Improvement of ICD-Therapie by Catecholamines and Beta-Blockers for the Prevention of Sudden Cardiac Death

J. PELLA, P. KALIST, L. FEDÁKOVÁ, E. KOMANOVÁ
Third Internal Clinic, Louis Pasteur Hospital, Pavol Jozef Šafárik University, Košice, Slovakia

Summary

We analysed the function of the implantable cardioverter defibrillator (ICD) and modification of their therapeutic programme before and after application of a b-blocker. The study group consisted of 25 patients. Electrophysiological examinations were performed in all patients before ICD implantation. Twenty patients suffered from coronary heart disease with an average ejection fraction in the range of 40 % and five patients had dilated cardiomyopathy with an ejection fraction of about 30 %. There were no contraindications for the treatment with b-blockers in any patient. According to a randomized study concept, 11 patients received the b_1 selective blockers metoprolol and bisoprolol. From 14 patients who received no b-blockers, one patient switched to the b-blocker group during the study. The maximum 24-hour dose of b-blocker was 250 mg metoprolol or 10 mg of bisoprolol respectively. The positive impacts on the ICD function were: easier termination of tachycardia, decreased number of shocks, and decreased frequency of ventricular tachycardia and ventricular fibrillation episodes. Cardiac compensation was improved and overall anginal pain significantly reduced. The patients were followed up to 5 years. In the ICD group with b-blockers there were no deaths, but in the other group three patients died suddenly – two after acute myocardial infarction and one due to unknown reasons.

Key Words

Implantable cardioverter-defibrillator (ICD), catecholamines, β-blocker

Introduction

Increased blood pressure and disturbances of lipid and glucose metabolism have shown to be independent risk factors of sudden cardiac death and stroke. Hypertension is one of the significant cardiovascular disease risk factors [1,2]. The sympathetic nervous system plays an important role in the blood pressure regulation and its augmented activity is considered to be a primary precursor of hypertension both in human and animal experiments [3-8]. Already in 1987, Coumel outlined the relation between the substrate, ventricular tachycardia (VT) and ventricular fibrillation (VF) mechanisms and the sympathetic nervous system [3]. The impact of VT on the plasma level of the humoral transmitter of the sympathetic nervous system, norepinephrine (NE), was studied by our study group [9]. In general, the neurohumoral model of heart failure, pathogenesis of increased blood pressure, and coronary heart disease is generally accepted today [10-12].

The aim of this paper is to discuss whether it is convenient to combine ICD and β-blockers in order to improve treatment of sudden cardiac death. Our work also included evaluation of plasma levels of NE. We deem that the evaluation and interpretation of NE plasma levels is crucial, because β-blockade as a pharmacological treatment is based on large multicenter trials [3,4,12,13]. β-blockers have a firm place in the treatment of heart failure with coronary heart disease and increased blood pressure. Patients with ICD usually take amiodarone as antiarrhytmic drug. Many of these patients have concomitant diseases such as cardiac decompensation, arterial hypertension, diabetes mellitus, and other. β-blockers offer significant benefits in

these patients, yet we had no experience in using ß-blockers as antiarhytmics together with ICD. We started our 5-year trial with the aim to demonstrate that β-blockers improve cardiac remodeling and are useful also in the treatment of concomitant diseases.

Materials and Methods

Twenty-five patients with an indication for ICD implantation participated in the study. They received a Phylax 03, Phylax 06, Microphylax, or Phylax AV ICD unit (Biotronik, Germany). Each patient underwent electrophysiological examination according to standard methodology [14]. The patients suffered from coronary heart disease, hypertension, and disorders of lipid and glucose metabolism. Twenty patients presented with coronary heart disease and an average ejection fraction of 40 %, while five patients had dilated cardiomyopathy with an ejection fraction of 30 %. Arrhythmogenic right ventricular dysplasia, idiopathic VF, and congenital long QT-syndrome were found in none of the patients. There were no contraindications for β-blocker treatment.

According to a randomized study protocol, 11 of 25 patients with implanted ICDs received metoprolol asparate, succinate and bisoprolol. Metoprolol was introduced into the clinical practice as the first β_1-selective β-blocker in 1975 [15]. Because one patient switched from the non β-blocker to the β-blocker group, only 13 patients did not receive any β-blocker during the course of the study (Table 1).

