TOPICAL REVIEW

Endocrine activation in tachycardias

Lukac P, Lukacova S, Vigas M, Hatala R

*Department of Arrhythmias, Cardiology Clinic, Slovak Cardiovascular Institute, Bratislava. Slovakia.***lukacpe2@hotmail.com**

Abstract

This article reviews the complex character of neuroendocrine response to paroxysmal tachycardia. While the endocrine influences in arrhythmogenesis are well perceived by the cardiologists, less attention has been paid to influence of tachycardia on neuroendocrine activation. However, this may significantly alter the clinical course of tachycardias and its responses to pharmacotherapeutic interventions. Main characteristics of hormones with direct relationship to cardiovascular system (ANP, AVP, catecholamines, angiotensin and others) are listed with description of regulation of their secretion and main biological effects, especially with regard to regulation of circulation. Changes in hemodynamics during tachycardia with accompanying changes in ANP, AVP renin-angiotensin-aldosterone system, sympatho-neural and sympatho-adrenal activation are reviewed. Further research and understanding require more complex approach and concentration on interrelationship of different regulatory hormones in tachycardia. ***(Fig. 2, Ref. 96.)***

Key words: tachycardia, hemodynamics, hormone, neuroendocrine system.

The endocrine and cardiovascular systems are closely interrelated. Heart and endothelium have important endocrine and paracrine functions producing important hormones and biologically active substances. On the other hand, cardiovascular system is the target for multiple hormonal regulations. Participation of certain hormones in the process of arrhythmogenesis is well known. Arrhythmogenic effects of thyroid hormones in thyrotoxicosis or catecholamines in pheochromocytoma are well known and have been recently reviewed (Viskin et al., 2000). This overview focuses the reverse, less known interrelation: the endocrine activation during paroxysmal tachycardias.

Changes in circulation stimulate secretion of many hormones. Of all the cardiac diseases, endocrine activation has been studied probably most extensively in heart failure. Depending on its hemodynamic tolerability, similar mechanisms as in heart failure might operate in tachycardia and many aspects of the endocrine response are comparable. As paroxysmal tachycardias are usually relatively short-lasting due to therapeutic interventions, spontaneous cessation or death, fully blown neuroendocrine activation does not take place. It is especially due to this reason that the vast majority of studies on this topic deal with acute changes. However, this is not an absolute rule. Some supraventricular and ventricular tachycardias may compromise the patient also in the long run.

In the recent years, some work has been done showing besides the hemodynamic influences also direct relationship between arrhythmias and the endocrine system. This might be the secretion of atrial natriuretic peptide activated by electrical activation of atrial cardiomyocytes (Schiebinger and Linden, 1986). However, research on this topic has not been conclusive yet.

Tachycardia is a cardiac rhythm faster than 100 beats per minute. In order to avoid complicated classification of tachycardias which is not necessary to explain the aspects of endocrine activation, we shall distinguish only between supraventricular and ventricular tachycardias. Supraventricular tachycardias require for their initiation and persistence abnormal electrical activity of the atria and/or atrioventricular junction. Ventricular tachycardias do not require abnormal electrical activity of the atria and/or atrioventricular junction. In the majority of cases, supra-

Department of Arrhythmias, Cardiology Clinic, Slovak Cardiovascular Institute, Bratislava, and Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava

Address for correspondence: P. Lukac, MD, Dept of Arrhythmias, Slovak Cardiovascular Institute, Pod Krasnou horkou 1, SK-833 48 Bratislava 37, Slovakia.
Phone: +421.2.59320398, Fax: +421.2.59320656

ventricular tachycardias show narrow QRS complex, while the QRS complex is wide in ventricular tachycardias. Atrial fibrillation, the most common supraventricular tachyarrhythmia, has a special position. We shall deal with this arrhythmia in depth in a separate section.

The endocrine response evoked by paroxysmal tachycardia depends on several factors:

(a) hemodynamics during the tachycardia,
(b) duration of the episode,
(c) administered therapy, both pharmacological and electrical,
(d) the rate of atrial electrical activity.

We shall deal with the latter in the section on atrial natriuretic peptide.

Hemodynamic effects of tachycardia

Physiological sinus tachycardia has positive impact on hemodynamics. A good model for studying the effects of pathological tachycardias is cardiac pacing because both conditions represent ectopic rhythms unresponsive to physiological regulation. Although changes of rate of a healthy heart in the range from 40—50 beats per minute to 160—170 beats per minute during atrial stimulation significantly lower stroke volume, they have little impact on cardiac output and blood pressure (Ross et al., 1965; Ota et al., 1987), as explained by equation:

cardiac output = stroke volume x heart rate.

Stimulation with higher rates causes a decrease in cardiac output and blood pressure. This decrease is caused by:

(a) decreased ventricular filling secondary to shortening of diastole and absence of correctly timed atrial systole.

(b) absence of sympathetically mediated physiological increase of contractility.

In the majority of pathological tachycardias, the temporal relationship between atrial and ventricular systole is impaired. Correctly timed atrial systole augments cardiac output in direct relationship to heart rate (Ruskin et al., 1970; DiCarlo et al., 1987; Sganzerla et al., 1989; Hamer et al., 1985). It prevents the transmission of high enddiastolic pressures from the left ventricle to the left atrium (Rahimtoola et al., 1975; Tsai et al., 1988). During atrial contraction against closed atrioventricular valves, atrial and venous pressures suddenly rise (cannon a waves) (O'Rourke and Braunwald, 1998). The affected patients typically report palpitations especially in the neck, a finding typical for atrioventricular nodal reentry tachycardia.

Patients with structural heart disease may dramatically respond to heart rates otherwise well tolerated by healthy hearts. Tachycardia may even at relatively low heart rates elicit ischemia with resulting systolic and diastolic dysfunction (Thadani et al., 1979; Linhart et al., 1969). Patients with dilated cardiomyopathy with low inotropic reserve fail to demonstrate enhancement in systolic and diastolic function during rapid atrial pacing, which typically takes place in normal hearts (Feldman et al., 1988). Asynchronous ventricular contraction in ventricular tachycardias or in supraventricular tachycardias with aberrant intraventricular conduction might have deleterious hemodynamic consequences in such hearts which do not depend on the loss of atrial contribution or the occurrence of mitral regurgitation (Nakano, 1964).

