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Neurohumoral Control of Heart Rate

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1. Introduction

It is well known that the heart generates and conducts electrical impulses, leading to a rhythmical contraction of the cardiac muscle. In normal situations, the atria contract about one sixth of a second ahead of ventricular contraction, allowing the filling of the ventricles before they pump the blood through the lungs and peripheral circulation. Additionally, all portions of the ventricles contract almost simultaneously, which is essential for a most effective pressure generation in the ventricular chambers. This rhythmical and conductive system is susceptible to damage by heart disease, especially by ischemia of the cardiac tissues. The result is often an abnormal heart rhythm and sequence of contraction of the heart chambers, leading to a reduction in pumping effectiveness, even to the extent of causing death (Hall, 2011).

Heart rate (HR) is not a static hemodynamic parameter but instead changes over time in response to physical and mental demands. HR is normally determined by spontaneous and periodic depolarizations of the sinoatrial node, the frequency of which is modulated by the sympathetic and parasympathetic divisions of the autonomic nervous system, the intrinsic cardiac nervous system, reflexes, and respiration. These neural systems also partially control cardiac contractility and conduction of electrical activity through the heart. As a result, HR (chronotropism), contractility (inotropism), and conduction (dromotropism) are adjusted to meet the changing needs of the body (Feldman et al, 2010).

2. Electrical activity of the heart

The properties of automaticity and rhythmicity are intrinsic to the cardiac tissue and considered a very complex phenomenon and, besides cellular mechanisms, integrative different factors are involved in cardiac pacemaking. The cardiac electrical events are initiated with changes in the permeability of the cell membrane, mainly to Na^+, K^+ and Ca^{2+} ions. Changes in cell membrane permeability alter the rate of ion passage across the membrane with the opening and closing of ion channels. Two main types of action potentials are observed in the heart: (A) fast action potentials, that occur in the normal myocardial fibers in the atria and ventricles and in the specialized conducting fibers (Purkinje´s fibers) and (B) slow action potentials, which are found in the sinoatrial (SA) node, the natural pacemaker of the heart, and in the atrioventricular (AV) node, the specialized tissue involved in conducting the cardiac impulse from atria to ventricles (Bouman and Jongsma, 1986).

In mammalian, the region of the heart that ordinarily generates impulses at the greatest frequency is the SA node. In humans, it lies in the groove where the superior vena cava joins the right atrium. It is a small, roughly rectangular region at the edge of the right atrium, bounded on two sides by the superior and inferior vena cava and on the other two by the interatrial septum and the crista terminalis, a part of the right atrial muscle over whose endocardial surface the pacemaking tissue of the SA node extends (Brown, 1982). The intact sinoatrial node is a heterogeneous structure and contains 2 principal types of cells: 1) small, round cells, which have few organelles and myofibrils; and 2) slender, elongated cells, which are intermediate in appearance between the round and the ordinary atrial myocardial cells. The round cells are probably the pacemaker cells, whereas the transitional cells probably conduct the impulses within the node and to the nodal margins (Verheijck et al., 2011; Verheijck et al., 2004; Tellez et al, 2006).

In the SA node cells, the upstroke of action potential is less steep, the plateau is not sustained and the depolarization is more gradual. However, the principal distinguish feature of a pacemaker resides in resting phase. In nonautonomic cells, the resting potential is constant, whereas in a pacemaker fiber there is as low depolarization that proceeds at steady rate until a threshold is attained, and then an action potential is triggered (Brown, 1982; Berne and Levy, 2009). In the pacemaker cells of the SA node the diastolic depolarization is attributed to at least 3 ionic currents: (1) an inward current (I_f), induced by hyperpolarization; (2) an inward Ca^{+2} current, (I_{Ca}); and (3) an outward K^+ current, I_K . The inward current (I_f) is carried mainly by Na^+ and the current is conducted through specific channels that differ from the fast Na^+ channels. This current becomes activated during the repolarization phase of the action potential, as the membrane potential becomes more negative than about -50mV. The more negative the membrane potential becomes at the end of repolarization, the greater is the activation of the I_f current. The second current responsible for diastolic depolarization is the slow inward current. This current is composed mainly of Ca^{+2} and therefore it is referred to as the Ca^{+2} current, (I_{Ca}). This Ca^{+2} current is carried mainly by T-type Ca^{+2} channels. Once the Ca^{+2} channels become activated, the influx of Ca^{+2} into the cell increases and accelerates the rate of diastolic depolarization, which then leads to upstroke of the action potential. The progressive diastolic depolarization mediated by the 2 inward currents, I_f and I_{Ca}, is opposed by a third current, an outward K^+ current, I_K . This efflux of K^+ tends to repolarize the cell after upstroke of the action potential. The outward K^+ current continues well beyond the time of maximum repolarization, but it diminishes throughout the end repolarization. Hence the opposition of I_K to the depolarizing effects of the 2 inward currents (I_{Ca} and I_f) gradually decreases (Brown, 1982; Berne and Levy, 2009).

From the SA node the cardiac impulse spreads radially throughout the right atrium along ordinary atrial myocardial fibers, at a conduction velocity of approximately 1m/sec. A special pathway, the anterior interatrial myocardial band, conducts the impulse from the SA node directly to the left atrium. Tree tracts, the anterior, middle, and posterior internodal pathways, constitute the principal routes to the conduction of the cardiac impulse from the SA to AV node. The AV node contains the same two cell types as the SA node, however the round cells are sparser and elongated cells preponderate. The AV node has been divided into three functional regions: 1) the AN region, the transitional zone between the atrium and the remnant node; 2) the N region, the midportion of the AV node; and 3) the NH region, the upper portion of the specialized conducting system for the ventricles. Usually, the AV node and the bundle of His constitute the only pathways to action potential conduction from atria to ventricles. The

conductive system passes subendocardially down the right side of the interventricular septum for about 1cm and divides into the right and left bundle branches. The right bundle branch is a direct continuation of the bundle of His and it proceeds down the right side of the interventricular septum. The left bundle branch, which is considerably thicker than the right, arises almost perpendicularly from the bundle of His and cross the interventricular septum. The right bundle branch and the two divisions of the left bundle branch ultimately subdivide into a complex network of conducting fibers called Purkinje´s fibers, which ramify over the subendocardial surfaces of both ventricles (Brown, 1982).

In the myocardium, the action potential generation includes 5 distinct phases: 1) Phase 0: the chemical and electrostatic forces both favor the entry of Na^+ into the cell through fast Na^+ voltage-gated channels to generate the upstroke; 2) Phase 1: the chemical and electrostatic forces both favor the efflux of K^+ through transient outward current (I_{to}) channels to generate early, partial repolarization; 3) Phase 2: during the plateau, the net influx de Ca^{2+} through L-type Ca^{2+} voltage-gated channels is balanced by the efflux of K^+ through rectifier (I_k), inwardly rectifying (I_{k1}) and I_{to} channels; 4) Phase 3: the chemical forces that favor the efflux of K^+ through I_k, I_{k1},I_{to} channels predominate over the electrostatic forces that favor the efflux of K^+ through these same channels; 5) Phase 4: the chemical forces that favor the efflux of K^+ through I_k and I_{k1} channels exceed very slightly the electrostatic forces that favor the influx of K^+ through these same channels (Berne and Levy, 2009).

