

DOCTORAL THESIS

**SHORT AND LONG TERM EFFECT OF NON-
PHARMACOLOGICAL RATE CONTROL ON
SYMPTOMATIC ATRIAL ARRHYTHMIA REFLECTED BY
THE CARDIO-PEPTIDE SERUM LEVEL CHANGES**

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1. INTRODUCTION

Supraventricular tachycardia, related to several cardiac and extracardiac diseases, may appear independently of age. These may develop in some of the individuals of the corresponding structural cardiac disease groups, while in other cases they do not appear. The clinical significance of this is determined by complications and haemodynamical effects caused by arrhythmia.

Sustained supraventricular arrhythmia with high ventricular rate, of which the most frequent clinical arrhythmia is atrial fibrillation (AF), may result in tachycardiomyopathy, and ultimately heart failure (HF). Its exact pathophysiology and molecular background is still subject to research. Catheterized rate control ablation or modulation of the atrio-ventricular node proved to be an effective therapy in the treatment of atrial fibrillation of drug refractory, or pharmacologically not tolerated nature, due to side effects.

Both literature and the results of our work group confirm that supraventricular tachyarrhythmia (SVT) cause an elevation in endogenous peptide serum levels, namely endothelin-1 (ET-1), big endothelin (BET), atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP). Several results were published after MAZE surgeries, or cardioversion of atrial fibrillation about the decrease of serum ANP and BNP levels for short and long term alike. Certain authors related the decrease of natriuretic peptide levels to the improvement of cardiac pumping function, as a result of the restoration of sinus rhythm.

Depending on the type of the arrhythmia – often along with the subsistence of irregular atrial activity –, catheterized rate control (RC) ablation (ABL) and pacemaker implantation ensure regular and normofrequent ventricular functioning. This procedure assures a patent approach for the examination of cardiopeptides in the clinically effective treatment of symptomatic SVTs.

This study was aimed at the examination of changes in the serum proANP (ANP), NT-proBNP (BNP), the endothelin system, and clinical parameters during drug refractory, permanent supraventricular tachyarrhythmia, and followed by their non-pharmacological rate control, for short and long term alike.

2. OBJECTIVES

Our aim was the examination of short and long term effects of non-pharmacological rate control in sustained symptomatic atrial arrhythmia, reflected by the changes of certain cardiopeptides.

Our objective was:

1. the examination of short term changes in serum ET-1 and BET plasma levels after non-pharmacological rate control of supraventricular tachyarrhythmia.
2. the long-term examination of endothelin-1, big endothelin, ANP, and BNP serum levels during drug refractory atrial fibrillation, followed by its non-pharmacological rate control after 1 month.
3. study whether the cardiopeptides are suitable for the diagnosis of heart failure developing along with atrial fibrillation.
4. the long-term examination of patient's clinical parameters during drug refractory atrial fibrillation, followed by its non-pharmacological rate control after 1 month.
5. detect whether the pacemaker implantation procedure has an effect on the changes of cardiopeptide serum levels.

3. METHODS

3.1. Short-term effects of rate regulation on plasma endothelin and BET level changes for patients with tachyarrhythmia

3.1.1. Patients

The 22 patients included into the examination had suffered from sustained symptomatic atrial arrhythmia – atrial fibrillation, atrial flutter, atrial tachycardia, or sinus tachycardia – lasting for more than three months, but no more than six months. Their ventricular rate was permanently above 100/min, which had been verified by a Holter-EKG monitor. Echocardiographic examination measured a left ventricular ejection fraction (EF) of values between 35% and 50%. Exclusion criteria were defined for – extant valvular disease; diastolic ventricular diameter above 60 mm measured by echocardiographic monitoring, from the direction of the parasternal longitudinal axis; extant nephropathy, where creatine plasma level is $>120 \mu\text{mol/liter}$; significant comorbid states; recurring arrhythmia within 24 hours.

	Group I.	Group II.	Group III.	Control group
No. of patients	9	7	6	13
Type of procedure	AV ablation (PM implantation was 2 months ago)	AV ablation and PM implantation	AV modification	PM implantation
Duration of procedures (min)	35.2 ± 6.7	45.5 ± 11.4	33.7 ± 7.8	30.4 ± 7.7
Men/women	4/5	3/4	5/1	7/6
Mean age (years)	64.6 ± 2.9	68.4 ± 6.1	59.5 ± 6.2	66.1 ± 6.7
Ejection fraction (%)	40.0 ± 3.5	40.7 ± 2.97	45.8 ± 2.1	45.5 ± 3.9
NYHA stage	2.4 ± 0.1	2.4 ± 0.3	2.0 ± 0.2	2.4 ± 0.2
Underlying diseases	CAD: 3 DCM: 2 none: 4	CAD: 2 DCM: 2 none: 3	CAD: 3 DCM: 1 none: 2	CAD: 8 none: 5
Basic rhythm	AF: 7 FL: 1 AT: 1	AF: 4 FL: 2 AT: 1	FL: 4 AT: 1 ST: 1	SR: 13 (no SVT)
Spontaneous rate before procedure (1/min)	110–170 (no PM rhythm)	100–160	110–160	50–90
Rate after procedure (1/min)	70–80 (PM rhythm)	70–80 (PM rhythm)	70–90 spontaneous rhythm)	60–80 (PM rhythm)

Table 3: Data of the arrhythmia groups and the control group.