Two weeks after ICD implantation, evaluation of NE was performed in seven patients from the non β-blocker group, using the high performance liquid chromatography [16-18]. The peripheral plasmatic NE from the cubital vein was obtained from patients after 30-minutes resting in the supine position. Pharmacological treatment was limited to diuretic and anticoagulant drugs. No antiarrhythmics, β-blockers, or ACE inhibitors were allowed. After taking the above-described basal sample from the cubital vein, we stimulated in the right ventricular apex for 5 minutes at a cycle length of 600 ms. Then, we drew another sample of plasmatic NE from the cubital vein.

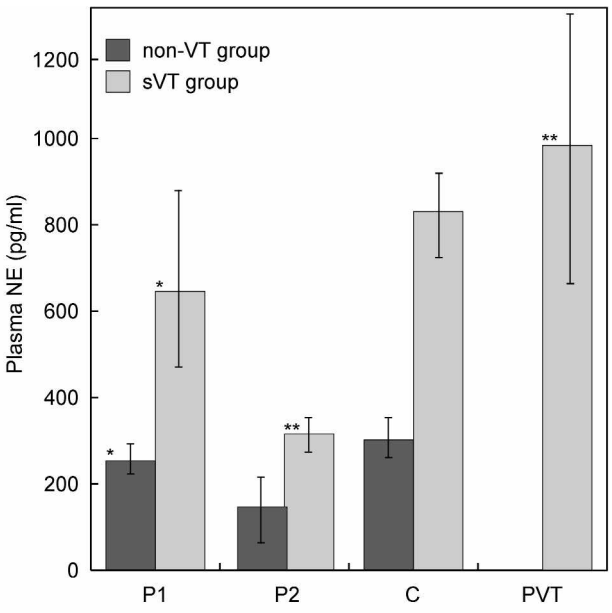
We statistically evaluated the sole NE (not dopamine or epinephrine) on the basis of our previous experience [9], because NE itself is minimally influenced by emotional stress.

	Patients with β-blocker	Patients without β-blocker
Randomization	11	14
Study duration	12	13
Mortality (5 years)	–	3

Table 1. Number of patients in the study group.

Results

In our previous study involving NE measurements, there was a statistically significant difference in peripheral plasmatic NE from left cubital vein during the basal conditions between the sVT and non-VT group (Figure 1, for detailed description see reference [9]). The intracardiac plasmatic NE concentration in the right atrium was significantly higher in both groups compared to the peripheral value of NE measured from the cubital vein sample. During VT, the value of peripheral NE in the cubital vein increased significantly from the baseline value ($P < 0.001$). In the present



P1	from left cubital vein
P2	from left cubital vein after ventricular stimulation
C	from right atrium after ventricular stimulation
PVT	from left cubital vein after 5 min sVT

Figure 1. Norepinephrine (NE) concentrations for patients without ventricular tachycardias (non-VT) and with sustained tachycardias (sVT) from reference [9]. The difference (*) and (**) were statistically significant ($P < 0.001$).

Patient	Before stimulation (pg/ml)	After stimulation (pg/ml)
PKA1	2467	461
PLE1	4985	413
PFA1	706	158
PRU1	949	141
PKO1	1200	219
PVA1	1513	296
PFR1	938	302

Table 2. Values of norepinephrine concentrations before and after stimulation in seven patients from the non-b-blocker group. The difference is statistically significant (P < 0.001).

study, we verified our previous results [9] and obtained statistically significant decrease of the basal peripheral plasmatic NE after 5 minutes of ventricular stimulation (P < 0.001, Table 2).

In 13 patients taking no β-blockers, three patients died suddenly; two patients died due to cardiogenic shock following acute myocardial infarction and in one patient (who also had coronary heart disease) the cause of death remained unexplained. One patient from this group only began with β-blocker therapy in the course of the study. Conversely, all 12 patients with β-blocker treatment are alive, with the longest follow-up period being 5 years and the shortest 6 months. Administration of β-blockers facilitated termination of VT and VF (Figures 2 and 3). Cardiac decompensation, subjective complaints and hypertension were improved in all 12 patients. The number of tachycardia spells and episodes of angina pectoris were reduced. Figure 2 illustrates unsuccessful anti-tachycardia pacing in a patient before β-blocker treatment, which included repeated bursts of two extrastimuli, increasingly aggressive ramp sequences starting from three extrastimuli, and ramp sequences of 10 extrastimuli. The VT was eventually terminated by 18-J shock energy. Figure 3 shows the same patient after 3 months of β-blocker treatment, when VT was easily terminated by the first anti-tachycardia pacing program (two extrastimuli).