3. Neural control of HR

The peripheral circulation distributes the cardiac output to the various organs and tissues according to their individual metabolic or functional needs while maintaining arterial blood pressure within a relatively narrow range. Regional blood flows can be efficiently regulated at the local level by the intrinsic ability of vessels to respond to various mechanical forces (e.g., wall tension and shear stress) as well as chemical stimuli (e.g., tissue metabolites and O_2). However, a perfect regulation of the peripheral circulation cannot be achieved only by the local vascular control mechanisms, but require the coordinating activity of central neural outflow to the heart and blood vessels (Thomas, 2011). In this field, the autonomic nervous system plays an important role to normal cardiovascular control and changes in autonomic balance has been related to several cardiovascular disorders, such as cardiac arrhythmias and hypertension (Workman, 2010; Pagani and Lucini, 2001).

3.1 The autonomic nervous system and cardiovascular control

The autonomic nervous system is responsible for the involuntary control of most visceral organs, including the heart and the interactions between the sympathetic and parasympathetic limbs play a critical role in cardiac electrical stability and arrhythmias generation. In general, sympathetic activation has a profound arrythmogenic potential (Schwartz et al., 1978, Schwartz 1984). Experimental stimulation of sympathetic nerves or stellate ganglia induces ECG repolarization changes and reduces the fibrillation threshold, facilitating ventricular fibrillation (Yanowitz et al, 1966; Podrid et al, 1990), while the use of β-adrenergic blocking agents can improve survival in patients following myocardial infarction (Gottlieb et al, 1998). On the other hand, vagal activation has a powerful antifibrillatory effect (Vanoli et al., 1991; De Ferrari et al., 1994). Therefore, autonomic imbalance could become either proarrythmic or anti-arrythmic based on which of the two components is going to prevail (Schwartz and De Ferrari, 2011).

Preganglionic fibers of autonomic nervous system are originated from central nervous system (CNS) at the level of the brainstem or sacral spinal cord (parasympathetic fibers) and the thoracic or lumbar spinal cord (sympathetic fibers). Both parasympathetic and sympathetic preganglionic fibers release acetylcholine which binds to nicotinic receptors located in the cell bodies of postganglionic neurons, leading to action potential generation. This synapse occurs in autonomic ganglia located outside of the CNS (Thomas, 2011).
The axons of postganglionic neurons innervate the effector tissues, including cardiovascular tissues. Parasympathetic neurons are distributed much more heterogeneously throughout the heart than sympathetic neurons. The density of parasympathetic innervation in the sinoatrial (SA) and AV nodes is considerably higher than in the surrounding atrial or ventricular tissue (Vaseghi and Shivkumar, 2008). Cardiac sympathetic innervation of the heart includes innervation of the SA node and myocardial cells. Based on norepinephrine content studies, a gradient exists in sympathetic innervation from atria to ventricles and from base to apex of the heart, indicating that the atria are most densely innervated, but the ventricles are also supplied with a sympathetic network, most densely at the base (Vaseghi and Shivkumar, 2008). Regarding the neurotransmitters, postganglionic parasympathetic fibers release acetylcholine, which binds to muscarinic receptors on the target tissue, while postganglionic sympathetic fibers release norepinephrine, which binds to either α or β adrenergic receptors (Thomas, 2011).
The effects of sympathetic and parasympathetic neurons on HR will be based on changes in the ion currents of SA node action potential generation. Norepinephrine release from post ganglionic sympathetic neurons will increase the slope of diastolic depolarization in SA node by the enhancement of the resting potential, while acetylcholine release from parasympathetic postganglionic neurons will decrease the slope of diastolic depolarization by hyperpolarization of the resting potential (Verrier and Tan, 2009). Additionally, sympathetic stimulation increases the rate of conduction as well as the level of excitability in all portions of the heart and augments greatly the force of contraction of all the cardiac musculature. Maximal stimulation can almost triple the frequency of heartbeat and can increase the strength of heart contraction as much as twofold. On the other hand, parasympathetic stimulation to the heart decreases the excitability of the A-V junctional fibers between the atrial musculature and the A-V node, thereby slowing the transmission of the cardiac impulse into the ventricles (Guyton and Hall, 2006).
Given the ability to modulate both HR and stroke volume, the autonomic nerves provide an important mechanism to rapidly adjust cardiac output to meet short-term changes in the body's needs (cardiovascular reflexes). In humans, there is a good deal of tonic vagal discharge and a moderate amount of tonic sympathetic discharge, showing a parasympathetic prevalence on the heart. Additional vagal discharge can further reduce HR, consequently cardiac output, whereas additional sympathetic discharge can increase HR and stroke volume and augment cardiac output. Conversely, withdrawal of tonic vagal or sympathetic discharge has opposing effects to increase or decrease cardiac output, respectively (Thomas, 2011).

4. Cardiovascular reflexes

It is well known that the maintenance of arterial pressure at adequate levels to perfuse the tissues is a basic requirement for survival. In cardiovascular system, among the mechanisms that act buffering arterial pressure fluctuations we can highlight the role of the neural

reflexes. Such control is an important pathway to effect rapid changes in blood pressure and in the distribution of cardiac output that are essential to maintain a sufficient perfusion to vital organs, such as heart, brain and the kidney in face of physiological and environmental challenges. This rapid control of cardiovascular function is achieved through arterial and non-arterial reflexes that detect and correct changes in arterial blood pressure (baroreflex), blood volume (cardiopulmonary reflex) or chemical composition (chemoreflex) of the blood (Vasquez et al., 1997). It is important to notice that the effectiveness of these systems may be modulated by hormonal systems, such as angiotensin II and nitric oxide. The understanding of the key concepts about these reflexes under physiological conditions and the effects of hormonal substances on its functioning is an important step to clarify the development of arrhythmias.

4.1 Baroreflex

The baroreflex feedback loop is one of the most important mechanisms controlling arterial pressure. The main purpose of the baroreflex function is to provide a rapid and efficient stabilization of arterial blood pressure on a beat-to-beat basis by means of strategically located arterial sensors which are sensitive to high blood pressure and known as arterial baroreceptors. The baroreceptors endings are located in adventitia layer of carotid sinus and aortic arch with their soma located in the petrosal and nodose ganglia respectively. These receptors are mechano-sensitive and the distension of the vessels that occurs at each heart beat leads to action potential generation on these terminals which are transmitted to CNS, buffering arterial pressure fluctuations through changes in sympathetic and parasympathetic activity (Vasquez et al., 1997).

To achieve this precise control, the generated action potentials in each systole travel centrally to synapse onto neurons in the nucleus tractus solitarii (NTS) in the dorsal medulla. NTS neurons project to "higher" brain nuclei, as well as other nuclei in the brainstem that are critical for efferent sympathetic and parasympathetic activity (Loewy and Spyer, 1990). Projections from NTS are connected to the inhibitory neurons of caudal ventrolateral medulla (CVLM) that subsequently synapse to excitatory neurons in the rostral ventrolateral medulla (RVLM). RVLM exerts a tonic discharge upon the preganglionic sympathetic neurons, located in the intermediolateral column (IML) of the spinal cord (Kirkman and Sawdon, 2004). Therefore, activation of the baroreceptor afferents innervating the NTS causes excitation of neurons projecting to the CVLM, which in turn inhibits RVLM. These events lead to less activity from the RVLM to IML, reducing sympathetic efferent activity (Figure 1A). Several studies have demonstrated that disturbances in the normal functioning of these nuclei can be related to the development of arrhythmias. In example, Issa et al. (2005) showed that the central inhibition of the sympathetic drive using clonidine reduces the occurrence of ventricular tachycardia/ventricular fibrilation in a canine heart failure model.

