Plasma Norepinephrine and Ventricular Tachycardia

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Summary

In examining the effects of the autonomic nervous system on cardiac processes, the re-uptake of norepinephrine was examined in 17 patients parallel to an electrophysiologic exam. Levels of peripheral norepinephrine (from the left cubital vein) and central norepinephrine (from the lower region of the right atrium) were examined during sustained and non-sustained ventricular tachycardia. Through detailed multivariate analysis, it was discovered that the basic tendency was a decrease in the level of plasma norepinephrine on the periphery and an increase in the level of plasma norepinephrine intracardially after ventricular stimulation. These differences are statistically significant in patients with VT, whereas they are not significant in patients without VT. Levels of central norepinephrine increase remarkably in patients at risk of SCD. The clinical implications that result are: the right atrium when supplied abundantly and adrenergically appears to be a complex endocrine organ; plasma norepinephrine levels could be used for estimating the risk of SCD; intracardiac (right-heart) levels of norepinephrine influence heart rate variability, baroreflex sensitivity, QT interval, monophasic action potential, ventricular evoked response, and contraction dynamics; beta-blockers are advantageous in preventing SCD. In the future, an implantable cardioverter-defibrillator (ICD) could have a sensor for R-R and QT variability and "automatic pumps" for automatically releasing antiarrhythmic drugs together with a beta-blocker.

Key Words

ANS, re-uptake of norepinephrine, atrial contribution, beta-blockers, R-R variability analysis

Introduction

The autonomic nervous system (ANS) has an important influence on the heart rhythm. In 1987 Coumel described a functional and morphological relationship between the ANS and arrhythmias (Figure 1) [1]. Terminal adrenergic fibers have not only the property of producing and secreting norepinephrine but of also re-uptaking it (Figure 2). With the re-uptake of norepinephrine (and of other adrenergic neurotransmitters), a certain number of free signal molecules is always present in the plasma. Their number will depend on the number of adjacent adrenergic fibers, the number of surrounding target receptors, and the speed of production, secretion, re-uptake and degradation of signal molecules.

Using the method of fluorescent histochemistry, several authors had almost identical morphological findings in different animal species [3,5,7]. These findings concerned the predominant localization of adrenergic fibers placed subendocardially within the right atrium in the region of the superior vena cava (the auricle of the right atrium) and the region of the inferior vena cava (the tricuspid valve). Adrenergic fibers within the tricuspid valve of a rabbit are shown in Figure 3, and fibers within the papillary muscle of a pig are shown in Figure 4 [7].

The aim of our study was to establish plasma levels of norepinephrine during an electrophysiologic examination for ventricular tachycardia (VT). We chose norepi-

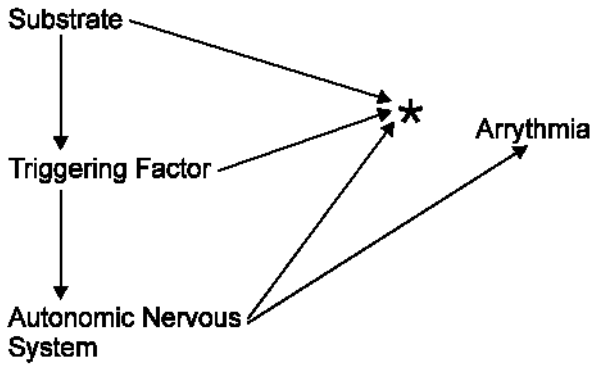

Figure 1. Relationship between autonomic nervous system and arrhythmia (Coumel,1987).

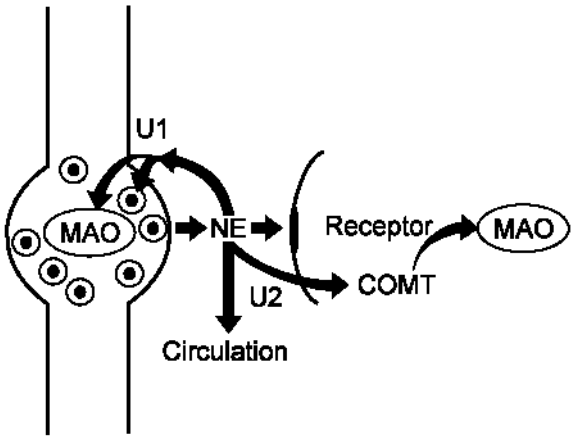

Figure 2. U1: Re-uptake of norepinephrine (NE). U2: Producing and secreting of norepinephrine (NE); monoamino-oxidase (MAO), catecholorthormethyltranspherasis. (COMT).

nephrine over other catecholamines (e.g., epinephrine, dopamine) because it is not influenced by stress during electrophysiologic examinations. Determining the norepinephrine was done parallel to the examination. As such, the procedure did not cause any extra load to the patients. In fact, the electrophysiologic examination was in no way prolonged by this endeavor.

Materials and Methods

We determined the plasma levels of catecholamines by high performance liquid chromatography (HPLC) with electromechanical detection in the liquid chromatograph produced by Hewlett Packard [8,9,10]. HPLC enables us to separate the single catecholamines from each other. We used dihydroxybenzylamine as the inner standard.

