Gender differences in the neurohumoral control of the cardiovascular system

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The cardiovascular system is regulated by many complex neurohumoral mechanisms which ensure the cardiac, cerebral and renal functions. The nervous control of the heart is mainly mediated by the vagal and sympathetic systems and by their interaction, known as the sympatho-vagal balance. An increased sympathetic tone is found in many abnormal situations, such as arterial hypertension, diabetes, chronic heart failure and myocardial infarction, and is associated with an increase in overall mortality. The hormonal control of the cardiovascular system is mediated by various substances such as renin-angiotensin, catecholamines, insulin and estrogens, that are themselves correlated with the autonomic nervous system. In contrast to men, fertile women show a predominant vagal tone. Sex-related differences in the neurohumoral control of the cardiovascular system have been demonstrated during physical effort and in the hemodynamic adaptation to orthostatism. They have been postulated to explain the lower mortality in women compared to men among hypertensive or chronic heart failure patients. Prospective studies are needed to better define the gender differences in the pathophysiological mechanisms underlying cardiovascular diseases, in order to refine prevention and therapy.

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Introduction

A complex nervous system controls the main activities of the heart and blood vessels, such as arterial pressure and heart rate and contractility, and thus ensures the cardiac, cerebral and renal functions[1]. If the balance between these various control mechanisms fails, many pathological situations may occur. A number of cardiovascular diseases, such as myocardial infarction, hypertension and heart failure, are associated with alterations in the nervous system with an increase in sympathetic activity and a consequent worsening in prognosis[2,3]. Humoral mechanisms regulate slower cardiovascular adaptations, such as blood volume, hydrosaline homeostasis, myocyte growth, etc.[4].

Cardiovascular activities are normally regulated by the interaction between the sympathetic and vagal systems; the activation of one inhibits the other, and vice versa. This mechanism is known as the sympatho-vagal balance. Peripheral signals gathered by chemo- and baroreceptors are transmitted by the afferent vagal and sympathetic nerves to the cerebral centers. Thus, the neural control of the heart and vascular tone is mainly supplied by sympatho-vagal activity and is regulated by peripheral and central negative feedback. It controls involuntary functions and drives rapid changes of cardiovascular variables, such as heart rate, blood pressure and cardiac output.

Many physiological conditions are controlled by the neuroendocrine system: physical effort, psychological stress, postural changes, temperature variations, circadian rhythms, and hormonal cycles. These mechanisms have been studied for a long time both in health and disease; while differences between the two sexes have been clearly demonstrated in normal situations, only few studies exist, and many uncertainties still remain, concerning disease.

Autonomic nervous control of the cardiovascular system

Baroreflex sensitivity expresses the relation between variations in systemic arterial pressure and those in heart rate. It represents the capacity to activate a vagal reflex in response to sympathetic stimulation, and vice versa[5]. Arterial peripheral baroreceptors, stimulated by an increase in systemic blood pressure, inhibit afferent sympathetic activity and increase vagal stimulation leading to a reduction in heart rate, and vice

versa. In normal young adults, normal values are about 15 ms/mmHg.

Heart rate variability (HRV) is a relatively simple index used to evaluate the sympatho-vagal balance of the heart. In the time domain, SDNN measures the 24 hour variance of the RR intervals. The frequency domain evaluates the power of low (0.03-0.15 Hz) and high (0.16-0.40 Hz) frequency spectral components, an expression of vagal and sympathetic activity, respectively.

A reduction in baroreflex sensitivity and/or in HRV occurs in both sexes with age and in many cardiovascular diseases, such as hypertension, diabetes, myocardial infarction, and chronic heart failure[6,7]: an increase in sympathetic tone correlates significantly with an increase in the risk of death[2,3].

Hormonal control of the cardiovascular system

The renin-angiotensin system (RAS) is certainly the best known endocrine system regulating cardiovascular function. Many other substances such as aldosterone, natriuretic peptides (atrial natriuretic peptide-ANP, brain natriuretic peptide-BNP), vasopressin, insulin, thyroid and sexual hormones act as "cardiac hormones". The RAS plays a fundamental role in hydrosaline homeostasis, as well as in the control of peripheral resistance. The natriuretic peptides ANP and BNP, when stimulated by different substances such as catecholamines, endothelin, or by an increase in atrial wall tension, cause an increase in diuresis; they also reduce peripheral vascular resistance. The counter action brought about by catecholamines determines substantial peripheral vasoconstriction and an increase in heart rate and arterial pressure. Arginine vasopressin is a vasoconstrictor and water-retaining hormone; high levels of arginine vasopressin may also contribute to dilutional hyponatriemia in severe heart failure. Insulin has numerous effects on the cardiovascular system, the most important being vasodilation, increased catecholamine release and sympathetic activation[8]. Estrogens produce many protective effects on endothelial, coagulation, lipid and fibrinolytic factors, which may explain the reduced cardiovascular risk in fertile women. On the other hand, androgens seem to determine peripheral vasoconstriction[9]. In women, an androgen excess causes obesity and insulin resistance.

