The Role of Coronary Reactivity Testing in Women with no Obstructive CAD

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Abstract

Purpose of the review: Two-thirds of women with signs and symptoms of ischemia and no obstructive coronary artery disease have abnormal coronary reactivity. These women are challenging to assess, diagnose and manage because of a lack of evidence-based guidelines. Furthermore, they are considered to be at “low risk” by most physicians, often receive no specific therapy and tend to be dismissed from sub-specialty care.

Recent findings: Coronary reactivity testing is considered the reference-standard for evaluation of epicardial and microvascular coronary function in response to various vasoactive agents. It provides a comprehensive vascular function assessment for diagnosis, a guide for management, and has prognostic benefit that outweigh the risk of the procedure. We recently demonstrated the prognostic value of assessing coronary vascular reactivity in women with signs and symptoms of ischemia, especially those with no obstructive CAD.

Summary: Invasive CRT is a feasible, useful method to identify CMD and risk stratify women with INOCA. It has a comparable safety record to other invasive procedures. Future research is directed at optimizing patient selection, streamlining of invasive CRT methods using user-friendly catheters to enhance feasibility in the routine clinical setting, and optimizing treatment protocols, with clinical trials designed to evaluate outcomes.

Keywords

- coronary reactivity; endothelial function; microvasculature; coronary flow reserve; cardiovascular outcome

Introduction

Cardiovascular disease is the leading cause of death in women; over 400,000 women in the United States die annually from cardiovascular disease, predominantly from ischemic heart
disease (1). Despite advances, over half of all women with symptoms and/or signs of ischemia undergoing coronary angiography have no obstructive coronary artery disease (CAD) (2–5). Two-thirds of these women have coronary microvascular dysfunction (CMD) (6). These patients are challenging to assess, diagnose and manage because of a lack of evidence-based guidelines (5).

Although CMD has been documented to predict adverse cardiovascular events, including myocardial infarction, hospitalization for heart failure, and cardiac death (7–13) for over two decades, these women are considered to be at “low risk” by most physicians, often receive no specific therapy and tend to be dismissed from sub-specialty care. We have also documented that these women have coronary endothelial dysfunction (14), have more extensive but non-obstructive coronary atherosclerosis by intravascular ultrasound (IVUS) (15), exhibit endothelium-independent CMD (11, 16), and evidence of myocardial ischemia (11). CMD with ischemia on stress testing and persistent angina for >1 year identifies a group of women at the highest risk for adverse outcomes (17, 18). Estimates from the ACC-NCDR and the Women’s Ischemia Syndrome Evaluation (WISE) databases indicate that there are at least 3–4 million women in the United States alone with signs/symptoms of ischemia but no obstructive CAD who incur health-care costs similar to obstructive CAD (19, 20).

We recently demonstrated the prognostic value of assessing coronary vascular reactivity in women with signs and symptoms of ischemia, especially those with no obstructive CAD (7). Coronary reactivity testing is considered the reference-standard for evaluation of epicardial and microvascular coronary function in response to various vasoactive agents. It provides a comprehensive vascular function assessment for diagnosis, a guide for management, and has prognostic benefit that outweigh the risk of the procedure.

**Coronary Reactivity Testing**

While standard coronary angiography excludes significant CAD in patients with signs and symptoms of ischemia, it is not a functional test because it does not evaluate coronary reactivity. Therefore, comprehensive coronary physiological assessment is useful in patients with ischemia and no obstructive CAD (INOCA) to identify the underlying etiology for their symptoms. While there are now standard definitions of coronary vasomotor disorders established by the Coronary Vasomotor Disorder International Summit (COVADIS) (21, 22), there are no established unified protocols between catheterization laboratories for evaluating coronary vascular function, and it is not routinely performed. Additionally, the study requires experienced interventional operators familiar with the protocols and techniques (5).

