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Gender differences in the severity and extent of coronary artery disease

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ABSTRACT

Objective: To investigate whether women presenting with suspected angina would show less severe coronary artery disease in than men as determined by the extent score.
Methods: We examined 994 participants of the Australian Heart Eye Study presenting for coronary angiography in the investigation of chest pain from June 2009 to February 2012. People were excluded if there was a history of coronary artery bypass surgery, previous stenting procedure or incomplete angiogram scoring. An extent and vessel score was calculated using invasive coronary angiography. Normal coronary arteries were defined as having no luminal irregularity (Extent score = 0). Obstructive coronary artery disease was defined as a luminal narrowing of greater than 50%.
Results: Women compared to men without infarction had a lower burden of CAD with up to 50% having normal coronary arteries in the 30–44 year group and 40% in the 45–59 year group. Compared to men, women with chest pain had lower mean extent scores (19.6 vs 36.8; $P < 0.0001$) and lower vessel scores (0.7 v 1.3; $P < 0.0001$). Although the mean extent score was lower in women than men with myocardial infarction, this was not statistically significant (34.8 vs 41.6 respectively; $P = 0.18$).
Conclusion: There is a marked difference in coronary artery disease severity and burden between females and males presenting for the investigation of suspected angina. Women are more likely to have normal coronary arteries or less severe disease than age-matched men, particularly if they do not present with myocardial infarction.

1. Introduction

Cardiovascular disease, in particular coronary disease, is the leading cause of mortality in women. In fact, women are more likely to die following a myocardial infarct than men [1]. Despite this, the pattern of coronary artery disease (CAD) is substantially different between men and women [2]. Up to 60% of women and 30% of men who present with angina have either normal arteries or non-obstructive lesions [3–5]. Women present with less obstructive epicardial stenoses and more diffuse atherosclerosis and microvascular dysfunction [6]. Women can display evidence of ischemia on functional assessment (such as pressure wire studies, myocardial perfusion imaging and magnetic resonance imaging) without obstructive epicardial coronary disease. This may be unrelated to the presence of Framingham risk factors [7–9]. Women also demonstrate a higher prevalence of atherosclerosis with positive remodeling and preserved lumen size as demonstrated by intravascular ultrasound [9,10].

The Australian Heart Eye Study (AHES) was a large cross-sectional study of patients presenting for coronary angiography in the investigation of chest pain at Westmead Hospital, Sydney, Australia. It was developed to study the relationship between gender and both retinal vascular disease and CAD. We investigated the anatomical relationship between angiographically proven CAD and gender in this population using the extent score. The extent score reflects the proportion of the coronary tree with angiographically detectable atherosclerotic disease, scaled according to the functional significance of the involved artery [11]. There are no studies to our knowledge that use the extent score to describe the anatomical burden of CAD in men compared to women. We hypothesized that women with chest pain would show less severe CAD in all age groups than men.

2. Methods

2.1. Study population

The Australian Heart Eye Study (AHES) recruited patients presenting to Westmead Hospital for the assessment of suspected CAD between

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June 2009 and January 2012. Patients were both internally and externally referred for investigation and the decision to pursue angiography was made by the referrer who was unaware of any subsequent participation in the study. Participants were consented to the study prior to or following invasive coronary angiography, and included 1680 patients, who were interviewed to obtain data on demographic characteristics, medical history and behavioral habits. The presence of risk factors was determined either by physician diagnosis or treatment for the medical condition. Medical records were reviewed to obtain medication use and confirm medical history. Of the 1680 examined in this study, a total of 398 participants were excluded because they had a previous history of coronary artery bypass grafting ($n = 191$) and/or previous coronary artery stent ($n = 298$). If there was incomplete background information or if an extent score was not able to measured due to suboptimal angiogram quality, these participants were also excluded. A total of 994 participated (712 men and 282 women). Of those presenting with chest pain, 221 (187 men and 34 women) were diagnosed with myocardial infarction. This was based on symptoms of ischemia, characteristic electrocardiographic findings, elevation in cardiac troponin enzyme.

The study protocol conforms to the ethical guidelines of the 1975 declaration of Helsinki and ethical approval was obtained from the Western Sydney Local Health Network Human Research Ethics Committee (Westmead).

2.2. Coronary angiography image acquisition and analysis

Diagnostic coronary angiography was performed via a femoral or radial approach using a catheter of known dimension. The technique employed was determined by vascular accessibility of the patient and operator preference. Selective coronary injections were filmed in standard projections with a Siemens Bi-Plane radiographic unit (Siemens Healthcare, Germany). All angiograms were filmed at 15 frames/s and cine runs were stored at the time of acquisition in DICOM format.