NYHA: New York Heart Association classification; CAD: coronary artery disease; DCM: dilatative cardiomyopathy; Null: in the background of arrhythmia, no other disease can be verified; FL: atrial flutter; AT: atrial tachycardia with a transition of 2:1 ratio; ST: sinus tachycardia; AF: atrial fibrillation; AV: atrio-ventricular; PM: pacemaker.

Patients were divided into 3 groups:

In group number 1 ($n = 9$), PM implantation was performed 1 month before the ablation. The pacemakers programmed to demand function initiated the activation process only after the performance of AV ablation, when the ventricular rate fell below the programmed base

frequency. In group number 2 ($n=7$) PM implantation was performed simultaneously with ablation. For the members of group number 3 ($n = 6$) AV node ablation was performed without PM implantation (table 3).

One control group ($n = 13$) with clinical parameters similar to those mentioned above was also examined. The patients in this control group received DDD PM implantation due to carotis sinus hyperesthesia ($n = 10$) and third grade AV block ($n = 3$). They had observable sinus rhythm and no SVT was present in their medical history, therefore no ablation treatment was necessary (table 3).

3.1.2. Comparison of Patient Groups

There was no significant difference between the patient groups regarding age, ejection fraction, New York Heart Association (NYHA) stage, underlying diseases, and the ventricular rate of SVT (table 3). In patient group number 3, the ratio of male patients was higher than in the other groups.

3.1.3. AV Node Ablation and Pacemaker Implantation

For our patients, temperature controlled radiofrequency AV node ablation or modification was applied in the cases of atrial fibrillation, atrial flutter, atrial tachycardia with 2:1 transition, and in one case sinus tachycardia. In this process two catheters – a diagnostic and an ablation catheter – were conducted via the right atrial, His, right ventricular, sinus coronarius, and tricuspid ring positions. The position of the catheters was monitored using an X-ray image amplifier and an intracardial electrogram, by means of a Biotronik EP Control system (Biotronik GmbH, Berlin, Germany).

Pacemaker implantation is necessary after each AV node ablation procedure. In the case of AV node modification pacemaker implantation is needed only in the case of permanent bradycardia.

Dual layer (DDD) PMs (Actros DR, Axios DR; Biotronik GmbH) were implanted into patients with sustained atrial fibrillation and atrial flutter 2 months before AV node ablation, or simultaneously with it. The electrodes were conducted via the left cephalic vein, or the subclavian vein into the right atria and the right ventricle. The generators were placed into an infraclavicularry configured pocket on the left side. In the group of patients with atrial flutter, atrial tachycardia, or sinus tachycardia, for those who were subjected to AV-node modification, no PM therapy was necessary in our current study.

3.1.4. Measurement Methods for Serum ET-1 and BET Levels

Blood samples were collected from the cubital vein directly before the ablation and/or PM implantation procedure, then 5 minutes and 24 hours after the procedure.

For ET and BET measurement, plasma taken from centrifuged (3000/min) blood from peripheral veins by a native tube pretreated with EDTA, was then preserved on -80°C until use.

ET-1 and BET levels were measured by means of immunoprecipitation, as well as the application of lyophilized rabbit anti-human endothelin and anti-human big-endothelin antibodies (BIOMEDICA, Cat. N° Bi-40011, Bi-40012 Vienna, Austria), together with PVDF membrane application and Western-blot techniques. The membranes were analyzed using Bioscan v.1.01 software (Bioscan, Washington, DC).

3.1.5. Statistical Analysis

The calculations were performed using SPSS 12.0 software (SPSS, Chicago, IL). Providing the data followed normal distribution, the results were given in the form of average \pm average-deviation (mean value \pm SEM). In the case of normal distribution a one or two-sample Student t-probe was used for the comparison of two patient groups. Changes regarding time were obtained by the ANOVA method, optimized for recurring measurements. For comparisons of incidences per patient groups we used the chi-square test. Significance was established at the generally accepted $p < 0,05$ value.

3.2. Short and Long Term Effect of Non-pharmacological rate control reflected by cardio-peptide serum level changes

3.2.1. Patients

The 20 patients for the study were selected on the basis of having a permanent, Holter EKG-certified average ventricular frequency of over 100/min lasting for more than 12 month, and where the sinus rhythm could not be maintained either by multiple cardioversion, or by administering drugs. Pharmacological rate control also proved to be either ineffective (with beta-blocking verapamil; in case of heart failure, beta-blocking digitalis), or due to the side effects, intolerable.

Exclusion criteria were assigned for broad QRS (> 120 ms) nephropathy (serum creatine level $> 120\mu\text{mol/l}$), or other known severe disease of the same category (e.g. pneumopathy, hepatic disease, stroke, tumor-related disease). The clinical data of the patients are shown in table 4.

