The effect of hormone replacement therapy on the left ventricle systolic and diastolic function in postmenopausal women with coronary artery disease

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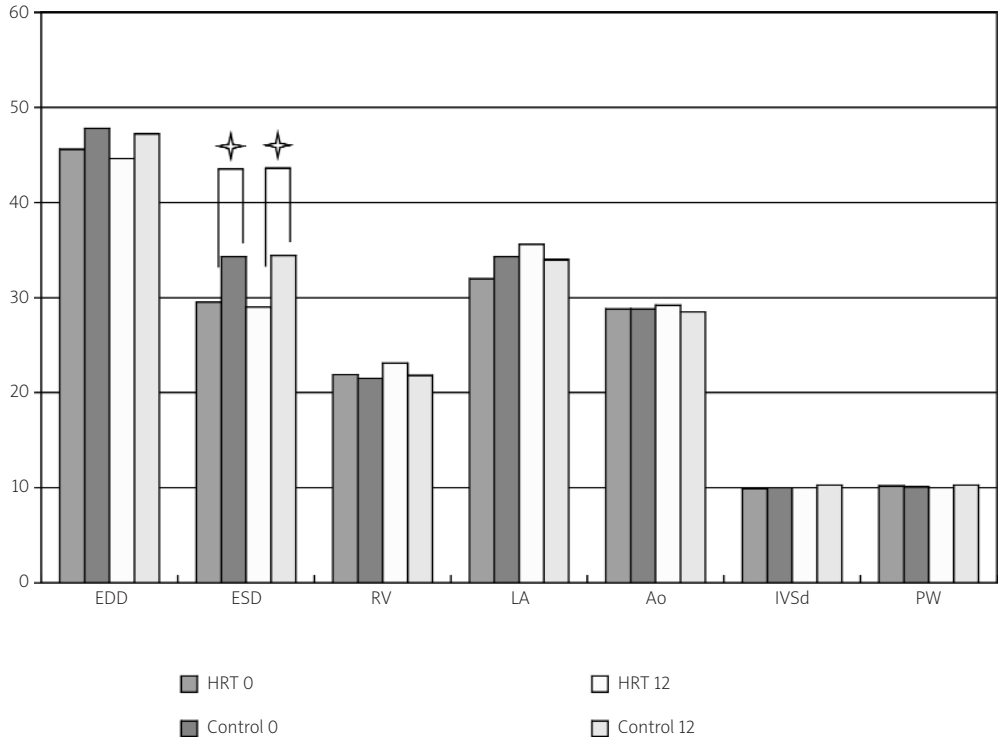
Abstract

Introduction: The aim of this study was to evaluate the effect of hormone replacement therapy (HRT) on the left ventricle systolic and diastolic function.
Materials and methods: Fifty-six postmenopausal women with proven coronary artery disease (CAD) were enrolled into the study (31 were assigned to HRT and 25 were matched as a control group). Clinically both groups were comparable. All patients had standard 2D and Doppler echocardiography study at the baseline and after 12 months of follow up.
Results: The heart geometry and wall thickness did not change significantly in both groups and were comparable after 12-months of follow-up: EDD: 45.6±6.0 to 44.6±8.1 vs. 47.8±7.1 to 47.2±4.4; ESD: 29.5±7.1 to 29±8.8 vs. 34.3±6.7 to 34.4±7.7; RV: 21.9±6.1 to 23.1±7 vs. 21.5±5.8 to 21.8±3.2; LA: 32±4.7 to 35.6±7.9 vs. 34.3±4.2 to 34±4.4; Ao: 28.8±3.3 to 29.2±4.5 vs. 28.8±2.2 to 28.5±3.4; IVS: 9.9±1.4 to 10±1 vs. 10±1.3 to 10.3±1.6; PW: 10.2±1.1 to 10±1 vs. 10.1±1.6 to 10.3±1.4. Left ventricle systolic and diastolic parameters did not change significantly in both groups and were comparable after 12-months of follow-up: LVEF (%): 64.3±13.4 to 68.4±14.9 vs. 56.6±12.5 to 59.9±13; ESV (ml): 35.3±39.8 to 40.4±57.2 vs. 42.9±23.9 to 38.6±16.4; IVRT (ms): 120.9±22.8 to 112.2±15.4 to 112.8±27.7 to 109.3±12.8; E: A: 1.17±1.17 to 1±0.48 vs. 0.97±0.41 to 0.94±0.35; DCT (E) (ms): 152.4±70.6 to 150.2±50.9 vs. 149.3±69.1 to 176.8±61.4; EDV (ml): 84.9±62.6 to 98.3±69.7 vs. 96.9±43.6 to 96.1±26.9.
Conclusions: Short term transdermal HRT has no effect on the left ventricle systolic and diastolic function in women with CAD.