Discussion

Sudden cardiac death is caused by ventricular tachycardia in more than 90 % of cases. Those include different types of tachyarrhythmias: sustained VT, slow

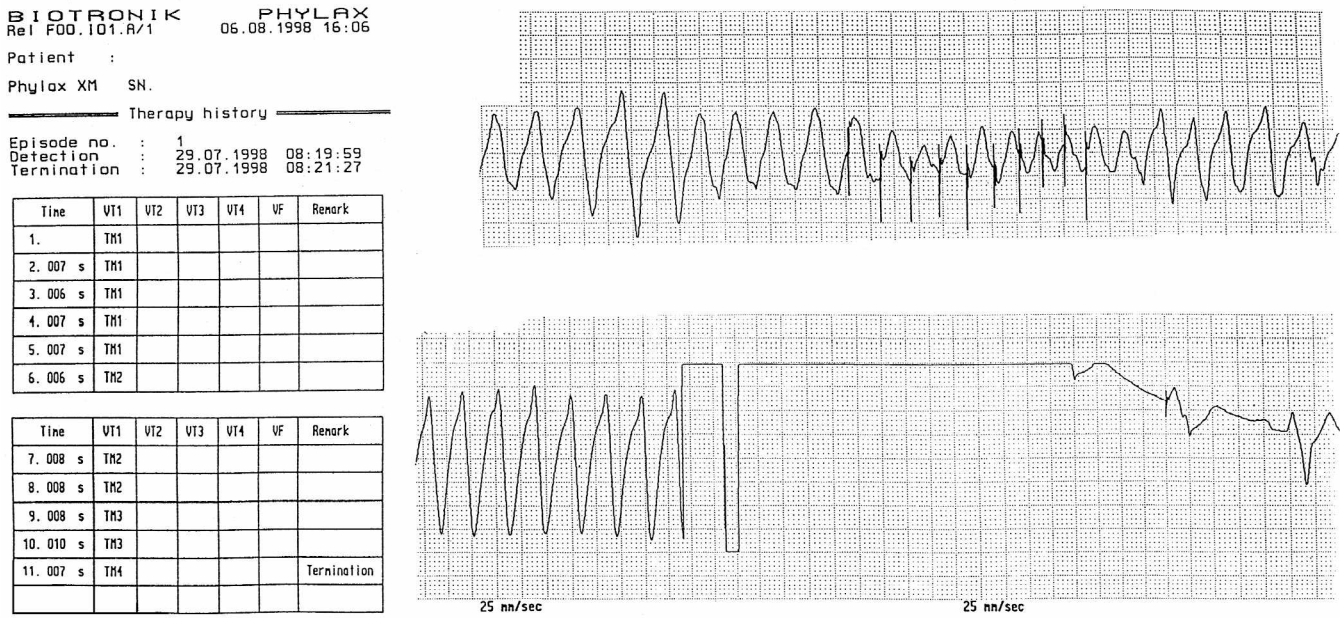


Figure 2. Antitachycardia pacing before treatment with b-blockers: repeated burst of two extrastimuli (TM1 programme, no ECG record available), increasingly aggressive ramp sequences starting from three extrastimuli (TM2 programme, no ECG record available), and ramp sequence with 10 extrastimuli (TM3 programme, first line of ECG recording), which all failed to terminate the ongoing ventricular tachycardia. At last, the tachycardia was terminated by 18-J shock energy (TM4 programme, second line of ECG recording).

or fast VT, ventricular flutter, VF and proarrhythmia - for instance torsade des pointes. It is very important to stratify patients according to the risk of sudden cardiac death. VT or VF must always be verified by an electrophysiological examination. According to the recent NASPE recommendations, the main contraindications for the ICD therapy include conditions allowing VT to be treated by other modalities.