	All patients	Control group	SUBGROUPS				
			According to underlying disease			According to heart failure	
			DCM	IHD	OTHER	Heart failure	Without heart failure
patient no.	20	13	7	5	8	9	11
age (year)	63.9±3.1	66.1±2.6	67.0±3.1	63.2±2.9	61.5±3.2	64.9±8.1	63.1±7.9
male/female	10/10	7/6	6/1	2/3	2/6	6/3	4/7
EF (%)	41.8±3.2	45.5±3.1	31.7±2.2	45.0±2.2#	48.6±3.0#	33.6±5.8	48.5±7.0*
NYHA	2.5±0.7	2.4±0.7	2.9±0.6	2.2±0.7#	2.3±0.7#	2.8±1.7	2.2±1.5*
underlying disease	DCM: 7, IHD: 5, other: 8	IHD: 8, other: 5	—	—	—	CM: 7, other: 2	IHD: 5, other: 6
pre-intervention rhythm, fr (1/min)	Atrial fibrillation fr:102-170	sinus rhythm fr:50-70	Atrial fibrillation fr:113-170	Atrial fibrillation fr:106-140	Atrial fibrillation fr:102-160	Atrial fibrillation fr:113-170	Atrial fibrillation fr:102-160
post-intervention rhythm, fr (1/min)	PM rhythm, fr:75-90	PM rhythm, fr:60-80			PM rhythm, fr:75-90		

Table 4: Clinical data of the total number of patients (n=20), who received atrio-ventricular node ablation, followed by pacemaker implantation, and patients that constitute the control group (n=13). In the course of subgroup analysis the patient population of 20 members was further analyzed according to the existence of underlying diseases and heart failure.

p< 0,05 vs. DCM; * p< 0,05 vs. heart failure

DCM: dilative cardiomyopathy; IHD: ischemic heart disease; EF: ejection fraction; NYHA: New York Heart Association functional stage; fr: frequency, PM: pacemaker.

Further subgroup analysis of patients were performed on one hand according to underlying diseases, on the other hand according to diagnosed heart failure based on BNP levels. Heart failure was accounted for patients with control serum BNP level above 100 fmol/ml.

Subgroups According to Underlying Diseases

According to underlying diseases, three subgroups were designated: 1./ group with dilatative cardiomyopathy (DCM, n=7), 2./ coronary disease group (IHD, n=5), 3./ patients who can neither be categorized into the DCM, nor the IHD subgroup (EGYÉB, n=8). In the latter group the underlying disease was hypertension (n=5) and non-significant rheumatic mitral regurgitation (table 4).

Subgroups Based on Extant Heart Failure

The group of 1./ those with heart failure (HF, control BNP > 100fmol/l, n=9), and 2./ those without heart failure (no HF, control BNP < 100fmol/l, n=11) (table 4).

The Control group (n=13) received DDD pacemaker implantation as a result of carotis sinus hyperesthesia (n=6) and third grade AV block (n=7) (Actros DR, Axios DR; Biotronik GmbH&Co., Berlin). In no cases did certified atrial fibrillation occur to patients with sinus rhythm. In their cases no ablation procedure was performed (table 4)

3.2.2. Comparison of patient groups

By comparison of all patients to the control group, no significant difference was found regarding age, sex, ejection fraction, and NYHA stage at the beginning of the examination. In the course of the subgroup analysis, the DCM and the HF subgroup showed significantly lower initial ejection fraction and NYHA stage, compared to the IHD/OTHER and the non-HF subgroups, which derives from the aspects of the disease. The DCM subgroup was built up by significantly less women, while in the OTHER subgroup the number of women was dominant (table 4).

3.2.3. AV node ablation and PM implantation

For patients with permanent atrial fibrillation at rapid ventricular transition, we performed catheterized, temperature controlled radiofrequency AV-node ablation. During this we conducted 3-4 catheters via the right side femoral vein in addition with x-ray control, to the right atrial, His, ventricular, sinus coronarius, and tricuspid ring positions. For the recording of intracardial electrograms we applied the Biotronik EP Control system. Following the coagulation of the atrio-ventricular node, monocavity pacemaker was implanted into the patients (Axios SR; Biotronik GmbH&Co., Berlin). The electrode was conducted via the left side cephalic or subclavian vein to the left atrium and ventricle, placing the apparatus in the infraclavicular region.

3.2.4. Measurement of Serum Endothelin, ANP and BNP Levels

We took blood 4 times from the cubital veins: directly before the start of ablation (control period), then 10 minutes, 24 hours and 1 month after the intervention.

The plasma pretreated with EDTA (for ET, BET, and ANP measuring), and obtained from centrifuged peripheral venous blood was stored on -80°C until use.

The endothelin-1, big endothelin, ANP and BNP levels were measured using the ELISA (enzyme linked immunosorbent assay) method, with the application of standard kits (Endothelin (1-21) ELISA cat. no. BI-20052, BigEndothelin ELISA cat. no. BI-20072,

proANP (1-98) ELISA cat. no. BI-20892, NT-proBPN ELISA cat. no. BI-20852, Biomedica, Vienna, Austria)

3.2.5. Statistical Analysis

The temporal changes of endogenous peptides were analyzed – depending on the distribution of the data – either by paired T-test, or by Wilcoxon-test calculated by the prodromal sign of the differential grade. For the analysis of subgroups at the time phases we used the Kruskal-Wallis-test. We also used the Kruskal-Wallis-test for comparing the EF and NYHA values of subgroups, after which we examined the subgroups by pairs using the Mann-Whitney-test. In grouping the patients as having, or not having heart failure, the temporal comparison of subgroups and the analysis of EF and NYHA values were also performed by the Mann-Whitney test. The relation between the values of the serum levels and the EF, NYHA modifier was analyzed by Pearson's correlation. In case of multiple comparisons, the first specific error was controlled by the Bonferroni-method. For the calculations, SAS 9.1.3 software was used. The results were given in average \pm average distribution, and significance level was established at the commonly accepted $p < 0,05$ value.