Tachycardias are one of the precipitating factors of heart failure (Braunwald, 1998). Tachycardias influence hemodynamics in the arterial (forward) and venous (backward) beds. In the arterial bed typically a fall in blood pressure and cardiac output takes place. In more severe cases, especially in ventricular tachycardias, vital organ hypoperfusion ensues, often with the picture of shock, syncope or, in the worst case, sudden cardiac death. Similarly, influence on venous system may manifest with different severity. Depending on the origin of tachycardia, timing of atrial systole and presence or absence of structural heart disease, right and left atrial filling pressures in tachycardia may be elevated (in the majority of tachycardias), remain unchanged or fall (Roy et al., 1987). Pulmonary venous congestion leads to pulmonary edema, systemic venous congestion causes e.g. peripheral edema and hepatomegaly. Long lasting elevation of atrial pressures leads to atrial dilatation with accompanying secondary atrial arrhythmias, most often atrial fibrillation or flutter (Vaziri et al., 1994; Henry et al., 1976). Atrial dilatation and elevated pressures lead, according to Laplace's law to elevated wall tension, which is the main stimulus for activation of several endocrine functions.

Overview of hormones with direct relationship to cardiovascular system

Atrial natriuretic peptide (ANP)

ANP is synthesized in atrial cardiomyocytes. Immunohistochemical studies show higher production in the right atrium (Cantin et al., 1984). Synthesis in the ventricles is 20—50 times lower (Gerbes et al., 1994).

Regulation of secretion

Main stimulus for its secretion is elevation of pressures in the atria (Sato et al., 1986; Müller et al., 1986), or their distension (Ong et al., 1990). Important role is played by high peak pressure in the atria, e.g. secondary to already mentioned cannon a waves. In patients with complete atrioventricular block with implanted VVI pacemaker, baseline values of ANP were significantly higher in patients with sinus rhythm than in patients with atrial fibrillation (Kelly et al., 1997). This result is probably influenced also by lower secretion of ANP in degenerated atrial myocardium in patients with chronic atrial fibrillation (Van Den Berg et al., 1998) (for more detail see section „Endocrine activation in atrial fibrillation" of this article). A correlation between right atrial size and plasma ANP concentration has been shown in patients with congenital heart disease (Ross et al., 1988).

Rapid heart rate has been considered as one of the stimulating factors. However, several studies did not succeed in demonstrating direct relationship between plasma level of ANP and heart rate (Roy et al., 1987; Crozier et al., 1987). Theory, that

ANP secretion depends on atrial rate, has gained interest. Increase in atrial stimulation rate from 120 to 240 beats per minute led to significant increase in ANP secretion in isolated rat hearts (Schiebinger a Linden, 1986). A study by Fujiwara et al. (1993) showed, that fast atrial electrical activity in atrial fibrillation with up to 500 beats per minute *per se* leads to increased ANP secretion. Tan et al. (1993) report significant increase in ANP level during paroxysm of supraventricular tachycardia. On the other hand, increase in atrial stimulation rate from 120 to 176 beats per minute did not increase plasma level of ANP in men (Burnett et al., 1989). Thus, research on this topic remains controversial and presently does not allow for final answer.

ANP secretion is also stimulated by catecholamines via β and α1 receptors (Wong et al., 1988; Schiebinger et al., 1987). However, the results are controversial also in this point. ANP rises during physical stress and probably takes part in the regulation of cardiovascular response to stress (Follenius a Brandenburger, 1988), but the level of ANP did not correlate significantly with levels of norepinephrine (Cuneo et al., 1988) and the addition of a betablocker led to an increase and not decrease of ANP concentration (Tsai et al., 1988).

Mechanism of secretion and effects

Storage form of ANP is the pro-hormone proANP and its secretion is accompanied by mobilization of intracellular calcium. Pro-hormone 1—126 ANP gives rise to N-terminal ANP (1—98) and active form 28 hANP (99—126). Biological half-life of 28 hANP is 2.5—4.5 minutes (Lechleitner et al., 1991).

Antibodies against ANP cross-react with its pro-hormone which is secreted into circulation with a ratio 1:20. The measured value is so called immunoreactive ANP and its physiological value is 10—70 pg/ml (Lichardus and Lazúrová, 1993).

ANP receptors are located in the kidneys, zona glomerulosa of adrenals and in other tissues. After binding to membrane receptors guanylatcyclase is activated and cGMP in the cell rises. CGMP activates cGMP dependent proteinkinase, which is responsible for the peripheral effects of ANP. These include relaxation of smooth muscles, increase in endethelial permeability, negative inotropic effect on myocardium and others (Kahn et al., 1998).

Biological effects of ANP

ANP has important effects on cardiovascular system. In response to decreased cardiac output induced by ANP (decreased inotropy and venous return) systolic blood pressure falls. In some models of hypertension, ANP reduces peripheral vascular resistance, as shown by increase in skin blood flow (Bussien et al., 1986). Hemodynamic changes lead to sympathetic activation which counteracts ANP mediated vasodilation. In kidneys, ANP augments glomerular filtration rate and natriuresis (Laragh, 1985). Sympathetic nervous system and angiotensin II decrease the natriuretic effects of ANP.

ANP is the physiological contraregulatory mechanism of renin-angiotensin-aldosterone system. It decreases the production of renin and inhibits both basal and stimulated aldosterone secretion directly, via inhibition of sympathetic nervous system and via inhibition of the stimulatory effect of angiotensin II on the secretion of aldosterone (Cuneo et al., 1987; Struthers et al., 1986).

ANP lowers the secretion of vasopressin and its effects on permeability of collecting tubule (Brown et al., 1988). It blocks the effect of hypertonic saline load on secretion of vasopressin and thirst.

Brain natriuretic peptide (BNP)

BNP is synthesized in ventricles, binds to ANP receptors and also acts via guanylatcyclase (Hunt et al., 1994). As a consequence of lower affinity its degradation is slower than the degradation of ANP. It causes vasodilation, slightly lowers systolic blood pressure and significantly increases heart rate. It has natriuretic effects and inhibits renin-angiotensin-aldosterone system. Increased levels were measured in patients with heart failure. This fact may be useful in detection of early stages of heart failure (Gottlieb et al., 1989; Tsutamoto et al., 1999).

Vasopressin (AVP)

AVP is produced in supraoptic (NSO) and paraventricular (NPV) nuclei. Their axons lead mainly to the posterior pituitary where they store AVP and then release it into systemic circulation in response to neural stimuli from NSO. The secretion of AVP is regulated by osmotic and hemodynamic changes. Osmotically active substances (Na, K, glucose) influence secretion of AVP by creating gradient between extra- and intracellular space of osmoreceptor cells. Hemodynamic stimuli regulate AVP secretion only indirectly, they modulate functional properties of osmoregulatory system. Changes of circulating volume and blood pressure are recorded by high and low pressure receptors. Probably most important are the baroreceptors in the left atrium which react to even small changes in circulating blood volume (Reeves et al., 1998). Increased blood volume causes increase in afferent impulses to central nervous system. In NSO and NPV, they inhibit AVP secretion.

