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Coronary microvascular dysfunction is not associated with a history of reproductive risk factors in women with angina pectoris—An iPOWER substudy

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ABSTRACT

Background: Reproductive risk factors such as preeclampsia and recurrent miscarriages have been associated with adverse cardiovascular (CV) events. Underlying coronary microvascular dysfunction (CMD) may be a common denominator.

Purpose: We investigated whether a history of reproductive risk factors was associated with CMD in women with angina pectoris and no obstructive coronary artery disease (CAD).

Methods: Participants from the iPOWER study, including women with angina pectoris and no obstructive CAD (< 50% stenosis), were invited to complete an electronic survey regarding reproductive risk factors: recurrent miscarriages, gestational diabetes, preeclampsia, rhesus immunity, polycystic ovary syndrome and menopausal status as well as migraine and Raynaud phenomenon. CMD was assessed by transthoracic Doppler echocardiography with measurement of coronary flow velocity reserve (CFVR) during high-dose dipyridamole infusion, and analyzed in three categories with cut-off points at 2.0 and 2.5. Associations between CFVR and a history of reproductive risk factors were examined by age-adjusted trend test.

Results: The questionnaire was completed by 613 women (73% of those invited), of whom 550 had a successful CFVR measurement. There was no significant difference in baseline characteristics between participants and non-participants. Median (interquartile range (IQR)) age was 62.8 (54.8; 68.7) years, median (IQR) BMI 26.2 (23.2; 29.8) kg/m^2, and 81.5% were postmenopausal. We did not find any significant associations between any of the reproductive risk factors, Raynaud's phenomenon or migraine and CFVR.

Conclusion: The lack of association between coronary microvascular function and a history of reproductive risk factors, migraine and Raynaud's phenomenon suggests that a common vascular pathophysiological mechanism underlying these conditions is unlikely.

1. Introduction

In the past decades understanding of sex-related differences in the presentation of cardiovascular disease (CVD) has improved. Conditions leading to alterations in estrogen level such as menopause and polycystic ovary syndrome are associated with increased risk of CVD [1]. Studies have found that a history of recurrent miscarriages [2], gestational diabetes mellitus (GDM) [3] and pregnancy-induced hypertension [4] were associated with an increased risk of CVD. Some conditions such as Raynaud's phenomenon and migraine are found to have a female preponderance and further, migraine has been linked to increased cardiovascular risk among women [5,6]. A possible explanation for the increased occurrence of CVD in relation to the above mentioned conditions could be presence of coronary microvascular dysfunction (CMD). There is evidence of subclinical inflammation and early vascular dysfunction after delivery in women with a history of

Abbreviations: CVD, cardiovascular disease; CMD, coronary microvascular dysfunction; CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; FMD, clow mediated dilation; GDM, gestational diabetes mellitus; iPOWER, ImProve diagnOsis and treatment of Women with angina pEctoris and micRovessel disease; TTDE, Transthoracic Doppler echocardiography

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GDM and similarly, a maternal reaction in preeclampsia involves endothelial cell dysfunction caused by a stimulated inflammatory response [7–9]. CMD reflects a reduced ability of the coronary microvasculature to increase blood supply when oxygen demand is increasing and it can be assessed non-invasively by transthoracic Doppler echocardiography (TTDE) measuring coronary flow velocity reserve (CFVR) [10]. CFVR is a surrogate measure of coronary microvascular function in the absence of a coronary artery stenosis. CFVR is calculated as the ratio between coronary flow velocity (CFV) at maximal hyperemia and rest. CMD is closely linked to age, diabetes, hypertension and the metabolic syndrome [11]. Studies indicate that between 22% and 40% of patients with angina pectoris and no obstructive CAD have CMD and it has been demonstrated that a reduced CFVR is a strong marker of poor cardiovascular prognosis [12–16]. Prognostic studies have found cut-off values of CFVR of 2 and 2.5 to predict recurrent hospitalizations and death of cardiovascular causes [17,18].

We hypothesized that CMD assessed as impaired CFVR may constitute the link between reproductive risk factors and an increased risk of CVD, subsequently leading to increased morbidity and mortality in women with angina pectoris and no obstructive CAD.

2. Methods

2.1. Study population

Participants were included from the iPOWER (Improving diagnosis and treatment of women with angina pectoris and microvascular disease) cohort, comprised of Danish women aged 18–80 with angina pectoris and no obstructive CAD on invasive coronary angiography (< 50% epicardial stenosis). The iPOWER study is an ongoing study initiated in 2012, aiming at enrolling 2000 women. The present study is based on the first 1260 participants included between May 2012 and December 2015 [19].