At present, the neurohumoral model of chronic heart failure is well accepted, with various hormones known to be activated [12]. The potentially ensuing diuretic therapy often leads to hypokalemia as a result of renin-angiotensin system activation and secondary aldosteronism [12]. Together with the administration of various drugs – and not exclusively cardiotropic ones – hypokalemia may, among other things, lead to secondary prolongation of the QT interval. The majority of drugs and regulative hormones used for treatment of chronic heart failure and of ejection fraction < 30 % obstruct the I_{Kr} repolarising current, which plays an important role in the repolarisation of cardiomyocytes. Consequently, the QT interval will be prolonged. The I_{Kr} repolarising current is particularly sensitive to minimal oscillations of plasmatic values of potassium. The likelihood of VT is increased with an elevated sympathetic tone, minimal ischemia caused by coronary heart disease, as well as dysfunction of the endothelium (imbalance of endotheline I, its receptors, nitrates, various cytokines – interleukin 1) [3,5,6,10,11,13,17-20]. Particularly the relationship between coronary heart disease, increased sympathetic tone, lipid and glucose metabolism disorders and arrhythmogenesis was analysed [20]. The final answer to these complex neurohumoral relations and on the question whether antiarrhythmic therapy (e.g., amiodarone) is indicated in the prevention of sudden cardiac death in patients with coronary heart disease, or it is sufficient to apply only ICD therapy or both, can be only obtained through genetic evaluation. The aim of such evaluation would be to seek for the evidence of the latent mutations of gene coding, in particular the ones related to the I_{kr} repolarising current.

The objective of our paper was to assess whether the combination of β-blockers and ICDs is justified. We found that VT termination by anti-tachy pacing was in many cases easier after ß-blocker treatment. The big advantage of the treatment by second-generation selective β-blockers is seen in respect to coronary heart disease, hypertension, and chronic heart failure [6,9-12,18]. Although we had a small group of ICD patients available for the evaluation, we were able to demonstrate a significant difference in patient mortality.

Sympathetic activation in chronic heart failure and successful treatment of heart failure by β-blockers have recently been confirmed by several large multicenter studies. A few studies were even terminated early because of unambiguously positive influence on heart failure stage [3,13,21]. Nowadays, not only traditional preparations like digitalis or diuretics have their place in the therapy of heart failure, but also direct AT I receptor blockers, magnesium, competitive aldosterone antagonists (spironolactone), nitrates, and peripheral vasodilators are successfully applied in addition to β-blockers and ACE inhibitors. In our opinion, the most important role in heart failure and concomitant prevention of VTs is taken by effective β-blockade. VT may,

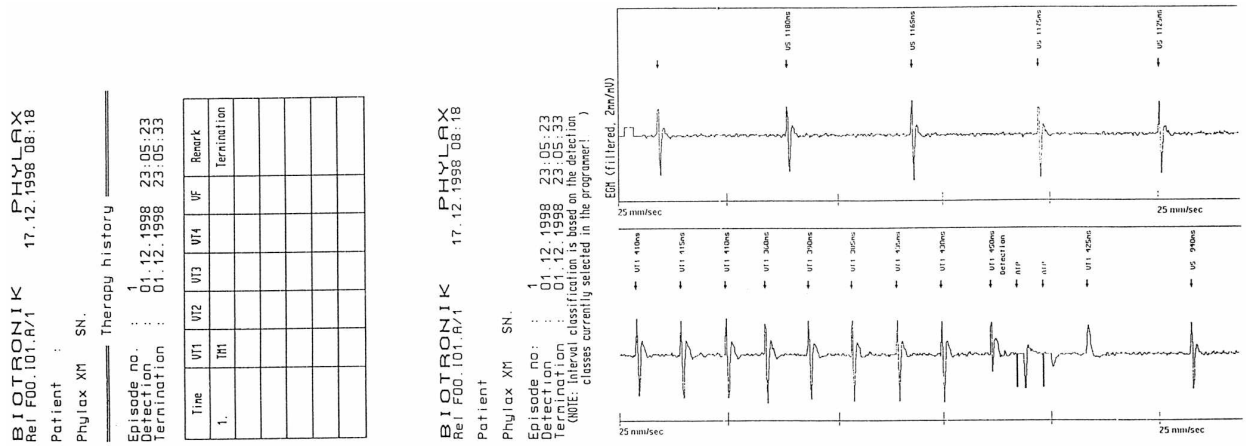


Figure 3. Successful antitachycardia pacing with just two extrastimuli at 3 months after beginning of the β-blocker treatment.

