Clinical Research

Nonatherosclerotic Coronary Artery Disease in Young Women

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ABSTRACT

Background: Nonatherosclerotic coronary artery disease (NACAD) is an important cause of myocardial infarction (MI) in young women but is often missed on coronary angiography, especially spontaneous coronary artery dissection (SCAD). The prevalence of NACAD in young women has not been described.

Methods: We retrospectively reviewed all coronary angiograms of women aged 50 years and younger at Vancouver General Hospital from December 1, 2009 to November 30, 2011. The angiograms were reviewed by 2 experienced interventional cardiologists, and reported as normal (<30% stenosis), atherosclerotic coronary artery disease (ACAD), or NACAD. NACAD was further characterized as SCAD, coronary fibromuscular dysplasia (FMD), ectasia, vasculitis, embolism, congenital anomaly, or unclear etiology.

Results: Of 7605 coronary angiograms performed, 177 were done in women aged 50 years and younger. The mean age was 45.4 ± 4.9 (range, 31-50) years, 76 of 177 (42.9%) presented with acute coronary syndrome, and 66 were troponin-positive. Ninety-seven (54.8%) women had normal arteries, 54 (30.5%) had ACAD, 23 (13.0%) had NACAD, and 3 (1.7%) had unclear etiology. Of those with NACAD, subsequent effect on long-term productivity and cardiovascular outcomes is substantial considering their young age of presentation.

Cardiovascular disease (CVD) is the leading cause of death in women in Canada and the United States. Although women are traditionally thought to be at lower risk for CVD and have disease onset a decade later than men, younger women suffering myocardial infarction (MI) are increasingly recognized and a population-based study has shown that women comprised 20% of MI patients younger than the age of 55. The mortality due to MI in young women is 2-fold higher than aged-matched men younger than 50 years of age, despite adjusting for age and other prognostic factors. Even though the estimated prevalence of heart disease in young women age younger than 55 is only 1%-3% in Canada, the cumulative
SCAD was observed in 16 (all troponin-positive and 13 of 16 had noncoronary FMD), and 2 had irregular beading suspicious of coronary FMD. Coronary vasculitis was suspected in 2, and 5 had coronary ectasia. Among women with MI (66/177), 19 (28.8%) had normal arteries (3 Takotsubo cardiomyopathy), 24 (36.4%) had ACAD, 20 (30.3%) had NACAD, 16 (24.2%) had SCAD, and 3 had unclear etiology.

Conclusions: NACAD was not rare among young women (aged 50 years and younger) undergoing coronary angiography and was an important cause of MI, accounting for 30%. SCAD was the most commonly encountered NACAD in young women, causing 24% of MIs. Women with reduced coronary flow reserve. The prevalence of NACAD is not known but is generally thought to be rare. Various forms of NACAD have been described, including spontaneous coronary artery dissection (SCAD), coronary fibromuscular dysplasia (FMD), ectasia, vasculitis, vasospasm, and congenital coronary anomaly.

At our institution, we diagnosed several cases of SCAD over a short time period, especially with the acquisition of optical coherence tomography (OCT) technology. This raised the suspicion that SCAD was previously undiagnosed because of the limitations of coronary angiography. The classic pathognomonic angiographic SCAD appearance is multiple radiolucent lumens and wall stains, but this is actually less frequently observed than luminal compression alone (in the absence of intimal tear) without wall stains. Such luminal compression typically appears as a diffuse smooth stenosis that might vary in severity and length, and thus can mimic atherosclerosis, which is a common reason for misdiagnosis of SCAD. Alternatively, this diffuse narrowing might be mild and/or affect distal arteries, which can be subtle and missed entirely by angiographers.

Therefore, considering the scarcity of knowledge on NACAD epidemiology and burden of disease, and the frequently missed diagnosis of SCAD, we sought to determine the prevalence of NACAD among young women (aged 50 years and younger) undergoing coronary angiography.