Gender differences in neurohumoral control of the cardiovascular system

Heart rate variability. With regard to the regulation of heart rate, women, in contrast to men of the same age, seem to have a predominant parasympathetic tone[10]. Kuo et al.[11] reported similar results in a population of normal subjects aged 49-70: HRV showed a predominance of parasympathetic over sympathetic tone in women and the opposite in men. They also demonstrated that the gender-related difference in vagal regulation diminishes after the age of 50, while the sympathetic dominance in men disappears significantly later. On the other hand, Jensen-Urstad et al.[12] showed that age, more than sex, influences HRV. Ramaekers et al.[13], using HRV, showed that cardiac autonomic modulation is significantly lower in healthy women compared to men because of a lower sympathetic activity. The authors postulated that this finding may provide an explanation for the protection against cardiovascular diseases observed in females. Actually, a low HRV is considered an independent marker of mortality risk. Umetani et al.[14] evaluated HRV in normal subjects ranging in age over 9 decades to define the influence of both age and sex. Under age 30, HRV was lower in females. After 30, the gender differences decreased and disappeared after age 50.

Response to exercise and postural changes. In addition to the above, even the response to physical effort is different between the two sexes. Women seem to have a higher risk of post-exercise orthostatic hypotension, due to a greater decrease in stroke volume and a lesser increase in total peripheral resistance during the recovery phase[15]. During sustained isometric contraction, in women, but not in men, epinephrine seems to play a minor role in the regulation of heart rate and blood pressure[16]. Significant differences between males and females have been found in response to standing, generally related to a greater decrease in thoracic blood volume on standing in females compared to males[17]. On standing, men show a greater increase in blood pressure and total peripheral resistance than women; cardiac output and stroke volume decrease more in men, while heart rate is similar[18]. During head-up tilt test, women show a greater increase in heart rate, a smaller increase in arterial pressure, and a significantly different muscle sympathetic nerve activity response. These factors may explain the reduced arterial pressure control during head-up tilt test in females[19]. The hypothesis that in women a lower orthostatic tolerance is associated with a lower responsiveness of the mechanisms regulating arterial pressure has been supported by the results of Convertino[20]. During various protocols of lower body negative pressure, a similar behavior of heart rate and total peripheral resistance was demonstrated at presyncope in both sexes, whereas stroke volume, cardiac output and mean arterial pressure were lower in females. The lower body negative pressure tolerance in females was associated with a reduced heart rate response to carotid baroreceptor stimulation, a lower baseline cardiac vagal activity, lower levels of norepinephrine, and a lower relative blood volume[20].

Neurohumoral cardiovascular control and disease. There are no prospective studies evaluating gender differences in the neurohumoral control of the cardiovas-

cular system in pathological conditions. A few observational and experimental data are available on arterial hypertension and heart failure. The cardiovascular risk in the hypertensive population seems to be higher in men than in women. Actually, at rest, women with hypertension have a higher heart rate, cardiac index, and pulse pressure, and a lower total peripheral resistance; during isometric stress, arterial pressure increases 50% more in men compared to women for any level of arterial pressure, while total peripheral resistance remains lower in women than in men[21]. Androgens seem to increase blood pressure via the RAS[22]. The renal vasoconstrictor response to AT_1/AT_2 differs between genders: it is increased in women, who show a different baroreflex reactivity during angiotensin infusion compared to men[23]. Experimental studies show that the components of the circulating, as well as of the tissue-based, RAS are markedly affected by gender. Angiotensin is upregulated by the oral administration of estrogens, whereas renin and angiotensin-converting enzyme AT_1 receptors are downregulated; while under experimental conditions the net effect of estrogen appears to suppress the RAS, the clinical setting may be more complex[24]. Radin et al.[25] studied male and female rats affected by hypertensive cardiac heart failure and demonstrated that, while male rats showed early activation of the RAS, females showed early activation of the endothelin vasopressor system; in the advanced stages of heart failure, the response of the RAS, endothelin and ANP systems were similar in the two sexes.

During the first 24 months after a myocardial infarction, female gender seems to be protective against arrhythmic death, but at the moment the reason remains unclear[26]. In women diastolic heart failure is more frequent, probably due to a higher prevalence of hypertension and diabetes, but the total mortality for chronic heart failure is lower in the female sex. It has not been proved that such a decrease in mortality is due to a different etiology or to differences in the autonomic control of the cardiovascular system. In women with congestive heart failure, left ventricular mass and natriuretic peptide concentrations seem to increase less than in men. These observations suggest gender differences in the myocardial adaptations to hemodynamic overload, in particular a faster induction of left ventricular hypertrophy during myocardial dysfunction in men[27].

Conclusions

The neurohumoral control of the cardiovascular system shows several gender differences. In comparison to men, a greater parasympathetic drive seems to characterize healthy women, at least during reproductive years. In physiological situations, the most relevant gender differences have been demonstrated during physical exertion, orthostatism and, in general, for the mechanisms underlying blood pressure regulation. Estrogens are thought to play an important cardiovascular protective role, not only through direct effects on the vascular endothelium, but also by interacting with the mechanisms regulating heart rate, arterial pressure, and the activation of the RAS. Prospective studies are needed to better define the presumed sex-related differences in the neurohumoral control of the cardiovascular system during pathological conditions, with the aim at differentiating prevention programs and therapy.

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