Key words: hormone replacement therapy, HRT, estrogens, menopause, coronary artery disease, CAD, echocardiography, systolic function, diastolic function.

Introduction

Differences in the course of coronary artery disease (CAD) in men and women were of particular interest during last decade. Morbidity rate of CAD among premenopausal women is significantly lower than among men and after menopause increases rapidly. The differences between genders concern not only morbidity, but symptomatology, disease course and risk factors impact. The most obvious cause of this state seems to be a difference in endocrine system function and its expiration during



– statistical significance
Ao – aortic annulus, EDD – end-diastolic dimension, ESD – end-systolic dimension, IVSd - interventricular septum thickness, LA – left atrium dimension, PW – posterior wall thickness, RV – right ventricle end diastolic dimension. Dimensions are presented in mm

Figure 1. Heart geometry

menopause. This fact provokes many investigators to seek for the new preventive and therapeutic strategies of CAD targeted to women. Based on numerous studies, hormone replacement therapy (HRT) seemed to be the solution, however the most recent studies stay in opposition to the previous observations [1-7]. In fact, it has been demonstrated that acute coronary events rate in the first year of HRT was even higher than in control groups [2, 7-9].

Beneficial effects of estrogens are being explained by their favourable vasomotor influence on the coronary and peripheral blood flow. Estrogens-related vasodilatation is mediated by nitric oxide, calcium antagonism and sympathetic modulation [10-15]. These effects reduce myocardial ischemia shortly after estrogens administration, but disappear soon after drug cessation [16, 17]. Prevention and inhibition of the atherosclerotic process is the other well-known estrogens action, mediated mainly by improving lipid profile. Enhanced coronary circulation and calcium antagonism caused by estrogens may increase myocardial relaxation as observed in several studies [18-21]. Other authors did not confirm these observations [22].

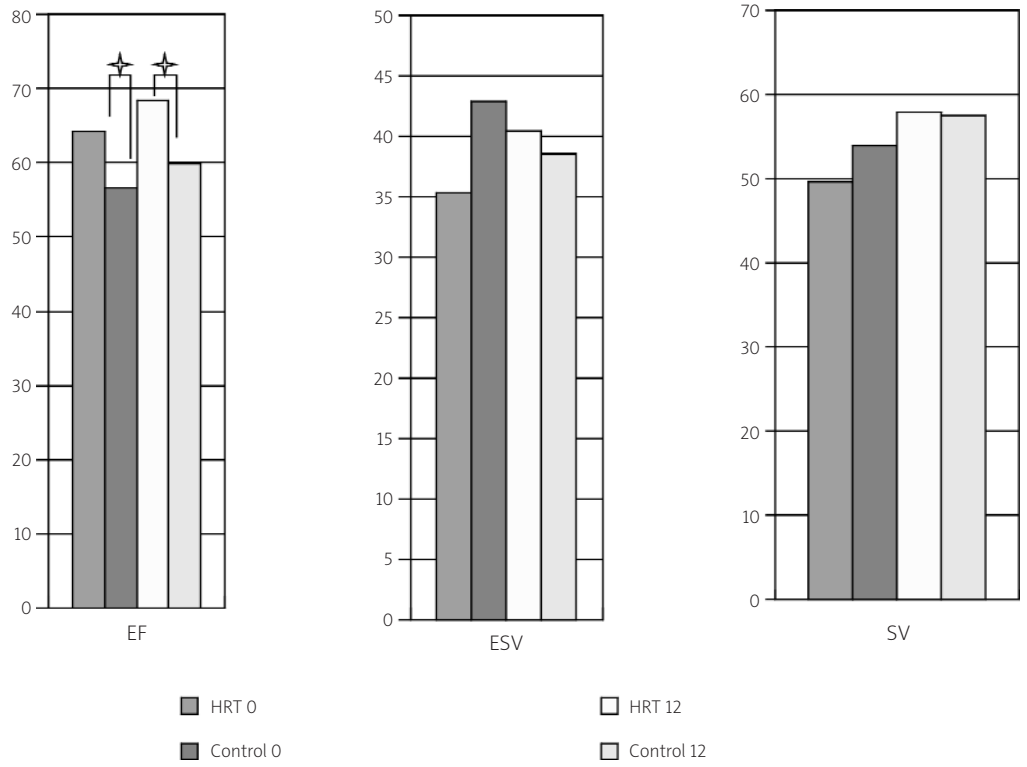
The aim of this study was to evaluate the effect of transdermal HRT on the left ventricle systolic and diastolic function in postmenopausal women with documented CAD.