Coronary reactivity testing has a comparable safety profile to coronary angiography and related procedures (23), and can be performed in an out- or inpatient settings. Patients withhold long-acting nitrates, caffeine, and any other vasoactive medications for 24 hours prior to testing, and avoid using nicotine and short acting nitroglycerine 4-hours before the procedure (7, 11, 23). Ideally, the test should include evaluation of both endothelium-dependent and independent pathways of epicardial and coronary microvasculature (5).
Endothelium-independent Microvascular Function Determination

This pathway can be assessed using different coronary vasodilatory indices (Figure 1):

1. **Coronary flow reserve (CFR):** CFR reflects the vasodilator capacity of the coronary vascular tree, predominantly the microcirculation. It can be determined using Doppler or a pressure-temperature–sensitive guidewire with thermodilution technique. If the Doppler technique is used, it is defined as the ratio of adenosine-induced hyperemic average peak velocity/baseline average peak velocity. With the thermodilution technique, it is defined as mean transient time (Tmn) at rest/Tmn at hyperemia in response to adenosine. Measurement of CFR\textsubscript{Doppler} is typically require maximum or near-maximum hyperemia, which can be assessed using either intravenous or intra-coronary adenosine. However, CFR in response to intravenous adenosine should be interpreted with caution due to the decrease in systemic blood pressure and increase in heart rate, which cause a relative decrease in coronary blood velocity and subsequently a lower CFR when compared to CFR in response to intracoronary bolus of adenosine (24, 25). In general, a CFR ≥2.5 is considered normal, although in women, CFR ≥2.32 in response to intracoronary adenosine is useful for prognosis (11). Yet, we recommend adjusting for systemic blood pressure and heart rate changes when adenosine is given intravenously (adjusted CFR= [CFR/resting blood pressure*heart rate] *10\textsuperscript{4}). Unlike CFR\textsubscript{Doppler}, only intravenous adenosine can be used to calculate CFR\textsubscript{thermodilution}, as it requires a steady state hyperemia for at least 30 seconds (25). CFR\textsubscript{Doppler} assessment is limited by the variability in velocity tracing from beat-to-beat, dependent on blood pressure and heart rate and affected by resting hemodynamics. Measurement of CFR\textsubscript{thermodilution} requires multiple manual injections of normal saline which can be a source of variability (25).

2. **Index of Microvascular Resistance (IMR):** IMR quantitatively reflects coronary microvascular resistance. It is derived from the thermodilution technique using a pressure wire with temperature sensor. It is calculated as the distal coronary pressure (Pd)*hyperemic Tmn (unit). It requires 3 injections of 3 mL of room temperature normal saline during hyperemia to calculate Tmn. An IMR <25U is considered normal (26). A limitation of IMR assessment is variability due the manual injections of saline.

3. **Hyperemic Microvascular Resistance (HMR):** HMR is assessed using a wire with combined pressure and Doppler sensor. It is calculated as the Pd/mean flow velocity during hyperemia (mmHg.cm\textsuperscript{-1}.s). The use of HMR is limited as there is no clear prognostic cutoff to identify those with normal versus abnormal coronary microvascular function.

Endothelial-dependent micro- and epicardial vascular function determination

Coronary blood flow and epicardial coronary artery diameter changes in response to intra-coronary acetylcholine (IC-Ach) are used to evaluate microvascular and epicardial coronary endothelial function (6, 7, 23, 26). Graded IC-Ach concentrations of 0.182 mcg/ml and 18.2
mcg/ml are infused manually or at rate of 2 ml over 2–3 minutes via mechanical infusion pump. In addition, if no significant coronary epicardial luminal stenosis, angina symptoms or significant EKG changes are observed during infusion of these lower doses of Ach, then epicardial coronary artery vasospasm provocation testing can be performed using higher dose intra-coronary acetylcholine bolus over 20 seconds (up to 200 mcg in the left anterior descending artery and up to 80 mcg in the right coronary artery) (22, 27). Due to the potential transient severe bradycardia associated with acetylcholine bolus injection at higher (200 mcg) doses, insertion of a temporary pacing wire in the right ventricle is often used (28, 29). A positive response to acetylcholine coronary artery vasospasm provocation testing is defined as >90% epicardial luminal narrowing with angina and EKG changes. Table 1 demonstrating the normal coronary endothelial function cutoffs in response to acetylcholine.

