Current State of Invasive Coronary Function Testing in Canadian Catheterization Laboratories: A National Survey

Short title: Invasive Coronary Function Testing in Canadian CCL

Laurie-Anne Boivin-Proulx MD MSc FRCPC1,2, Andrea Lavoie MD BSc FRCPC3, Eric Schampaert MD FRCPC4, Aun Yeong Chong MD1, Derek So MD FRCP1, Olga Toleva MD MPH5,6, Javier Escaned MD PHD2, Steve Miner MD FRCP7.

1. University of Ottawa Heart Institute, Ottawa, Canada.
2. Hospital Clínico San Carlos IDISSC, Complutense University of Madrid, Madrid, Spain.
3. Prairie Vascular Research Inc., Regina, Saskatchewan, Canada.
4. Sacré-Cœur Hospital, Montreal, Quebec, Canada.
5. Department of Cardiology, Emory University School of Medicine, Atlanta, Georgia, USA,
6. Emory Heart and Vascular, Emory University School of Medicine, Atlanta, Georgia, USA.
7. Southlake Regional Health Centre, Newmarket, Ontario, Canada.

Corresponding author:
Laurie-Anne Boivin-Proulx, MD MSc FRCP
University of Ottawa Heart Institute, 40 Ruskin St, Ottawa, ON K1Y 4W7, Canada,
Phone : 1-613-696-7000, Email: laurianneboivinproulx@gmail.com

Text: 1484 words (maximum 1500 words)
Despite the availability of technologies and guidelines recommendations, invasive coronary function testing (IFT) remains underperformed in patients with ischemia with no obstructive coronary artery disease (INOCA), but the current state of IFT in Canadian cardiac catheterization laboratories (CCL) remained unknown. Therefore, we conducted an survey among Canadian CCL directors (n=46). While most CCL directors believed that IFT should be performed in INOCA patients experience persisting symptoms or adverse clinical outcomes, only 19.6% (n=9) and 30.4% (n=14) of responding centers performed invasive assessment of the microvasculature and vasomotor function, respectively.

Around 40% of all patients with demonstrated ischemia non-invasive testing undergoing elective coronary angiography for the investigation of chronic coronary syndromes have no obstructive coronary artery disease (CAD), commonly known as INOCA. Despite the absence of obstructive CAD, INOCA is associated with a higher risk of mortality and morbidity, and impaired quality of life. The two main key endotypes of INOCA are structural coronary microvascular disorder (CMD) and coronary vasomotor disorders, the latter only diagnosable through invasive means. In the CORonary MICrovascular Angina (CorMicA) trial that included 151 patients with INOCA randomized to stratified medical therapy (guided by IFT) or standard care, only 17 (13.2%) patients had a normal coronary endothelial function: structural CMD, vasomotor disorders or both were identified in 78 (51.7%), 25 (16.6%) and 31 (20.5%) of patients, respectively. Guidewire-based coronary flow reserve (CFR) and/or microcirculatory resistance measurement (Class 2a, level of evidence B) and acetylcholine provocation testing (Class
2b, level of evidence B) is currently recommended in INOCA patients with persisting anginal symptoms to assess the presence of structural CMD and coronary vasomotor disorder.\textsuperscript{5} Despite the availability of technologies and guidelines recommendations, invasive coronary function testing (IFT), including guidewire-based CFR and/or microcirculatory resistance measurement and spasm provocation testing, remains underperformed in INOCA patients, but the current state of IFT in Canadian cardiac catheterization laboratories (CCL) remains unknown. Therefore, we conducted a survey among CCL directors to assess the state of IFT in Canadian CCL.

We conducted an online survey among Canadian CCL directors from January 11\textsuperscript{th} to May 5\textsuperscript{th}, 2024. All CCL directors responded to the survey (n=46). Respondents were from Ontario (n=18; 39.1\%), Quebec (n=15; 32.6\%), British Columbia (n=5; 10.8\%), Alberta (n=3; 6.5\%), Saskatchewan (n=2; 4.4\%), Manitoba (n=1; 2.1\%), Nova Scotia (n=1; 2.2\%) and New-Brunswick (n=1; 2.2\%). The authors confirm that patient consent is not applicable to this article, as no patient was directly involved in this survey.