Catecholamines act in the process of AVP secretion indirectly via changes in hemodynamics and directly as neurotransmitters. In NSO and NPV, nerve endings containing norepinephrine are present which stimulate the release of AVP via α1 receptor stimulation (Willoughby et al., 1987).

Intravenous administration of angiotensin II directly stimulates AVP producing neurons leading to stimulation of AVP secretion (Iovino et al., 1984). ACE-inhibitors block AVP release.

The negative feedback for AVP is probably ANP. On the other hand, AVP with its vasopressor action may stimulate the production of ANP (Manning et al., 1985).

Biological effects

Effects of AVP are mediated by means of two receptor types — V1 and V2. They are connected with different second messenger systems on the surface of target cells (Reichlin, 1998).

V1 receptors, called pressoric, are located mainly in the vessels. Their activation is coupled to changes in intracellular calcium. The result is vasoconstriction.

V2 receptors, called also antidiuretic, are coupled to cAMP second messenger system and are located in cortical and medullary part of renal collecting tubules and other parts of the nephron. AVP increases the permeability of epithelial cells for water which leads to its passage from the lumen into the interstitial fluid in the direction of osmotic gradient (Hebert et al., 1981).

Catecholamines

The autonomic nervous system is the fundamental regulatory mechanism of the cardiovascular system. It has two components, parasympathetic and sympathetic. Parasympathetic mediator is acetylcholine which is released from the efferent parasympathetic terminals in the vicinity of target organs. Sympathetic mediators are norepinephrine, epinephrine and dopamine. Catecholamines are synthesized in adrenal medulla, in adrenergic neurons, postganglionic sympathetic neurons and in the central nervous system. In adrenal medulla, predominantly epinephrine, but to a lesser extent also norepinephrine is synthesized. In postganglionic sympathetic fibres, norepinephrine production prevails.

The stimulus for the release of catecholamines is acetylcholine which is secreted from the terminals of preganglionic sympathetic fibres. Epinephrine is a marker of adrenal activity, while norepinephrine reflects the functional status of sympathetic nervous system (Young and Landsberg, 1998).

Biological effects

Epinephrine and norepinephrine act as mixed agonists. Their effect depends on the target organ and the distribution of adrenergic receptors in it. Their effect is mediated mainly by and receptors.

Adrenergic receptors are ubiqitous in the cardiovascular system. Afferent information is sensed by the high- and low-pressure baroreceptors which continously monitor the state of circulation. From there, inhibitory fibers lead to the brainstem where the sympathetic centers are located. Efferent fibers lead to arterioles, heart, kidneys and veins (Young and Landsberg, 1998).

α1 receptors are postsynaptic and cause contraction of smooth muscles. α1-adrenoceptor mediated venoconstriction augments venous return. Based on Frank-Starlings mechanism, increased ventricular filling causes an increase in ventricular contractility. α2 receptors are presynaptic autoreceptors which by means of negative feedback inhibit secretion of epinephrine and acetylcholine from nerve fibres. Postsynaptic α2 receptors lower blood pressure and heart rate. They act in the central nervous system (Milligan et al., 1994).

Direct cardiac effects are mediated by postsynaptic β1 receptors. Their activation leads to increased contractility, automaticity and conductance.

The impact of adrenergic activation on electrophysiological properties influences all the main mechanisms of arrhythmogenesis:

1. *Abnormal automaticity.* Normal automaticity of automatic cells and Purkinje fibers is caused by spontaneous diastolic depolarization. Sympathetic-mediated increased automaticity occurs in consequence to accelerated spontaneous diastolic depolarization by amplified hyperpolarization-activated pacemaker current (Brown et al., 1979). Abnormal automaticity in the working myocardium arises for example during acute ischemia when in response to increased extracellular K+ concentration diminished transmembrane potential and inactivation of sodium channels occurs. In this situation, calcium current is responsive for the excitability of the myocardium. Increased automaticity causes ectopic beats. Ectopy and increased heart rate may trigger malignant arrhythmias on the basis of reentry in the inhomogeneous milieu of ischemic myocardium (Kléber et al., 1978).

2. *Reentry.* Catecholamines accelerate impulse conduction through ischemic myocardium, shorten refractory period of normal myocardium and prolong refractory period of ischemic myocardium (Opthof et al., 1991; Opthof et al., 1993). This effect leads to a dispersion of repolarization which predisposes to reentrant arrhythmias. Atrioventricular nodal conduction improves and its refractory period shortens thereby facilitating the induction of supraventricular tachycardias dependent on the participation of atrioventricular node (atrioventricular nodal reentry tachycardia, atrioventricular reentry tachycardia).

3. *Triggered activity*. In patients with congenital long QT syndrome, early afterdepolarizations are the probable mechanism responsible for the start of malignant ventricular arrhythmias. Catecholamines play here an important role and antiadrenergic interventions improve the prognosis of patients (Schwartz and Locati, 1985). Catecholamines increase cytosolic calcium level through a mechanism dependent on cAMP predisposing to late afterdepolarizations (Lubbe et al., 1992).

These experimental results are corroborated by large clinical studies which demonstrate positive effect of betablockers on survival of patients with malignant ventricular tachyarrhythmias (Steinbeck et al., 1992), coronary heart disease after myocardial infarction (The Norvegian Multicenter Study Group, 1981), congestive heart failure (Packer et al., 1996), long QT syndrome (Schwartz and Locati, 1985), hypertrophic cardiomyopathy (Östman-Smith et al., 1999) and hypertension, i.e. in patients with high risk of malignant ventricular arrhythmias.

β2-adrenoceptors are predominantly located in trachea, bronchi, vessels, uterus etc. Their stimulation leads to smooth muscle relaxation.

