Anatomy and mechanical properties of baroreceptors

The carotid sinus constitutes an enlargement of the internal carotid artery at the site of its origin from the common carotid artery (Figure 1). This enlargement is due to the fact that at the specific point the wall of the vessel presents less muscle tissue[4] and more collagen (86%) compared to the common carotid artery (74%)[5].

Stimuli from each carotid sinus are transfered to a branch of the glossopharyngeal nerve (Hering's nerve) that includes sensory fibers from the carotid. The fibers of Hering's nerve are small (2-4 mm), myelinated[6] and most of their endings are at the tunica externa of the carotid sinus[7].

The stimulation threshold of the carotid sinuses with the use of static, non pulsatile, intravascular pressure is 60 mmHg in most of the species studied up to date[8]. The highest changes of reflexes are achieved at pressures of 175-200 mmHg as is seen from the changes they cause in the heart rate[9]. These findings are in accordance with those of other researchers who have used neuro-electric recordings in order to assess the action of the receptors. Such recordings have shown a direct relationship of the threshold and intensity of the carotid sinus stimulation to the changes in the function of autonomous efferent fibers[10]. When pressure is pulsatile, the stimulation threshold is 62 mmHg while there is a linear relationship between the action of Hering's nerve and the mean AP for pressures ranging from 80 to 180 mmHg[11]. However, the total gradient of the stimulation pressure of the carotid sinus and of the accompanying changes of RR interval is sigmoid[12] (Figure 2). Aside from the mean distending pressure, the rate of pressure change is equally important since it influences carotid reflexes at lower mean pressures[13].
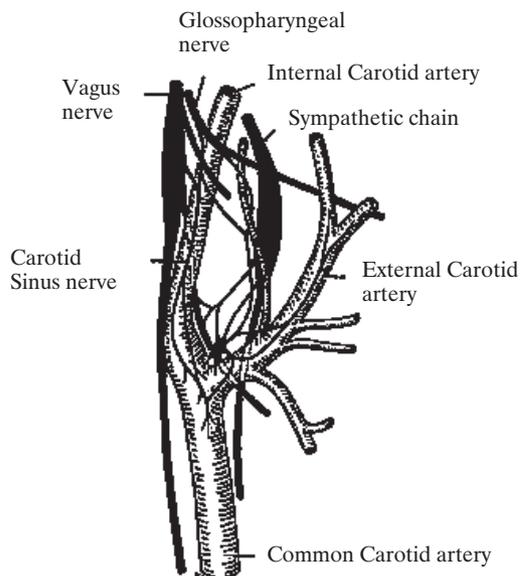
Figure 1. Carotid sinus and related neural structures in humans. The carotid sinus often includes the region of bifurcation and the initial segment of the external carotid artery.

Baroreceptors respond to stress changes and are stimulated by the deformation of the tunica externa of the vessel in which they are located. Whilst the mean intraluminal blood pressure as well as the range of pulse pressure play an important part in the action of reflexes, these seem to have an influence only if they cause deformation of the wall of the carotid sinus. The external pressure of the carotid sinus is an effective way to provoke such reflexes without changing the
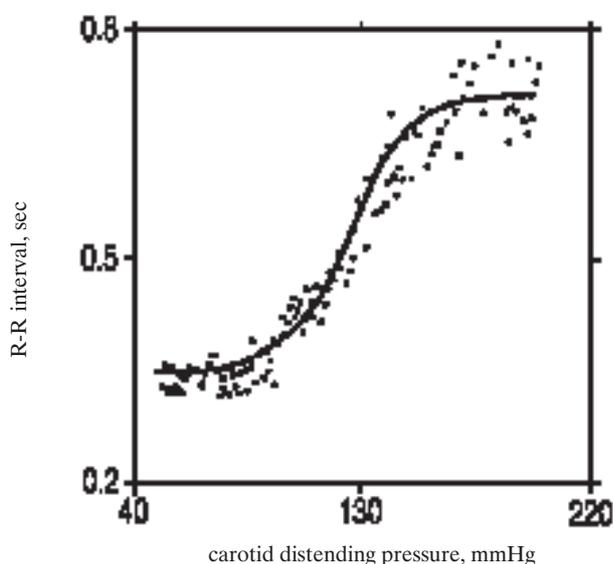
Figure 2. Relationship between carotid distending pressure and RR interval (Koch, 1931).