In parallel, NTS neurons also synapse onto preganglionic vagal neurons localized within nucleus ambiguus (NA) and in the dorsal motor nucleus of the vagus (DMNX, Figure 1A). These neurons dominate the neural control of HR under normal conditions and also influence the prognosis of many cardiovascular disorders, such as sudden cardiac death, ventricular fibrillation, and myocardial ischemia (Wand et al, 2001). The axons from preganglionic cardiac vagal neurons travel down the vagus nerve and synapse onto postganglionic cardiac vagal neurons in cardiac ganglia. The synaptic innervation of cardiac vagal neurons is therefore critical for the tonic and reflex evoked changes in cardiac vagal activity that control HR.

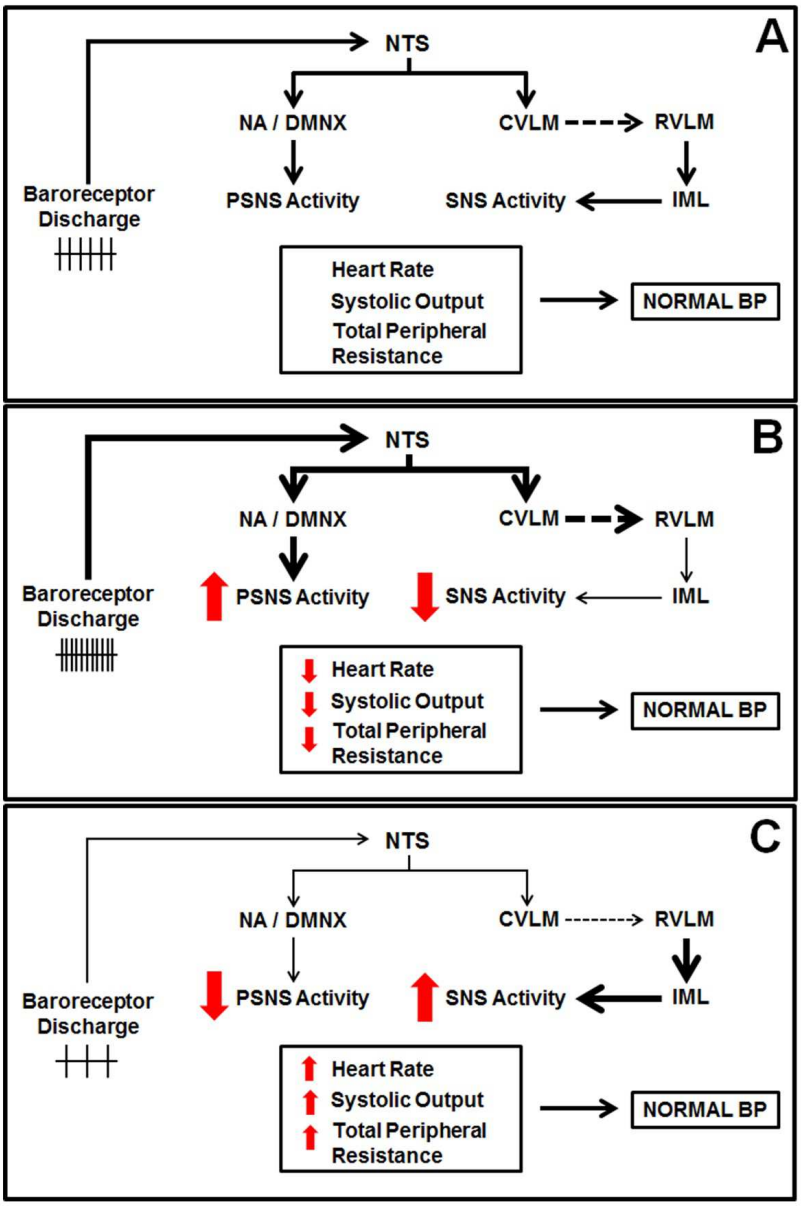

Fig. 1. Schematic diagram showing the baroreflex functioning during normal (A), increased (B) and decreased blood pressure (C). NTS: nucleus tractus solitarii, NA: nucleus ambiguus, DMNX: dorsal motor nucleus of the vagus, CVLM: caudal ventrolateral medulla, RVLM: rostral ventrolateral medulla, IML: intermediolateral column, PSNS: parasympathetic nervous system, SNS: sympathetic nervous system, BP: blood pressure. The continuous arrow and the dashed arrows indicate a stimulatory and an inhibitory synapse, respectively.

Therefore, when blood pressure rises, the baroreceptor afferent activity augments, leading to increased vagal activity and diminished sympathetic outflow. These effects will reduce HR and cardiac contractility, causing a decrease in cardiac output. Additionally, the fall the sympathetic activity to blood vessels also leads to vasodilation, diminishing the vascular resistance (Figure 1B). The reduced cardiac output and vascular resistance return blood pressure to its original level. On the other hand, a fall in blood pressure results in reduced baroreceptor afferent activity, causing a decrease in vagal activity and augmented sympathetic outflow (Figure 1C). These events increase cardiac output and vascular resistance, normalizing arterial blood pressure.
Experimentally, the baroreflex function can be evaluated through changes in arterial pressure. In bolus phenylephrine injections elicits increases in arterial pressure leading to reflex bradycardia and sodium nitroprusside injections reduces arterial pressure causing reflex tachycardia. Typical recordings of baroreflex evaluation are displayed in Figure 2.

4.2 Cardiopulmonary reflex

Despite the great importance of baroreflex in controlling arterial pressure, several investigations have demonstrated that the neural reflex of circulation also depends on cardiopulmonary reflex.
Cardiopulmonary receptors are found in low pressure portions of the circulation, such as walls of the atria and pulmonary arteries. These mechano-sensitive receptors are activated by the distension of the vessels walls, responding to changes in central blood volume (Thomas, 2011). The impulses arising from these receptors exert a tonic restraint on cardiac function and contribute to the physiological control of circulation. Cardiopulmonary reflexes are stimulated not only by changes in cardiac filling pressure but also by chemical agents, such as prostaglandins and serotonin (Vasquez et al., 1997). The cardiopulmonary fibers converge to the same pool of central neurons as the baroreceptors and act in a similar way (Spyer, 1990). Therefore, increased discharge of cardiopulmonary vagal afferent C fibers results in reflex enhancement of parasympathetic activity and decreased sympathetic outflow, leading to bradycardia, hypotension and apnea, also known as the Bezold-Jarisch reflex (BJR) (Kashihara, 2009). In addition, increased discharge of the cardiopulmonary receptors diminishes renal sympathetic outflow and pituitary release of vasopressin, thereby decreasing Na^+ and water reabsorption by the kidneys, increasing urine volume, and reducing blood volume. As changes in blood volume affect cardiac output and arterial pressure, this provides an additional mechanism by which the cardiopulmonary reflex contributes to blood pressure regulation (Thomas, 2011).
Interestingly, cardiopulmonary reflex may exert a tonic inhibitory influence in the arterial baroreflex sensitivity (Abboud and Thames, 1983). In pathological conditions, such as acute myocardial infarction, the reduction in baroreflex sensitivity could be explained by an increase in cardiopulmonary reflex sensitivity (Lacerda et al., 2007). Furthermore, the BJR activation might cause sudden cardiac death during ischemic injury (Robertson et al., 1985), since the overactivation of cardiopulmonary reflex together with baroreflex blunting might cause severe bradycardia and hypotension, placing the patient's life at risk due to the magnitude of sympathetic inhibition and vagal activation. These data demonstrate that the interplay between baroreflex and cardiopulmonary reflex may exert an important role in the progression of cardiovascular diseases and arrhythmias generation.