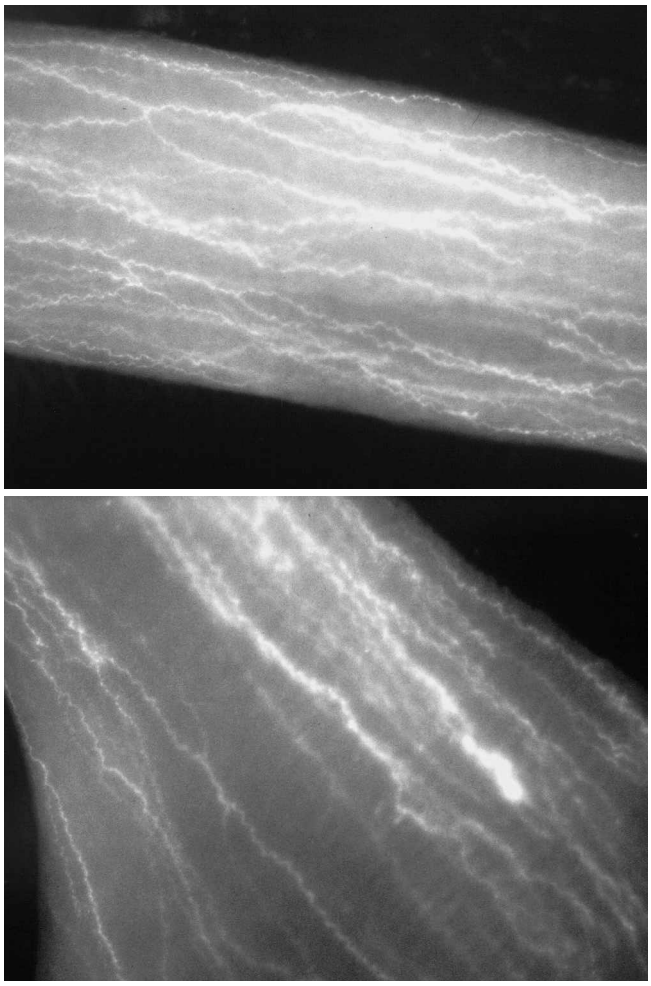


Figure 4. Adrenergic fibres in tricuspid valve of rabbits (above) and in chordae tendineae of pigs (below).

however, also be verapamil-sensitive, fascicular and ATP-sensitive. We can evoke a VT also by phosphodiesterase inhibitors, e.g., by theophylline overdose.

Already in 1987 Coumel registered and published his observations concerning the increasing rate of normal sinus rhythm one hour before occurrence of VT or VF [1]. In chronic heart failure, the risk of VT increases [10,11] and the local heart regulation of β_1- and β_2- receptors changes. Depending on the sudden cardiac death risk with respect to individual catecholamines (especially to NE), the sensitivity of the myocardium is up to 500-times higher compared with the healthy heart [12].

Similarly to aldosterone and angiotensin II, NE is involved in direct remodelling of the heart; these three hormones function as growth factors [12]. Once their serum level inside the heart is high enough, they may directly cause necrosis of cardiomyocytes. Necrosis of cardiomyocytes are replaced by fibrotic tissue, leading to heart remodelling.

From Figure 4 it can be deduced that the right atrium and in particular the tricuspid valve with chordae tendineae and the upper part of the right atrium behave as immediate sensors for the overall plasmatic amount of NE in the organism. This amount reaches the right atrium through the vena cava superior and inferior. According to reflex mechanisms [9], they can influence the sympathetic tone through monoaminoxidase and ortocatecholmethyltransferase (NE reuptake and uptake in adrenergic fibres of the right atrium, but finally in the whole heart). Their increased activity, especially if not suppressed by a β-blocker directly in the heart, is another possible triggering factor of VT. We therefore think that the correlation of our results from Figure 1 and Table 2 is correct, although we are aware that our patient population is relatively small. From the viewpoint of patient's compliance bisoprolol or metoprolol succinate in titrated doses are preferred. Although the results of combined therapy (ICD + β-blocker) are encouraging, it is necessary to conduct a larger multicentric study and experimental work to provide enough evidence supporting this hypothesis. The results in Table 2 are, however, so striking that they require at least a serious consideration. Attention should be devoted also to Figure 4: the finding of adrenergic fibres in these atypical places is a fact which can currently be stated, but has no logical explanation from a functional or anatomical viewpoint. Immunohistochemical findings in various mammals have confirmed the fact that the higher the basic heart rate in the experimental animal, the more adrenergic fibres are found in vascular-free chordae of the tricuspid valve [9].

Conclusion

Apart from electrical and mechanical functions, which are perfectly synchronised, the heart also has an important endocrinal function. The assumption, that it may be used in the future as a potential natural source of energy for operation of various artificial organs is, in our opinion, possible and an assumed vision of the future. The problems of cardioendocrinology lie in the nearest future together with the problems of molecular biology and genetics, including a difficult verification

of the latent gene mutations of somatic chromosomes in each individual that are resolved only with great difficulties. Initially it will have experimental and clinical meaning not only in arrhythmology but in the whole syndrome of cardiovascular diseases:

- Increased blood pressure;
- Coronary heart disease and myocardial infarction;
- Lipid and glucose metabolism disorders;
- Serum osmolarity disorders, coagulation disorders – platelets, electrolytes;
- Till now unknown relations – homocystein, urine acid;
- Genetics of atherosclerosis.