pressure in the sinus[14]. If we prevent the deformation of the carotid sinuses by placing a splint, then the changes of the intraluminal pressure on their own do not cause reflex provocation[15]. From the above, we understand why baroreceptor reflexes are influenced by changes in the distensibility or compliance of the sinus wall, caused by catecholamines, acidosis, hypoxia or their combination. Epinephrine infusion on the tunica externa of the carotid sinus increases the discharges from Hering's nerve[16]. This may be due to the contraction of the tunica muscularis of the sinus that causes deformation of the wall and activate the baroreceptors[17].

The aortic arch also contains a large number of baroreceptors whose behavior is completely different from the carotid sinus baroreceptors. In this case, the neuroreceptors are between the tunica media and the tunica externa of the vessel[18] and they seem similar to the ones of the carotid sinus. However, some of their nerve-endings are outside the outer third of the vascular tunica[8]. Electric stimulation of the aortic nerve in rabbits causes bradycardia and hypotension in a way similar to the one observed during stimulation of the Hering's nerve[1]. The pressure stimulation threshold of the aortic baroreceptors is higher than the one of the carotid baroreceptors (95 mmHg versus 62 mmHg) and the AP curve in relation to the activity of the aortic nerve shifts to the right, with the exception of the points of the highest and lowest pressure values, indicating in this way that the aortic receptors are much less sensitive than the carotid receptors for a given AP value[11]. Thus, aortic baroreceptors actually function as an anti-hypertensive mechanism and they remain relatively inactive when AP is within normal limits[19].

Normal action of baroreceptors

Baroreceptors receive AP changes through the mechanical distortion and the dilation of the vessel. This procedure takes place in three stages that include changes of the compliance and the glioelastic properties of the vessel, electric transformation of the mechanical stimulus and finally depolarization of the nerve-endings[20]. These stimuli are then transferred with cerebral syzygies IX and X to the medulla oblongata and more specifically to the nucleus of the solitary fasciculus. From there, by second class nerve fibers, they are transferred to the posterior part of the latero-ventricular segment of the medulla

oblongata, while by third class fibers they will finally be transferred to AP-controlling neurons at the anterior segment. Axons of these neurons reach the cellular bodies of the preganglionic sympathetic neurons of the intermediate-lateral nuclei of the spinal cord. The axons of the preganglionic neurons exit the spinal cord and are attached to the metaganglionic neurons in the ganglionic chain and the collateral ganglia as well as to the catecholamine secreting cells of the medulla of the adrenal glands. The axons of the metaganglionic noradrenergic neurons finally innervate the heart and the vessels[21]. Acetylocholine, serotonine, L-glutaminic, P substance and the Y neuropeptide have been proposed as neurotransmitters of this reflex arch[22].

Following extended increase of the AP, the action of baroreceptors is initially increased, and is reduced or modified over time as the AP reaches the value required. Furthermore, following a sudden increase of the AP, their action is depressed (postexcitatory depression) and their stimulation threshold is increased (reset). These changes occur rapidly (in sec or min) following the AP increase. The baroreceptors then (particularly those with myelinated fibers) continue to adjust at a slower rate and they practically return to normal levels even if the AP increase is extended and chronic[23].

Mechanisms regulating the action of baroreceptors

Several mechanisms have been proposed to explain baroreceptors' action regulation. Among these are:

I. Glioelastic relaxation of the vessel: AP increase causes distention of the vascular wall and distortion of the baroreceptors nerve endings. As soon as maximum AP is reached, the glioelastic relaxation may reduce the tension exerted on the nerve endings, despite the continuous increase of the vessel's diameter[24].

II. Activation of the $N\alpha^+$ pump: Inhibition of the $N\alpha^+$ pump with ouabain or K^+ solutions prevents or significantly reduces the post-excitatory depression and the resetting of baroreceptors following AP increase[25].

