Charles University

1st Faculty of Medicine

Study domain *Biomedical informatics*

Summary of the dissertation

Selected differences in pathophysiology of cardiovascular system in women

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Praha 2016

Doctoral study program in human physiology and pathophysiology

Charles University in Prague Academic Sciences of the Czech Republic

Field: Human physiology and pathophysiology

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení provědeckou činnost a zahraniční styky Dékanátu 1. lékařské fakulty

Contents

Abstrakt (česky)

V posledních letech byly prokázány významné rozdíly mezi muži a ženami ve výskytu kardiovaskulárních poruch včetně arytmií. Pohlavní rozdíly byly pozorovány v epidemiologii, patogenezi i klinických projevech různých arytmií. Menopauza je fyziologickou součástí procesu stárnutí u žen a je podmíněna přirozeným poklesem produkce estrogenu a progesteronu ve vaječnících. Dramatický pokles hladiny estrogenů v plasmě má vliv na mnoho tkání včetně kardiovaskulárního systému. Protože incidence ischemické choroby srdeční (ICHS) významně stoupá po menopauze, byla vyslovena hypotéza, že nižší výskyt ICHS oproti mužům stejného věku je u žen před menopauzou dán protektivním účinkem estrogenů. Avšak již od počátku devadesátých let byla publikována řada kontroverzních výsledků. Zatímco některé studie nalezly sníženou incidenci ICHS a sníženou kardiovaskulární mortalitu, jiné studie neprokázaly žádný efekt estrogenové terapie na výskyt ICHS po menopauze a některé studie dokonce nalezly pozitivní korelaci mezi hladinou estradiolu a kardiovaskulární mortalitou u žen nad 65 let věku.

Studie 1: Tato studie zkoumala možné pohlavní rozdíly v elektrofyziologických charakteristikách a výsledcích katetrizační ablace u pacientů s idiopatickou komorovou tachykardií z pravého výtokového traktu (RVOT-VT). Zjistili jsme, že ženy trpící RVOT-VT mají kratší QRS interval, nižší komorovou voltáž a více nízkovoltážních zón na volné stěně RVOT než muži se stejnou diagnózou. Ačkoliv mechanismus těchto rozdílů není jasný, naše výsledky ukazují pohlavní rozdíly v remodelaci komorového myokardu u pacientů s RVOT-VT. Volná stěna RVOT byla oblastí nápadnou tím, že nebyla v korelaci s rozdíly v incidenci komorové tachykardie. Z tohoto nálezu lze odvozovat, že nízké voltáže v této lokalitě jsou pravděpodobně spíše důsledkem než příčinou remodelace myokardu. Pokud se týká efektu katetrizační ablace, byl výskyt opakovaných ablací i výskyt rekurentních komorových tachykardií obdobný u obou pohlaví.

Studie 2: Cílem této studie bylo porovnat odpověď variability srdeční frekvence (HRV) na dva typy HST u postmenopauzálních žen a ukázat případný efekt HST krátce po začátku léčby. Signifikantně nižší výskyt spektrální síly v nízkofrekvenčním pásmu (LF) byl nalezen u léčených žen ve srovnání s neléčenými ženami a s muži stejného věku. HST léčba pouhým estrogenem byla v tomto směru účinná, zatímco žádný účinek HST na LF nebyl prokázán u kombinované HST estrogenem a progesteronem. Spektrální síla ve vysokofrekvenčním pásmu (HF) byla nižší u neléčených postmenopauzálních žen než u žen léčených estrogenovou HST a než u žen premenopauzálních, zatímco od žen léčených kombinovanou HST se významně nelišila. Zvýšené hodnoty HF byly prokázány i v kontrolním měření 2 měsíce po začátku HST estrogenem. Tyto výsledky naznačují, že vagová modulace srdeční frekvence typická pro mladší ženy se po menopauze stává podobnou vagové modulaci u mužů.

Abstract

It has become increasingly apparent in recent years that there are important differences of many cardiovascular disorders including ventricular tachycardias in men and women. Gender differences have been observed in the epidemiology, pathogenesis and clinical presentation of various ventricular arrhythmias. Physiological menopause occurs as a part of a woman's normal aging process being based on the natural cessation of estradiol and progesterone production by the ovaries. The dramatic fall in circulating estrogens levels at menopause impacts many tissues including cardiovascular system. Because the incidence of coronary heart disease (CHD) rises significantly after menopause, it has been hypothesized that women's CHD advantage before menopause (in comparison to men of the same age) could be due to the protective effects of estrogens. However, controversial results have been reported since early nineties until today. While some studies found reduction in the incidence of CHD and in mortality from cardiovascular diseases some other studies failed to provide any evidence for an independent role of estradiol levels in determining CHD in postmenopausal women and some studies even found positive association of endogenous estradiol with the risk of CHD among women above 65 years of age.

Study 1: This study explored possible gender differences in electrophysiological characteristics and catheter ablation outcome in idiopathic ventricular tachycardia from right ventricular outflow tract (RVOT-VT) patients. We have found that females suffering from RVOT-VT had shorter QRS duration, lower right ventricular voltage, and more low voltage zone in the RVOT free wall than males with the same diagnosis. Although the possible mechanisms are not clear, our findings suggest differences in ventricular remodeling between genders in patients with idiopathic RVOT-VT. The RVOT free wall was the prominent region, which was not associated with different ventricular tachycardia (VT) incidences. Those findings suggest that ROVT low voltage might be the remodeling result after VT, rather than its cause. Regarding an effect of the ablation, the acute success rate, repeated catheter ablation rate and VT recurrence rate were similar in both genders.