In spite of the high specificity and sensitivity of HPLC, close attention must be paid to the sampling and preanalytic preparation of the specimen. The patient is placed on a special diet that does not allow any medication for at least five days before the examination. The first step in the catecholamine measurement is the adsorption on Al_2O_3 which is specifically adjusted for determining catecholamines. After the adsorption on

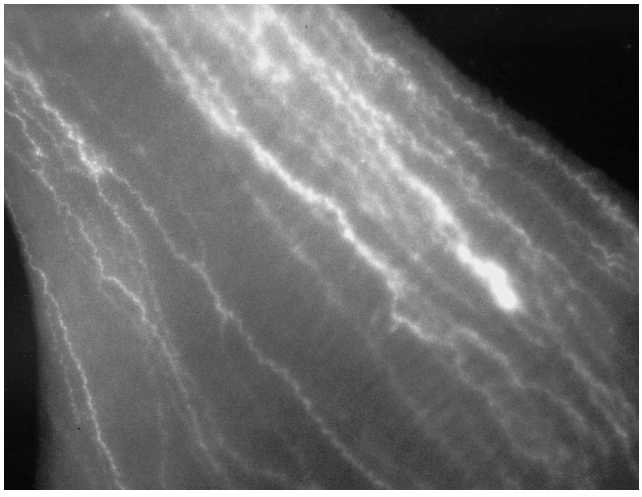

Figure 3. Adrenergic fibers in tricuspid valve of rabbits (Stopek,1995).

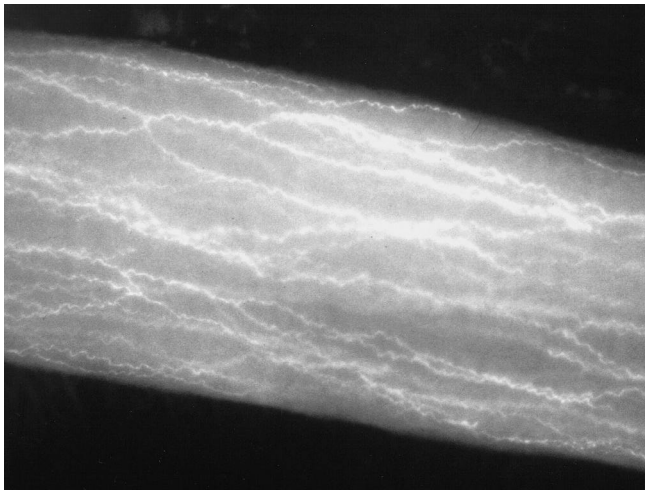

Figure 4. Adrenergic fibers in chordae tendineae of pigs (Stopek,1995).

Al_2O_3, catecholamines are eluated with 0.2 mol/L of acetic acid. The eluate is directly used for injection into HPLC. We separated the catecholamines on a Sperisorb ODS-2 (C-18) (250 x 5 μm) colony at a pH level of 4.0.

We used plasma levels of norepinephrine from simultaneously sampled specimens from the left cubital vein and, intracardially, from the region of the lower part of the right atrium (under the X-ray control). We have determined the level of statistical significance to be 5%.

The electrophysiological examination was performed through standard methods [4] and under the same circumstances, a strict diet and discontinuation of medication for at least five days before the start of examination.

The programmed ventricular stimulation included stimulation with one or two extrastimuli for basal frequency of ventricular stimulation of the length of cycle (600 ms and 500 ms). Continuous ventricular stimulation was realized by increasing the stimuli rate to 240 bpm. The intensity of the impulse was twice as high as the threshold level; the pulse width was 2 ms. We used stimulation in the apex of the right ventricle. In cases where VT could not be induced, we repeated the stimulation regimen in the region of the right ventricular outflow. Stimulation was performed by an external cardio-stimulator (UHS 20, BIOTRONIK).

The period of stabilization after inserting the electrodes was 10 minutes, and only after that was the basal peripheral value of norepinephrine taken from left cubital vein. The norepinephrine was detected in the left cubital vein during sustained ventricular tachycardia (sVT) after 5 minutes of VT (sampling was realized after the first induction of VT). Before the start stimulation protocol (after the basal sampling), we had stimulated the apex of the right ventricle for 5 minutes at a ventricular stimulation rate of 100 bpm, and we performed simultaneous sampling of norepinephrine from the left cubital vein and the right atrium.

Results

Patients were divided into three groups (Table 1). Group A consisted of patients without a previously documented history of VT. Patients were electrophysiologically examined for other reasons, and VT was not induced during these examinations. Ten patients from group B (n=4) and C (n=6) had a previous history of VT. We induced sustained VT (sVT) in group B and non-sustained VT (nsVT) in group C during the invasive examination. There were no statistically significant differences in age and gender between these groups. Among groups B and C, 7 patients had ischemic heart disease, 2 patients had dilated cardiomyopathy, and 1 patient had no structural heart disease. In group A, we found no morphological substrate for the heart disease.