Methods
We retrospectively reviewed all women aged 50 years and younger who underwent coronary angiography at Vancouver General Hospital (VGH) from December 1, 2009 to November 30, 2011. The baseline characteristics and medication use were recorded from the VGH cardiac catheterization database and clinical records. Patients with ACS or stable symptoms were included. The angiograms were reviewed meticulously by 2 experienced interventional cardiologists (J.S., E.A., or D.R.), who had each performed more than 10 thousand coronary angiograms. A consensus was attained on the etiology of the coronary artery stenoses. The coronary angiograms were reported as normal (<30% stenosis), atherosclerotic coronary artery disease (ACAD), NACAD, or unclear etiology (ACAD and NACAD could not be differentiated without adjunctive imaging). NACAD was further characterized as SCAD, epicardial coronary FMD, ectasia, vasculitis, vasospasm, embolism, or congenital anomaly (e.g., anomalous coronary artery origin, fistula).

SCAD was diagnosed on angiograms when 1 of the following 3 criteria were present: (1) characteristic multiple radiolucent lines separating true and false lumens, often with contrast dye hang-up (or staining) (type 1 angiographic SCAD) (Fig. 1); (2) diffuse (>20 mm) stenosis with abrupt proximal demarcation (might be subtle) from normal segments involving mid to distal arteries (type 2 angiographic SCAD) (Fig. 2) that did not respond to intracoronary nitroglycerin, and without atherosclerotic changes in other vessels or that subsequently were shown to be normalized on repeat angiograms; or (3) adjunctive intracoronary imaging (intravascular ultrasound or OCT) showing intramural hematoma with or without intimal tear. Epicardial coronary FMD was suspected on angiography when there was a diffuse beading pattern (string-of-beads appearance) not typical of atherosclerosis, and with confirmation of FMD involving at least 1 noncoronary territory. Coronary arteries were considered ectatic when the luminal diameter exceeded 1.5-fold the adjacent normal segment. Coronary vasculitis was suspected when patients had diffuse coronary artery narrowing in association with a systemic vasculitis condition. Coronary artery spasm was suspected when the coronary stenosis was relieved by intracoronary nitroglycerin, and confirmed with intracoronary acetylcholine challenge. Coronary embolism was suspected when there was abrupt occlusion of the coronary artery in the absence of atherosclerosis, with an identifiable embolic source (e.g., valvular thrombus or endocarditis, left ventricular thrombus, venous thrombus with atrial septal defect, or patent foramen ovale).

Patients with NACAD were approached to participate in the prospective Non-Atherosclerotic Coronary Artery Disease Registry at VGH for annual follow-up for 10 years to assess recurrent cardiovascular events. Patients with SCAD or suspected coronary FMD were screened for concomitant FMD involvement in noncoronary territories (renal, iliac, and cerebrovascular) with computed tomography angiography (CTA) or magnetic resonance angiography, if catheter
angiography was not already performed during their index procedures.

**Statistical analysis**

Baseline continuous variables were expressed as mean ± standard deviation, and baseline discrete variables were expressed as mean and percentages. Statistical analysis was performed with the SPSS software (IBM SPSS version 20).

**Results**

Of 7605 coronary angiograms performed at VGH during this 2-year period, 177 were performed in women aged 50 years and younger. The baseline characteristics are described in Table 1. The mean age was 45.4 ± 4.9 (range, 31-50) years, and average body mass index was 27.9. Coronary angiograms were done in 27.1% of these women because of ischemia on stress testing. Overall, 76 of 177 (42.9%) presented with ACS, and 66 of these (37.3%) had increased troponin levels.