III. Activation of the K^+ channels: The administration of specific K^+ channels inhibitor reduces the adaptation of baroreceptors without influencing their maximum potential[26].

IV. Hormones and local chemical agents such as:

a) Norepinephrine, that circulates in the blood or it is released by the endings of the sympathetic neurons of the carotid sinus and the aortic arch, may either reduce the action of baroreceptors, by reducing the diameter of the vessel due to vasoconstriction, or increase their sensitivity, acting directly on the nerve endings[27],

b) prostacyclin that seems to directly affect the baroreceptors since prostacyclin injection in the carotid sinus increase the sensitivity of the baroreceptors, without changing its diameter, while indomethacin reduces it. The reduction of baroreceptor sensitivity that is observed in atherosclerosis and hypertension may be due to the decreased prostacyclin production that characterizes such diseases[28],

c) nitrogen oxide (NO), which when injected in the carotid sinus increases the baroreceptor sensitivity regardless of its vasodilating action[29],

d) oxygen free radicals that seem to act only on atheromatic vessels since the administration of the anti-oxidant enzymes superoxide dismoutase and catalase increases the action of baroreceptors in atheromatic vessels but not in normal vessels[30] and

e) agents secreted by activated platelets in the carotid sinus area, that activate the baroreceptors leading to reflex abolishment of the sympathetic system and hypotension[31].

The influence of baroreceptors' stimulation on the heart, the sympathetic and parasympathetic nervous system

Baroreceptors may influence heart function in three different ways: a) with direct modification of the influence of the sympathetic and parasympathetic system on the myocardium, the sinus node, the conductive system and the peripheral vasomotor tone, b) with indirect effect on the afterload (that follows the changes in vascular resistance) and c) the preload (following reflex changes in the capacity of the veins).

Downing and Siegel[32] showed that the depolarization of the sympathetic nerves of the heart follows the rhythm of the heart beat; it increases during systole and is depressed during diastole. Following bilateral dissection of the vagal nerves as well as of Hering's nerves, the stimuli become random and cease to correlate with the arterial pulse wave. A reduction of the sympathetic tone was also shown by Ninomiya et al.[33] who determined the relative benefit from the action of baroreceptors, taking in account the intensity of the depolarization of the sympathetic nerves of the myocardium. The degree of sympathetic activity

was reduced to noise levels with a mean aortic pressure of 167 mmHg. In most of the cases, the sympathetic depolarization is regulated by stimuli that come from peripheral changes of the tension. However, during acute systemic hypoxia, where there is also significant increase of AP, the inhibitory action of baroreceptors is abolished and the heart sympathetic depolarization is more intense[32].

In general, the increased afferent activity of baroreceptors that is caused by AP increase inhibits the efferent vasomotor action of the sympathetic system, whilst the reduced afferent activity of baroreceptors stimulates the efferent vasomotor action of the sympathetic system. This is achieved through the inhibitory GABAergic neuronic connection between the posterior and the anterior segment of the latero-ventricular system of the medulla oblongata[21].

The increased activity of baroreceptors also stimulates afferent fibers, that extend from the nucleus of the solitary bundle to the dorsal motor nucleus of the vagal nerve and the ambiguous nucleus. This leads to an intensification of the action of the parasympathetic system that is conveyed to the heart through the vagal nerve. The nerve fibers of the vagal nerve are mainly located in the atria and the conductive system up to the level of the sino-atrial node[34]. Furthermore, cholinergic fibers enter the myocardium of the ventricles and it has been proven that the action of acetylocholinesterase in the ventricles is significant and that it is equal to one third of that of the atriums[35]. Thus, stimulation of the vagal nerve inhibits the sinus node cells and those of the conductive system, causing bradycardia[36] and reducing the intensity of the atrium systole[37]. The effect of the stimulation of the parasympathetic in the function of the ventricles is not clear. Certain researchers failed to show negative inotropic action in the ventricles[38] while others showed that electrical stimulation of the peripheral endings of the vagal nerves reduces the maximum developing pressure of the left ventricle, proving in this way that the parasympathetic fibers participate in the regulation of ventricular contractility[39]. This may be due either to a parasympathetic dependent reduction of the myocardial response to a given quantity of norepinephrine[40] or to the fact that the cholinergic activity changes the quantity of norepinephrine that is secreted for a given level of sympathetic activity[41].

