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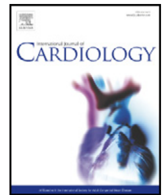

The cardiovascular effects of premature ovarian failure☆

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ABSTRACT

Background: Previous studies have shown that cardiovascular risk is increased in premature ovarian failure (POF). To determine the effects of POF on different parameters of cardiovascular health, we investigated the relationship between POF and circulating endothelial progenitor cells (EPC), endothelial function, carotid intima media thickness (CIMT) and left ventricular diastolic function.
Methods: We compared 23 female POF patients (mean age; 37.8 ± 10.8 years) with 20 gender and age-matched healthy controls. Circulating CD133(+)/34(+) and CD34(+)/KDR(+) EPCs were determined by using flow-cytometry. Ultrasound assessment of endothelial function by brachial artery flow-mediated dilatation (FMD) and CIMT was made. Left ventricular systolic and diastolic function was assessed by standard 2D and M-mode echocardiography and tissue Doppler velocities.
Results: Brachial artery FMD was significantly impaired in patients with POF compared with CG (6.3 ± 1.9% vs 10.4 ± 3.7%, $p<0.05$). Furthermore, circulating EPCs were lower among patients with POF compared to controls for CD133(+)/34(+) and CD34(+)/KDR(+) cells ($p<0.05$). There was a significant correlation between serum estradiol levels and EPC number (CD 133+/34+) ($r=0.329$, $p<0.05$). POF patients had increased CIMT compared to controls (0.67 ± 0.17 vs 0.43 ± 0.10, $p<0.05$). When diastolic functions were assessed, patients with POF had lower E_{peak}, A_{peak} and mitral CP and higher DT and IVRT ($p<0.05$, respectively).
Conclusion: Our findings indicate that endothelial function as well as circulating EPCs, CIMT and diastolic function are significantly affected in young women with POF which may have an adverse long-term effect on cardiovascular prognosis.

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1. Introduction

Premature ovarian failure (POF) is a disease characterized by amenorrhea and infertility before the age of 40 years due to premature depletion of ovarian follicles causing deficiency of sex steroids [1,2]. Approximately 1% of the women develop POF spontaneously by the age of 40 years [3]. POF may have important clinical implications since the early loss of sex steroids has been associated with cardiovascular (CV) diseases such as myocardial infarction (MI) and stroke [4,5].

Different imaging modalities have been used to assess CV health and are accepted as surrogate markers of CV risk [6]. Flow mediated vasodilatation (FMD) of the brachial artery is the most common method in the assessment of endothelial function and measures the changes in arterial diameter in response to increased blood flow by stimulating endothelial nitric oxide production [7]. It has been shown previously that endothelial function assessed by FMD is impaired in patients with POF [8]. Circulating endothelial progenitor cells (EPC) have recently been recommended as a novel biomarker of endothelial function showing a close relationship with FMD [9,10]. Circulating endothelial progenitor cells (EPC) originate from the bone marrow and play an important role in vascular homeostasis for both repair and regeneration of damaged endothelium [11]. Circulating EPCs may have an important contribution to estrogen-induced cardiac protection but they have not been studied in POF previously [12,13]. Also decreased EPCs may lead to accelerated vascular remodeling like increased CIMT due to chronic impairment of endothelial maintenance [14,15]. Polycystic ovary syndrome patients who have chronic anovulation and hyperandrogenism have been shown to have decreased EPC counts and increased CIMT [16,17].

In this study, we hypothesized that depletion of sex steroids may alter circulating EPCs thus impair endothelial function, CIMT and diastolic function. To this date, the effect of POF on circulating EPCs has not been evaluated.

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For this purpose, we compared the different indices of vascular health between patients with POF and regularly cycling healthy women.

2. Methods

2.1. Study population

Between October 2010 and February 2011 all eligible subjects with clinical and biochemical evidence of POF referred from Obstetrics and Gynecology Clinic were enrolled in the study. Patients were excluded from the study if they had acute or chronic infection, thyroid disorders or cardiovascular diseases including hypertension, ischemic heart disease, congestive heart failure, peripheral artery disease, valvular heart disease, cardiomyopathy and cardiac arrhythmia. Patients taking cardiovascular medication or drugs affecting FMD (e.g. hormone replacement) were also excluded. The control group consisted of 23 healthy voluntary subjects. Premature ovarian failure was diagnosed according to i) diagnosis of POF before 40 years, ii) history of amenorrhea for at least 4 months, and iii) two independent serum FSH levels above 40 mIU/ml. All patients underwent detailed gynecologic examination and karyotype analysis that patients without endometrial pathology or other than normal karyotype were excluded.