4. RESULTS

4.1. Short term effects of rate control for patients with tachyarrhythmia on plasma endothelin and BET level changes

4.1.1. Comparison of ET-1 and BET Levels of the Four Groups

There was no significant difference in plasma ET-1 and BET levels between the three arrhythmia groups in the period of examination (table 5). Furthermore, no significant difference in ET-1 and BET levels was measured in the control period between the three arrhythmia groups and the Control group. Compared to the values of the Control group, ET-1 levels were significantly lower in the first and the third patient groups in the 24 hour measurement periods (table 5).

4.1.2. Changes in ET-1 levels during the observation time

In the first patient group ET-1 levels decreased significantly at the 5 minute and 24 hour measurements, while in the third group at the 24 hour measurements, compared to the control period (table 5). In the meantime, no significant changes were observable in the Control group during the period observed.

	Group I.	Group II.	Group III.	Control group
ET control (fmol/ml)	0.66 ± 0.13	0.93 ± 0.32	0.68 ± 0.12	0.50 ± 0.17
ET 5 min (fmol/ml)	0.50 ± 0.12*	0.77 ± 0.12	0.61 ± 0.14	0.58 ± 0.24
ET 24 hrs (fmol/ml)	0.29 ± 0.14*,#	0,61 ± 0.15	0.34 ± 0.12*,#	0.68 ± 0.33
Big ET control (fmol/ml)	0.80 ± 0.20	1.34 ± 0.49	1.12 ± 0.64	0.90 ± 0.20
Big ET 5 min (fmol/ml)	0.78 ± 0.28	1.28 ± 0.60	1.02 ± 0.56	0.93 ± 0.24
Big ET 24 hrs (fmol/ml)	0.67 ± 0.26	0.81 ± 0.49	0.78 ± 0.74	0.95 ± 0.30

Table 5: Measurement results of ET and BET levels in the 24 hour interval.

ET: endothelin, Big ET: Big endothelin

*p < 0,05 vs. control period; #p < 0,05 vs. Control Group

4.1.3. Changes in Big ET levels during the observation time

BET levels showed no significant change in any of the arrhythmia groups, nor they changed significantly in the control group during the observation time.

4.2. Short and Long-Term Effect of Non-Pharmacological Rate Control of Atrial Fibrillation Reflected by Endogenous Peptide Serum Level Changes

Compared to the results obtained in the control periods, the ET-1 serum level showed significant decrease in all patients who received AV node ablation followed by pacemaker implantation, in the observed periods (figure 5/a.).