Renin-angiotensin-aldosterone system

Aldosterone is produced in the zona glomerulosa of the adrenal cortex. Main stimulus for the release of aldosterone is renin. Renin is formed in the juxtaglomerular cells of the afferent arterioles and in the macula densa of the distal tubules. The baroreceptors of the juxtaglomerular apparatus react to the activation of vascular stretch receptors and the receptors of macula densa to low sodium concentration in tubular fluid. Molecular-biological studies revealed the production of renin and other components of renin-angiotensin-aldosterone system in many other tissues besides the kidneys, namely in myocardium and vascular wall (Dostal et al., 1992; Sawa et al., 1992). Experimental studies however proved the dependence of the local pro-

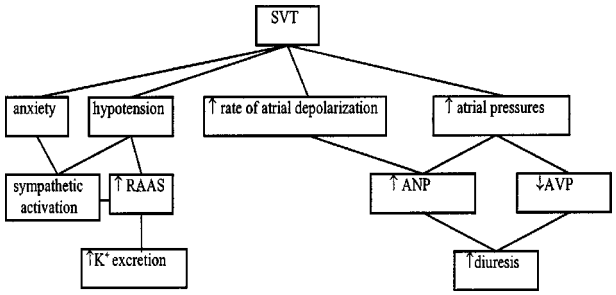

Fig. 1. Endocrine activation in paroxysmal supraventricular tachycardia. SVT — paroxysmal supraventricular tachycardia, RAAS — renin-angiotensin-aldosterone system, K+ — potassium, ANP — atrial natriuretic peptide, AVP — vasopressin.

duction on renal renin which is picked up from the circulation and catalyzes intracellular transformation of angiotensinogen to angiotensin I (Danser et al., 1994). In liver, angiotensinogen is cleaved by renin to angiotensin I, which is concerning vasoconstriction inactive (Obdržálková a Križanová, 1998). In the lungs, angiotensin converting enzyme cleaves two aminoacid rests of angiotensin II giving rise to angiotensin II. Angiotensin II directly stimulates aldosterone secretion in the adrenals.

Biological effects

Angiotensin II acts after binding to angiotensin receptors 1 (AT1) and 2 (AT2) on the cell membrane. It causes vasoconstriction. Proliferative effects of angiotensin II have been demonstrated also (Kuželová et al., 1998). Aldosterone amplifies the growth and proliferative effects of angiotensin II (Takeda and Miyamori, 1995).

There is close relationship between the sympathetic nervous system and renin-angiotensin-aldosterone system. Animal experiments have shown that circulating angiotensin II not only inhibits central and peripheral vagal activity but also raises sympathetic tone (Potter, 1981; Zimmerman, 1981). On the other hand, renin release is stimulated by ß-adrenergic activation.

Aldosterone maintains intravascular volume and homeostasis by retention of sodium and excretion of potassium and hydrogen ions in the kidneys. Target tissues are epithelial cells of the renal collecting tubules.

Endocrine activation in paroxysmal supraventricular tachycardia (Fig.1)

Paroxysmal supraventricular tachycardia (SVT) is typically a disease occuring in structurally normal hearts. Its mechanism is most commonly reentry mediated by dual atrioventricular nodal pathways or accessory atrioventricular pathways. The majority of SVT's has a short R-P interval. Hemodynamically this means that atrial systole occurs during ventricular systole. In supraventricular tachycardias with long R-P interval, atrial systole correctly precedes ventricular systole.

Several studies which did not distinguish between SVT with long and short R-P intervals came to the conclusion that SVT leads to a fall in cardiac output and systolic blood pressure, while the pressures in right and left atria rise (Tsai et al., 1988). In a study by Sganzerla et al. (1989), in contrary to SVT with short R-P interval, there was no fall in systolic blood pressure and cardiac output in long-RP tachycardia. Very recently published study by Hamdan et al. (2001) concluded that superior maintenance of hemodynamic stability during long-RP tachycardia is accompanied by reduced sympathoexcitation. However, both forms of SVT led to fall in blood pressure and increased central venous pressure and sympathetic nerve activity.

Increase in atrial pressures during SVT stimulates ANP release (Schiffrin et al., 1985; Müller et al., 1986). ANP rises 30 minutes after the induction of SVT and the values return to normal 30 minutes after its termination (Fujii et al., 1991).

In contrary to the proven relationship between atrial pressures and the level of ANP, the relationship between heart rate and ANP level is less clear (Roy et al., 1987; Mookherjee et al., 1991). The influence of heart rate and atrial pressures is difficult to distinguish, because they rise in parallel during SVT (Schiebinger and Linden, 1986; Burnett et al., 1989; Fujiwara et al., 1993).

Activation of pressure receptors in the left atrium leads to inhibition of AVP secretion. Its blood level falls in SVT. In early recovery phase, sudden rise in AVP level occurs, probably caused by a fall in atrial pressures after restoration of sinus rhythm and continued water diuresis (Fujii et al., 1991).

Level of aldosterone, the contraregulatory hormone in water homeostasis, increases, as well as the level of norepinephrine (Theodorakis et al., 1996; Fujii et al., 1991).

Complex endocrine activation, above all increased ANP and low AVP levels during the arrhythmia cause profound changes in water and electrolyte handling. In the kidneys, glomerular filtration rises by 50 % and plasma renal flow by 20 %. Other changes include increases in diuresis and natriuresis and a fall in urinary osmolality. Potassium excretion rises especially in the recovery phase. Creatinine clearance increases up to 30 minutes after the termination of SVT (Fujii et al., 1991; Tsai et al., 1988). The clinical correlate of all these changes is polyuria, which is often one of the leading symptoms of SVT.

Endocrine activation in atrial fibrillation

Atrial fibrillation (AF) is the most common persistent arrhythmia in the adult population. Its prevalence is 0.3—0.5 % and increases with age. In the population over 60 years of age, its incidence is 2—4 % (Van Wagoner et al., 1997).

Arterial hypertension, congestive heart failure, valvular heart disease, coronary heart disease and hyperthyroidism all pre-

dispose to atrial fibrillation. It is frequent after heart surgery. Coronary artery bypass grafting is post-operatively complicated by an episode of AF in 5—40 % (Dimmer et al., 1998). Idiopathic AF, where the cause is unknown, represents 6—16 % of the cases. In some patients, influence of autonomic nervous system on AF initiation and maintenance can be demonstrated (Coumel, 1994).

From the electrophysiological point of view, AF is characterized by an irregular atrial electrical activity on the basis of multiple wavelets of reentry with a rate of more than 350/minute (Konings et al., 1994). Ventricular response is also irregular and depends on the state of the conduction system.

Longer duration of AF causes persisting electrophysiological and histological changes called electrical remodelling. These changes predispose to reentrant activation and lead to self-perpetuation of AF — the concept of „AF begetting AF" (Wijffels et al., 1995). Signs of calcium overload have been noted in fibrillating atrial cardiomyocytes. Administration of a calcium channel blocker led to inhibition of electrical remodelling which argues for the causal involvement of calcium overload in this process (Goette et al., 1996). The role of calcium ions as a second messenger in the regulation of ANP production is known and ANP secretion may parallel the electrophysiological changes in the atria. Calcium channel blockers suppress ANP production in isolated atrial cardiomyocytes and their administration to patients with chronic AF was associated with lower ANP production (Ambler and Leite, 1994; Van Den Berg et al., 1998). ANP level is inversely related to the duration of atrial fibrillation (Van Den Berg et al., 1998). Degenerative changes in the atria depend on the duration of AF. On the basis of these facts there is hope that ANP level, additional to the duration of AF, could have prognostic implications for the maintenance of sinus rhythm after cardioversion of AF. Indeed, in one study, ANP level and its rise during stress test were higher in patients, in whom cardioversion was successful (Theodorakis et al., 1996).