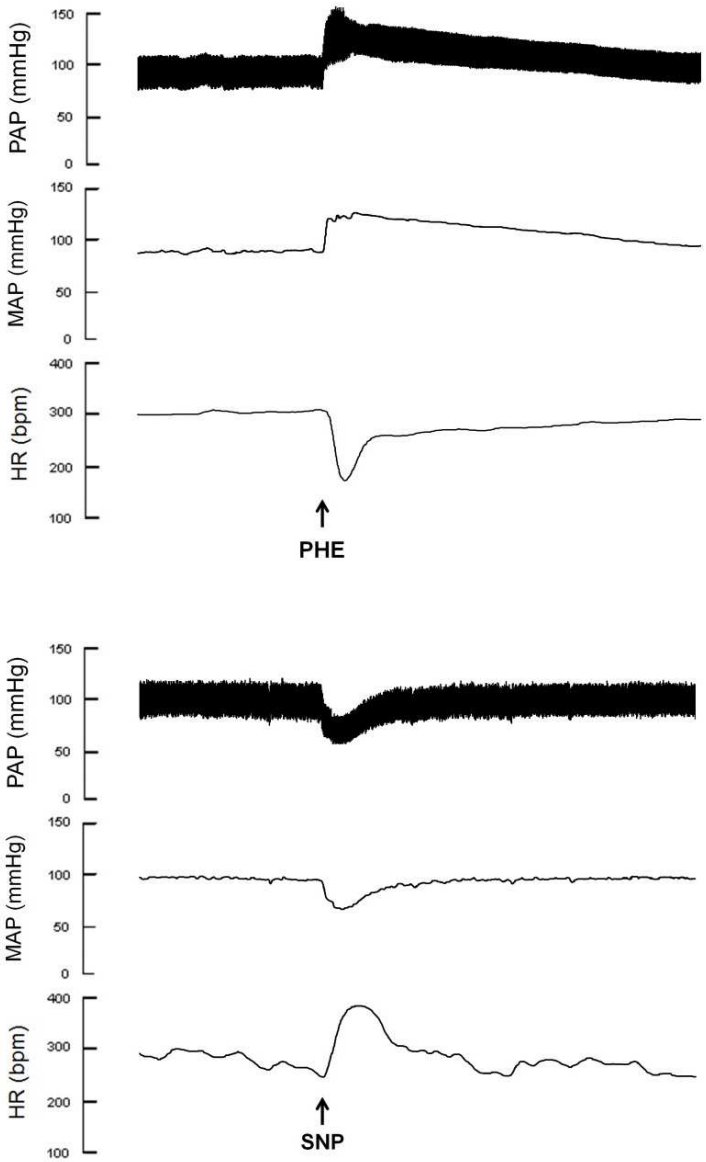

Fig. 2. Typical recordings of baroreflex evaluation in anesthetized rats. The phenylephrine-induced increase in arterial pressure leads to reflex bradycardia (upper panel) and the sodium nitroprusside-induced decrease in arterial pressure results in reflex tachycardia (lower panel). The images were generously provided by Professor Helder Mauad from Federal University of Espirito Santo, Brazil. Data from Pedrosa et al., 2009. PAP: pulsatile arterial pressure, MAP: mean arterial pressure, HR: heart rate, PHE: phenylephrine, SNP: sodium nitroprusside.

Experimentally, the cardiopulmonary reflex function can be evaluated through phenylbiguanide injections. Figure 3 shows typical recordings of changes in arterial pressure and HR during cardiopulmonary reflex test.

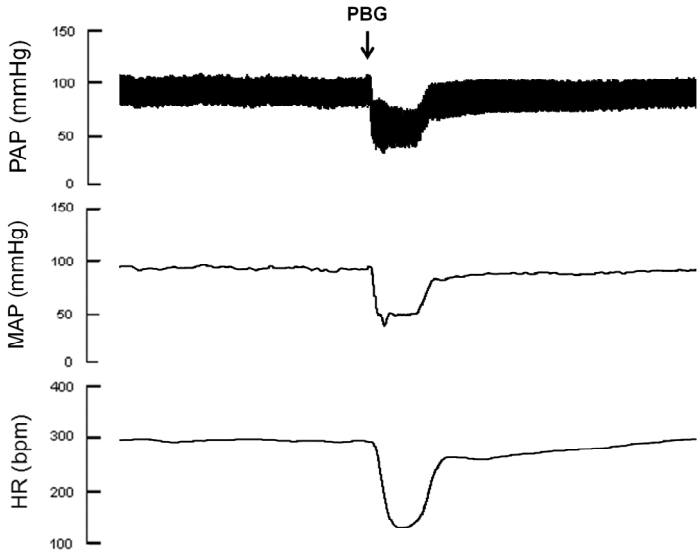

Fig. 3. Typical recordings of cardiopulmonary reflex evaluation in anesthetized rats. The activation of cardiopulmonary receptors is achieved by intravenous phenilbiguanide injections. The images were generously provided by Professor Helder Mauad from Federal University of Espirito Santo, Brazil. Data from Pedrosa et al., 2009. PAP: pulsatile arterial pressure, MAP: mean arterial pressure, HR: heart rate, PBG: phenybiguanide.

4.3 Arterial chemoreflex

The peripheral chemoreflex is considered one of the main mechanisms of control of the ventilatory responses to the changes in arterial O_2 and CO_2 concentrations. The peripheral chemoreceptors located in the carotid and aortic bodies, with afferents to the respiratory center in the medulla oblongata and the NTS, respond primarily to hypoxia (Guimarães et al., 2009). These chemo-sensitive receptors constantly receive information of arterial pO_2, pCO_2 e pH through a thin artery originated in the middle of the bifurcation of the common carotid artery that maintains these cells in close contact with blood gases (Vasquez et al., 1997). Increases in the firing rate of these neurons lead to a simultaneously activation of sympathetic outflow to blood vessels and increased vagal activity to the heart (Kara et al., 2003). Therefore, the excitation of the peripheral chemoreceptors produces an increased minute ventilation, systemic vasoconstriction and hypertension. The primary HR response to chemoreceptor stimulation is a parasympathetic mediated-bradycardia, but this mechanism is usually apparent only in the absence of ventilation. In the presence of the normal ventilatory response to hypoxia, tachycardia is generated by a lung inflation reflex that inhibits vagal outflow to the heart (Marshall, 1994). It is interesting to notice that, if blood pressure is within its normal range, the chemoreflex does not evoke a powerful cardiovascular response because of the predominant effect of the arterial baroreflex.