The baroreceptor reflex indirectly affects the endocrine system through the activation of the sympathetic system and more specifically: a) increases the secretory activity of the adrenal glands medulla although the increase of catecholamines contributes slightly to AP increament, b) activates the renine-angiotensin-aldosterone system leading to the direct contraction of the smooth muscle fibers of the vessels as well as Na^+ and water retention with an increase of the volume of the extracellular space, and finally c) the increased vasomotor activity causes increase of vasopresin through a reflex arch from the medulla oblongata to the hypothalamus. Vasopresin increases the total volume of water in the body, thus contributing to the restoration of the extracellular volume, although its contribution is relatively small[21].

We conclude that the baroreceptor reflex constitutes a powerful mechanism of negative retrograde AP regulation that aims at normalizing its changes. This is achieved directly by a reflex inhibition of sympathetic activity, activation of the parasympathetic system and increase of vascular resistance and heart rate and indirectly by renin and vasopresin secretion that, in turn, influence AP regulation. These regulating mechanisms are very important for homeostasis, both in normal as well as in pathological conditions.

Experimental methods for the calculation of baroreceptor sensitivity

Several methods and techniques have been used for the measurement of baroreceptors sensitivity in humans and can be divided in two main groups. The first one includes methods that cause artificial (mechanical or pharmacological) stimulation of the baroreceptors and the second one involves normal variations of AP and the heart rate. The ideal test for the control of baroreceptors must be safe, easy to use, non-invasive, with low failure rates and high repeatability. Unfortunately, all methods used up to date fail in at least one of these parameters.

a) The Oxford method

The first description of a practical method of baroreceptors assessment was made by Smyth et al. in 1969[42], who intravenously administered AP-increasing agents (initially angiotensin II and then phenylephrine hydrochloride). Each measurement of systolic AP was correlated with the respective RR interval, during which it occurred or with the one that followed. Using linear regression analysis on these pairs, the RR interval prolongation curve was formed towards the systolic AP, the gradient of which was
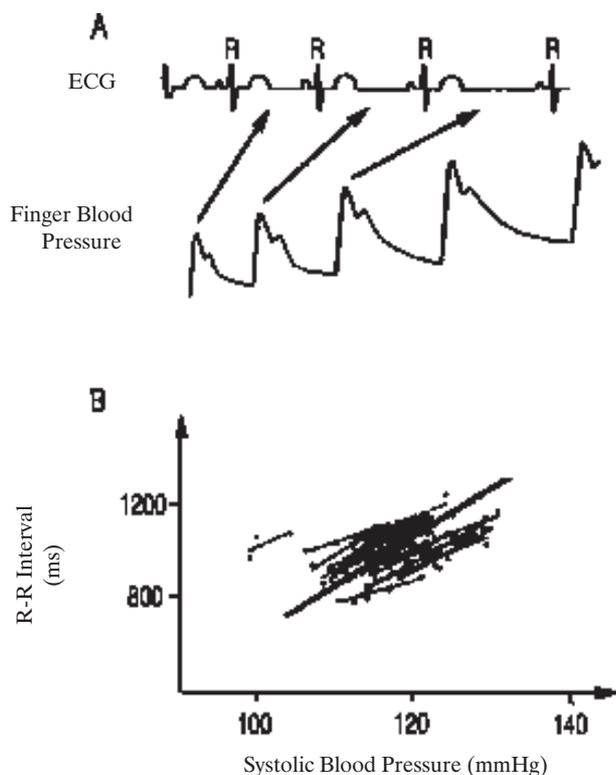
Figure 3. A schematic representation of the selection of spontaneous baroreflex sequences. It shows 3 beats of consecutively increasing systolic pressure associated with prolonging RR interval. The average regression slope (heavy line) is termed the spontaneous baroreflex sensitivity (Parlow et al, 1995).

defined as baroreflex sensitivity (BRS). Since the linear part of the curve is wide in men, moderate increases of the AP value (of 20 mmHg) are limited to that area of the curve. Initially, AP measurement was carried out in an invasive way with the insertion of an intra-arterial catheter, a fact that limited the broad use of the method. Finally, with the development of devices such as Finapress (a type of photoplethysmograph), that measure AP per heart beat, in a non invasive way, larger patient groups can be studied. The BRS value that is calculated in a non-invasive way is almost the same as the BRS value that is calculated with the invasive method[43].