The angiographic findings are described in Table 2. Most of these young women, (97/177; 54.8%), had normal coronary arteries, of which 3 were diagnosed with presumed Takotsubo cardiomyopathy (stress cardiomyopathy). There were 54 of 177 (30.5%) with ACAD and 23 of 177 (13.0%) with NACAD. The most common NACAD abnormality was SCAD, which was observed in 16 young women, accounting for 69.6% of NACAD. All patients with SCAD presented with troponin-positive ACS and 13 of 16 (81.3%) were found to have FMD in noncoronary vascular territories (renal, iliac, or cerebrovascular arteries). Thirteen of these SCAD patients had type 2 angiographic appearance without arterial wall stain, of which 4 had OCT showing intramural hematoma, and 6 had repeat coronary angiograms performed (at a mean 1.36 years) that all showed angiographic healing (Fig. 1). Only 3 of 16 of diagnosed SCAD cases had type 1 angiographic appearance of multiple radiolucent lumen or wall stains.

Other NACAD diagnoses were identified in a minority of patients only. Two women had suspected epicardial coronary FMD with irregular beading pattern (Supplemental Fig. S1), but screening of other vascular territories was not performed in an out-of-province patient, and the other patient did not have FMD on computed tomography angiography of the renal, iliac, or cerebrovascular arteries. Suspected coronary vasculitis (Supplemental Fig. S2) was observed in 2 women with extensive diffuse narrowing: one with underlying pulmonary aspergillosis plus eosinophilia, and the other had systemic lupus erythematosus. Coronary ectasia was observed in 5 women (1 who also had irregular coronary stenosis suggestive of coronary FMD), and 1 had coincidental FMD of her iliac artery. Three women had coronary artery stenosis that could not be distinguished between ACAD or NACAD.

Among young women with troponin-positive ACS (66/177), the most commonly encountered abnormality was ACAD in 24 of 66 women (36.4%), followed by NACAD affecting 20 of 66 women (30.3%), and followed by normal coronary arteries encountered in 19 of 66 women (28.8%). With respect to NACAD in patients with troponin-positive ACS, 16 of 66 (24.2%) had SCAD, 1 of 66 (1.5%) had suspected epicardial coronary FMD, 2 of 66 had suspected coronary vasculitis, and 3 of 66 had coronary ectasia. Three women had unclear etiology on angiogram for their ACS. Follow-up was available in 14 of 16 patients with SCAD (2 were lost to follow-up); there was no in-hospital or follow-up mortality, but 1 patient had recurrent MI 11 days after coronary stenting.

**Discussion**

We reviewed the coronary angiograms of all young women aged 50 years and younger who underwent angiography over a 2-year period at our institution. We found that NACAD was an important diagnosis observed in 13% of these patients, especially those who presented with troponin-positive ACS, of whom
NACAD accounted for approximately 30% of the diagnoses. SCAD was the most frequently observed form of NACAD, accounting for approximately 70% of NACAD. In fact, among patients who presented with troponin-positive ACS, SCAD accounted for almost a quarter of these MIs in young women. SCAD is an underdiagnosed condition that is frequently missed on coronary angiography, which resulted in this condition being reported as rare by the medical community. In aggregate, there were <800 cases of SCAD reported in the literature to date since the first case report in 1931; most of these consisted of case reports or small case series. The overall prevalence of SCAD is rare, being diagnosed in only 0.2%-1.1% of patients undergoing coronary angiography. In our series, we diagnosed SCAD in 16 out of 177 (9%) coronary angiograms performed in young women aged 50 years and younger at our institution over a 2-year period. SCAD was also reported to be a rare cause of ACS (0.1%-4%) and sudden cardiac death (0.4%). The prevalence of SCAD appeared greater among unstable patients with ACS (3%-4%) than stable patients (0.3%). Vanzetto et al. reported that the prevalence of SCAD is greater in young women with MI, in their retrospective series of 23 SCAD found on reviewing 11,605 angiograms. They found a SCAD prevalence of 8.7% in young women aged younger than 50 years with ACS, and 10.8% in young women with ST-elevation MI. The management of SCAD is typically conservative without revascularization unless patients have ongoing ischemia, but there are no randomized data to definitively guide management with regard to revascularization or medical therapy.