ANP level is higher in AF of short duration than in sinus rhythm (Berglund et al., 1990). There was no correlation between ANP and the size of the left atrium in AF (Mookherjee et al., 1991; Theodorakis et al., 1996; Fujiwara et al., 1993; Dimmer et al., 1998).

There is little data published on the influence of AF on secretion of other hormones. Increased level of aldosterone and non-significant changes in epinephrine, norepinephrine and AVP in comparison to patients in sinus rhythm have been observed, i.e. changes which are not surprising in well tolerated AF with good control of ventricular rate (Berglund et al., 1990).

Apart from ANP, neither neuroendocrine response to cardioversion has been adequately studied. Published studies concern mainly electrical cardioversion. Atrial pressures significantly fall after electrical cardioversion (Rowlands et al., 1967; Arakawa et al., 1995). The levels of ANP and its second messenger — cGMP also fall. They return to normal 15 minutes to 4 hours after electrical cardioversion (Petersen et al., 1988; Arakawa et al., 1995; Fujiwara et al., 1993; Roy et al., 1987; Lechleitner et al., 1991; Mookherjee et al., 1991; Müller et al., 1986). On the other hand,

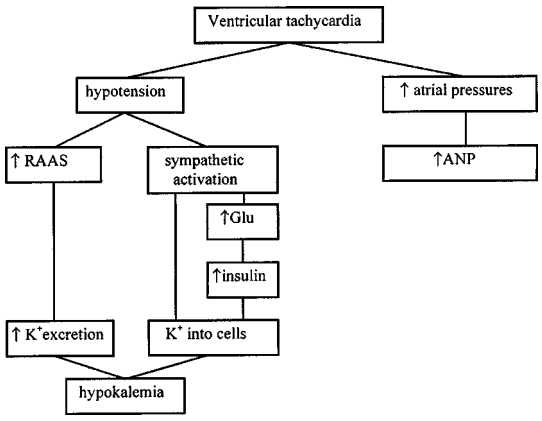

Fig. 2. Endocrine activation in ventricular tachycardia. Abbreviations as in Figure 1. Glu — glucose.

following pharmacological cardioversion, normal values were achieved only after 7 days (Müller et al., 1986).

In the study by Florkowski et al. (1996), significant rise in plasma cortisol with maximum at 30 minutes, ACTH and AVP at 5 minutes and prolactin at 10 minutes after electrical cardioversion were noted. Our study confirmed these findings. The most pronounced change in pituitary hormone release was observed in plasma prolactin levels which increased significantly during the whole time period after the cardioversion studied. Cardioversion resulted in rise in plasma cortisol and renin activity observed at 20 minutes. Though the blood glucose and C-peptide concentrations did not change, plasma insulin levels rose at 5 and 20 minutes. Electrical cardioversion failed to change significantly growth hormone, aldosterone and catecholamine levels. Thus, electrical cardioversion induces a specific neuroendocrine activation (Lukáč et al., 2000).

Endocrine activation in ventricular tachycardia (Fig. 2)

ANP level rises in ventricular tachycardia (Crozier et al., 1987; Ellenbogen et al., 1988), the increase being stronger than in SVT. The increase is explained by higher atrial pressures in ventricular tachycardia. Right atrial pressure positively correlates with the level of ANP (Ellenbogen et al., 1988). Ventricular tachycardia is often associated with hypotension which probably leads to additional hormonal activation. In ventricular tachycardia, first norepinephrine and epinephrine, afterwards glucose followed by insulin rise (Ellenbogen et al., 1990). Probably these endocrine changes elicit hypokalemia, which is often observed following resuscitation from ventricular tachycardia and ventricular fibrillation (Salerno et al., 1993).

During paroxysmal tachycardias activation of the neuroendocrine system is predominantly mediated by hemodynamic changes. ANP is the major player in these complex regulatory me-

chanisms but clinically relevant are also changes of the renin-angiotensin-aldosterone system, AVP, catecholamines and other hormones. There is ambient space for further laboratory and clinical research, which should improve our understanding of these clinically important interrelations between cardiovascular and neuroendocrine systems.

References

1. Ambler SK, Leite MF: Regulation of atrial natriuretic peptide secretion by α1-adrenergic receptors: The role of the second messenger pathways. J Mol Cell Cardiol 1994; 26: 391—402.

2. Arakawa M, Miwa H, Kambara K, Ohno M, Kagawa K, Nishigaki K, Ito Y, Kawada T, Hirakawa S: Changes in plasma concentrations of atrial natriuretic peptides after cardioversion of chronic atrial fibrillation. Amer J Cardiol 1992; 7: 550—552.

3. Arakawa M, Miwa H, Noda T, Ito Y, Kambara K, Kagawa K, Nishigaki K, Kano A, Hirakawa S: Alternations in atrial natriuretic peptide release after DC cardioversion of non-valvular chronic atrial fibrillation. Europ Heart J 1995; 16: 977—985.

4. Berglund H, Boukter S, Theodorsson E, Vallin H, Edhag O: Raised plasma concentration of atrial natriuretic peptide are independent of left atrial dimensions in patients with chronic atrial fibrillation. Brit Heart J 1990; 64: 9—13.

5. Braunwald E: Heart failure. P. 1287—1298. In: Fauci AS et al (Eds.): Harrison's principles of internal medicine. 14. New York, McGraw—Hill 1998, 2569 p.

6. Brown HF, DiFrancesco D, Noble D: How does adrenaline accelerate the heart? Nature 1970; 280: 235—236.

7. Brown J, Forsling ML, Valdes G, Slater JD, Dollery CT: Antagonism of V2-receptor effect of antidiuretic hormone by atrial natriuretic peptide in man. Experientia 1988; 15: 513—516.

8. Burnett JC, Osborn MJ, Hammill SC, Heublein DM: The role of frequency of atrial contraction versus atrial pressure in atrial natriuretic peptide release. J Clin Endocrinol Metab 1989; 69: 881—884.

9. Bussien JP, Biollaz J, Waeber B, Nussberger J, Turini GA, Brunner HR, Brunner-Ferber F, Gomez HJ, Otterbein ES: Dose-dependent effect of atrial natriuretic peptide on blood pressure, heart rate and skin blood flow of normal volunteers. J Cardiovasc Pharmacol 1986; 8: 216—220.

10. Cantin M, Gutkowska J, Thibault G, Milne RW, Ledoux S, MinLi S, Chapeau C, Garcia R, Hamet P, Genest J: Immunocytochemical localization of atrial natriuretic peptide in the heart and salivary glands. Histochemistry 1984; 80: 113—127.