In this method, the baroreceptors stimulation is done in a physiological way, since the stimulus is AP increament. However, it is thought that AP changes occur exclusively on the linear part of the curve and that only a small part of the sigmoid curve can be determined with this method.

A variation of this method takes into account the tachycardia that is related with AP decrease following administration of vasodilating agents (sodium nitroprusside or nitroglycerine)[44]. BRS values that are measured following AP increase are significantly higher than those following same degree AP reduction. This difference may be related with the fact that baroreceptors are firmly connected with the wall of the carotid sinus[45].

b) The Valsalva maneuver

The Valsalva maneuver (effort of intense expiration with closed glottis) has an evident influence on the cardiovascular system. Patients usually expire in a manometer, achieving in this way stable pressure (e.g. 40 mmHg) for 10-15 sec. The fourth stage of the procedure, where there is an AP increase and a reduction of the heart rate, can be used for BRS calculation[46].

Aside from the baroreceptors stimulation, the maneuver causes significant changes in venous return, which influence intra-cardiac receptors and receptors in the thoracic wall that are sensitive to tension, thus causing cardiovascular changes that are independent from the baroreceptors[47]. This technique has relatively high failure rates either because patients find the method particularly difficult or because AP is not satisfactorily increased at the end of the maneuver. Moreover, this method has very low reproducibility[48].

c) Neck suction method

The first description of this method was in 1957 by Ernsting and Parry[49] who were the first to apply suction on a neck air chamber to selectively activate the carotid baroreceptors and to cause slowing of the heart rate. The device they used includes an air chamber that can exert positive as well as negative pressure on the neck for brief time periods[50].

This method is better than the pharmacological one since it is non aggressive and exerts a rapid stimulus directly on the neck. In this way, we avoid the stimulation of other regulatory systems and it can be used even when patients hold their breath (to reduce the influence of breathing on the measurements). With this method, we can study the total activity of the baroreceptors, from threshold to maximum point of action. Neck suction, may cause changes in venous return from the vessels of the head or even change the action of aortic baroreceptors with results contrary to the anticipated, while on the other hand it requires very specialized equipment.

There are three BRS assessment methods that are based on the changes of the AP and of the heart

rate at rest: the sequence or spontaneous method, the method of spectral analysis and the control breathing method.

d) The sequence or spontaneous method

This method was first described by Bertinieri at al. in 1985[51]. Brief AP recording periods (5-10 min) are used in conjunction with recording of the RR interval per heart beat while the patient is at rest. A software program then undertakes the task of identifying: a) the periods of three or more consecutive beats during which systolic AP is increased by at least 1 mmHg per beat, while the RR interval is progressively getting longer and b) the periods of three or more consecutive beats during which systolic AP is decreased by at least 1 mmHg per beat, while the RR interval is progressively reduced. These periods are drawn in a graph and the gradient of the linear curve that is formed by all the lines constitutes the BRS (Figure 3).

In a later description of this method in non anesthetized cats[52] the authors introduced a threshold for the RR interval of 4 ms, that was increased to 6 ms for humans[53]. Ever since it was first presented, this method is used in patients with high threshold range both for AP as well as for the RR interval.

e) The spectral analysis method

AP and RR interval variation at rest based on the frequency-domain is achieved with the use of auto-regressive modeling[53-55]. When all the parameters of this formulation are assessed (calculated on the basis of Akaike's criteria), a dynamic spectrum of normal[54] density is created by all the time series. This also constitutes one of the disadvantages of the method. If the wrong settings are chosen, the dynamic spectrum will not accurately represent the one of the real system. A few parameters will create a system that will not be detailed, while a setting that will use many parameters will produce a spectrum with fictitious peaks[55,56].