All angiograms were masked to patient name and diagnosis. Analysis was performed offline by a cardiologist (author J.C.) blinded to the results of the adjunctive investigations. Two orthogonal views were examined in end-diastole to maximize contrast enhancement and vessel diameter. The image with the most severe stenosis was used for each evaluated segment of the coronary artery tree. For each segment, the severity of obstruction was documented using several grades: normal, 1–25%, 25–50%, 50–74%, 75–99% and 100% (occluded). Each lesion that was visually scored as greater than 50% luminal obstruction in a vessel that was ≥1.5 mm diameter, was further analyzed using validated computerized edge-detection software (QCAPLUS, Sanders data Systems, Palo Alto, California, USA) to allow more accurate assessment and classification of lesion severity. Catheters of known diameter were used for calibration. Coronary angiograms were scored according to two methods. The analyzing cardiologist was masked to patient medical history and investigation results.

1) Vessel score: A vessel score was calculated based on the number of vessels with significant obstructive coronary disease. The 2011 American College of Cardiology (ACC) taskforce definition uses 50% stenosis to define significant vessel disease [12]. This definition was used for the left main coronary artery, right coronary, left anterior descending and left circumflex arteries. Scores ranged from 0 to 4, depending on a finding of vessels with greater than 50% stenosis [13]. Left main artery stenosis was scored as double vessel disease.
2) Extent score: This score, proposed by Sullivan et al. defines the proportion of the coronary artery tree involved by angiographically detectable coronary atheroma [11]. The proportion of each vessel involved by atheroma, identified by lumen irregularity, was multiplied by a factor for each vessel, related to the length of that vessel. The scores for each vessel were added to give a total score out of 100. This percentage represents the proportion of the coronary intimal surface area containing coronary atheroma [11].

To assess the inter-observer and intra-observer variation in the coronary angiography analysis, 40 random cases were selected. None of the observers participated in the selection of the angiograms and were masked to patient name and diagnosis. We used the Bland Altman method to evaluate reproducibility and inter-observer reliability of the extent score [14]. The bias was 0.15 (limit of agreement −1.77 to 2.06) for intra-observer reproducibility. For inter-observer difference the bias was 0.076 (limit of agreement −1.74 to 1.25).

2.3. Statistical analysis

Continuous variables are presented as means (SD or SE) and categorical variables are presented as proportions (%). SAS statistical software (SAS Institute, Cary NC) version 9.2 was used for analyses. The Bland Altman method was performed to evaluate the inter- and intra-variability of the Extent score grading. Analyses performed included t-tests, chi-squared (χ^2)-tests and generalized linear models, binary and generalized logistic regression models. Pearson's correlation coefficients were used to correlate the discontinuous and non-normally distributed data. We performed a Kolmogorov–Smirnov test for extent scores that showed a significant difference between gender ($P < 0.0001$) with women having lower scores than men. We chose to stratify all analyses by sex and age for this study. Both continuous and categorical data were used to present the extent score. Multivariable logistic regression models (binary and generalized) were used to assess the association between gender, age and extent scores. Extent scores were expressed as ordinal categories ranging from 0 (no disease) to 1, 2, and 3 (corresponding to the first, second and third tertiles among those who had disease). The tertile ranges for extent score were 0.3 to 10.7, 11.1 to 33.6 and 33.7 to 100 for the female population and 0.7 to 25.5, 25.7 to 59.6 and 59.6 to 100 in the males. Independent t-tests were used to compare the extent and vessel scores between infarct and non-infarct groups and in our models, data were adjusted for the potential influence of significant covariates: age, mean arterial blood pressure, body mass index, dyslipidemia, smoking, hypertension, presence of type 2 diabetes and treatment with calcium-channel blockers and nitrates. P-values <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

The study cohort was predominantly male (73%) with an average age of 60.3 years and Caucasian background (Table 1). Men were more likely to give a history of smoking. In contrast, more women had a history of dyslipidemia, hypertension and diabetes. Body mass index and waist to height ratio were both greater in women ($P < 0.0001$).

3.2. Angiographic scoring and correlations by gender

The mean extent and vessel scores were higher in men than women (Table 2). Correlation analysis showed a strong positive linear relationship between each of the scoring systems used. The correlation was higher in men ($r = 0.78$–0.94, $P < 0.0001$) than in women ($r = 0.67$–0.9, $P < 0.0001$). Compared to women, men had significantly increased the odds of having an extent score not equal to zero (Table 3).

3.3. Extent scores and relationship to gender and age

Fig. 1 is a graphical representation of the extent scores by age and gender. There were proportionally more women with normal coronary arteries than men and a slow tapering with age. By contrast, men had a lower proportion of normal arteries and had significant coronary