Study 2: The aim of this study was to compare the responses of heart rate variability (HRV) with two different types of hormonal substitution therapy (HT) in post-menopausal women (cross-sectional study) and to reveal an effect of HT shortly after beginning of its administration (follow-up study). Significantly lower portion of the low frequency power (LF) was found in premenopausal women when compared to untreated postmenopausal women and men. Treatment by estrogen only was proved to decrease the LF% while no effect on HRV was observed in women treated with combination of estrogen and progesterone. Also the high frequency power (HF) was lower in postmenopausal women than in premenopausal women and women treated with estrogen only while in women treated with combined hormonal therapy the average value did not significantly differ from that of untreated postmenopausal women. The follow-up study also proved increase of HF already after two months of estrogen substitution therapy. These results suggest that higher vagal modulation of heart rate that seems typical for younger women becomes after menopause similar to that of men.

Keywords : sex differences, menopausal, cardiovascular disease, pathophysiology of menopause, sex hormones, estrogen, progesterone, androgens, testosterone.

List of Abbreviations

ARVC/D	Arrhythmogenic right ventricular cardiomyopathy / Dysplasia, page 11
AV	Atrioventricular, page 8
CAD	Coronary artery disease, page 9
Chrs	Autosomal chromosomes, page 9
ChrX	Chromosomes X, page 9
ChrY	Chromosomes Y, page 9
CHD	Coronary heart disease, page 20
CRT-D	Cardiac resynchronization therapy-defibrillator device, page 8
CSE	Cystathionine-γ-lyase, page 9
3D	3 dimensions, page 10
ECG	Electrocardiography, page 10
EF	Ejection fraction, page 11
eNOS	Endothelial nitric oxide synthase , page 9
EPS	Electrophysiological study, page 11
FFT	Fast Fourier transformation, page 13
HF	High-frequency, page 13
HPA	Hypothalamic-pituitary-adrenal, page 9
HRT	Hormone replacement therapy, page 10
HRV	Heart rate variability, page 13
HT	Hormone therapy, page 12
IOTVA	Idiopathic outflow tract ventricular arrhythmias, page 19
LBBB	Left bundle branch block, page 8
LF	Low-frequency, page13
LF/HF	Low-frequency to high-frequency power ratio, page 13
LV	Left ventricular, page 11

LVAD	Left ventricular assist device, page 8
MSY	Male-specific region of the Y chromosome, page 9
NO	Nitric oxide, page 9
PI3K/AKT	Phosphoinositide 3-kinase/serine/threonine protein kinase, page 8
RBBB	Right bundle branch block, page 13
RV	Right ventricular, page 11
RVOT-VT	Ventricular tachycardia from right ventricular outflow tract, page 8
SHR	Spontaneously hypertensive rat, page 9
VF	Ventricular Fibrillation, page 8
VT	Ventricular Tachycardia, page 8
VT/VF	Ventricular tachycardia/ ventricular fibrillation, page 8

1. Introduction

Cardiovascular diseases remain the primary cause of death worldwide. In the US, deaths due to cardiovascular disease for women exceed those of men. While cultural and psychosocial factors such as education, economic status, marital status and access to healthcare contribute to sex differences in adverse outcomes, physiological and molecular bases of differences between women and men that contribute to development of cardiovascular disease and response to therapy remain underexplored. Therefore, we need to discover some theories to do the best forecast, diagnosis, treatment and post-therapeutic prognosis between women and men. For instance, women tend to present with longer-lasting episodes of atrial fibrillation, with a faster ventricular response and a higher incidence of cardio-embolic complications. The predominance of atrioventricular (AV) nodal reentrant supraventricular tachycardia with a higher prevalence in women–2:1 compared to men. (Rodriguez et al. 1992) The prevalence of the use of antihypertensive agents is higher among middle-aged women than among men. Notably, in the United States, hypertensive women use more diuretics and angiotensin receptor blockers than men, whereas hypertensive men more often receive beta-blockers, calcium channel antagonists, or inhibitors of angiotensin-converting enzyme. (Cadeddu et al. 2016) Drug-induced torsade de pointes and symptomatic long QT syndrome have a female predominance.(Wolbrette et al. 2002) A clear trend to a higher incidence of bleeding complications has been consistently reported in women, which might be related to a more frequent over-dosage of antithrombotic treatment in women than in men. (Gutiérrez-Chico & Mehilli. 2013) Anticoagulants are less frequently used in women (David and Christine. 2010) Women are at higher risk than men for AF-related thromboembolism off warfarin (Fang et al. 2005) Women with ischemic heart disease and women with left bundle branch block (LBBB) who received cardiac resynchronization therapy-defibrillator device (CRT-D) had the lowest incidence of ventricular tachycardia/ ventricular fibrillation (VT/VF) or death when compared to men. The risk of stroke after left ventricular assist device (LVAD) implantation varies based on sex, with a higher risk in female patients. (Morris et al. 2015)

However, seldom study mentioned that idiopathic ventricular tachycardia from right ventricular outflow tract (RVOT-VT) has any sex different in cardiologic tissues patterns. Our study find RVOT-VT that females had shorter QRS duration, lower right ventricular voltage, and more low voltage zone in the RVOT free wall than males. Although the possible mechanisms are not clear, our findings suggest differences in ventricular remodeling between genders in patients with idiopathic RVOT-VT. The RVOT free wall was the prominent region, which was not associated with different ventricular tachycardia (VT) incidences. Those findings suggest that ROVT low voltage might be the remodeling result after VT, rather than the cause. We also concern that what kind of arrhythmic treatment methods can reduce the sex differences in prognosis. We used 3D mapping ablation which can indeed choice precise position to let prognosis better.