**Endothelium-independent epicardial vascular function determination**

This pathway can be assessed by evaluating the coronary epicardial diameter change in response to intra-coronary injection of glyceryl trinitrate (nitroglycerine). To date, there is no study showing a strong relationship between endothelium-independent epicardial function and adverse outcome. However, Von mering et al. demonstrated that women with cardiovascular events during follow-up had less dilation in coronary artery diameter in response to nitroglycerine (14).

**CRT Safety**

The safety of the invasive CRT was assessed in women with signs and symptoms of ischemia, who are suspected to have coronary microvascular dysfunction (23) in 293 women. Two women had serious adverse events related to the procedure, including one who had coronary artery dissection and the other who had a non-ST segment myocardial infarction associated with coronary vasospasm. In addition, two women had non-serious events, including transient air micro-embolism and deep venous thrombosis on the side of the groin access site more than 30 days after testing. Overall, the risks of the test (1.4%) was lower than the risk of adverse cardiovascular events (up to 16% over a median of 9.7-year follow-up).

Coronary vasospasm testing includes bolus injection(s) of higher doses of intra-coronary acetylcholine (20 to 200 mcg) over 20 seconds (27, 30), which is associated with higher risk of arrhythmias (about 7%) (31). Lee et al. using a total dose of 108 mcg intra-coronary acetylcholine infusion over 3 minutes demonstrated no coronary vasospasm (defined as decrease in coronary artery diameter by 90% in response to acetylcholine). In the coronary microvascular angina (CorMicA) study (32), a bolus of intra-coronary acetylcholine was given to the left coronary artery (100 mcg) and the right coronary artery (50 mcg) and reported 17% coronary vasospasm. Similarly, Sheikh et al. (33) reported 33% of their cohort developed coronary vasospasm in response to rapid bolus injection of acetylcholine. There is no head-to-head comparison of slow infusion versus bolus injection of high dose acetylcholine.
Prognosis

Endothelium-independent coronary microvascular function and outcome

We previously demonstrated in the original WISE study (34) that endothelium-independent coronary microvascular dysfunction is associated with major adverse outcomes over a median follow-up of 9.7 years (7). In women with no obstructive CAD and after adjustment to risk factors (age, diabetes, hypertension, dyslipidemia and smoking), a decrease of 0.1 in CFR was associated with an 8% increase in hazard of adverse cardiovascular events (HR: 1.08; 95% CI: 1.01 to 1.16; p =0.036) (Figure 2) (7). Women with CFR <2.32 had higher rates of adverse cardiovascular events compared to those with normal CFR (p=0.008). Multiple studies included men with various follow-up durations showed similar results (Table 2).

Endothelium-dependent coronary vascular function and outcome

Furthermore, following adjustment to traditional cardiovascular risk factors (age, diabetes, hypertension, dyslipidemia and smoking), for each 10% reduction CBF in response to acetylcholine, there was a 12% significant increased risk of all-cause mortality (HR: 1.12; 95% CI: 1.01 to 1.24; p = 0.038), and 12% increase in adverse cardiovascular events (HR: 1.12; 95% CI: 1.03 to 1.22; p < 0.01). Similarly, in women with minimal or no CAD, every 10% decrease in CBF was associated with a 23% increase in risk of all-cause mortality (HR: 1.23; 95% CI: 1.04 to 1.45; p = 0.015), and 16% increase in adverse cardiovascular events (HR: 1.16; 95% CI: 1.05 to 1.28; p = 0.003). Women with epicardial coronary artery constriction in response to acetylcholine, indicating endothelium-dependent epicardial artery dysfunction, have significant increased risk of hospitalization due to angina (Figure 3).