In all subjects, a detailed cardiovascular and systemic examination was performed at the beginning of the study including demographic data and anthropometric measures including weight, height, and BMI. Blood samples were obtained after an overnight fasting and the serum levels of triglyceride (TG), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and fasting glucose were determined using commercially available assay kits (Hitachi P800, Holliston, Massachusetts, USA) at the time of cardiovascular evaluation. Also serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and progesterone levels were measured in all patients.

Informed consent was taken from each patient and the study was approved by the local ethics committee.

2.2. Blood sampling, immunofluorescence staining and flow cytometry

Peripheral blood samples were taken after a 12-h overnight fasting. A 20-ml sample of arterial blood was taken from the antecubital vein to the citrate containing glass tubes for the isolation of endothelial progenitor cells and kept at room temperature for less than 2 h until analysis. Peripheral blood mononuclear cells were isolated from these samples by Ficoll Histopaque density centrifugation (Histopaque-1077, Sigma-Aldrich, St. Louis, MO, USA). Following washing with phosphate buffered saline twice, viability of the recovered cells was determined by Trypan Blue staining (Merck, Germany).

Cell suspension was initially incubated with Fc-gamma receptor blocking rabbit IgG antibodies followed by incubation with fluorescein isothiocyanate conjugated CD34 antibody (eBioscience, San Diego, CA, USA) and PerCp conjugated antibodies against human KDR (BioLegend, San Diego, CA, USA). Control stainings were performed with isotype matched and species specific antibodies. Incubation was followed by washing and fixation in 1% paraformaldehyde after exclusion of debris and platelets.

FACS Calibur flow cytometry device (Becton Dickinson, NJ, USA) containing an argon ion laser was used for flow cytometric analysis. Two color fluorescence, SSC and FSC diagrams were used to count 100,000 cells per sample. CD133, CD34 and KDR positivity was analyzed in the defined cell population. Data derived were analyzed in CellQuest software in Macintosh G3. SSC/FSC mapping methods were used for analysis as described before [18].

2.3. Brachial artery FMD

Brachial artery diameter measurements were performed by an investigator who was blinded to the experimental conditions. Measurement of FMD using brachial artery reactivity was performed by two-dimensional gray-scale and color-flow Doppler and vascular imaging using an echocardiography (Vivid 5, GE Vingmed, Horten, Norway) machine with a 10-MHz vascular ultrasound probe as described before [19]. On the day of the study, participants fasted 6 h and all medications were withheld. After resting in the supine position for 10 min in a quiet air-conditioned room, the non-fistulated arm brachial artery was prepared for measurements. The brachial artery was scanned longitudinally at 2–5 cm above the antecubital crease. This location was marked on the skin and all subsequent measurements were performed at the same location. To calculate FMD, percent diameter changes were determined as follows: (diameter after reactive hyperemia − baseline diameter)/baseline diameter × 100. To avoid confounding effects of arterial compliance and its cyclic changes in dimension, all measurements were obtained at the peak of the R-wave of the electrocardiogram [20]. The mean diameter of the brachial artery was determined at baseline and then continuously for up to 5 min after reactive hyperemia.

2.4. Assessment of CIMT

CIMT was measured by a single experienced specialist blinded to the clinical data of the patients. Intima-media thickness is defined as the distance between the media–adventitia interface and the lumen–intima interface and measured using a duplex ultrasound system with a 10 MHz scanning frequency in the B-mode, pulsed Doppler mode, and color mode using Vivid 5 (GE Vingmed, Horten, Norway). Carotid IMT was measured at the far wall of the right and left common carotid arteries 10 to 20 mm proximal to the carotid bulb. The mean CIMT was calculated from five measurements on each artery.