There are several pathways where sex hormones can effect human being cardiovascular system to produce original sex differential pathophysiology between women and men. The mechanisms of sex differential pathophysiology of cardiovascular system between women and men that can be the following theories or hypotheses. The rapid signaling cascade activation and long term respond are the two major pathways revealing how sex hormone to effect cardiovascular system whose results can be found out from human being. However, some unclear mechanisms may need reference animal model experiment to hypothesize human being condition. Firstly, the gene expression theory of human sex hormone to modulate cardiovascular system is described differences between women and men. For instance, the phosphoinositide 3-kinase/serine/threonine protein kinase (PI3K/AKT)-

dependent endothelial nitric oxide (NO) synthase (eNOS) activation pathway to protect cardiovascular system can proved by some authors. They publish that progesterone increases NO synthesis in human vascular endothelial cells through activation of membrane progesterone receptor-α. (Pang et al. 2015) Secondly, the hypothesis of cardiac cells contain sex hormone receptors whose dominant activity are tendency differentially towards sexual difference from animal model. Hydrogen sulfide, generated in the myocardium predominantly via cystathionine-γ-lyase (CSE), is cardioprotective. Some authors study has shown that estrogens enhance CSE expression in myocardium of female rats. The present study aims to explore the mechanisms by which estrogens regulate CSE expression, in particular to clarify the role of estrogen receptor subtypes and the transcriptional factor responsible for the estrogenic effects. (Wang et al. 2015) Thirdly, the hypothesis of Y chromosome effect from animal model. Like autosomal chromosomes (Chrs), the sex chromosomes (ChrX; ChrY) are thought to have once been identical pairs that were free to recombine and exchange genetic material. Recently, studies on the human Y chromosome have also demonstrated that genetic variation within the male-specific region of the Y chromosome (MSY) could play a part in determining cardiovascular risk in men, confirming the notion that the increased risk for coronary artery disease (CAD) in men (Molina et al. 2016) Genes located on the Y chromosome from the spontaneously hypertensive rat (SHR) are associated with the renin-angiotensin system. (Sampson et al. 2014) Finally, the sex hormone can also combination with neuroendocrine and other neurotransmitters to effect cardiovascular system including blood pressure, heart rate, gender differential anxiety respond and so on. For instance, sex comparisons in the functional and molecular aspects of the hypothalamic-pituitary-adrenal (HPA) axis, through various phases of activity, including basal, acute stress, and chronic stress conditions. Additional systems impinging on the HPA axis that contribute to sex differences include the monoamine neurotransmitters norepinephrine and serotonin. (Goel et al. 2014) Sex hormones can also exert differential effects on a variety of sensitive tissues like the reproductive tract, gonads, liver, bone and adipose tissue, among others. In the brain, sex hormones act as neuroactive steroids regulating the function of neuroendocrine diencephalic structures like the hypothalamus. (Sotomayor-Zarate et al. 2014).

Therefore, we consider whether Estrogen is cardio-protection for women throughout their whole life or not. Hot flashes is one of the common syndromes of perimenopausal women. It is thermoregulatory and cardiovascular changes generally lasts 1 to 5 minutes, and skin temperatures rise because of peripheral vasodilation. We want to know how the relationship between female sex hormones (Estrogen and Progestrone) with their heart rate variability.

2. Hypothesis

One of the hypothesis is that sex differences in electrophysiological characteristics of idiopathic ventricular tachycardia original from right ventricular outflow tract. We also predict that we use 3 dimensions (3D) mapping ablation which can indeed choice precise position to let prognosis better. Another hypothesis is Estrogen can stablize menopausal women's heart rate variability.

The particular goals of this thesis are :

- To investigate whether sex differences in electrophysiological characteristics when idiopathic ventricular tachycardia is happened and its prognosis after suitable therapy.
- To elucidate Estrogen can modulate menopausal women's heart rate variability.

This thesis tried to discuss the hypothesis in different areas of RVOT-VT and hormone replacement therapy (HRT). Their application were identified during the work. (1) Gender differences in electrophysiological characteristics of idiopathic ventricular tachycardia original from right ventricular outflow tract (2) Estrogen can modulate menopausal women's heart rate variability

It try to finds answers to the following additional questions :

- *Assume that estrogen has a cardio-protective effect, whether idiopathic ventricular tachycardia from right ventricular outflow tract (RVOT-VT) is a sex difference or not ?*
- *How to compare the prognosis of catheter ablation in patients suffering from idiopathic RVOT-VT between men and women ?*
- *Do women are tend to have frequent ventricular tachycardia initiation during hormonal flux ?*
- *Do sex hormones really effect menopausal women's cardiac rate variability because menopausal hot flashes can be cured by Estrogen ?*
- *What is the difference cardiac rhythm between men, pre-menopause and menopause women if give Estrogen or combine with Progesterone ?*

There were the ideals to give clinical recommendation from our new concepts in order to make best therapy of RVOT-VT and application of cardiovascular HRT in hospital.