These results reinforce the prior finding by Halcox et al (35), which suggested impaired microvascular dilatory response in response to IC-Ach as a measure of endothelium-dependent microvascular reactivity is associated with development of adverse cardiovascular events. Furthermore, Schachinger et al (36) showed that subjects with cardiovascular events during follow-up (median of 7.7 years) had significant increase in vasoconstriction and blunted increase in coronary blood flow in response to intracoronary acetylcholine infusion. However, both studies included “soft” events; such as: elective coronary and peripheral revascularizations. Suwaidi et al (12), found that patients with severe coronary endothelial dysfunction, defined as epicardial constriction >20% in response to acetylcholine, had more adverse cardiovascular events, compared to those with epicardial artery dilatation. The events rate in this study was low and majority of them were revascularization events.

Knowledge Gaps

Knowledge gaps exist in understanding the most appropriate patient selection, protocol guidelines and CRT-specific pathway-directed therapy. There are multiple physiological indices capable assessing the same pathway (e.g. endothelium-independent CMD can be assessed using CFR, IMR, HMR). COVADIS is working to further understand and provide evidence-based protocols for definitions of CMD for testing and treatment. For example, the CorMicA study provides initial guidance to clinicians on how and when to perform
reactivity testing, as well as the utility of a treatment protocol based on the CRT findings which improves angina as measured by the Seattle Angina Questionnaire (32). Further work to understand the underlying pathophysiology and potentially developing more effective therapies is needed. Finally, current guidelines do not specifically address treatment of CMD within INOCA population. A large randomized multicenter, prospective, randomized, blinded outcome study evaluating intensive medical therapy (high intensity statin, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers) vs. usual care in 4,422 symptomatic women with INOCA, is underway (Women’s Ischemia TReatment Reduces Events In Non-Obstructive CAD [WARRIOR]-NCT03417388).

Conclusions

Invasive CRT is a feasible, useful method to identify CMD and risk stratify women with INOCA. It has a comparable safety record to other invasive procedures. While women with endothelium-independent CMD are at risk of adverse cardiovascular events, those with endothelium-dependent CMD are at higher risk of both death and adverse cardiovascular events during follow up. Future research is directed at optimizing patient selection, streamlining of invasive CRT methods using user-friendly catheters to enhance feasibility in the routine clinical setting, and optimizing treatment protocols, with clinical trials designed to evaluate outcomes.

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References


Key Points:

- Two thirds of women with ischemia and no obstructive coronary artery disease have coronary microvascular dysfunction.
- Coronary microvascular dysfunction is linked to adverse cardiovascular outcome.
- Invasive coronary reactivity testing is a feasible, safe, useful method to identify microvascular dysfunction and risk stratify women with ischemia and no obstructive coronary artery disease.
Figure 1: Schematic of Physiological Assessment of endothelium-independent Coronary Microvascular Function.

Pd: mean distal coronary pressure; CFR: coronary flow reserve; IMR = the index of microcirculatory resistance; HMR: hyperemic microcirculatory resistance; and Tmn = mean transit time.

CFR = Mean hyperemic flow velocity/mean resting flow velocity
     = Resting Tmn/hyperemic Tmn

IMR = Pd at maximal hyperemia X hyperemic Tmn

HMR = Pd/mean hyperemic flow velocity

(Tmn: an inverse correlate to absolute coronary flow)
Figure 2: Relationship Between Endothelium-Independent Coronary Microvascular Function and Cardiovascular Events.
(A) Kaplan-Meier analysis showing percentage of women surviving free from the major adverse cardiovascular event (MACE) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and heart failure during long-term follow-up stratified by coronary flow reserve (CFR). (B) Kaplan-Meier analysis showing percentage of women with no obstructive coronary artery disease (CAD) stratified by CFR surviving free from MACE during long-term follow-up. (Source: AlBadri et al. J Am Coll Cardiol. 2019; 73: 684–693) (7).
Figure 3: Relationship Between Endothelium-Dependent Epicardial Coronary Artery Function Stratified by Change in Coronary Artery cross-sectional area (CSA) in Response to Intra-Coronary Acetylcholine (IC-Ach) and Hospitalization due to Angina.