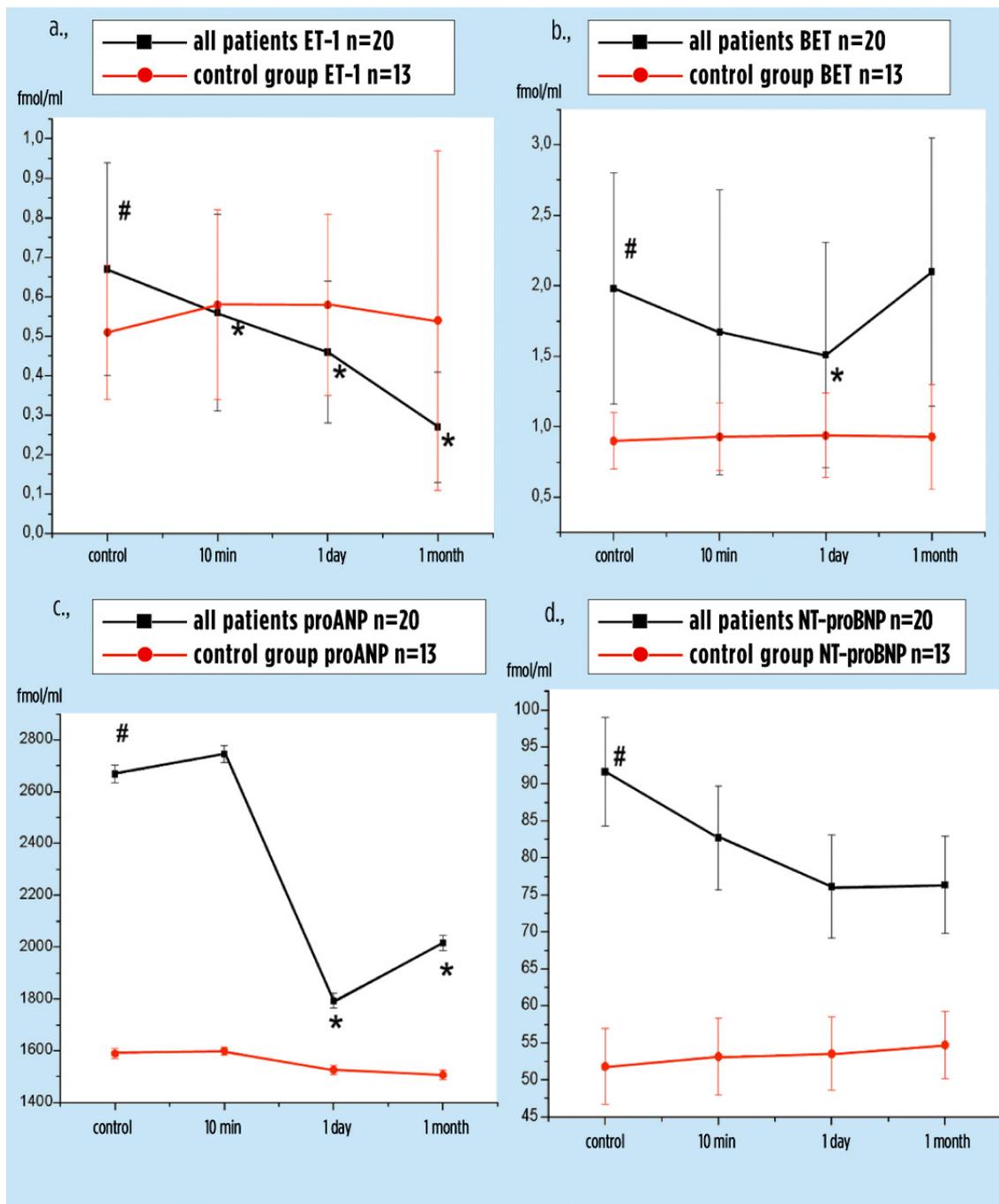


Figure 5: Changes of cardio-peptide serum levels of all patients and the control group, during the 1 month tracing period.

* $p < 0,05$ control period vs. change

$p < 0,05$ all patients vs. control group in the control period

Compared to the initial values, significantly lower serum levels were detected during the measurement of big endothelin in the one day period (figure 5/b.). In the course of ANP examination, significantly lower serum levels were found in the one day and one month periods, compared to the initial values (figure 5/c.). In the meantime, tendentious, but not

significant decrease of BNP values could be observed after the one month tracing period (figure 5/d). The endogenous peptide levels of the control group showed no significant change, compared to the control values (figure 5/a-d). Control ET-1, BET, ANP and BNP levels, measured for all patients with atrial fibrillation, proved to be significantly higher than the initial values of the control group, without atrial fibrillation (figure 5/a-d).

4.2.1. Subgroup analysis

4.2.1.1. Temporal changes of endogenous peptide serum levels

According to the subgroup analysis based on underlying diseases, the ET-1 level of DCM and IHD patients decreased to a significant extent, compared to the control values, in the 1 day and 1 month periods, whereas for the patients of the OTHER subgroup, they changed significantly only in the 1 month periods (figure 6/a.). Big endothelin levels, on the other hand, showed no significant change in any of the subgroups in the course of the observation (figure 6/b.).

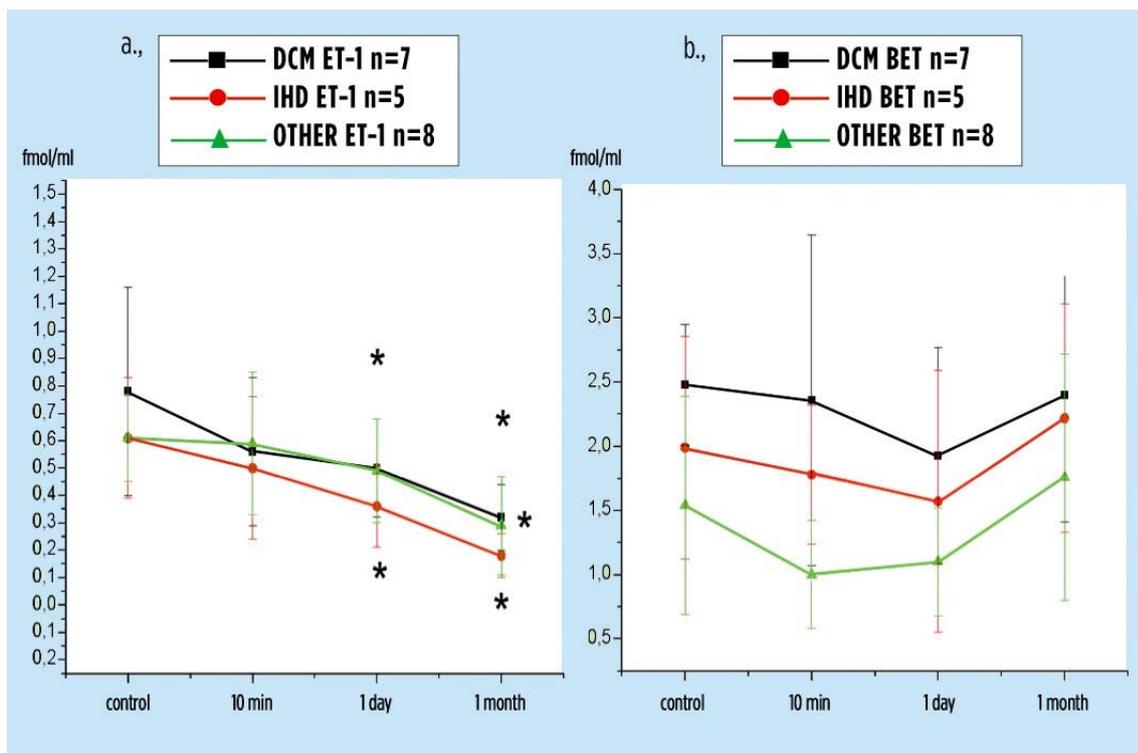


Figure 6/a-b: ET-1 and BET serum level changes in the subgroup analysis based on underlying diseases, during the 1 month tracing period.