However, if blood pressure is low, generally below 80 mmHg, activation of the chemoreflex potentiates the vasoconstriction evoked by the baroreflex and helps to restore blood pressure to normal (Thomas et al., 2011).
The role of chemoreflex in cardiac arrhythmias have been already demonstrated. Patients with survived ventricular arrhythmias show significantly decreased chemoreflex sensitivity (Hennersdorf et al., 1997). The chemoreflex sensitivity is also considered as a marker of increased risk for ventricular tachyarrhythmias, since it shows a high positive predictive power in patients with prior myocardial infarction and who previously survived ventricular tachyarrhythmias (Hennersdorf et al., 2002). Central sleep apnea, which is associated with absent respiratory effort and results from instability in the chemoreflex control of breathing, is thought to predispose to cardiac arrhythmias generation (Leung et al., 2009).
Experimentally, the chemoreflex function can be evaluated through potassium cyanide injections. Figure 4 shows typical recordings of changes in arterial pressure and HR during chemoreflex test.

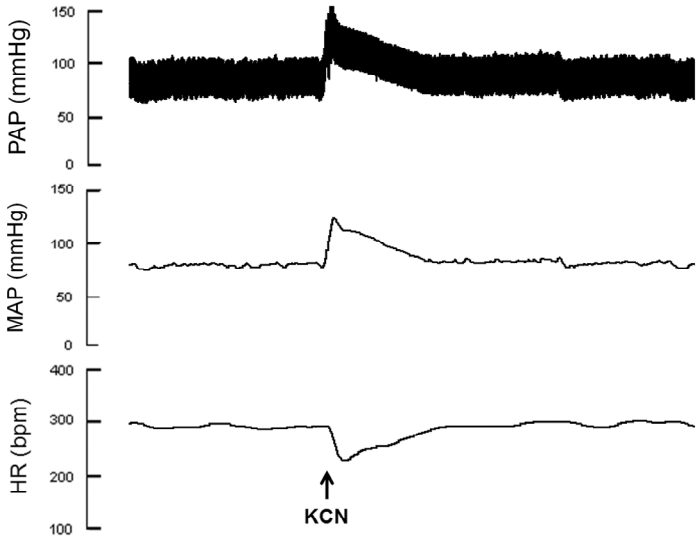

Fig. 4. Typical recordings of chemoreflex evaluation. The activation of chemoreflex is achieved by intravenous potassium cyanide injections. The images were generously provided by Professor Helder Mauad from Federal University of Espirito Santo, Brazil. Data from Pedrosa et al., 2009. PAP: pulsatile arterial pressure, MAP: mean arterial pressure, HR: heart rate, KCN: potassium cyanide.

5. Humoral control of HR

Several investigations have demonstrated that humoral systems can play a pivotal role in maintaining cardiac electric activity homeostasis and changes in their production and/or action pathways may contribute to various disorders in cardiac excitability. Additionally, the humoral systems can also modulate the autonomic nervous system and cardiovascular reflexes, demonstrating the importance of these substances in cardiovascular functioning.

5.1 Estrogen

The sexual hormones are related mainly with the control of reproductive function, however they can also modulate the cardiovascular function. Estrogen is the main female sex hormone in both humans and animal models. It is produced in the granulosa cells of the ovarian cortex through the conversion of androgen precursors by the aromatase enzyme, which in turn is modulated by the hormonal hypothalamic-pituitary axis (Filicori, 1986). The protective effects of estrogen on cardiovascular function have been already demonstrated by several investigations. Indeed, estrogen replacement therapy reduces the incidence of coronary artery disease (Rowland & Fregly, 1992; Farhat et al., 1996). Corroborating these data, Moyses et al. (2001) showed that estrogen treatment in ovariectomized female rats restored coronary vasodilation produced by serotonin in isolated hearts, and a bolus injection of 17ß-estradiol elicited a transient vasodilatory response in male and female normotensive (Santos et al., 2004) and spontaneously hypertensive rats (Santos et al., 2010).

It has been already demonstrated that estrogen levels are also related with the development of cardiac arrhythmias. During the menstrual cycle, estrogen levels rise and fall in women and these fluctuations are related with more frequent episodes with a longer duration of supraventricular tachycardia (Rosano et al., 1996). During perimenopause there is a marked decrease in ovarian estrogen production that is associated with an increase in HR (sinus tachycardia) and an enhancement in the frequency of palpitations and non-threatening arrhythmias, such as premature ventricular contractions (Rosano et al., 1996; Asplund and Aberg, 2003). During menopause a further decline in estrogen occurs and this event is associated with irregular heartbeats, palpitations, spasmodic chest pain and nightmares in women from 40 to 64 years old (Asplund and Aberg, 2003). Corroborating this data, hormonal replacement therapy (HRT) may decrease palpitations and other symptoms such as hot flashes, insomnia, and sweating (Grady et al., 2002). On the other hand, the Heart and Estrogen/Progestin Replacement Study (HERS) found no benefit to reduce cardiovascular events in women on HRT, which may even increase risk of thromboembolism during the first year (Grady et al., 2002). HRT has also being associated with lengthening the QT interval, although the relevance of this finding is not known (Gokce et al., 2005). Therefore, more investigations are necessary to better elucidate the benefits of HRT in preventing cardiac arrhythmias generations.

The mechanisms by which estrogen may affect the development of cardiac arrhythmias include changes ion channels expression and/or activity. Most of the studies demonstrate that estrogen exerts antiarrhythmic effects, possibly by acting the L-type Ca2+ channels, contributing to its cardioprotective actions (Nakajima et al., 1999). Ulrich et al (2007) demonstrated that estrogen inhibits ICaL through direct interactions of the steroid with the channel protein in a rate dependent way, leading to a decreased contraction. However, estrogen can also upregulates the sodium-calcium exchanger (NCX1) through a genomic mechanism mediated by estrogen receptors (ER), contributing to the enhanced propensity to early after depolarizations in female hearts (Cheng et al 2011).

It is well established that estrogen can cross the blood brain barrier and be accumulated in regions of the brain to bring about changes in neural activity, including in autonomic functions (Lee and McEwen, 2001). This modulation may occur via activation of ERs, since ER mRNAs expression have been identified in central areas controlling cardiovascular function such as, NTS, CVLM, RVLM and IML (Spary et al, 2009).

Several studies have demonstrated the effects of estrogen on cardiovascular reflexes. In ovariectomized female rats, intravenous estrogen supplementation significantly reduced sympathetic tone within 30 minutes and significantly increased parasympathetic tone within 5 minutes of administration (Saleh and Connel, 2000). Corroborating these findings, Flues et al (2010) demonstrated that ovariectomized rats supplemented with 17β estradiol presented an exacerbated vagal tonus when compared to ovariectomized rats. This study also showed that ovarian hormones deprivation induced a higher sympathetic activity to the heart. Additionally, Minson et al (2000) reported an increase of baroreflex sensitivity (BRS) in phases of menstrual cycle with estrogen preponderance. An enhanced BRS is associated with an increase in parasympathetic and/or a decrease in sympathetic tone (Rovere et al, 2000), and the degree of BRS depression is significantly correlated to an increased likelihood of cardiac arrhythmogenesis (Saleh et al, 2003). Taken together, those data indicate a beneficial effect of estrogen in autonomic balance and in arrhythmias prevention.