Table 1:
Definitions of Coronary Microvascular and Epicardial Coronary Artery Dysfunction

<table>
<thead>
<tr>
<th>Pathways</th>
<th>Microvascular dysfunction</th>
<th>Epicardial coronary artery dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelium-independent</td>
<td>CFR in response to adenosine &lt;2.5 (in Women &lt;2.32)</td>
<td>Change in coronary artery diameter in response to nitroglycerin &lt;20%</td>
</tr>
<tr>
<td>Endothelium-dependent</td>
<td>Change in CBF in response to acetylcholine ≤50%</td>
<td>Change in coronary artery diameter in response to acetylcholine ≥50%</td>
</tr>
<tr>
<td>Coronary vasospasm</td>
<td>• Chest pain + ECG changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Change in coronary artery diameter in response to acetylcholine &gt;90%</td>
<td></td>
</tr>
</tbody>
</table>

CFR: coronary flow reserve; CBF: coronary blood flow.

### Table 2:
Outcome studies examining endothelium-independent microvascular function

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study Size</th>
<th>Study population</th>
<th>Methods</th>
<th>Outcome measure</th>
<th>Follow-up</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pepine et al(11) (WISE) 2010</td>
<td>189</td>
<td>Women, angina/ ischemia most with non-obstructive CAD</td>
<td>Intracoronary Adenosine-CFR Doppler flow wire</td>
<td>Death, nonfatal MI, nonfatal stroke, HF hospitalization</td>
<td>5.4 y (mean)</td>
<td>P=0.003</td>
</tr>
<tr>
<td>Britten et al(37) 2004</td>
<td>120</td>
<td>Chest pain or referred for single vessel revascularization</td>
<td>IC papaverine or Adenosine-CFR Doppler flow wire</td>
<td>Cardiac death, ACS, revascularization,</td>
<td>7.3 years (Median)</td>
<td>P=0.019</td>
</tr>
<tr>
<td>Von Mering et al(14) (WISE) 2004</td>
<td>163</td>
<td>Women, angina/ ischemia</td>
<td>Intracoronary Adenosine-50% change in Coronary CSA</td>
<td>Death, MI, nonfatal stroke, HF Hospitalization, revascularization</td>
<td>48 months (median)</td>
<td>NS</td>
</tr>
<tr>
<td>Schanchinger et al(36) 2000</td>
<td>147</td>
<td>Chest pain or referred for single vessel revascularization</td>
<td>IC papaverine or adenosine- flow mediated dilation</td>
<td>Death, MI, unstable angina, stroke and revascularization</td>
<td>7.7 years (Median)</td>
<td>0.004</td>
</tr>
<tr>
<td>AlBadri et al(7) (WISE) 2019</td>
<td>224</td>
<td>Women, angina/ ischemia most with non-obstructive CAD</td>
<td>Intracoronary Adenosine-CFR Doppler flow wire</td>
<td>Death, nonfatal MI, nonfatal stroke, HF hospitalization</td>
<td>9.7 years (Median)</td>
<td>0.008</td>
</tr>
<tr>
<td>Halcox et al(35) 2002</td>
<td>308</td>
<td>Chest pain or evidence of ischemia</td>
<td>Intracoronary Adenosine-change in coronary vascular resistance</td>
<td>Death, MI, unstable angina, stroke and revascularization</td>
<td>40.7 months (Median)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CAD, coronary artery disease; CFR, coronary flow reserve; HF, heart failure; IC, intracoronary; MI, myocardial infarction; and WISE, Women’s Ischemia Syndrome Evaluation.