11. Coumel P: Paroxysmal atrial fibrillation: Role of the autonomic nervous system. Arch Mal Coeur 1994; 87: 55—62.

12. Crozier IG, Ikram H, Nicholls MG, Nicholls MG, Espiner EA, Yandle TG: Atrial natriuretic peptide in spontaneous tachycardias. Brit Heart J 1987; 58: 96—100.

13. Cuneo RC, Espiner EA, Nicholls MG, Yandle TG: Exercise induced increase in plasma atrial natriuretic peptide and effect of sodium loading in normal man. Horm Metab Res 1988; 20: 115—117.

14. Cuneo RC, Espiner EA, Nicholls MG, Yandle TG, Livesey JH: Effect of physiological levels of atrial natriuretic peptide on hormone secretion: inhibition of angiotensin-induced aldosterone secretion and renin release in normal man. J Clin Endocrinol Metab 1987; 65: 765—772.

15. Danser AHJ, Van Kats JP, Admiral PJJ: Cardiac renin and angiotensins. Uptake from plasma versus in situ synthesis. Hypertension 1994; 24: 37—48.

16. Di Carlo LA, Morady F, Krol RB, Baerman JM, de Buitler M, Schork A, Sereika SM, Schurig L: The hemodynamic effects of ventricular pacing with and without atrioventricular synchrony in patients with normal and diminished ventricular function. Amer Heart J 1987; 114: 746—752.

17. Dimmer C, Tavernier R, Gjorgov N, Van Nooten G, Clement DL, Jordaens L: Variation of autonomic tone preceding onset of atrial fibrillation after coronary artery bypass grafting. Amer J Cardiol 1998; 82: 22—25.

18. Dostal DE, Rothblum KN, Chernin MI, Cooper GR, Baker KM: Intracardiac detection of angiotensinogen and renin: a localized renin-angiotensin system in the neonatal rat heart. Amer J Physiol 1992; 263: C838—C850.

19. Ellenbogen KA, Rogers R, Walsh M, Mohanty PK: Increased circulating atrial natriuretic factor (ANP) release during induced ventricular tachycardia. Amer Heart J 1988; 116: 1233—1238.

20. Feldman MD, Alderman JD, Aroesty JM, Royal HD, Ferguson JJ, Owen RM, Grossman W, McKay RG: Depression of systolic and diastolic myocardial reserve during atrial pacing tachycardia in patients with dilated cardiomyopathy. J Clin Invest 1988; 82: 1661—1669.

21. Florkowski CM, Crozier IG, Nightingale S, Evans MJ, Ellis MJ, Joyce P, Donald RA: Plasma cortisol, PRL, ACTH, AVP and corticotrophin releasing hormone responses to direct current cardioversion and electroconvulsive therapy. Clin Endocrinol 1996; 44: 163—168.

22. Follenius M, Brandenburger G: Increase in atrial natriuretic peptide in response to physical exercise. Europ J Appl Physiol 1988; 57: 159—162.

23. Fujii T, Kojima S, Imanishi M, Ohe T, Omae T: Different Mechanisms of polyuria and natriuresis associated with paroxysmal supraventricular tachycardia. Amer J Cardiol 1991; 68: 343—348.

24. Fujiwara H, Ishikura F, Nagata S, Beppu S, Miyatake K: Plasma atrial natriuretic peptide response to direct current cardioversion of atrial fibrillation in patients with mitral stenosis. J Amer Coll Cardiol 1993; 22: 575—580.

25. Gerbes AL, Dagnino L, Nguyen T, Nemer M: Transcription of brain natriuretic peptide and atrial natiuretic peptide genes in human tissues. J Clin End Met 1994; 78: 1307—1311.

26. Goette A, Honeycutt C, Langberg JJ: Electrical remodeling in atrial fibrillation. Circulation 1996; 94: 2968—2974.

27. Gottlieb SS, Kukin ML, Ahern D, Packer M: Prognostic importance of atrial natriuretic peptide in patients with chronic heart failure. J Amer Coll Cardiol 1989; 13: 1534—1539.

28. Hamer AW, Zaher CA, Rubin SA, Thomas P, Mandel WJ: Hemodynamic benefits of synchronized 1:1 atrial pacing during sustained ventricular tachycardia with severely depressed ventricular function in coronary heart disease. Amer J Cardiol 1985; 55: 990—994.

29. Hebert SC, Schafer JA, Andreoli TE: Effects of antidiuretic hormone (ADH) on solute and water transport in the mammalian nephron. J Membr Biol 1981; 58: 1—19.

30. Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, Epstein SE: Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation 1976; 53: 273—279.

31. Hunt PJ, Richardus AM, Espiner EA, Nicholls MG, Yandle TG: Bioactivity and metabolism of C-type natriuretic peptide in normal man. J Clin End Met 1994; 78: 1428—1435.

32. Iovino M, Steardo L: Vasopressin release to central and peripheral angiotensin II in rats with lesion of the subfornical organ. Brain Res 1984; 322: 365—368.

33. Kahn CR, Smith RJ, Chin WW: Mechanism of action of hormones that act at the cell surface. P. 95—143. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR (Eds.): Williams textbook of endocrinology. 9. Philadelphia, W.B. Saunders Company 1998, p. 1819.

34. Kelly PA, McAuly-Hunter E, Astridge P, Lowry PJ, Perrins EJ, Kaye GC: Failure of plasma atrial natriuretic peptide levels to increase during exercise in patients with chronic atrial fibrillation. Pacing Clin Electrophysiol 1997; 320: 10—16.

35. Kléber AG, Janse MJ, van Capelle FJL: Mechanism and time course of S-T and T-Q changes during acute regional myocardial ischemia in the pig heart determined by extracellular and intracellulat recordings. Circulat Res 1978; 42: 603—613.

36. Konings KTS, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA: High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994; 89: 1665—1680.

37. Kuželová M, Tumová I, Švec P: Antagonisty angiotenzínových receptorov-perspektívne liečivá srdcovo-cievneho systému. Slovakofarma Revue 1998; 8: 97—103.

38. Laragh JH: Atrial natriuretic hormone, the renin-aldosterone axis, and blood pressure-electrolyte homeostasis. New Engl J Med 1985; 21: 1330—1340.

39. Lechleitner P, Genser N, Mitterschiffthaler G, Puschendorf B, Dienstl F: Atrial natriuretic peptide and cyclic guanosine monophosphate response to cardioversion of atrial flutter or fibrillation. Amer J Cardiol 1991; 68: 837.