* $p < 0,05$ control period vs. change;

$p < 0,05$ DCM vs. IHD and DCM vs. OTHER

DCM: dilatative cardiomyopathy; IHD: ischemic heart disease

Compared to the initial values, serum ANP levels showed significant decrease in the DCM (1 day, 1 month) and the OTHER subgroups (1 day) [figure 6/c].

At the same time, BNP serum levels decreased to a significant extent only at the 1 month sampling of the DCM subgroup, compared to initial values (figure 6/d).

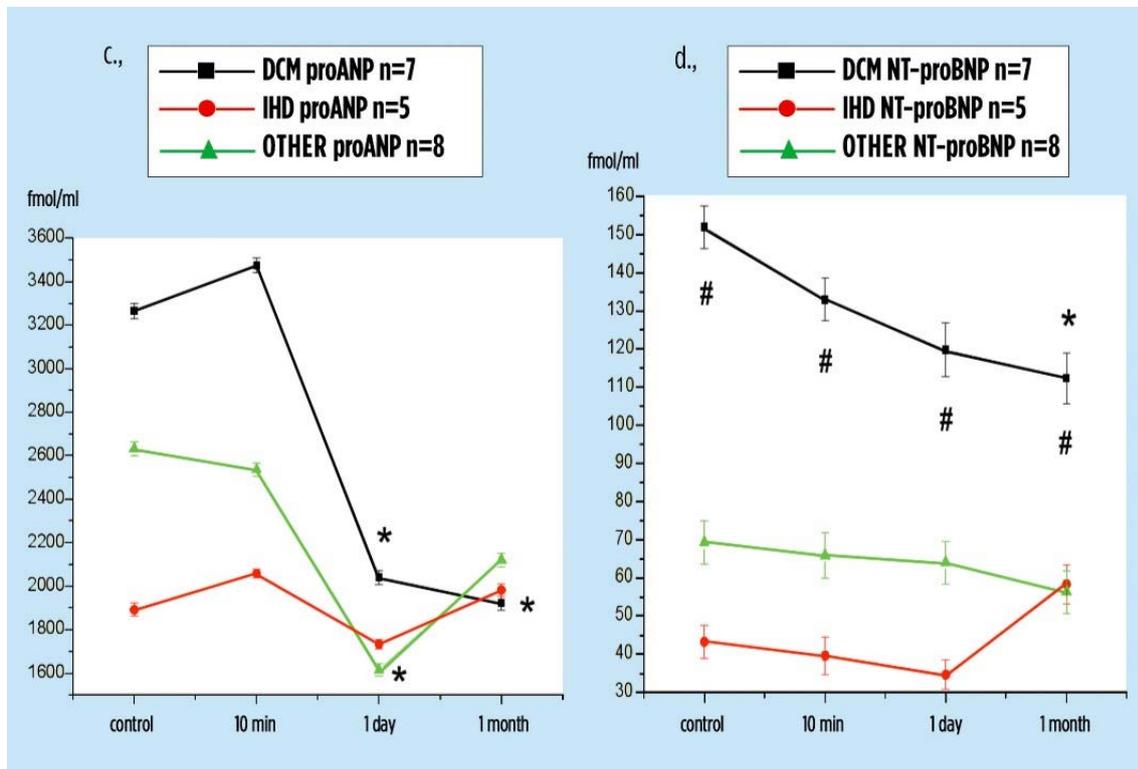


Figure 6/c-d: ANP and BNP serum level changes based on the underlying diseases subgroup analysis during the 1 month tracking period.

* $p < 0,05$ control period vs. change;

$p < 0,05$ DCM vs. IHD and DCM vs. OTHER

DCM: dilatative cardiomyopathy; IHD: ischemic heart disease

Based on the results of subgroup analysis on HF and non-HF patients, grouped according to BNP levels, the serum ET-1 values showed significant decrease at 1 month in the HF subgroup, while that of the non-HF subgroup decreased significantly at 1 day and 1 month periods, compared to control values (figure 7/a).

In contrary, big endothelin levels showed no significant change during the tracing period (figure 7/b).

In the HF subgroup, ANP levels decreased to a significant extent at 1 day and 1 month, while in the non-HF subgroup, it was achieved at the 1 day period, compared to initial values (figure 7/c).

In the meantime, BNP serum levels showed significant decrease only at the 1 month values of the HF subgroup (figure 7/d).