3. Methods

We need two population of patients to find two major research aim.

3.1 Study population of RVOT-VT

93 patients with idiopathic ventricular tachycardia from right ventricular outflow tract (RVOT-VT) (mean age 38.7±15.5 years) were enrolled into the study between January 2011 and September 2013. There was no difference between sex in age of disease onset, diabetes mellitus, hyperlipidemia, previous syncope episodes or family history of ventricular arrhythmias. The diagnosis of VT was documented either by 12-lead resting electrocardiogram (ECG) or by 24-hour ambulatory ECG according to Holter. Cardiac catheterization excluded the possibility of coronary artery disease. All patients were examined using transthoracic echocardiography at the time of diagnosis and all other heart diseases, such as dilated cardiomyopathy, were excluded. Right ventricular (RV) function, regional RV wall motion, as well as left ventricular (LV) function, LV wall motion and LV ejection fraction (EF) were evaluated. RV dysfunction was defined as regional RV akinesia, RV dyskinesia, RV aneurysm, or RV EF less than 40%. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) was excluded by Task-Force criteria (Marcus et al. 2010). Monomorphic VT was defined as VT with a uniform beat-to-beat surface QRS morphology. Electrocardiographic criteria were employed to identify VT origin, and in all patients included into the study the VTs were confirmed to be of RVOT-VT type (Arya et al. 2007).

3.1.1 Electrophysiological study and electromechanical mapping

We performed simultaneous electromechanical mapping during electrophysiological study (EPS) using the NavX mapping system (NavX, St. Jude Medical, St. Paul, MN, USA). The mapping procedure included pace mapping during sinus rhythm, endocardial activation mapping, identification of diastolic potentials and entrainment mapping during VT. Entrainment was performed to identify the critical component of the VT circuit and for guidance of selective ablation. We used endocardial activation-sequence mapping to record the earliest endocardial activity and diastolic potentials during VT. Continuous recordings of RV endocardium voltage were done during sinus rhythm, and abnormal areas were defined as voltage setting of $\leqq$1.5 mV on bipolar electrocardiogram. Scar zones were defined by a voltage setting < 0.5 mV, whereas areas with voltage between 0.5 mV and 1.5 mV were evaluated as low voltage zones. This facilitates the delineation of the culprit substrate for VT. We performed catheter ablation in those patients with inducible VT with standard radiofrequency energy delivered through 4-mm tipped deflectable ablation catheters. Twelve patients did not receive catheter ablation because relevant clinical VT was not induced during EPS. Acute success was defined by the absence of any inducible VT at the end of the catheter ablation procedure via electrical stimulation with or without isoprenaline. ECGs were checked soon after EPS or catheter ablation.

After hospital discharge, the first outpatient follow-up time was arranged two weeks later and further follow-up visits were scheduled at three-month intervals. Surface ECGs and 24-hour holter ECG exams were arranged during serial outpatient follow-up. VT with RVOT origins documented on ECGs or 24-hour holter ECG exams was classified as VT recurrence.

All measurements were performed in the morning between 8 a.m. and 12 a.m. In our study we have used only standard measurement procedures, more detailed description of methods is available in cited papers (Hummel et al. 1994, Tada et al. 2004).

3.1.2 Statistical analysis

Continuous variables are expressed as mean ± standard deviation and the comparisons between continuous data were performed using Student's t test. Comparisons of categorical data were performed using a Chi-square test with a Yates' correction or Fisher's exact test. Statistical significance was established at a p value of < 0.05. All statistical analyses were performed using commercial statistical SPSS version 17.0 software (SPSS, Chicago, IL, USA).

3.2. Study population of hormone therapy (HT)

The cross-sectional study was performed on 925 volunteers. The whole cohort was composed of three groups: premenopausal women, postmenopausal women (at least two years from the last menstrual period) and men at the same age as postmenopausal women. The volunteers were recruited from healthy population who live in the same Datong District of Taipei, Taiwan, R.O.C. The group of postmenopausal women was divided randomly into three subgroups: women without any hormonal treatment, women treated by conjugated estrogen (Premarin at 0.625 mg/day) and women receiving combined hormone replacement (Covina at estradiol 2 mg + norethisterone acetate 1 mg/day). Both subgroups with hormone therapy (HT) were treated continuously, group E (estrogen only) continuously by conjugated estrogen, group E+P repeatedly by estrogen only in first 14 days of 28-days periods and by combination of estrogen and progestin in second halves of 28-days periods.

The follow-up study included only postmenopausal woman with estrogen replacement therapy and postmenopausal woman with combined HT receiving the hormone therapy for at least two consecutive months. The exclusion criteria were cardiovascular diseases, arterial hypertension, diabetes mellitus, asthma, smoking, neurological or psychiatric diseases and any medication that have been reported to affect heart rate (like for instance autonomic blockers). Also postmenopausal women receiving HT or contraceptives before menopausal symptoms were excluded from the study. Before the experiment, objects had no participation in any strenuous exercise, drinking, smoking, drinking caffeinated beverages and taking sleeping pills or tranquilizers.