BRS is measured with α-index that is the square root of the ratio between the RR interval variability and the AP in the frequency zone that interests us. It is generally accepted[57] that the α-index can be measured only when the square of the in-phase values of the RR interval and of the AP, as these are calculated with the use of cross-spectral analysis, is higher than 0.5.

f) Control breathing method

Breathing plays an important role in cardiovascular regulation but its effect on BRS measurement has been ignored. It has, however, been proven that controlled breathing improves the correlation between α-index and BRS that is calculated with the administration of phenylephrine. Based on these data, Davies et al. described, very recently, a new method of BRS calculation, using a controlled breathing protocol[58]. According to this protocol, the patient is directed with the help of a screen to breathe at a rate of 0.1 Hz. The heart rate is recorded with the use of ECG, AP is recorded with the Finapress device and the number of breaths is recorded with the use of plethysmography. Initially, patients are followed for 30 sec in order to ensure that they follow correctly the protocol, before we start recording for 5 minutes duration. The signals of the RR intervals and of the AP that are received in this way are passed through a simple digital filter (time domain) where time processing takes place and we thus take the part of the signal in the frequency that interests us (0.1 Hz). BRS, calculated with this method, is equal to the ratio of the mean range of RR intervals' variation to the mean range of AP variations (Figure 4). The authors
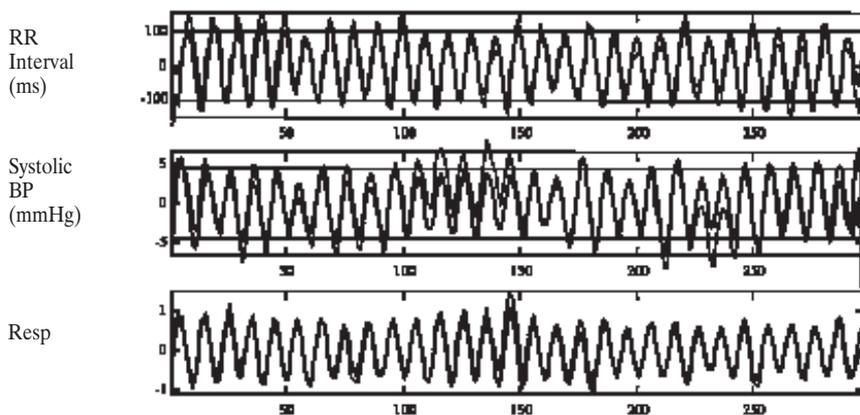
Figure 4. Assessment of baroreflex sensitivity using time domain analysis during controlled breathing. The dotted line shows the measured signal and the continuous line the filtered signal (Davies et al, 1999)

showed that this method is very simple in its application and the best reproducibility and the lowest failure rates as compared to all other methods mentioned above[58].

Baroreceptors in several cardiovascular diseases

The role of baroreceptors in hypertension

It seems that BRS is reduced in hypertension but its participation in the onset of the disease has not been defined. AP was found at 112.7 mmHg, in dogs, to whom the carotid and aortic baroreceptors had been denervated, while it was only 101.6 mmHg in the controls[59]. Significant instability was also noted in AP values with stable variation of 125 mmHg, as compared to 50 mmHg in the control group. Some of these animals did not present any predisposition to continuous increase of the AP even after a long follow-up (15 months). However, baroreceptors seem to contribute to maintaining AP. Studying dogs with nephrogenic hypertension, McCubbin et al.[60] showed that the type of depolarization of the carotid and aortic depressor nerve was not different between hypertensive dogs and healthy controls. The pressure threshold on the carotid sinus, required for the depolarization of the nerve fibers was 60 mmHg in the controls and 120 mmHg in hypertensive dogs. Thus, the baroreceptors system preserves its ability to offset acute AP changes in higher AP values. In this way, it contributes to persisting hypertension and does not react to its action. This result may be attributed either to the de-activation or loss of low threshold fibers[61,62] or to compliance changes of the carotid sinus wall[63].