5.2 Testosterone

Testosterone, the major androgenic hormone is synthetized and released by the Leydig cells in the testis. It also gives rise to two other potent androgens: dihydrotestosterone and 5-alfa-androstenediol. Epidemiological and clinical studies indicate that testosterone status influence cardiovascular physiology and pathophysiology (Golden et al., 2002; Er et al., 2007).

The effects of testosterone on cardiac electric activity have been poorly investigated. Sanchez et al. (2009) showed that the acute administration of 5-alpha-dihydrotestosterone elicited a negative chronotropism effect and increased SA node recovery time, which could improve cardiac performance. The authors also suggested that this effect might be due to an interaction with the underlying mechanisms involved in the pacemaker activity (Mangoni and Nargeot, 2008) such as T-type Ca^{2+} channel and inward rectifier currents and a functional interaction with ionic pumps of plasma membranes. On the other hand, the acute treatment with testosterone enhanced the spontaneous beating frequency of cultured neonatal cardiomyocytes, which was associated with an increase in the level of expression of T-type Ca^{2+} channels (Michels et al., 2006). It has also been reported that androgens produce changes in the male heart phenotype and on electrophysiological properties, such as shortening of the QT interval in males after puberty (Rautaharju, 1992; Lehmann, 1997; Locati et al., 1998). These contradictory data may be related to different basal HR values among various mammalian species, and more studies are necessary to better elucidate the role of testosterone on cardiac electric activity.

Most of the research concerning the effects of gonadal hormones on the cardiovascular reflexes has focused on 17β-estradiol. However, other studies have provided evidence that androgens (including testosterone) play an important role in the control of cardiovascular function by modulation of cardiovascular reflexes (Caminiti et al., 2009). Steroids can cross the blood–brain barrier and act on the central nervous system, where androgen receptors in the central cardiovascular regulatory regions, such as NA and DMNX (Peuler et al., 1990; Pouliot et al., 1996) have been demonstrated. Therefore it is possible that androgens may act on brainstem vagal preganglionic neurons to modulate cardiomotor vagal activity. In accordance with this data, El-Mass et al. (2001) have shown that in male rats, castration caused a significant attenuation of baroreceptor control of reflex bradycardia versus no effect on reflex tachycardia. Testosterone replacement increased BRS to phenylephrine in castrated rats and restored reflex bradycardic

responses to levels similar to those of sham-operated rats. The muscarinic blockade by atropine in sham-operated rats caused a substantial reduction in BRS to phenylephrine, an effect that was significantly attenuated by castration and restored to sham-operated levels after testosterone replacement, suggesting that testosterone facilitates baroreceptor control of reflex bradycardia. Moreover, the modulatory role of testosterone on baroreflex responsiveness appears to involve, at least partly, enhancement of cardiac vagal efferent activity. Corroborating these data, a long-term testosterone therapy (6 weeks) improves the baroreflex sensitivity in men with chronic heart failure (Caminiti et al., 2009). The blockade of androgen receptor with flutamide attenuates the enhancement of baroreflex bradycardia in sexually mature male rats, indicating that the effects of testosterone on BRS depend on the involvement of the androgen receptor (Ward and Abdel-Rahman, 2006).

Besides the testosterone-induced effects on baroreflex, this sexual hormone may also modulate the cardiopulmonary reflex and the chemoreflex. Bissoli et al (2009) demonstrated that long-term treatment (8 weeks) with supraphysiological doses of nandrolone decanoate reduces the sensitivity of BJR control of HR in male rats. The effects of testosterone on BJR seem to be time-dependent, since the same treatment for 4 weeks had no effects on BJR nor the basal HR (Andrade et al., 2008). Pereira-Junior et al. (2006) showed that 10 weeks of high-dose nandrolone decanoate treatment leads to dysfunction in tonic cardiac autonomic regulation, with marked impairment of parasympathetic cardiac modulation and sympathetic hyperactivity. Regarding the chemoreflex, data from castrated male cats suggest that testosterone increases the hypoxic and hypercapnic ventilatory responses and augmented carotid body sensitivity to hypoxia (Behan et al., 2003). In adult rats, however, castration had no effect on the ventilatory response measured at the end of hypoxia (Joseph et al., 2002). On the other hand, Bairam et al. (2009) demonstrated that gonadectomy increased the acute breathing frequency response to hypoxia in neonatal rats. Because the rapid increase in breathing frequency is attributed to peripheral chemoreceptor activation, these data suggest that testosterone attenuates carotid body function. Although several studies demonstrated contradictory results about the benefic or malefic effects of testosterone on the modulation of cardiovascular reflexes, the characterization of the mechanisms could lead to a better understanding of the effects of testosterone in cardiovascular system and to the development of new therapies.

5.3 Nitric oxide (NO)

Since the discovery of the signaling properties of nitric oxide (NO) (Ignarro et al. 1987), it has been suggested that this important molecule may be involved in many physiological processes, such as the control of cardiovascular function. NO is a free radical synthesized from L-arginine by three isoforms of nitric oxide synthase (NOS): NOS1 (neural), NOS2 (inducible), and NOS3 (endothelial) and all three isoforms have been shown to influence autonomic neural function in some manner (Schultz, 2009). NO generated at nerve synapses diffuses in an autocrine and paracrine way to influence both presynaptic and postsynaptic events on excitatory and inhibitory synapses. NO exerts its cellular actions by binding to guanylyl cyclase to activate cGMP production, which remains the only fully recognized physiological signal transduction mechanism for NO. In central neurons, cGMP then can have diverse effects on neuronal excitability. Cyclic GMP can directly bind to and modulate cyclic nucleotide-gated ion channels, bind to phosphodiesterases to impair cAMP hydrolysis, or most prominently, activate cGMP-dependent protein kinase which can

directly or indirectly leads to phosphorylation of effector proteins or ion channels (Schultz, 2009).

The effects of NO on baroreflex have been already demonstrated by several investigations. Meyrelles et al (2003) have shown that adenovirus-mediated eNOS delivery to carotid sinus adventitia leads to a diminished baroreceptor activity. NO seems to have an inhibitory effect on sodium currents in baroceptor neurons (Li et al., 1999) and activates calcium dependent potassium channels, leading to membrane hyperpolarization (Bolotina et al., 1994).

Besides NO effects on baroreceptor afferents, NO also exerts effects on central nuclei regulating baroreflex function.

Intracerebroventricular injections of L-NAME (an inhibitor of NO synthases) caused an enhancement in baroreflex sensitivity, indicating that NO may exert an inhibitory effect upon baroreflex (Matsumura et al, 1998). This inhibition appears to occur in both sympathetic and parasympathetic component of baroreflex. Liu et al (1996) demonstrated that NO synthase blockade with L-NNA causes an increase in the baroreflex gain, which is prevented by L-arginine injections. This augmented sensitivity is blocked by the use of atropine, indicating an inhibitory effect of NO on the parasympathetic component of the reflex. NO also seems to exert sympatoinhibitory effects, as demonstrated by Zanzinger et al (1995) who show that L-NNA administration leads to an increased basal sympathetic tonus. On the other hand, Dias et al. (2005) demonstrated a stimulatory effect of NO in the central nuclei controlling cardiovascular function. In this study, the renal sympathoinhibition induced by activation of baroreceptors and cardiopulmonary receptors is attenuated by the microinjection of L-NAME in the NTS. The same investigators also demonstrated that NO increases the number of discharges evoked by excitatory amino acids in NTS neurons that receive vagal afferent inputs, and action potentials induced by iontophoretic application of AMPA in the NTS was reduced by L-NAME, indicating a excitatory effect of NO in this nucleus (Dias et al., 2003). Some studies also showed no effects of NO on baroreflex function. eNOS gene therapy did not alter baroreflex sensitivity and autonomic balance in C57 mice and was not able to prevent the increase in sympathetic tonus and the decrease parasympathetic activity to the heart in hypertensive mice (Gava et al., 2008).