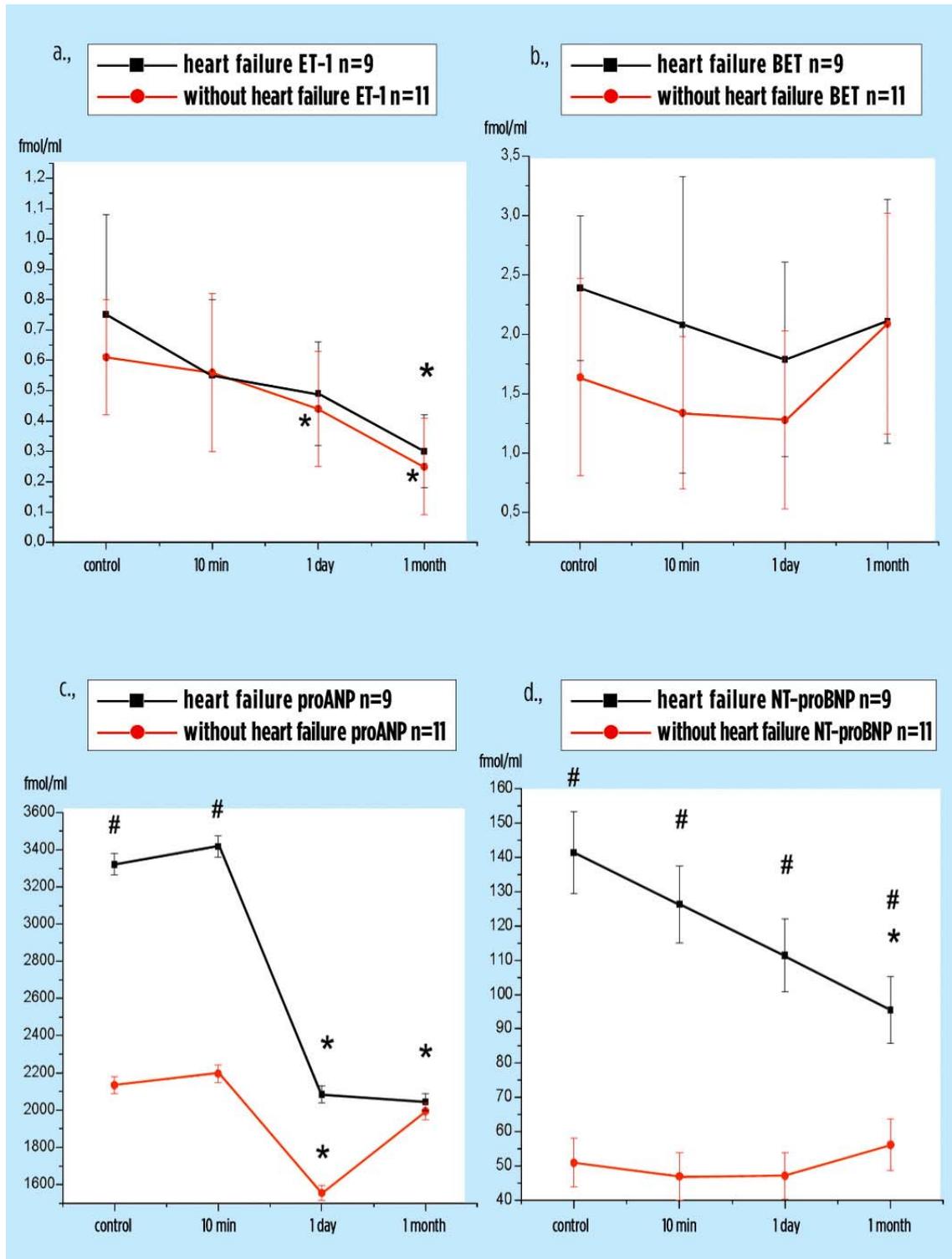


Figure 7: Changes of endogenous peptide serum levels in the subgroup analysis of patients with heart failure and without heart failure, based on their BNP levels, during the 1 month tracing period.

* $p < 0,05$ control period vs. change

$p < 0,05$ heart failure vs. no heart failure

4.2.1.2. Comparison of Endogenous Peptide Levels of Individual Groups

During the comparison of peptide levels in certain time phases, the BNP levels of DCM patients were significantly higher compared to the BNP levels of IHD and OTHER subgroups, measured in the respective time periods (figure 6/d).

Out of the 3 subgroups divided according to underlying diseases the ANP levels of DCM patients were significantly higher at the control and the 10 minute periods, than the ANP values of the IHD group. These differences are no longer observable at the 1 day and the 1 month ANP values. (figure 6/c).

No significant difference occurred between the 3 subgroups regarding ET-1 and BET values in the given periods (figure 6/a-b).

Likewise, no significant difference was found in the ET-1 and BET levels of the HF and non-HF subgroups in the respective time periods. On the other hand, the control and 10 minute ANP values had proven to be higher in the HF subgroup in comparison with those without heart failure (figure 7/a-c). Similarly to the DCM subgroup, the BNP levels of patients with heart failure were at all times higher than the respective values of the non-HF subgroup (figure 7/d).

4.2.2. The Effect of Rate Control on Clinical Parameters

Table 6 demonstrates the ejection fraction and NYHA functional stage of the control group, all the patients, and the subgroups, in the time phase of the control and the 1 month period. The clinical data of the control group did not show any significant changes during the time of the examination. We experienced the improvement of all patients' ejection fraction and NYHA stage during the 1 month of inspection, compared to the control period.

4.2.2.1. Subgroup Analysis

In the course of subgroup analysis on the basis of underlying diseases, the pump function and functional stage of DCM patients both showed significant improvement, while in the OTHER subgroup, only the increase of ejection fraction was detected after the 1 month period. On the contrary, in the IHD subgroup no parameter changed at the time of the examination.