The role of baroreceptors in the prognosis of post-infarction patients

Scwartz and Stone indicated for the first time the significance of BRS in the prognosis of arrhythmias, using an experimental dog model with sudden death simulation[64]. In that model, in the presence of healed anterior myocardial infarction, physical exercise caused a normal raise of the sympathetic activity combined with acute ischemia of the lower wall of the myocardium[65]. During the ischemic period, approximately half of the dogs presented ventricular fibrillation (sensitive) and the other half non fatal arrhythmias (resistant). Researchers reached two conclusions: a) dogs with a previous myocardial infarction had less baroreceptors sensitivity than

healthy controls and b) the sensitivity values before the ischemic episode were significantly lower in sensitive than in resistant dogs[64]. The ventricular fibrillation risk increased from 20% (for dogs with BRS >15 ms/mmHg) to 91% (for dogs with BRS <9 ms/mmHg).

These findings led to clinical studies in order to assess the prognostic value of BRS in post-infarction patients. The first of these studies, by La Rovere et al. in 1988[66], examined BRS in 78 patients one month after the first infarction. During two years follow-up, 7 patients died (4 because of sudden death). BRS in the deceased patients was significantly lower than in the survivors. The mortality of patients with BRS <3 ms/mmHg was 50% whilst only 3% in patients with a higher BRS. There was no correlation between BRS and ejection fraction, something that indicates that low BRS is not only due to the impaired function of the left ventricle. This was also verified by another study where BRS was found to be the most potent prognostic factor for persisting ventricular tachycardia than the variation of the heart rate and the signal average ECG[67,68].

The largest clinical study conducted in post-infarction patients was the ATRAMI study (Autonomic Tone and Reflexes After Myocardial Infarction)[69]. It aimed at assessing BRS (method of phenylephrine administration) and the variation of the heart rate in 1284 patients, 16 days after a myocardial infarction. During follow-up (21±8 months), 49 patients died or had at least one episode of cardiac syncope due to ventricular fibrillation. Patients with low variation (SDNN <70 ms) and BRS values (<3.0 ms/mmHg) presented a higher relative risk of cardiac death, reaching 3.2 and 2.8 respectively. These studies proved that BRS measurement after an infarction plays a significant part in the prognosis of such patients.

Baroreceptors sensitivity and heart failure

BRS reduction has been widely described both in animals as well as in humans with heart failure[70,71,72]. Despite all that, there is only little information regarding the prognostic value of BRS in chronic heart failure. In a study of 35 patients who were followed-up for 4 years, Osterziel et al. showed that BRS measured with the neck suction technique was lower in patients who died as compared to the one of the survivors. However, in multivariant analysis, only systolic AP and noradrenaline levels constituted independent prognostic markers[73].
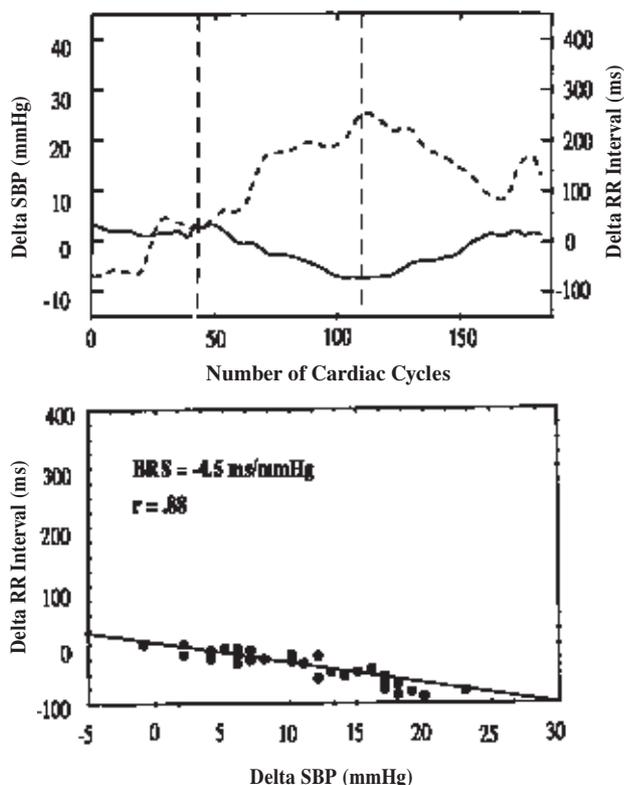
Figure 5. Example of BRS assessment in a patient with a tachy-cardic response to phenylephrine administration. As a result, the BRS is negative (Mortara et al, 1997).