In addition to the brain, emerging evidence suggests that NO can also influence sympathovagal function at the site of the end-organ itself, acting in sympathetic ganglia or vagal neurons. Neuronal nitric oxide synthase is localized in both intrinsic cardiac vagal neurons and stellate sympathetic ganglia innervating the SA node, indicating an important role NO in modulating of peripheral neuronal function (Herring and Paterson, 2009). In cholinergic neurons, NO seems to act increasing acetylcholine release through stimulation of soluble guanylate cyclase. The resultant generation of cGMP causes phosphodiesterase-3 inhibition, increasing cAMP-PKA dependent phosphorylation of N-type calcium channel and calcium-induced exocytotic release of acethycholine (Herring & Paterson, 2001). However, in the AV nodal cells, NO regulates AV excitabilility by muscarinic cholinergic attenuation of ICa-L (L-type calcium current), the mechanism likely involves the cGMP-stimulated phosphodiesterase (Han et al., 1997). In sympathetic ganglia, NO reduces the release of noradrenaline through a soluble guanylate cyclase–cGMP dependent pathway that reduces calcium influx (Schwartz et al. 1995; Wang et al. 2007), probably via stimulation of PDE2 and/or protein kinase G (Herring and Paterson, 2009). Despite some contradictory results, the role of NO in the modulating HR it is well established and the implication of changes in the NO production and/or activity for cardiovascular disease development remains an intriguing possibility of new targets for treating arrhythmias.

5.4 Renin-angiotensin-aldosterone system (RAAS)

The RAAS is a peptidergic cascade with endocrine characteristics and is considered one of the most important systems that participate of cardiovascular control. In the classical view of RAAS, angiotensinogen, an alfa-glycoprotein, is released from the liver and is cleaved in the circulation by the enzyme renin that is secreted from the juxtaglomerular apparatus of the kidney to form the decapeptide angiotensin I (Ang I). Ang I is then transformed into to the octapeptide angiotensin II (Ang II) by angiotensin converting enzyme (ACE), a membrane-bound metalloproteinase, which is predominantly expressed in high concentrations on the surface of endothelial cells in the pulmonary circulation. Ang II, considered the main effector peptide of the RAAS, acts on specific receptors (AT_1 and AT_2), for example, to induce vasoconstriction on vascular smooth muscle cells or to stimulate the release of aldosterone from the adrenal cortex (Paul et al., 2006).

Several lines of evidence suggest that Ang II may exert a direct modulation on cardiac ionic channels. Experiments have shown that stimulation of AT_1 receptor result in the inhibition of transient outward potassium channel in myocytes from rat or canine ventricle (Shimoni and Liu, 2003; Yu et al., 2000). Ang II also increases cardiac L-type Ca^{2+} current (ICaL) in isolated cat myocytes (Aiello and Cingolani, 2001). In this view, the RAAS activation may therefore significantly contribute to the pathogenesis of cardiac arrhythmias. On the other hand, Ang II decreased the current density of L-type Ca^{2+} current in SA node cells and reduces the auto rhythm of SA node cells via enhancing slowly activated delayed rectifier K^+ currents and reducing ICaL. Therefore, the elevated levels of Ang II may be involved in the occurrence of SA node dysfunction in cardiac pathophysiology (Sheng et al., 2011).

Numerous studies already demonstrated that Ang II plays a pivotal role in the neural regulation of cardiovascular system. High concentrations of AT_1 receptor and fibers with Ang II immunoreactivity have been described in the dorsomedial and ventrolateral areas of the medulla (Allen et al., 1998; Averill and Diz, 2000). It is well known that Ang II causes an increased sympathetic drive, particularly by means of central mechanisms. In dogs, acute (21 h) and chronic (5 days) infusion of Ang II caused a two- to threefold increase in Fos-Li immunoreactivity in the NTS and CVLM, leading to a baroreceptor suppression of sympathoexcitatory cells in the RVLM (Lohmeier et al, 2002). Lesions at either the area postrema or the subfornical organ attenuate angiotensin II-based hypertension, indicating a direct central sympathoexcitatory action of Ang II (Collister and Hendel, 2003; Collister and Hendel, 2005). Corroborating these data, experimental models of angiotensin II-dependent hypertension present an augmented sympathetic drive (Peotta et al., 2007) and patients with chronic angiotensin-dependent renovascular hypertension have generally demonstrated higher sympathetic levels, correlated with circulating angiotensin II concentrations (Grassi e Esler, 2002). Besides Ang II effects on sympathetic drive, this peptide also exerts effects on the parasympathetic component of the reflexes. Borges et al. (2008) demonstrated that mice with renovascular hypertension presented diminished cardiac vagal activity, and together with an enhanced cardiac sympathetic activity, contributed to a reduced baroreflex sensitivity in this animal model of hypertension. Moyses et al. (1994) also demonstrated a reduced cardiac vagal activity in renovascular hypertensive rats.

Although Ang II is considered the major effector of RAAS system, growing evidence have demonstrated an important role of angiotensin-(1-7) in cardiovascular regulation. This

molecule can be formed from Ang I and Ang II fragments through an angiotensin-converting enzyme (ACE) independent pathway (Santos et al., 2007). It has been demonstrated that Ang-(1-7) actions are often contrary to those described for Ang II (Benter et al., 1993). In fact, regarding the neural control of circulation, several studies have provided evidence that endogenous Ang-(1-7) enhances the baroreceptor reflex bradycardia, while Ang II attenuates it (Campagnole-Santos, 1992; Sakima et al., 2007). The beneficial effect of Ang-(1-7) on cardiovascular reflexes was also demonstrated by Oliveira et al (1996) who showed that the central infusion of a selective Ang-(1-7) antagonist attenuates baroreflex and blocks the improvement in the reflex bradycardia produced by Ang-(1-7). The specific binding of Ang-(1-7) to its receptor (Mas receptor) seems to be a basic requirement for the maintenance of normal arterial blood pressure and cardiovascular reflex control, since Mas-knockout mice presented hypertension and altered cardiovascular reflexes (Moura et al., 2010).

5.5 Natriuretic peptides (NPs)

The NPs play an important role in the regulation of cardiovascular homeostasis maintaining blood pressure and extracellular fluid volume. There are four major natriuretic peptides (NPs) that have been isolated: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and Dendroaspis-type natriuretic peptide (DNP). NPs exert their biological effects by binding to three distinct cell surface receptors denoted NP receptors A, B and C (NPR-A, NPR-B and NPR-C) (Rose and Giles, 2008).