Our study reported an even greater prevalence of SCAD, involving 9% of young women aged 50 years and younger undergoing coronary angiography, and 24.2% of these young women who presented with MI. We believe that this is due to

Table 1. Patient baseline characteristics (N = 177)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>45.2 ± 4.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.3 ± 8.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.4 ± 19.7</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.9 ± 7.2</td>
</tr>
<tr>
<td>GFR, mL/min/1.73 m²</td>
<td>84.7 ± 21.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20.5%</td>
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<tr>
<td>Dyslipidemia</td>
<td>40.1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40.1%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15.8%</td>
</tr>
<tr>
<td>Previous MI</td>
<td>9.0%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6.2%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10.7%</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>2.8%</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>8.5%</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>7.3%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.4%</td>
</tr>
<tr>
<td>Abnormal stress test</td>
<td>27.1%</td>
</tr>
<tr>
<td>Stable angina or atypical chest pain</td>
<td>57.1%</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>42.9%</td>
</tr>
<tr>
<td>Troponin positive</td>
<td>37.3%</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; GFR, glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention.
improved recognition of SCAD on coronary angiography at our institution, especially of the type 2 angiographic form, which is not as familiar or easily recognizable compared with type 1 angiographic SCAD (multiple radiolucent lumen and wall stains). In fact, we found that a type 2 SCAD appearance (diffuse and smooth stenosis) is more frequently observed than the pathognomonic multiple radiolucent lumen and wall stains, as was reported by others.10 This emphasizes the need to improve recognition of type 2 angiographic SCAD, and that angiographers should strongly consider intracoronary imaging with OCT or intravascular ultrasound to improve SCAD diagnosis. In several cases, repeat coronary angiograms were performed after the initial SCAD event showing angiographic healing of the dissected arteries, which also helped differentiate SCAD from atherosclerotic stenosis. Of note, 13 of 16 of patients with SCAD were found to have FMD in other vascular arteries, similar to our previous report.22

Other forms of NACAD were seen much less frequently. We found an unusual “beading” irregular pattern of diffuse stenosis in 2 patients highly suspicious of coronary FMD (1 with concomitant ectasia), however, screening CTA did not reveal FMD in other vascular territories (although we recognize that the resolution of CTA is often inadequate to diagnose FMD) in 1 patient, and the other patient was not screened for FMD because she was from another province. Unfortunately, intracoronary imaging was not performed in these patients, which might be helpful for coronary FMD diagnosis.23 There were 2 patients with extensive coronary arterial narrowing, thought due to coronary vasculitis related to their systemic inflammatory condition (lupus, and pulmonary aspergillosis with eosinophilia), however, this is speculative because no histology was available.

Limitations

Our study was retrospective and limited by chart review and the available angiographic images. There was also potential selection bias of women who were chosen for and underwent coronary angiography (ie, higher-risk patients who died before coronary angiography or lower-risk patients chosen for noninvasive management were not represented in our study). Furthermore, there was low utilization of intra-coronary imaging, and a few patients had coronary disease that could not be differentiated between atherosclerotic or non-atherosclerotic forms. There was no histologic confirmation of the underlying pathology, and thus diagnosis of NACAD was based on consensus from expert review of angiograms. Therefore, the results from this study are hypothesis-generating and confirmation is required from more rigorous prospective studies.

Conclusions

Among young women aged 50 years and younger undergoing coronary angiography, NACAD is not rare and is observed in 13% of these patients, of which approximately 70% were due to SCAD. In particular, SCAD accounts for almost a quarter of young women presenting with MI. These observations need to be confirmed in larger prospective studies, but do highlight the need to improve the diagnosis of SCAD on angiography.

Disclosures

The authors have no conflicts of interest to disclose.

References


Supplementary Material
To access the supplementary material accompanying this article, visit the online version of the Canadian Journal of Cardiology at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2014.01.011.