2.5. Echocardiography

Standard echocardiographic imaging was performed in the left lateral decubitus position in the parasternal and apical views. Two-dimensional, M-mode, pulsed and color flow Doppler echocardiographic examinations of all subjects were performed by the same examiner with a commercially available machine (Vivid 5, GE Vingmed, Horten, Norway, 2–4 mHz phased array transducer) who was blinded to the clinical details of the subjects in the study and control group. During echocardiography, a one-lead electrocardiogram was recorded continuously. Left ventricle end-diastolic (LVEDD), left ventricle end-systolic (LVESD), right ventricular end diastolic (RV) and left atrial end-systolic (LA) diameters were measured from M-mode in the parasternal long-axis views according to the standards of the American Society of Echocardiography [21]. Left ventricular ejection fraction (LVEF), and fractional shortening (FS) were calculated using M-mode echocardiography. In case of reduced endocardial definition, LVEF was estimated visually by the examiner. Three consecutive cycles were averaged for every parameter.

Mitral inflow indices were obtained by pulsed-wave (PW) Doppler from the apical 4-chamber view to assess LV filling according to the recommendations of the American Society of Echocardiography [22]. Those measurements of mitral inflow included the peak early filling (E_{peak}) and late diastolic filling (A_{peak}) velocities, the E/A ratio, deceleration time (DT) of early filling velocity, and the isovolumic relaxation time (IVRT) measured by placing the cursor of CW Doppler in the LV outflow tract to simultaneously illustrate the end of aortic ejection and the onset of mitral inflow. Mitral flow color propagation velocity (CP) was measured as the slope of the first aliasing velocity during early filling, measured from the mitral valve plane to 4 cm distally into the LV cavity.

Doppler tissue imaging echocardiography was performed by transducer frequencies of 3.5–4.0 MHz, adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15–20 cm/s was reached, and using the minimal optimal gain. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. The pulsed-wave TDI was performed in the apical views by placing a 3 mm sample volume at the level of left ventricular lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus. The sampling window was positioned as parallel as possible with the myocardial segment of interest to ensure the optimal angle of imaging. Peak systolic (S′), early (E′) and late diastolic myocardial velocities (A′) were recorded. Several cardiac cycles were evaluated and the best three consecutive cycles were analyzed and averaged.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.6. Statistical analysis

Continuous variables were expressed as mean ± SD and categorical variables were expressed as percentages. Categorical variables were analyzed by chi-square test. Comparisons of continuous variables between the two groups were performed using the independent samples t-test. Mann–Whitney test was used to compare the mean values of the EPC counts in patients with and without POF. To test the reproducibility, $CD133^+/34^+$ and $CD34^+/KDR^+$ cell counts were determined in 20 subjects under similar conditions on the same day, which revealed a close correlation ($r = 0.90$ and $r = 0.84$ respectively, $p < 0.05$). Coefficient of variation (CV%) has been estimated according to the Poisson distribution and calculated on the basis of 20 analyses performed in duplicate. Cumulative intra-assay CV% was 6%. The total sample of 43 subjects achieves 92% power to detect differences among the means versus the alternative of equal means using a χ^2 test with a 0.05 significance level. Intra-observer agreement for brachial artery FMD and CIMT measurements were very large; simple agreement was 94% and Kappa (K) 1/4 0.84–0.98 ($p < 0.001$) for FMD and 95% and K 1/4 0.89–0.97 ($p < 0.001$). Statistical analyses were performed using SPSS statistical software (version 15.0; SPSS Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant.

3. Results

In this study we enrolled a consecutive subset of 20 female patients consecutively diagnosed as POF (mean age; 37.8 ± 10.8 years) and 23 gender, body mass index (BMI) and age-matched control healthy female subjects (mean age; 35.4 ± 8.6 years). There were no differences in risk factors including systolic–diastolic blood pressure, fasting plasma glucose and serum lipid profile. Serum estradiol levels were lower and FSH and LH levels were higher in POF patients. Baseline demographic, clinical and endocrinologic characteristics of the studied samples are summarized in Table 1.

3.1. Circulating EPCs

Circulating EPCs were higher in control subjects compared to patients with POF for CD133 +/34 + (cell percent, 0.95 ± 1.19 vs 0.74 ±

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