The practical endpoint of the work is that plasma level of NE in peripheral blood may help in stratification of patients risk of sudden cardiac death. Patients with high basal level of NE have a poor prognosis. Application of ICD in combination with a blockers is advantageous in prevention of sudden cardiac death, providing that the β-blockade is not contraindicated in the concerned patient.

References

[1] The Sixth Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Int Med. 1997; 157: 2413-2452.

[2] 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension. Guidelines Subcommittee. J Hypertens. 1999; 17: 151-183.

[3] Coumel P. The management of clinical arrhythmias. An overview on invasive versus non-invasive electrophysiology. Europ Heart J. 1987; 8: 92-99.

[4] Dawber TR. The Framingham study. The epidemiology of atherosclerotic disease. Cambridge: Harvard Univ Press. 1980: 87.

[5] Dominguez LJ, Barbagallo M, Jacober SJ, et al. Bisoprolol and captopril effects on insulin receptor tyrosine kinase activity in essential hypertension. Am J of Hypertension. 1997; 10: 1349-1358.

[6] Izzo JL, Junior Jr. Sympatoadrenal activity, catecholamines, and the pathogenesis of vasculopathic hypertensive target - organ damage. Am J of Hypertension. 1989; 2: 305-312.

[7] Julius S. Sympathetic hyperactivity and coronary risk in hypertension. Hypertension. 1993; 21: 866-893.

[8] Julius S. Introduction to the Solvay symposium. Journal of Human Hypertension. 1997; 11: 1-2.

[9] Pella J, Stopek D, Rybárová E, et al. Plasma norepinephrine and ventricular tachycardia. Prog Biomed Res. 1998, 3: 202-206.

[10] Meredith IT, Brouughton A, Jennings GL, et al. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. N Engl J Med. l991; 325: 618-624.

[11] Olsson G, Rehnquist N. Ventricular arrhythmias during the first year after acute myocardial infarction: influence of long-term treatment with metoprolol. Circulation. 1984; 69: 1129-1134.

[12] Pepper GS, Lee RW. Sympathetic activation in heart failure and its treatment with ß blockade. Arch Int Med. 1999; 159: 225-234.

[13] CIBIS Investigators and commites.A randomized trial of ß blockade in heart failure,The cardiac insufficiency bisoprolol study-(CIBIS). Circulation. l994; 90: 1765-1773.

[14] Josephson JE. Clinical cardiac electrophysiology. Techniques and interpretattions. Second edition. Philadelphia: Lea and Febiger. 1993: 839.

[15] Kendall M, Rydén L. Metoprolol CR ZOK. J Clin Pharmacol. 1990; 30: 1.

[16] Svendsen H, Greibrokk T. High performance liquid chromatographic determination of biogenic amines. J Chromatogr. 1981; 212: 153-166.

[17] Svendsen H,Greibrokk T. High performance liquid chromatographic determination of biogenic amines. J Chromatogr. 1981; 213: 429-437.

[18] Watson E. Liquid chromatography with electromechanical detection for plasma norepinephrine and epinephrine. Life Sci. 1981; 28: 493-497.

[19] Cowie MR,Mosterd A,Wood DA,et al. The epidemiology of heart failure. Eur Heart J. 1997; 18: 208-225.

[20] Palatini P, Julius S. Association of tachycardia with morbidity and mortality:pathophysiological considerations. Journal of Human Hypertension. 1997; 11: S19-S27.

[21] Folkov B. Autonomic nervous system in hypertension. In: Swales J (editor). Textbook of Hypertension. Oxford: Blackwell Scientific Publishing. 1994: 427-438.

[22] Schaldach M. Therapy of atrial tachyarrhythmia by cardiac pacing. Prog Biomed Res. 1998; 3: 177-183.

Contact
Peter Kalist, MD
Third Internal Clinic
Louis Pasteur Hospital
Medical faculty of the
Pavol Jozef Šafárik University
Rastislavova 43
040 01 Košice
Slovakia
Telephone: +421 95 615 2170
Fax: +421 95 615 2199
E-mail: kalist@hotmail.com