40. Lechleitner P, Genser S, Hauptlorenz S, Putensen C, Mitterschiffthaler G, Artner-Dworzak E, Puschendorf B, Dienstl F: Verhalten von atrialen natriuretischem Peptid (ANP) und zyklischem Guanosinmonophosphat (cGMP) bei der Kardioversion. Z Kardiol 1991; 80: 574—579.

41. Lichardus B, Lazúrová I: Nátriuretické hormóny. P. 505—516. In: Kreze A, Langer P, Klimeš I, Lichardus B (Eds.): Praktická endokrinológia. 1. Bratislava, Slovak Academic Press 1993, 549 p.

42. Linhart JW, Hildner FJ, Barold SS, Lister JW, Samet P: Left heart hemodynamics during angina pectoris induced by atrial pacing. Circulation 1969; 40: 483—492.

43. Lubbe WF, Podzuwei T, Opie LH: Potential arrhythmogenic role of cyclic adenosine monophosphate (AMP) and cytosolic calcium overload: Implications for prophylactic effects of beta-blockers in myocardial infarction and proarrhythmic effects of phosphodiesterase inhibitors. J Amer Coll Cardiol 1992; 19: 1622—1633.

44. Lukáč P, Kšinantová L, Lukáčová S, Hatala R, Pecháň I, Kvetňanský R, Vigaš M, Ježová D: Neuroendocrine activation in response to dc cardioversion of atrial fibrillation induces significant hypokalemia. Abstract O 077, 39, 8th alpe Adria Cardiology Meeting, May 24—24, 2000, Portorož, Slovenia.

45. Manning PT, Schwartz D, Katsube NC, Holmberg SW, Needleman P: Vasopressin-stimulated release of atriopeptin: endocrine antagonists in fluid homeostasis. Science 1985; 229: 395—397.

46. Milligan G, Svoboda P, Brown CM: Why are there so many adrenoceptor subtypes? Biochem Pharmacol 1994; 48: 1059—1071.

47. Mookherjee S, Anderson G, Jr, Smulyan H, Vardan S: Atrial natriuretic peptide response to cardioversion of atrial flutter and fibrillation and role of associated heart failure. Amer J Cardiol 1991; 67: 377—380.

48. Müller FB, Erne P, Raine AEG, Kiowski W, Resink TJ, Burkart F, Buhler FR: Sekretion des atrialen natriuretischen Peptids: Abhängigkeit vom Vorhofdruck und systemischen Blutdruck. Schweiz Med Wschr 1986; 116: 1610—1612.

49. Nakano J: Effects of atrial and ventricular tachycardias on the cardiovascular dynamics. Amer J Physiol 1964; 206: 547—552.

50. The Norvegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. New Engl J Med 1981; 304: 801—807.

51. O'Rourke RA, Braunwald E: Physical examination of the cardiovascular system. P. 1231—1237. In: Fauci AS et al (Eds.): Harrison's principles of internal medicine. 14. New York. McGraw-Hill 1998, 2569 p.

52. Obdržálková D, Križanová O: Štruktúra renín—angiotenzínového systému a jeho význam v organizme. Čs Fyziol 1998; 47: 104—114.

53. Ong AC, Handler CE, Slater JD: Atrial natriuretic peptide release responds to atrial stretch and not to atrial pressure: observations during pericardiocentesis in a young woman. Europ Heart J 1990; 11: 368—371.

54. Opthof T, Coronel R, Vermeulen JT, Verberne HJ, van Capelle FJ, Janse MJ: Dispersion of refractoriness in normal and ischemic canine ventricle. Effects of sympathetic stimulation. Cardiovasc Res 1993; 27: 1954—1960.

55. Opthof T, Misier AR, Coronel R, Vermeulen JT, Verberne HJ, Frank RG, Moulijn AC, van Capelle FJ, Janse MJ: Dispersion of refractoriness in ventricular myocardium. Effects of sympathetic stimulation. Circulat Res 1991; 68: 1204—1215.

56. Östman-Smith I, Wettrell G, Riesenfeld T: A cohort study of childhood hypertrophic cardiomyopathy. Improved survival following high-dose beta-adrenoceptor antagonist treatment. J Amer Coll Cardiol 1999; 34: 1813—1822.

57. Ota K, Kimura T, Ito M, Inoue M, Shoji M, Shinoda S, Nagashi M, Matsui K, Iitake K, Yoshinaga K: The effect of short-lasting atrial pacing on the release of atrial natriuretic peptide, vasopressin, and methionine enkephalin in man. Acta End (Copenh) 1987; 116: 235—240.

58. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH: The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. New Engl J Med 1996; 334: 1349—1355.

59. Petersen P, Kastrup J, Vilhelmsen R, Schötten HJ: Atrial natriuretic peptide in atrial fibrillation before and after electrical cardioversion therapy. Europ Heart J 1988; 9: 639—641.

60. Potter EK: Angiotensin inhibits action of vagus nerve at the heart. Brit J Pharmacol 1981; 75: 9—11.

61. Rahimtoola SH, Ehsani A, Sinno MZ, Loeb HS, Rosen KM, Gunnar RM: Left atrial transport function in myocardial infarction, importance of its booster pump function. Amer J Med 1975; 59: 686—694.

62. Reeves WB, Bichet DG, Andreoli T: Posterior pituitary and water metabolism. P. 341—387. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR (Eds.): Williams textbook of endocrinology. 9. Philadelphia. W.B. Saunders Company 1998, 1819 p.

63. Reichlin S: Neuroendocrinology. P. 165—248. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR (Eds.): Williams textbook of endocrinology. 9. Philadelphia. W.B. Saunders Company 1998, 1819 p.

64. Ross J, Linhart JW, Braunwald E: Effects of changing heart rate in man by electrical stimulation of the right atrium. Circulation 1965; 32: 549—558.

65. Ross RD, Daniels SR, Dolan LM, Young CA, Meyer RA: Determinants of plasma atrial natriuretic factor concentrations in congenital heart disease. Amer J Cardiol 1988; 62: 785—788.

66. Rowlands DJ, Logan WFWE, Howitt G: Atrial function after cardioversion. Amer Heart J 1967; 74: 149—160.

67. Roy D, Paillard F, Cassidy D, Bourassa MG, Gutkowska J, Genest J, Cantin M: Atrial natriuretic factor during atrial fibrillation and supraventricular tachycardia. J Amer Coll Cardiol 1987; 9: 509—514.

68. Ruskin J, McHale PA, Harley A, Greenfield JC: Presure-flow studies in man: Effects of atrial systole on left ventricular function. J Clin Invest 19790; 49: 472—478.