Material and methods

A hundred and fifty postmenopausal women with proven CAD after coronary angiography between 1996-2000 were screened, seventy-two interviewed and finally fifty-six were enrolled into the study (31 were assigned to HRT and 25 were matched as a control group). Clinically both groups were comparable. All patients had standard 2D and Doppler echocardiography study at the baseline and after 12 months of follow up. Menopause was defined as at least 6-month interval since last menstruation and plasma FSH >30 iu/l. CAD diagnosis was confirmed by coronary angiography with al least one >50% narrowing of the main coronary artery. The other inclusion criteria: age 50-65, BMI <32, lack of hormone therapy contraindications or any severe condition influencing 12-month survival rate, written informed consent.

The study was funded by Medical University, Ethics Committee permission was obtained.

Thirty-one consecutive patients (mean age 57.4±5.4) were assigned to HRT, then 25 were matched as a control group (mean age 56.2±7.7). Both groups (HRT vs. control) were comparable concerning risk factors, progression and symptoms of CAD, past revascularisation rate: hypercholesterolemia 96.8% vs. 80%, hypertriglycerydemia 45.2 vs. 56%, diabetes 12.9%



✧ – *statistical significance*
EF (%) – ejection fraction, ESV (ml) – end-systolic volume, SV (ml) – stroke volume

Figure 2. Systolic function parameters

vs. 24%, hypertension 58.1% vs. 60%, smoking 71% vs. 60%, positive family history 71% vs. 52%, BMI 26.9±3.5 vs. 27.5±3.3; past myocardial infarction (MI) 61.3% vs. 84% (QMI 36.8% vs. 33.3 %, anterior MI 42.1% vs. 61.9%); angina CCS I° 58.1% vs. 52%, CCS II° 25.8% vs. 16%; heart failure NYHA I° 22.6% vs. 32%, NYHA II° 6.5% vs. 12%; number of narrowed vessels >50% – 1.9±0.9 vs. 1.7±0.9, maximum stenosis 84.2±18.8% vs. 82.5±24.9%, left ventricle ejection fraction (LVEF) on ventriculography 61.8±15% vs. 62±15.7%; past percutaneous transluminal angioplasty (PTCA) – 48.4% vs. 32%; past coronary artery bypass grafting (CABG) – 19.4% vs. 12%. Basic pharmacotherapy before inclusion and at the end of the study did not differ between groups: beta-blockers 64.5% and 80.6% vs. 60% and 76%, acetylsalicylic acid 80.6% and 87.1% vs. 84% and 84%, calcium antagonists 29% and 29% vs. 40% and 40%, statins 35.5% and 74.2% vs. 28% and 68%, fibrates 29% and 0% vs. 32% and 8.0%, ACE-inhibitors 35.5% and 48.4% vs. 32% and 44%, nitrates 83% and 87.1% vs. 68% and 72%.

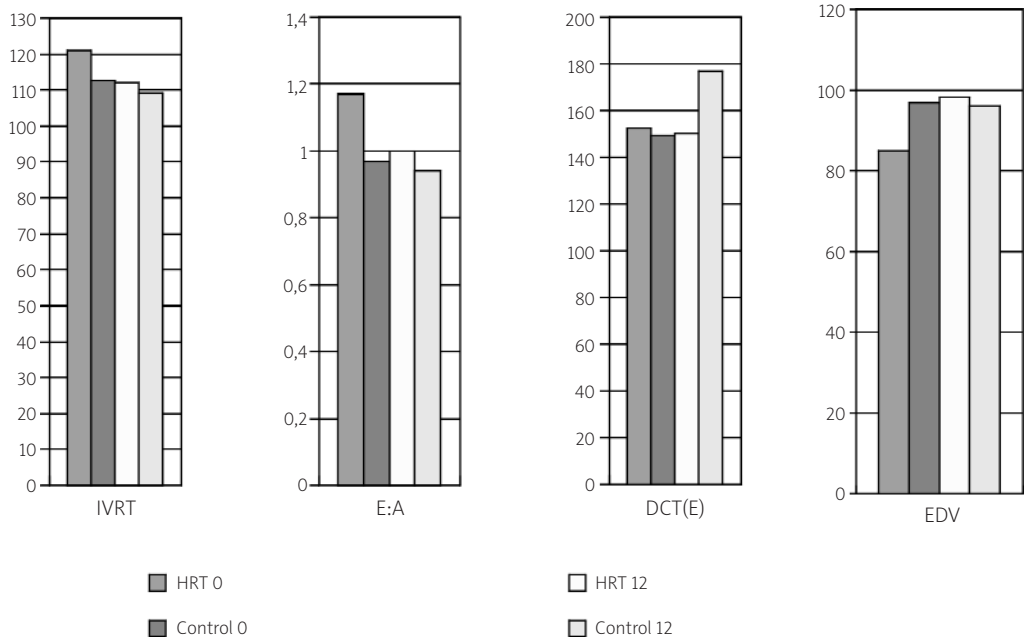
All patients had a standard 2D and Doppler echocardiography study (Hewlett-Packard Sonos 1000; 2.5 MHz electronic probe) at the baseline and after 12 months of follow up. The heart geometry measurements and systolic/diastolic function assessment were conducted in short and long axis left parasternal view, two and four chamber view, according to the American Society of the Echocardiography recommendations [23].

