Peripheral arterial disease, gender, and depression in the Heart and Soul Study

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Background: **Despite the high prevalence of peripheral arterial disease (PAD) in women, risk factors for PAD in women are not well understood.**
Methods: **Gender-specific risk factors for PAD were examined in a prospective cohort study of 1024 patients (184 women and 840 men) with stable coronary artery disease who were recruited between 2000 and 2002. Logistic regression models were used to evaluate associations between traditional and nontraditional risk factors and PAD in men and women.**
Results: **PAD was found in 11% of women and in 13% of men. Women with PAD had a similar prevalence of traditional risk factors (hypertension, hyperlipidemia, and smoking) compared with women without PAD and were significantly more likely to suffer from depression than women without PAD. Men with PAD were more likely to have hypertension, diabetes mellitus, a history of smoking, a worse lipid profile, and higher levels of inflammatory biomarkers than men without PAD. A multivariate model showed depression was the strongest independent factor associated with PAD in women, whereas smoking and elevated fibrinogen were independently associated with PAD in men.**
Conclusions: **The current findings suggest there are gender differences in risk factors for the development of PAD. Further research is needed to understand the role of depression in PAD. (J Vasc Surg 2014;60:396-403.)**

Peripheral arterial disease (PAD) is a significant cause of morbidity and mortality and has recently been recognized as a global pandemic.[1] PAD is under-recognized and under-treated in women, even though there appears to be an increasing population burden of PAD in women.[2,3] In fact, in the 2010 United States Census, the prevalence of PAD was higher in women than in men.[4] Despite the high prevalence of PAD in women, women are under-represented in contemporary PAD studies,[5,6] and risk factors for PAD in women have not been extensively studied. In view of this, the American Heart Association issued a scientific statement calling for further research to study PAD in women.[4]

Traditional cardiovascular disease (CVD) risk factors are more prevalent in men with PAD than in women with PAD,[7,8] suggesting that other risk factors might be involved in the pathophysiology of PAD in women. That women are at increased risk for depression[9-11] compared with men is well known, and we recently demonstrated that depression was a strong and independent risk factor for PAD.[12] Others have shown that among patients with PAD, those with depression have worse functional outcomes, greater need for revascularization, and have poorer quality of life outcomes and a higher risk for adverse events after revascularization.[13-16] Research has also indicated that women with PAD aged <65 years are particularly vulnerable to experiencing depressive symptoms and that these symptoms seem to be accompanied with high rates of smoking.[17]

The associations between depression and psychosocial factors with PAD have not been extensively investigated.

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A better understanding of patients' psychosocial profiles might identify risk factors that can be addressed to mitigate patients' depressive symptoms and their cardiovascular risk. The Heart and Soul Study was designed to study the association between psychologic disorders and cardiovascular events, including PAD, in outpatients with stable coronary artery disease (CAD). In this study, we investigated the gender-specific prevalence of traditional CVD, psychologic, and social risk factors for PAD. We hypothesized that women with PAD would have a different risk factor profile, including psychosocial factors, compared with men with PAD.

METHODS

Study population. The Heart and Soul Study was designed to study the association between psychologic disorders and cardiovascular events in outpatients with stable CAD. Detailed methods have been previously described.[18] Briefly, the investigators performed a prospective cohort study of 1024 subjects with known coronary heart disease (CHD) who were recruited between 2000 and 2002 and followed up for 10 years.

At the baseline examination, participants completed a structured diagnostic interview for depression, an extensive questionnaire, electrocardiogram, 6-minute walk test, and full exercise treadmill testing with stress echocardiography. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Participants also completed 24-hour ambulatory Holter monitoring to determine heart rate variability and collected 24-hour urine for measurement of creatinine, free cortisol, and catecholamines. Fasting blood was drawn, and samples of serum, plasma, DNA, and 24-hour urine were stored in a specimen biorepository at −80°C.

After 5 years of follow-up, 667 participants (>80% of survivors) completed a repeat examination that included a structured diagnostic interview for depression, questionnaire, electrocardiogram, exercise treadmill test, fasting blood draw, and 24-hour urine collection. Participants were also contacted annually to inquire about cardiovascular events, which were confirmed by review of medical records. Follow-up information was available for >99% of the study participants.

With regards to inclusion criteria, the investigators used administrative databases to identify outpatients with documented CAD at two Department of Veterans Affairs Medical Centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System), one university medical center (University of California, San Francisco), and nine public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had known CHD documented by at least one of the following: a history of myocardial infarction (MI), angiographic evidence of at least 50% stenosis in one or more coronary vessels, prior evidence of inducible ischemia by treadmill or nuclear testing, or a history of coronary revascularization.

Related to exclusion criteria, 15,438 patients with CHD were identified from administrative databases and mailed an invitation to participate. Of the 2495 patients who returned a form indicating that they would be interested in participating, 505 could not be reached by telephone, and 370 were excluded because they had a history of MI in the prior 6 months (treadmill test contraindicated), deemed themselves unable to walk 1 block (treadmill test not useful), or were planning to move out of the local area within 2 years (unavailable for follow-up). Of the 1620 patients who were confirmed eligible, 596 declined to participate, and 1024 (63%) enrolled.

Between September 11, 2000, and December 20, 2002, 1024 participants were enrolled and were followed up for a mean 7.2 ± 2.6 (standard deviation) years. Of those, 134 were found to have PAD (21 women and 113 men), defined by self-report of this diagnosis on entering the study in 84 (men, 8%; women, 9%); by diagnosis by a physician during hospitalization in 56 (men, 6%; women, 4%); by ultrasound imaging or angiographically demonstrated obstruction or ulcerated plaque (>50% of diameter or >75% of x-sectional area) of the iliac arteries or below in 40 (men, 4%; women, 3%); by surgery, angioplasty, or thrombolysis for PAD in 40 (men, 4%; women, 2%); or by exertional leg pain relieved by rest in 23 (men, 2%; women, 2%).

Study measurements. All participants completed a baseline examination that included an interview, fasting venous blood sample collection, a standardized medical history questionnaire, echocardiography, exercise treadmill testing, 24-hour ambulatory Holter monitoring, and a 24-hour urine collection. Age, sex, race, education level, and medical history were determined by self-report questionnaire. Height and weight were measured by a standardized protocol, with body mass index calculated as weight (kg)/height (m^2). Participants were instructed to bring their medication bottles to their enrollment visit, and study personnel recorded all current medications. Medications were categorized using Epocrates Rx (Epocrates Inc, San Mateo, Calif). None of the data presented >5% missing variables. Questionnaires were reported as missing if ≥30% of the individual items were missing. Otherwise, the total score was divided by the proportion answered to account for missing data. The appropriate Institutional Review Boards approved the protocol, and all participants provided written informed consent for participation in the study.

Blood samples. Fasting blood samples were obtained during the morning of the enrollment visit. Levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were determined from plasma and serum samples. These biomarkers were chosen because of their association with disease severity in PAD.[19-22] Levels of hsCRP were measured using the Integra assay (Roche, Indianapolis, Ind) or (owing to a change at the laboratory) the Extended Range assay (Beckman Coulter Ireland Inc, Galway, Ireland). Prior testing demonstrated high correlation of these two methods.[23] We used the Quantikine