3.2.1 Patients examinations

A detailed overall examination including basic biochemistry was performed before the beginning of the study and all participants were informed about the purpose of the study and all procedures before obtaining their written consent. All ECG examinations were performed between 8 a.m. and 3 p.m. Before every ECG examination the participants were ordered rest in a supine position for at least 5 minutes in a separate quiet room. One electrode was affixed to the sternal edge of the left second intercostal edge, the other one to the midclavicular line in the fourth intercostal space. The examination was realised at standard conditions under complete physical and mental rest, participants were asked to keep laying quietly and breathing normally but not to go to sleep. ECG signals were recorded by an 8-bit analogue to digital convertor with a sampling rate of 256 Hz, analysed on-line, and stored on the IBM-PC

hard drive. Software used for processing of the signal first identified each QRS complex by a spike detection algorithm and then excluded all premature beats and all beats not corresponding to the standard QRS template.

Non-parametric spectral analysis of the heart rate variability (HRV) was performed using fast Fourier transformation (FFT) and for attenuation of the leakage effect a Hamming operator was used. Such obtained power spectrum was computed to get standard frequency domain measurements (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996) which include: total variance, low-frequency power (LF), high-frequency power (HF) and low-frequency to high-frequency power ratio (LF/HF). All these variables were then logarithmically transformed in order to correct for the skewness of the distribution (Kuo et al. 1999).

3.2.2 Statistical analysis

The data were expressed as means ± standard error. For statistical analysis one-way ANOVA and Fisher's least significant difference test were used. Differences were considered to be statistically significant at $p < 0.05$.

4. Results

We divided two parts of above results individual to mention our discovery.

4.1 Result of RVOT-VT study

The findings of are the following mentions :

4.1.1 Electrocardiographic and echocardiographic differences

No differences existed between genders in respect to percentage of atrial arrhythmias and QTc prolongation. We found an right bundle branch block (RBBB) pattern of QRS in four male patients (13.3%) and five female patients (7.9%), which was not statistically significant. The QRS width was longer in men comparing to women (99.9 ± 19.4 ms vs. 88.4 ± 20.7 ms, p = 0.02). The incidence of T-wave inversion in right precordial leads (V_1 to V_3) indicated no statistical differences between genders. Twenty male patients (66.7%) presented with clinically documented VT, while 50 female patients (79.4%) did. Most of them had monomorphic VT. Only two male patients and three female patients had multiple monomorphic VT or polymorphic VT. There was no difference in LVEF between both genders. Twenty-one percent of male patients had RV dysfunction compared to 19% of female patients (p = 0.85). The percentage of RV dyskinesia was similar for male and female patients (13.8% vs. 20.6%, p = 0.43).

4.1.2 Electrophysiology study and electro-anatomic mapping

Male patients were found to have higher mean RV voltage than female patients (3.7 ± 0.9 mV vs. 3.0 ± 0.7 mV, p = 0.03). Analyzing scar zones and low voltage zones at RVOT and RV, females had more low voltage zones at the RVOT free wall (27% vs. 6.7%, p = 0.02) as compared with males. The percentage of low voltage zones in other areas was similar between

both genders (male vs. female, RVOT septum, 10% vs. 12.7%, p = 0.50; RV body free wall, 16.7% vs. 30.2%, p = 0.17; RV body septum, 6.7% vs. 0.6%, p = 0.10). There was no statistical difference in the percentage of scar zone distribution between male and female (RVOT free wall, 6.7% vs. 15.9%, p = 0.18; RVOT septum, 3.3% vs. 7.9%, p = 0.37; RV body free wall, 13.3% vs. 23.8%, p = 0.24; RV body septum, 6.7% vs. 0, p = 0.10)

4.1.3 The outcome after 3D catheter ablation

In total, 81 patients passed catheter 3 dimensions (3D) mapping ablation (23 male and 58 female patients), and the mean follow up time was 26.9 months (26.9 ±32.8 months). The acute success rate was similar in the two studied groups (73.9% vs. 65.5%, p = 0.47). Despite the fact that most patients had monomorphic VT, multifocal ablation sites were needed in 7 male patients and 13 female patients. We tried to analyze the sites where ablation was successful and the correlation with frequencies of scar zone or of low voltage zone and there were no differences between male and female patients. The ablation performed according to the result of pacemap locations was successful in 34.8% of male patients and 36.2% of female patients. The overall VT recurrence rate was likewise similar between the two groups (26.1% vs. 27.6%, p = 0.89). Three male and five female patients had to pass catheter ablation a second time

4.2 Result of HT study

The average heart rate (±SD) in the group of women treated by conjugated estrogen [64.6 (±3.5) min^{-1}] was significantly lower than in premenopausal women [73.1 (±3.9) min^{-1}] and also than in women treated by the combined hormone replacement therapy [81.4 (±4.6) min^{-1}]. The heart rate of women treated by conjugated estrogen was comparable with that of men. No significant difference was observed between premenopausal women and postmenopausal women without any hormonal treatment. Significantly lower portion of the low frequency power (LF%) was found in premenopausal women [46.9 (±2.7) nu] when compared to untreated postmenopausal women [54.3 (±2.9) nu] and men [55.2 (±3.0) nu]. Treatment by estrogen alone significantly decreased the low frequency power ratio [40.1 (±2.1) nu] while no similar effect was observed in women treated with combination of estrogen and progesterone [57.2 (±3.1) nu]. Also the high frequency power was lower in postmenopausal women [4.16 (±0.16) ms^2] than in premenopausal women [4.79 (±0.22) ms^2] and women treated with estrogen only [4.98 (±0.25) ms^2] while in women treated with combined hormonal therapy the average value [3.99 (±0.21) ms^2] did not significantly differ from that of untreated postmenopausal women. The corresponding results were consistently found in low-frequency to high-frequency power ratio: the values in premenopausal women [0.04 (±0.12)] and women treated by estrogen [-0.25 (±0.16)] were significantly lower than values found in untreated postmenopausal women [0.36 (±0.12)] and women treated by combined hormonal therapy. [0.48 (±0.16)]