2.2. Basic assessment

Basic assessments were done as part of the iPOWER main-study. Assessments were conducted by trained professionals through personal interviews and questionnaires. Demographic and clinical data, including cardiovascular risk factors (age, body mass index, smoking status, hyperlipidemia, diabetes and hypertension), pre- peri- or menopausal status, cause of menopause (natural, hysterectomy, oophorectomy, oophoro-hysterectomy or other reason) and number of years since the last menstrual period was collected. A dichotomized variable was created from menopausal status combining pre- and perimenopausal participants vs. postmenopausal participants. Participants who reported to be perimenopausal at study inclusion, but > 58 years of age (n = 13) were excluded. Similarly, participants who were premenopausal but > 55 years of age (n = 2) and those who were postmenopausal of natural causes < 36 years (n = 4) were excluded, due to a risk of typing errors. For postmenopausal women, “age at menopause” was calculated subtracting number of years since the last menstruation from the date the participant was included in the study. Participants who were hysterectomized (not oopherectomized) were excluded because of uncertainty about the exact age at menopause (n = 63).

2.3. Coronary flow velocity reserve

Echocardiographic examinations of CFVR were done as part of the iPOWER main-study. CFV was measured by TTDE of the left anterior descending (LAD) artery during rest and high dose dipyridamole stress (0.84 mg/kg over 6 min) as previously described [20]. CFV was measured by pulsed-wave Doppler as a laminar flow signal directed toward the transducer. Probe position was adjusted to align the ultrasound beam direction as parallel to LAD flow as possible. Images of CFV were acquired at rest (minimum three images of three cardiac cycles for all patients) and throughout the dipyridamole infusion and up to 3 min after infusion had terminated until flow had reached peak velocity. The echocardiographic examinations were performed with a Vivid E9 cardiovascular ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway) with a 2.7–8-MHz transducer (GE Vivid 6S probe). If visualization of the LAD was challenging, and the echocardiographer judged that contrast enhancement could improve visualization, contrast (SonoVue; Bracco Imaging, Milan, Italy) was given intravenously in refract doses of 1 mL during the examination. After the examination, intravenous theophylline (maximum dose, 220 mg) was administered to relieve side effects of dipyridamole. Before examination, patients were instructed to abstain from caffeine and food containing significant amount of methylxanthine (coffee, tea, chocolate, cola, and bananas) for 24 h. Medications containing dipyridamole were paused for 48 h, long-lasting nitroglycerin, anti-ischemic agents, and antihypertensive medication for 24 h, and short-lasting nitroglycerin 1 h before the examination. All CFVR measurements were evaluated for quality and only measurements of good quality were included in the analysis [20]. Previous studies have shown a good intra-operator CFVR repeatability and excellent inter-analyzer reproducibility [19,21].

2.4. Questionnaire

Participants were invited to complete an electronic questionnaire (SurveyXact) to obtain information on potential cardiovascular risk factors specific to women. The questionnaire included questions on previous pregnancies, number of deliveries and miscarriages before and after week 12 and whether the participant had experienced difficulties conceiving. Furthermore, information regarding complications during pregnancy was obtained (preeclampsia, GDM or rhesus incompatibility). Patients who did not know their rhesus blood type were grouped with patients who answered “no” to the question pertaining to rhesus incompatibility in the study questionnaire. A positive response was followed by specific questions validating the response. Information on polycystic ovary syndrome (PCOS) was acquired by questions regarding irregular menstruation, and a positive response was followed by a question confirming that a diagnosis of PCOS was given. Participants were questioned about symptoms of Raynaud’s phenomenon (episodic pallor and cyanosis of fingers in response to cold stimuli) and migraine, and if they responded positively they were asked if they were diagnosed with either condition. Further, they were asked about prescriptions of migraine medication and frequency of migraine attacks. Missing information (< 0.2%) was not included in the analysis. For a complete list of all exact questions included in the questionnaire, please see Appendix 1 in Supplementary material.

2.5. Statistical analysis

Continuous variables with normal distributions are expressed as mean ± standard deviation (SD). Variables with skewed distributions are expressed as median and interquartile range (IQR). For categorical variables count in percent is used. Distribution normality was assessed graphically. The participants were grouped in three according to CFVR-values with cut-off points of 2 and 2.5 according to cut offs used by prognostic studies [17,18]. Continuous variables with a normal distribution were compared using ANOVA. Categorical variables were compared using Pearson's chi-squared or Fisher's exact test. Patient characteristics were compared across CFVR group by trend test (age adjusted logistic regression for binary outcomes or linear regression analysis for continuous outcomes). For pregnancy dependent variables only women with a history of pregnancy were included.

To explore whether each variable was a predictor of reduced CFVR, age adjusted multiple regression analyses was performed with natural logarithmically transformed CFVR as a continuous outcome variable. Explanatory variables with a significance level < 0.2 in univariate analysis were included and discarded at a cut-off level of $p \geq 0.10$.