The HRT group received 50 µg transdermal 17-β estradiol twice a week and 5 mg oral medroxyprogesteron acetate every other day. All women stayed under gynaecological care.

Data distribution was estimated by Shapiro-Wilk test, and was normal. Results were presented as mean ± standard deviation (x±SD). *t*-Student' test was used in statistical analysis with its modification for related variables. Qualitative variables were compared with exact Fischer' test. Statistical significance was considered if $p<0,05$. Excel 7.0 and CSS Statistica 5.1 software were used.

Results

The heart geometry: left ventricle end-diastolic dimension (EDD), right ventricle end diastolic dimension (RV), left atrium dimension (LA), interventricular septum thickness (IVSd), posterior wall thickness (PW) and aortic annulus (Ao) was comparable in studied groups, and did not change during follow-up. Left ventricle end-systolic dimension (ESD) did not change during follow-up, but was higher before and at the end of the study in the control group ($p=0.010$ and 0.027) – Figure 1.



IVRT (ms) – isovolumetric relaxation time, E:A – mitral flow E/A ratio, DCT(E) (ms) – E wave deceleration time, EDV (ml) – end-diastolic volume

Figure 3. Diastolic function parameters

Mean values of LVEF (Simpson' formula) did not change during follow-up in either group. At start and after 12 moths LVEF was lower in the control group (p=0.032 and 0.029). Left ventricle end-systolic volume (ESV) and stroke volume (SV) were similar and stable – Figure 2. Left ventricle diastolic function parameters: isovolumetric relaxation time (IVRT), mitral flow E/A ratio, E wave deceleration time (DCT (E)), end-diastolic volume (EDV) did not differ between groups and stayed unchanged after 12 months – Figure 3.

Discussion

Myocardial ischemia causes gradual and abrupt (MI) loss of contractile elements, which are replaced by fibrotic tissue. These changes affect systolic as well as diastolic function of the heart. Echocardiographic assessment of these parameters in CAD patients has become a standard procedure. Revascularisation and pharmacotherapy may essentially improve systolic and diastolic left ventricle function in many patients. Diastolic function may be influenced by such compounds as calcium antagonists and ACE inhibitors. Estrogens are believed to act similarly due to their effects on arterial wall resembling calcium antagonists, but the reports on this topic are often contradictory [18-22].

High LVEF values are remarkable in both groups (38,7% HRT patients and 16% of control group had no MI; in most cases there were nonQ wave MIs: 63.2% and 66.7% respectively). ESD was higher, LVEF (echocardiography) was lower before and at the end of the study in the control group. LVEF measured on ventriculography was however comparable in both groups. This discrepancy is a result of various rates of anterior/inferior MIs in groups, which influences measurement. In echocardiography LVEF is estimated out of septum, apex and lateral wall contractility, while in ventriculography apex, anterior and inferior wall are taken into account.

In studied populations transdermal, combined HRT had no effect on systolic nor diastolic function. Lack of expected effects may be results of: a) real lack of such an action, b) too low estrogen dose, c) use of the synthetic gestagen. Observed *in vitro* effects are not always reproducible *in vivo*. Large evidence of favourable estrogens effects speaks against such a conclusion. Dosage (days per week, day time), route of administration (oral, transdermal, subcutaneous, local – intrauterine device) and therapy initiation time since menopause seem to be crucial. On the other hand proven acute effects after drug administration may disappear during long-term treatment. Higher doses of estrogens are more effective in cholesterol lowering, but are more likely to induce severe side effects (thromboembolic events, breast cancer, liver and gall bladder dysfunction), which essentially limits use of this therapy. Conducting HRT, gestagen use is obligatory in women with preserved uterus to avoid endometrial hypertrophy and cancer. However, there are some publications that indicate that gestagens, especially synthetic ones, attenuate or even abolish many favourable effects of estrogens [24-27]. Currently, after publications of a few big multi-centre

trials, recent HRT schemes are contraindicated in patients with CAD [2-4, 8]. Potential benefit of modulating endocrine system in women in order to prevent atherosclerosis needs further investigations.

Conclusions

Short term, combined, transdermal HRT has no significant effect on the left ventricle systolic and diastolic function assessed by echocardiography in postmenopausal women with CAD.

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