A summary of the findings of the survey is represented in Figure 1. Guidewire-based CFR and microcirculatory resistance measurement is performed in 19.6\% (n=9) of responding centers, with 88.9\% (n=8) using a thermodilution-based technique and 11.1\% (n=1) using a doppler-based technique. Sixty-five percent (64.9\%; n=24) of responding centers who did not performed invasive assessment of the coronary microvasculature could refer to a nearby institution for guidewire-based CFR and microcirculatory resistance measurement: 37.5\% (n=9), 50.0\% (n=12) and 12.5\% (n=3) reported a waiting time at
the referral institution of less than 3 months, 3 to 6 months and more than 6 months, respectively. Among centers who did not perform invasive assessment of the coronary microvasculature, 19 (51.4%) responding centers were planning to do so in the future, while 18 (48.6%) responding centers did not. Twenty-eight percent (28.3%; n=13) of responding centers had access to non-invasive modalities for the assessment of the microvasculature at their institution, which were stress cardiac positron emission tomography with myocardial blood flow reserve (MBFR), cardiac magnetic resonance with MBFR and stress transthoracic echography with coronary flow velocity reserve in 61.5% (n=8), 30.8% (n=4) and 7.7% (n=1) of the cases, respectively. Forty-six percent (46.2%; n=6), thirty-eight percent (38.4%; n=5) and fifteen percent (15.4%; n=2) reported a waiting time for non-invasive assessment of the microvasculature of less than 3 months, 3 to 6 months and more than 6 months, respectively. Fifty-nine percent (58.7%; n=27) of respondents believed that invasive assessment of the microvasculature should be offered initially to patients with INOCA, while 41.3% (n=19) did not. If empiric therapy was chosen as the initial strategy, respondents believed that invasive assessment of the microvasculature should be considered if the patients experiences daily (n=12; 26.1%) or weekly (n=30; 65.2%) symptoms or major cardiac adverse events (n=4; 8.7%).

Invasive assessment of coronary vasomotor disorders is performed in 30.4% (n=14) of responding centers, with 71.4% (n=10) using acetylcholine and 28.6% (n=4) using ergonovine as provocation agents. Two percent (2.2%; n=1) and thirteen percent (13.0%; n=6) stopped performing invasive assessment of coronary vasomotor disorders because of an adverse event and the acetylcholine shortage, respectively. Sixty-three percent (62.5%;
n=20) of responding centers who did not performed invasive assessment of coronary vasomotor disorders could refer to a nearby institution for provocation testing: 35.0% (n=7), 45.0% (n=9) and 2.0% (n=4) reported a waiting time at the referral institution of less than 3 months, 3 to 6 months and more than 6 months, respectively. Among centers who did not performed invasive assessment of coronary vasomotor disorders, 12 (37.5%) responding centers were planning to do so in the future, while 20 (62.5%) responding centers did not. Seventy-eight percent (78.3%; n=36) of respondents believed that invasive assessment of the vasomotor function should be offered initially to patients with INOCA, while 21.7% (n=10) did not. If empiric therapy was chosen as the initial strategy, respondents believed that invasive assessment of the microvasculature should be considered if the patients experiences daily (n=9; 19.6%) or weekly (n=29; 63.0%) symptoms or major cardiac adverse events (n=7; 15.2%). The indication for performing invasive coronary function testing, which may include invasive assessment of the microvasculature and vasomotor function, is set by an interventional cardiologist in the majority of cases (84.1%; n=37) or by a clinical cardiologist alternatively (15.9%; n=7).