69. Salerno DM, Katz A, Dunbar DN, Fjeldos-Sperbeck K: Serum electrolytes and catecholamines after cardioversion from ventricular tachycardia and atrial fibrillation. Pacing Clin Electrophysiol 1993; 16: 1862—1871.

70. Sato F, Kamoi K, Wakiya Y, Ozawa T, Arai O, Ishibashi M, Yamaji T: Relationship betweeen plasma atrial natriuretic peptide levels and pressure in man. J Clin End Metab 1986; 63: 823—827.

71. Sawa H, Tokuchi F, Mochizuki N: Expression of angiotensinogen gene and location of its protein in the human heart. Circulat Res 1992; 86: 138—146.

72. Sganzerla P, Fabbiocchi F, Grazi S, Cipolla C, Moruzzi P, Guazzi MD: Electrophysiologic and haemodynamic correlates in supraventricular tachycardia. Europ Heart J 1989; 10: 32—39.

73. Schiebinger RJ, Baker MZ, Linden J: Effect of adrenergic and muscarinic cholinergic agonists on atrial natriuretic peptide secretion by isolated rat atria. Potential role of the autonomic nervous system in modulating atrial natriuretic peptide secretion. J Clin Invest 1987; 80: 1687—1691.

74. Schiebinger RJ, Linden J: Effect of atrial contraction frequency on atrial natriuretic peptide secretion. Amer J Physiol 1986; 251: H1095—H1099.

75. Schiffrin EL, Gutkowska J, Kuchel O, Cantin M, Genest J: Plasma concentration of atrial natriuretic factor in a patient with paroxysmal atrial tachycardia. New Engl J Med 1985; 2: 1196.

76. Schwartz PJ, Locati E: The idiopathic long QT syndrome. Pathogenetic mechanisms and therapy. Europ Heart J 1985; 6: D103.

77. Steinbeck G, Andresen D, Bach P, Haberl R, Oeff M, Hoffmann E, von Leitner ER: A comparison of electrophysiologically guided antiarrhythmic therapy with beta-blocker therapy in patients with symptomatic, sustained ventricular tachyarrhythmias. New Engl J Med 1992; 327: 987—992.

78. Struthers AD, Anderson JV, Payne N, Causon RC, Slater JD, Bloom SR: The effect of atrial natriuretic peptide on plasma renin activity, plasma aldosterone, and urinary dopamine in man. Europ J Clin Pharmacol 1986; 31: 223—226.

79. Takeda R, Miyamori I: Endocrine and auto-paracrine factors in the pathogenesis of primary hypertension. Review. Hypertens Res 1995; 18: 171—179.

80. Tan SY, Nolan J, Craig K, Swainson CP: Supraventricular tachycardia, atrial pressure, atrial natriuuretic peptide and polyuria — a necessary sequence? J Intern Med 1993; 233: 415—417.

81. Thadani U, Lewis RJ, West RO, Chiong MA, Parker JO: Clinical, hemodynamic and metabolic responses during pacing in the supine and sitting position in patients with angina pectoris. Amer J Cardiol 1979; 44: 249—256.

82. Theodorakis GN, Markianos M, Kouroubetsis CK, Livanis EG, Paraskevaidis IA, Kremastinos DT: Clinical, adrenergic and heart endocrine measures in chronic atrial fibrillation as predictors of conversion and maintanance of sinus rhythm after direct current cardioversion. Europ Heart J 1996; 17: 550—556.

83. Tsai RC, Yamaji T, Ishibashi M, Takaku F, Pang SC, Yeh SJ, Lee YS, Hung JS, Wu D: Atrial Natriuretic Peptide During Supraventricular Tachycardia and Relation to Hemodynamic Changes and Renal Function. Amer J Cardiol 1988; 61: 1260—1264.

84. Tsai RC, Yamaji T, Ishibashi M, Takaku F, Hsu ST, Lai CY, Yeh SJ, Hung JS, Wu D, Lee YS: Effect of beta-adrenergic blockade on plasma levels of atrial natriuretic peptide during exercise in humans. J Cardiovasc Pharmacol 1988; 11: 614—618.

85. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Mabuchi N, Hayashi M, Ohnishi M, Sawaki M, Fujii M, Horie H, Sugimoto Y, Kinoshita M: Plasma brain natriuretic peptide level as a marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction. Europ Heart J 1999; 20: 1799—1807.

86. Usberti M, Federico S, Cianciaruso B, Federico S, Di Minno G, Ungaro B, Ardillo G, Pecoraro C, Cerbone AM, Cirillo F, Pannain M: Effects of angiotensin II on plasma ADH, PGE2 synthesis and water excretion in normal man. Amer J Physiol 1985; 248: F254—F259.

87. Van Den Berg M, Crijns JGMH, Van Veldhuisen DJ, Van Gelder IC, De Kam PJ, Lie KI: Atrial natriuretic peptide in patients with heart failure and chronic atrial fibrillation: Role of duration of atrial fibrillation. Amer Heart J 1998; 135: 242—244.

88. Van Den Berg MP, Tuinenburg AE, van Veldhuisen DJ, De Kam PJ, Crijns JGMH: Cardioversion of atrial fibrillation in the setting of mild to moderate heart failure. Int J Cardiol 1998; 63: 63—70.

89. Van Wagoner DR, Pond AL, Mc Carthy PM, Trimmer JS, Nerbonne JM: Outward K+ current densities and Kv 1.5 expression are reduced in chronic human atrial fibrillation. Circulat Res 1997; 80: 772—781.

90. Vaziri SM, Larson MG, Benjamin EJ, Levy D: Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation 1994; 89: 724—730.

91. Viskin S, Fish R, Roth A, Schwartz PJ, Belhassen B: QT or not QT? New Engl J Med 2000; 343: 352—356.

92. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA: Atrial fbrillation begets atrial fibrillation. Circulation 1995; 92: 1954—1968.

93. Willoughby JO, Jervois PM, Menadue MF, Blessing WW: Noradrenaline, by activation of α1-adrenoceptors in the region of the supraoptic nucleus, causes secretion of vasopressin in the unanesthetized rat. Neuroendocrinology 1987; 45: 219—226.

94. Wong NL, Wong EF, Au GH, Hu DC: Effect of alpha- and beta-adrenergic stimulation on atrial natriuretic peptide release in vitro. Amer J Physiol 1988; 255: E260—E264.

95. Young JB, Landsberg L: Catecholamines and adrenal medulla. P. 665—728. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR (Eds.): Williams textbook of endocrinology. 9. Philadelphia. W.B. Saunders Company 1998, 1819.

96. Zimmerman BG: Adrenergic facilitation by angiotensin: Does it serve a physiological function? Clin Sci 1981; 60: 343—348.

Received July 15, 2001.
Accepted August 17, 2001.