Groups	Number	Male/Female	Age of Patients
A	7	5/2	47.1 ± 13.6
B (sVT)	4	3/1	57.3 ± 10.2
C (nsVT)	6	3/3	60.8 ± 15.1

Table 1. A: Patients without ventricular tachycardia. B: Patients with sustained ventricular tachycardia (sVT). C: Patients with nonsustained ventricular tachycardia (nsVT).

The plasma norepinephrine values in pg 1 ml in single specimens in all 3 groups of patients: values of peripheral norepinephrine (P_1, P_2, PVT) and central norepinephrine from the right atrium after the ventricular stimulation (c) are listed in Table 2. The detailed multivariate analysis is illustrated in Table 3. The basic tendency is a decrease in the level of plasma norepinephrine on the periphery and an increase in the level of plasma norepinephrine intracardially after ventricular stimulation. These differences are statistically significant in patients with VT, whereas they are not significant in patients without VT (group A). The statistically significant difference in the basal levels of plasma norepinephrine are between groups A and B.

Discussion

Sudden cardiac death (SCD) is caused by ventricular tachyarrhythmias in 90% of all cases. Those include VT and/or ventricular fibrillation (VF) or ventricular flutter (VFL). Thus, it is very important to stratify patients according to the risk of SCD. Electrocardiographic methods (e.g., conventional ECG, Holter, R-R and QT variability), late ventricular potentials and programmed ventricular stimulation are of high predictive value. The left ventricular ejection fractions below 40% increase the risk of SCD, this parameter also has a predictive value for assessing the risk of SCD.

Samples	Value pg/1 ml P_1	Value pg/1 ml P_2	Value pg/1 ml c	Value pg/1 ml PVT
Groups				
A	254.2 ± 32.7	147.6 ± 83.5	302.0 ± 47.2	
B (sVT)	645.6 ± 207.2	315.7 ± 41.1	831.0 ± 102.5	984.2 ± 374.2
C (nsVT)	467.2 ± 110.2	252.0 ± 48.1	1558.5 ± 358.5	

Table 2. P_1: Norepinephrine (NE) from left cubital vein-basal value. P_2: NE from left cubital vein-after ventricular stimulation for 5 min, frequency 100/bpm. c: NE from right atrium-after ventricular stimulation. PVT: NE from left cubital vein-after 5 min sVT.

The peripheral and central plasma norepinephrine levels results enable us to stratify patients with a risk of SCD as well. There is a statistically significant difference in the basal, peripheral plasma norepinephrine level, and this difference increases with diagnostic ventricular stimulation: central norepinephrine increases remarkably in patients with a risk of SCD.

Within the context of our results, we think that the application of beta-mimetics followed by programmed ventricular stimulation has probably a higher sensitivity but not a higher specificity and higher predictive value for SCD risk assessment as does the basal diagnostic ventricular stimulation (without the application of beta-mimetics). Yet our results also state that the antiarrhythmic drug with the best prospects of lowering the risk of SCD is a beta-blocker [5]. In the future, an implantable cardioverter-defibrillator (ICD) could have a sensor for R-R and QT variability and "automatic pumps" for automatically releasing antiarrhythmic drugs together with the beta-blocker. These suggestions of R-R and QT variability are based upon observations by Coumel, who studied the change of these parameters and the periodical increase in frequency of normal sinus rhythm as early as one hour before the onset of VT [1]. With this approach, energy resources could be conserved. The feedback system using the adrenergic stimulation of myocardial cells in the apex of the right ventricle is based on the production, secretion and re-uptake of catecholamines. At present, the natural feedback system is successfully used in the permanent pacemaker therapy of bradycardic disorders [6].

Clinical Implications

1. We can state that from the aspect of functional morphology the right atrium of the heart when supplied abundantly and adrenergically appears to be a complex endocrine organ. On the basis of reflex mechanisms, as well as by the secretion of chemical signal

Statistic evaluation

AP_1 vs AP_2 : NS	BP_1 vs BP_2 : NS	Cp_1 vs CP_2 : $p < 0{,}001$
AP_1 vs Ac : NS	BP_1 vs Bc : NS	Cp_1 vs Cc : $p < 0{,}001$
BPVT vs BP_2 : $p < 0,001$	BPVT vs AP_2 : $p < 0,001$	BPVT vs CP_2 : $p < 0,001$
AP_1 vs BP_1 : $p < 0,001$	Ac vs Bc : NS	
AP_1 vs CP_1 : NS	Cc vs Ac : $p < 0,005$	

Table 3. Statistical evaluation: multivariate analysis.

molecules (e.g., norepinephrine), the right atrium participates significantly in the cardiac activity.
2. According to our results, we may assume that plasma norepinephrine levels could be used for estimating the risk of SCD.
3. Intracardiac (right-heart) levels of norepinephrine influence heart rate variability, baroreflex sensitivity, QT interval, monophasic action potential, ventricular evoked response, and contraction dynamics. These intracardiac levels of norepinephrine could be better used in clinical medicine in future.
4. We assert the advantage of beta-blockers in preventing SCD.

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