The follow-up study also proved the increase of high frequency power already after two months of estrogen substitution therapy [4.86 (±0.14) ms^2 vs. 4.19 (±0.15) ms^2]. The present study aimed to compare the responses of HRV with two different types of hormonal substitution therapy (HT) in postmenopausal women (cross-sectional study) and to reveal an effect of HT shortly after beginning of its administration (follow-up study). Simultaneously we compared the HRV between postmenopausal women and men at corresponding age. The

only significant differences are in the age of premenopausal women in comparison to all other groups and in the body height of men in comparison to all women groups.

5. Discussion

We divided two parts of above results individual to mention our discussion.

5.1 Discussion of RVOT-VT study

The present study was focused on sex differences in electro-anatomic characteristics and catheter ablation in RVOT-VT, which according to the authors' best knowledge, have never been previously reported.

5.1.1 Main findings

Females were proved to have more low voltage zone in the RVOT free wall, lower mean RV voltage, and shorter QRS duration as compared with males. The acute success rate, repetitive ablation rate and VT recurrence rate did not differ between genders.

5.1.2 Sex differences in electrophysiological characteristics

Differences in electrophysiological characteristics between genders have been reported in several recent studies. Women have been noted to have higher heart rates at rest, longer corrected QT intervals, shorter sinus node recovery time, and longer ventricular effective refractory periods compared with men (Bernal and Moro 2006). Differences in gender hormones may explain some of these findings, but precisely how is still not well understood. For instance, variations in arrhythmia frequency with respect to the menstrual cycle have been observed. In addition, an increase in arrhythmia frequency or the new onset of arrhythmias has been noted during pregnancy (Yarnoz and Curtis 2008). Differences have also been documented in the incidence and prevalence of specific arrhythmias, including atrial fibrillation, other various supraventricular tachycardias, and sudden cardiac death. Gender differences in pulmonary vein and left atrium action potential characteristics were noted in the animal study (Tsai *et al.* 2011). In the human beings, female gender with atrial fibrillation could predict the presence of superior vena cava ectopic beats (Lee *et al.* 2005). Women have also a higher prevalence of multiple accessory pathways and orthodromic atrio-ventricular re-entrant tachycardia in the case of pre-excitation syndrome (Huang *et al.* 2011). In atrioventricular nodal re-entrant tachycardia, both the antegrade fast and slow pathways effective refractory periods in women were significantly shorter than those in men (Suenari *et al.* 2010). Gender-specific differences exist in the incidence and age distribution of the various types of VT (Nakagawa *et al.* 2002). Nevertheless, limited information was noted from currently available literature. Women were found to have longer ventricular effective refractory periods in comparison to men (Liu *et al.* 2004). Women have also higher incidence of congenital and acquired long QT syndrome, but less ventricular tachycardia/fibrillation-related sudden cardiac death (Bernal and Moro 2006). In idiopathic ventricular tachycardia including RVOT-VT, gender-specific differences exist in the incidence and age distribution. The incidence of RVOT-VT in female is higher than that in males (Bernal and Moro 2006) but gender was not associated with the outcome after catheter ablation (Tanaka *et al.* 2011).

Moreover, the same authors have reported that in the patients with idiopathic ventricular arrhythmias, males are prone to have tachycardia induced cardiomyopathy.

5.1.3 Mechanisms of gender differences

Several mechanisms have been proposed to explain the gender differences in arrhythmias, and one of those is associated with sex hormones (Chen *et al.* 1999). Sex hormones could regulate the expression of cardiac ion channels. Progesterone increases delayed rectifier K+ current (Iks) through the nitric oxide production pathway and prevents cyclic adenosine monophosphate enhancement of L-type Ca2+ current (Rosano *et al.* 1996). Other possible mechanisms are different distributions of ion channels between genders. James *et al.* (2004) reported gender-related differences in ventricular myocyte repolarization in the guinea pig. They have found in their study that IKs and inward rectifier K^+ current were different between genders regardless of menstrual cycle. Gaborit *et al.* (2010) further reported that male and female human hearts had significant differences in ion-channel subunit composition, with female hearts showing decreased expression of a number of repolarizing ion-channels. The autonomic nervous system could also play the role. Autonomic regulation, contributing to different cardiac electrophysiology (Kapa *et al.* 2010, Yang *et al.* 2013) might explain gender differences in various arrhythmias (Dart *et al.* 2002, Hu *et al.* 2009, Morillo *et al.* 1994). Arg16Gly in β2-adrenoceptor is significantly associated with idiopathic ventricular outflow tract tachycardias in the Chinese Han population (Ran *et al.* 2010) which suggests the possible roles of sympathetic system in the RVOT-VT. In summary, gender differences might be attributed to multiple factors.