Mortara *et al.* assessed the BRS with the pheny-lephrine administration method in 282 patients with sinus rhythm who were referred for heart trans-plantation. The mean BRS value was 3.9 (4.0) ms/mmHg, while 22 patients presented tachycardia as a result of the baroreceptors stimulation and thus presented negative sensitivity values (Figure 5). After a mean follow-up of 12 months, 53 patients died of cardiac death (15 because of sudden cardiac death), 5 presented an aborted cardiac arrest and 20 needed immediate transplant (admission in the intensive care unit and cardiovascular support with the use of intraortic balloon). The mortality rates were higher for patients with BRS <1.3 ms/mmHg than for patients with higher values. BRS remained an important mortality factor in the multivariant analysis too, that included NYHA class, ejection fraction of the left ventricle, RR interval and maxi-mum oxygen consumption[74].

The causes of BRS reduction in chronic heart failure include baroreceptors degeneration, increas-ed yielding-in of the carotid sinus wall (due to inc-rease of sodium and water content) and the centrally originating changes of the baroreceptors[75]. Digitalis may play some part in the changes of the autono-mous nervous system that occur in heart failure. Intravenous infusion of glycosides in animals with-out heart failure increased the activity of Hering's nerve, which was accompanied by a reduction of the intensity of the cardiac systole. Following bilateral dissection of Hering's nerve, glycosides led to in-crease of both the intensity of the cardiac systole and of the AP[76].

Baroreceptors sensitivity and congenital heart diseases

We know that patients with congenital heart disease have a reduced sympathetic response to fatigue, which indicates the importance of the autonomous nervous system. However, BRS in these patients had not been studied up to date. Ohuchi et al.[77] have recently been engaged in a research effort, compar-ing BRS (phenylephrine administration method) in patients following surgery for atrial septal defect and in patients who had undergone surgery for the reconstruction of the right ventricular outflow tract. They used as controls patients with Kawasaki syn-drome without coronary artery stenosis. The baro-receptors' sensitivity was found reduced in both groups of patients, in particular in the second group, as compared to the controls. In this group, BRS was negatively correlated both with the total number of surgeries and with age during surgery. Also, it was higher in patients without previous palliative sur-geries and it was correlated with the duration of post-operative follow-up. Finally, in patients with atrial septal defect, BRS is reduced one month after surgery and it is increased in the first year, reaching levels higher than the pre-operative ones. To the contrary, in patients of the second group, BRS was reduced in the first month but it presented stati-stically significant increase in the first year following surgery. Such changes were attributed to sympa-thetic denervation of the myocardium which takes place during surgery and it seems that the enervat-ion rehabilitation is slow or uncertain.

A comparison of the BRS in operated patients with Fallot tetralogy and in healthy controls was also performed by our own team, making use of non - invasive methods. Preliminary results showed that patients who had been operated on had clearly reduc-ed sensitivity for all methods compared to healthy

controls. Reduced BRS is not related to the patients' age during surgery and the years that have elapsed, nor is it related with known survival markers such as the QRS wave duration. Since sudden death constitutes the most severe complication in these patients, it may be that BRS measurement will provide us with useful information for their prognosis[78].

From all the above, it becomes evident that baroreceptors play an important part in the normal regulation of the circulatory system. It is also proven that the de-regulation of the baroreceptors' reflexes contributes to the pathogenesis of several cardiovascular diseases. Finally, from the BRS measurement, useful conclusions can be drawn for the prognosis of such diseases. Modern cardiological research, recognizing the importance of baroreceptors, is oriented towards the discovery of new and more accurate methods of sensitivity calculations and the investigation of their relationship with other regulatory systems of the circulatory system.

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