The ejection fraction and NYHA stage of the HF and non-HF subgroups both showed significant improvement after the 1 month period (table 6).

	Ejection fraction (%)		NYHA	
	control	1 month	control	1 month
Control group	45.5±3.1	45.8±2.9	2.4±0.7	2.3±0.7
All patients	41.8±3.2	44.9±3.1*	2.5±0.7	2.0±0.6*
DCM	31.7±2.2	35.1±2.3*	2.9±0.6	2.1±0.6*
IHD	45.0±2.2 #	48.2±2.4 #	2.2±0.7 #	1.8±0.7
OTHER	48.6±3.0 #	51.4±2.8* #	2.3±0.7 #	1.9±0.6
Heart failure	33.6±5.8	37.3±6.1*	2.8±1.7	2.1±1.5*
Without heart failure	48.5±7.0 §	51.1±7.2* §	2.2±1.5 §	1.8±1.3*

Table 6: Change of ejection fraction and NYHA stage per patient groups during the 1 month tracing period.

* p<0,05 control vs. 1 month

p<0,05 DCM vs. IHD; DCM vs. OTHER

§ p< 0,05 vs. heart failure

DCM: dilatative cardiomyopathy; IHD: ischemic heart disease; NYHA: New York Heart Association functional stage

In the control phase the examination of EF and NYHA stages in all subgroups, patients with DCM proved to have lower ejection fraction than both the IHD and the OTHER subgroups. This difference remained extant also at the one month control.

Similar results were obtained by examining the HF and non-HF patients (table 6).

The ejection fraction showed negative (correlation coefficient 0,64; p<0,01), while the NYHA stage showed positive (correlation coefficient 0,62; p<0,01) correlation with the control serum BNP values.

5. CONCLUSIONS

1. Based on our study it can be assumed that atrial and ventricular degeneration caused by sustained SVT may generate the relative decrease of ET-1 production in patients suffering from moderate heart failure.
2. It was demonstrated that after the non-pharmacological rate control of SVT, a decrease of ET-1 plasma level occurs to a significant extent, within 24 hours, independently of the initial plasma-concentration values.
3. In our clinical studies it was proven that rate control with AV node ablation and PM implantation performed on patients suffering from atrial fibrillation with high ventricular rate

resulted in an improvement of the pumping function of the heart and the functional stage of patients, with major emphasis on patient subgroups with DCM and heart failure.

4. It was demonstrated that parallel to these changes, the concentration of some of the endogenous peptides – and according to our results, in the case of patients suffering from permanent, lasting atrial fibrillation – concentration of peptides showing higher initial serum level concentration are also under change. Thus an early and lasting decrease of serum endothelin-1 levels was detected in all patients and the subgroups alike.

5. In contrary, big endothelin serum level of patients with atrial fibrillation showed only a temporary change in the case of patients with atrial fibrillation, showing no significant decrease in any of the examined subgroups, after the rate control. During the non-pharmacological rate control of SVT, no considerable BET plasma level change was detected.

6. The rate control of atrial fibrillation resulted in an early – and in the HF and DCM groups in a lasting – moderation of ANP levels. Contrary to ANP levels, the production of BNP decreased significantly only in the DCM and HF groups.

7. The phenomenon, where despite the residual atrial activity and increased atrial pressure the ANP level decreased after ablation, may be denoted to its possible role of acute ventricular volume regulation, and the increased ventricular representation of the ANP synthesis.

8. The initial, pre-intervention measured outstandingly high ANP and BNP levels for DCM and HF patients support our research hypothesis about both peptides having a predictive role in the diagnosis of heart failure in patients with atrial fibrillation.

9. The considerable, post-RC clinical improvement and the significant decrease of ET-1 level in patients who are in NYHA II. stage, but were grouped into the non-HF group based on their BNP level, raises the question whether ET-1 may have a predictive role in the diagnosis of heart failure with atrial tachyarrhythmia, but without structural deviation. All these necessitate further studies.

10. The results of the control group have proven that the pacemaker implantation procedure modified the biosynthesis of neither the endothelins, nor the natriuretic peptides.

6. REFERENCES OF OWN PUBLICATIONS

6.1. Publications Used for the Dissertation

1. **Dézi, Cs A**, Szűcs A, Szűcs G, Róka A, Kiss O, Becker D, Merkely B. (2006) Short-Term Effect of Rate Control on Plasma Endothelin Levels of Patients with Tachyarrhythmias. *Exp Biol Med*, 231:852-856.
2. **Dézi, Cs A**, Szűcs G, Kiss O, Szűcs A. (2007) Long Term Effect of non-pharmacological rate Control on Atrial Fibrillation Reflected by the Changes of Cardio-Peptide Serum Levels. *Card Hung*, In print.

6.2. Thematically Related Publications

3. Szűcs A, Róka A, Soós P, Szilágyi Sz, Vágó H, Keltai K, **Dézi CA**, Gellér L, Merkely B. (2004) Effect of Incessant Ventricular Tachyarrhythmias on Serum Endothelin and Big-endothelin Levels. *J Cardiovasc Pharmacol* 44: S402-406.

6.3. Book Related to the Topic

4. **Dézi Cs A**. What you have to know about the pacemaker. *Gyógy-ír, Győr*. (1996)