This survey is the first to examine the current state of IFT among Canadian CCL and it identified important findings. First, only 19.6% and 30.4% of responding centers perform invasive assessment of the microvasculature and vasomotor function, respectively. While non-invasive diagnostic modality is currently available for coronary vasomotor disorders, only 28.3% of responding centers had access to a non-invasive alternative for the assessment of the microvascular function. Second, despite the low performance of IFT, most responders believed that IFT should be offered to INOCA patients if they experience
daily or weekly symptoms, or an adverse event. Third, responders believed in majority that the indication for IFT in INOCA patient should be set by the interventional cardiologist, underlying the importance of the involvement of interventional cardiologist in the care of INOCA patients.

It has been well established that the majority patients with angina in the absence of coronary artery disease have an abnormal coronary function, and that performing IFT to explore microcirculatory and vasomotor disorders increases the diagnostic yield in this population. Recently, the CORonary MICrovascular Angina (CorMicA) trial demonstrated that tailored treatment guided by the results of IFT leads to a significant reduction in anginal symptoms and an amelioration in the quality of life, compared with conventional, non-guided medical therapy. The CorMicA trial also reinforced the fact most INOCA patients have an abnormal coronary function, with structural CMD, vasomotor disorders or both identified in 78 (51.7%), 25 (16.6%) and 31 (20.5%) of patients, respectively, as well as the safety of IFT, with no major adverse event reported in the trial. The improvement in patient well-being associated with stratified medicine including IFT with linked medical therapy is reflected in the current guidelines who recommend guidewire-based CFR and/or microcirculatory resistance measurement (Class 2a, level of evidence B) and acetylcholine provocation testing (Class 2b, level of evidence B) in INOCA patients with persisting anginal symptoms. While performing IFT in INOCA patients may positively impact symptoms, quality of life, and healthcare costs by reducing repeated testing as a result of symptoms persistence, it has not been showed to impact major
adverse cardiac events, as no therapy is currently proven to mitigate the increased mortality
and morbidity observed in this population.\(^2\)

Low implantation of invasive diagnostic pathways to investigate microcirculatory
or vasomotor disorders is often cited in the literature, but no other country has assessed the
state of IFT in their CCLs. Therefore, this survey is one of the first to prove that
performance of IFT remains low across CCL, despite that CCL directors believe that IFT
should be performed in INOCA patients experiencing persisting symptoms or and adverse
event. While the reasons behind the low adaptation of IFT are unexplored, one can
hypothesize that several factors can contribute to the relatively low performance of IFTs,
such as insufficient CCL time, the absence of billing codes for IFT, budgetary constraints
in Canadian CCL, the recent approval of Coroflow (Coroventis Research, Sweden) by
Health Canada, concerns regarding the safety of IFT, the absence of evidence that proves
that diagnostic strategy linked to therapy improves patients morbidity and mortality, etc.
Future research should focus on investigating the factors that may explain poor uptake of
IFT among INOCA patients, in order to identify potential solutions that favor the
performance of IFT in Canadian CCL and the development of efficient referral pathways
for INOCA patients.

In conclusion, despite that most CCL directors believed that IFT should be
performed in INOCA patients experience persisting symptoms or adverse clinical
outcomes, a small proportion of Canadian CCLs is currently performing IFT, with little
access to non-invasive assessment of the microvasculature.
Acknowledgements

The authors want to acknowledge Dr Morton J Kern (professor of medicine, University of California, Irvine, USA) for his valuable contributions to the design and dissemination of the results of this survey. Laurie-Anne Boivin-Proulx is supported by a grant from the University of Ottawa Heart Institute Foundation and the Whit & Heather Tucker Endowed Funds (Ottawa, Canada).

Funding Sources

None.

Disclosures

None.

Patient Consent

The authors confirm that patient consent is not applicable to this article, as no patient was directly involved in this survey.
References


Figure 1. Current State of Invasive Coronary Function Testing in Canadian Catheterization Laboratories.
Invasive assessment of the microvasculature

- 89% thermodilution-based technique
- 11% doppler-based technique
- 65% can refer nearby for invasive microvasculature assessment
- 28% have access to an non-invasive alternative at their institution

Invasive assessment of the vasomotor function

- 71% provocation with acetylcholine
- 29% provocation with ergonovine
- 63% can refer nearby institution for invasive vasomotor function assessment