5.1.4 The outcome after 3D catheter ablation

The gender differences in outcomes after catheter ablation for different arrhythmias have been recently reported. For instance, outcomes of catheter ablation for atrial fibrillation in women were worse than in men, probably due to later referral and older age in the women in reported study (Santangeli *et al.* 2011). Similar ablation results regarding differences between the genders were observed in atrioventricular nodal and atrioventricular reentrant tachycardia. With regard to idiopathic VTs, no gender-related differences in outcome of catheter ablation have been found (Tanaka *et al.* 2011). This study also shows that successful ablation rates, recurrence rates, and necessary repetitive operations were similar between genders. Idiopathic RVOT-VT is a relatively benign ventricular arrhythmia, and prognosis should rely on underlying conditions and comorbidities, rather than on the arrhythmia itself. Ventura *et al.* (2007) reported decennial follow-up in 133 patients (77 females; 39±13 years) with RVOT-VT for 135±68 months and 127 (95 %) survived, while six (5 %) died but from noncardiac diseases. In this study, ablation was performed in middle-aged groups with relatively few comorbidities and preserved left ventricular function. The modern technique of catheter ablation has a high success rate and low complications, which explains why the acute success rate and recurrence rate didn't differ between the two groups. The recent study also revealed gender difference in mutation carriers in the lamin A/C gene (LMNA) when male had a worse prognosis due to a higher prevalence of malignant ventricular arrhythmias and end-stage heart failure (van Rijsingen *et al.* 2013).

5.2 Discussion of HT study

The present study aimed to compare the responses of HRV with two different types of hormonal substitution therapy (HT) in postmenopausal women (cross-sectional study) and to reveal an effect of HT shortly after beginning of its administration (follow-up study). Simultaneously we compared the HRV between postmenopausal women and men at corresponding age. The characteristics of the groups involved in our study are summarized in Table 1, the only significant differences are in the age of premenopausal women in comparison to all other groups and in the body height of men in comparison to all women groups. Decline in short-term indexes of HRV is associated both with ageing and with declined estrogen levels after menopause (Neves *et al.* 2007). Higher high-frequency power in premenopausal women in comparison to age-matched men was found by Kuo and al. (1999). This finding was confirmed by Liu *et al.* (2003) and moreover they have proved that these gender-related differences disappear after menopause. Our results fully correspond to these findings as we have not found any difference between postmenopausal women and men, but significant differences between premenopausal women and both men and postmenopausal women.

These results suggest that higher vagal modulation of heart rate that seems to be typical for younger women becomes after menopause similar to that of men. Responsibility for this phenomenon lies fully in ovarian hormones what was reported by Mercuro *et al.* (2000) who searched for effect of oophorectomy in premenopausal women on HRV. In their study comparing healthy women before and after oophorectomy with age-matched women who underwent hysterectomy with ovarian conservation they concluded that surgical menopause induced a decline in cardiac vagal modulation with a recovery of the baseline condition after 3 months of estrogen replacement therapy. This result suggests a crucial role of estrogen in the autonomic nervous control of the heart rate. On the other hand it is known that progesterone has a number of potential adverse effects on the cardiovascular system (Rosano GM 2000, Lantto *et al.* 2012) and our results support the concept that progesterone effect attenuates the benefit of unopposed estrogen replacement therapy in post-menopausal women. In order to confirm our hypothesis of a reverse effect of progesterone on HRV we used different types of HT. Although there are many possible HT regimens described in literature we choose only two standard prescriptions in order to make the study transparent. For comparison of effects of these two types of HT on the heart rate autonomic control we used spectral analysis of HRV. This method has been used since the late 1960s. Power spectral density analysis provides information on how power (variance) distributes as a function of frequency. (Carter *et al.* 2003). The advantages of nonparametric methods, such as the fast Fourier transform, are the simplicity of the algorithm used and the high processing speed. HRV as a powerful tool for the estimation of cardiac autonomic modulations is associated with three major physiological factors, which primarily reflect changing level of both parasympathetic and sympathetic neural control of the heart: oscillatory fluctuations in blood pressure, frequency oscillations due to thermal regulation and respiration. HRV may therefore be considered an output variable of a feedback network that is continuously monitored and regulated by the autonomic nervous system.

Our study showed that HRV differences among the groups were related to the differences of heart rate. This phenomenon could have both mathematical (shorter RR intervals mean that also their fluctuations are lower and thus also less identifiable) and physiological background (tachycardia is generally associated with increased sympathetic and decreased parasympathetic tone). We suppose that decreased heart rate and simultaneously increased high frequency power and very low value of lnLF/HF, that was identified in our study, fully correspond to the described changes in the tones of the autonomic nervous system. Moreover

it was proved that clinical usefulness of HRV is relatively independent on the heart rate differences (Kautzner *et al.* 1998).