Several studies demonstrated that NPs affect the electrophysiology of the heart (Rose et al., 2004) and central nervous system (Trachte et al., 2003; Rose et al., 2005). Voltage-clamp studies demonstrated that CNP can inhibit L-type Ca^{2+} current (ICa-L) through NPR-C binding. This inhibition involves a decrease in adenylyl cyclase activity, which leads to reduced intracellular levels of cAMP (Rose et al., 2003). These results were also demonstrated in isolated myocytes from mouse SA node, that express several cAMP-sensitive currents, including ICa-L (DiFrancesco, 1993). Corroborating these data, inhibition of adenylyl cyclase decreases HR and increases the P–R interval, suggesting that the atrioventricular conduction system is slowed following the activation of NPR-C. These data are consistent with other studies demonstrating a key role for L-type Ca^{2+} channels in the intrinsic regulation of SA node function and the determination of HR (Zhang et al., 2002; Mangoni et al., 2003). The molecular mechanism(s) by which CNP–NPR-C effects are compartmentalized in animal models SA node myocytes is not clear and will require further investigation.

In addition to their effects on cardiac electric activity, NPs also exert effects on cardiovascular reflexes. Thomas et al. (2001) showed that ANP, BNP and CNP enhance bradycardic responses to cardiopulmonary chemoreceptor activation in conscious sheep. On the other hand, Tallarida et al. (1991) demonstrated that intravenous infusion of ANP did not substantially change the baroreflex cardiocirculatory responses to loading and unloading carotid and aortic baroreceptors. Some of the reported discrepancies may be attributed to the dose of ANP, preparation (e.g., synthetic peptide vs. atrial extract) or to experimental conditions (e.g., anaesthetized vs. conscious). The target site(s) for the NPs action on cardio-cardiac vagal reflexes is not clear and more studies are necessary to better elucidate the mechanisms involved in NP-induced changes in cardiovascular reflexes.

5.6 Thyroid hormones (TH)

Variations from euthyroid status affect virtually all physiological systems and the effects on the cardiovascular system are particularly pronounced (Levey and Klein, 1990). Hyperthyroidism causes tachycardia and cardiac arrhythmias whereas bradycardia, reduced cardiac output, and slowed relaxation result from hypothyroidism (Klein and Ojamaa, 2001). The actions of TH are mediated by two nuclear TH receptors (TRs)- α and- β, encoded by two separate genes (Yen, 2001). TR-α1 isoform represents 70% of the TRs and serves an important role in cardiac development (Mai et al., 2004) and the regulation of heart rate and contractility (Dilmann, 2010; Macchia et al., 2001). Corroborating these data, Wikström et al. (1998) demonstrated that TR-α1 knockout mice presented a 20% reduction in HR and a prolonged relaxation time. The molecular explanation for these results includes a diminished expression of the hyperpolarization activated cyclic nucleotide-gated potassium channel 2, which plays a pivotal role for pacemaking (Macchia et al., 2001).

Changes in thyroid status are associated with changes not only in cardiac and vascular function but also in autonomic regulation of the cardiovascular system (Levey and Klein, 1990). In example, Foley et al. (2001) evaluated the effect of thyroid status on arterial baroreflex control of lumbar sympathetic nerve activity (LSNA) and HR in conscious rats. The authors report that rats with hypothyroidism exhibit blunted baroreflex mediated increases in LSNA and HR and a downward shift in baroreflex control of HR compared with euthyroid rats. On the other hand, rats with hyperthyroidism presented normal baroreflex function and sympathetic tone to the vasculature. Although hypothyroidism has been associated with sympathovagal imbalance, current literature shows conflicting results with either increased sympathetic activity (Cacciatori et al., 2000), decreased sympathetic modulation (Gallet et al., 2008) or an increased vagal tone (Xing et al., 2001).

As observed, there is a complex relationship between humoral factors, neural systems (CNS and autonomic nervous system) and cardiac electric activity (Figure 5) and disturbances in these interactions may be related with the development of arrhythmias.

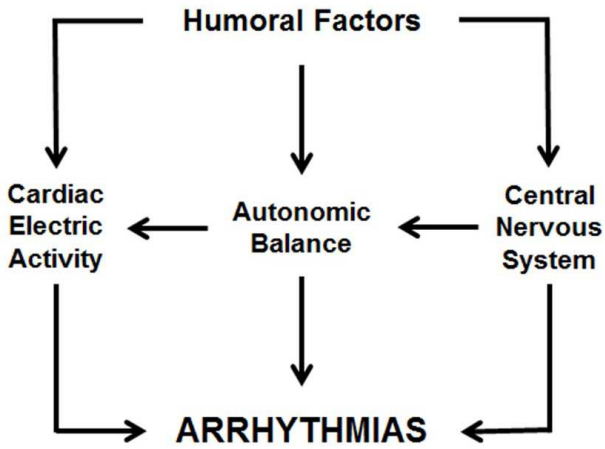

Fig. 5. Schematic diagram showing the interactions between humoral factors, cardiac electric activity, autonomic balance and central nervous system and their role in arrhythmias generation.

6. Perspectives

As observed, the normal control of HR depends on a complex interaction between neural and humoral factors and disturbances on these systems are strongly related with arrhythmias generation. The formation of an action potential in the SA node and its propagation throughout the heart involves several ion channels, mainly Na^+, K^+ and Ca^{+2}, and can be modulated by sympathetic and parasympathetic activation. The central outflow of autonomic nervous system is generated mainly in the brainstem and it involves the participation of diverse nuclei, such as NTS, CVLM and RVLM. The neuronal activity of these structures can be modulated by several hormones, including estrogen, testosterone, nitric oxide, angiotensin II, angiotensin (1-7), natriuretic peptides and thyroid hormones. Besides its effects on CNS, hormones can also regulate the release of neurotransmitters, the expression of ion channels and the activity of membrane transporters. Taken together, these data demonstrate the importance of neural and humoral systems in controlling cardiovascular function and brings out the possibility of new drug targets to treat arrhythmias.

7. Acknowledgments

We would like to acknowledge Professor Helder Mauad from Federal University of Espirito Santo - Brazil, who generously provided the typical recordings of baroreflex, cardiopulmonary reflex and chemoreflex evaluation displayed in Figure 2, 3 and 4.

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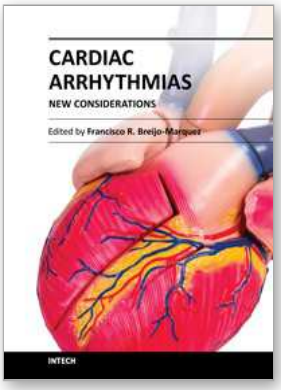

Cardiac Arrhythmias - New Considerations

Edited by Prof. Francisco R. Breijo-Marquez

ISBN 978-953-51-0126-0
Hard cover, 534 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

The most intimate mechanisms of cardiac arrhythmias are still quite unknown to scientists. Genetic studies on ionic alterations, the electrocardiographic features of cardiac rhythm and an arsenal of diagnostic tests have done more in the last five years than in all the history of cardiology. Similarly, therapy to prevent or cure such diseases is growing rapidly day by day. In this book the reader will be able to see with brighter light some of these intimate mechanisms of production, as well as cutting-edge therapies to date. Genetic studies, electrophysiological and electrocardiographyc features, ion channel alterations, heart diseases still unknown , and even the relationship between the psychic sphere and the heart have been exposed in this book. It deserves to be read!

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