Animal studies and observational studies have suggested that the use of HT in postmenopausal women could be beneficial with regards to the development of CHD (Adams *et al.* 1990, Grodstein *et al.* 1996, Arnal *et al.* 2006). On the other hand a possible association between estrogens and higher risk of cardiovascular mortality started to be discussed in many recent studies both with negative (Barret-Connor and Goodman-Gruen, 1995) and positive (Scarabin-Carré *et al.* 2012) conclusions. One possible reason for different results could be the time of measurement. Most published measurements as well as our measurements were performed between 8 a.m. and 3 p.m. when sympathetic activity dominates over the parasympathetic one. One of recently published papers studied the effect of estrogen HT on nocturnal HRV and found that HT has a slightly but distinctively attenuating effect on some nocturnal nonlinear measures of HRV, especially on complexity of heart rate dynamics, suggesting that estrogen HT may have potentiallydeleterious effects on cardiovascular health during sleep (Virtanen *et al.* 2008). Another possible reason for different results could be different age of postmenopausal women in these studies. While in younger postmenopausal women no association between estradiol levels and cardiovascular risk was found in postmenopausal women over 65 years a positive association between estrogens and progression of atherosclerotic process was identified. Our results proved a positive shift of HRV parameters toward more beneficial values regarding the cardiovascular risk in postmenopausal women treated with estrogens but not in women treated by combined therapy with estrogens and progesteron. But more particularly prospective studies are needed to confirm or definitely reject the theory of protective effects of estrogen HT in postmenopause or to define an age-limit for beneficial effects of this therapy.

6. Conclusion

It means that some relationship between sex hormones and cardiovascular systems by above two experiments. Sex hormones and gender differences have been reported to be associated with the occurrences of ventricular arrhythmias. Some authors investigated the relationship between sex hormones and idiopathic outflow tract ventricular arrhythmias (IOTVA) in adult male patients. (Hu et al. 2009) They suggested that IOTVA might be associated with the reduction of estradiol level even if adult in male patients. IOTVA, including left and right ventricular outflow tract, are dued to cyclic adenosine monophosphate (cAMP)-mediated calcium-dependent delayed after depolarizations. (Jiang et al. 2012) Meanwhile, estrogen replacement therapy could inhibit significantly the count of ventricular arrhythmias in the postmenopausal patients with IOTVA. Their conclusion revealed that estrogen replacement therapy may be a potential therapeutic approach for IOTVA besides postmenopausal patients. (Jiang et al. 2012) IOTVA has been demonstrated to have a unique arrhythmogenic substrate and electropharmacological profile, including RVOT and LVOT arrhythmias. The most common forms of idiopathic ventricular arrhythmias arise from the RVOT. (Hu et al. 2011) Therefore, we need to know the present study provides further evidence of the sex differences in electroanatomical mapping findings. Females had shorter QRS duration, lower right ventricular voltage, and more low voltage zone in the right ventricular outflow tract (RVOT) free wall than males. Although the possible mechanisms are not clear, our findings suggest differences in ventricular remodeling between genders in patients with idiopathic ventricular tachycardia from right ventricular outflow tract (RVOT-VT). The RVOT free wall was the prominent region, which was not associated with different VT incidences. Those findings suggest that ROVT low voltage might be the remodeling result after VT, rather than the cause. The outcome after catheter ablation was similar between genders, what corresponded with the previous report (Tanaka *et al.* 2011).

Measurement of heart rate variability (HRV) is an established method to assess the activity of the autonomic nervous system. A literature review was performed a decrease of the vagal dominance on the heart from the follicular to the luteal cycle phase, although some studies asserted no change. The intake of oral contraceptives appeared not to alter the vagal modulation of the heart. (von Holzen et al. 2016) Our research is corresponding with all recent investigations which agreed on a decline of HRV towards higher sympathetic control after menopause. (Von Holzen et al. 2016) Different menopausal hormone therapy approaches showed a supporting impact of estrogen on HRV in most studies. Further research is needed to demonstrate how this process might be attenuated by different menopausal hormone therapies. (von Holzen et al. 2016) Prescription of hormone replacement therapy (HRT) should never be made only for cardiovascular risk reduction. However, when symptom-related and other indications are present, HRT is appropriate and well tolerated in the early years after menopause with onset at a normal age. (Whayne and Mukherjee. 2015)

Estrogen is important throughout women's whole life. Not only it may regulate human utero-placental blood flow in a tissue-specific manner which can regulate vascular tone in the uterine circulation is a key determinant of appropriate utero-placental blood perfusion and successful pregnancy outcome (Corcoran et al. 2014), but also estrogen can improve menopausal women's heart rhythm. The impact of hot flashes and various forms of hormone therapy on health-related quality of life and sexual well-being in recently postmenopausal women. Estradiol or an estradiol-medroxyprogesterone acetate combination similarly alleviates hot flashes and improves health-related quality of life in relation to elimination of hot flashes. (Savolainen-Peltonen et al. 2014) In a cohort of healthy, drug-naive, postmenopausal women, HRT seems to positively affect glomerular filtration and is

associated with lower values of left ventricular mass and aortic root size, thus offering a further mechanism through female hormones exert cardioprotection. (Vitolo et al. 2015)

Multiple clinical studies including randomized trials and observational studies converge with animal experimentation to show a consistency that HRT decreases coronary heart disease (CHD) risk and overall mortality in primary prevention when HRT is started at the time of or soon after menopause. The totality of data supports the "timing" hypothesis that posits that HRT effects are dependent on when HRT is started in relation to age and/or time-since-menopause. The totality of data shows that HRT decreases CHD and overall morality when started in women who are less than 60 years old and/or less than 10 years postmenopausal, providing a "window-of-opportunity". Further evidence shows that women who start HRT when in their 50s and continued for 5-30 years that there is an increase of 1.5 quality-adjusted life-years (QALYs). (Hodis & Mack. 2014) HRT decreases the risk of colon cancer but increases a woman's chance of developing breast cancer. Short-term use of low-dose HRT remains a valid option for management of menopausal symptoms, especially hot flushes. (Takiya & Umland et al. 2003)

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