Recommendations for advancing the care of Canadians living with refractory angina pectoris: A Canadian Cardiovascular Society position statement

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Refractory angina (RFA) is a debilitating disease characterized by severe, unremitting cardiac pain (1,2). This pain or discomfort, by definition, is resistant to all conventional treatments for coronary artery disease (CAD) including nitrates, calcium channel and beta-adrenoceptor blockade, vasculoprotective agents, percutaneous coronary interventions and coronary artery bypass grafting (1,2). Patients living with RFA have a low annual mortality rate of 3% but suffer from a severely impaired health-related quality of life (3). They typically experience recurrent and sustained pain, poor general health status, psychological distress, impaired role functioning, activity restriction and inability to self-manage (4-7). As more patients survive primary and subsequent cardiac events, the global prevalence of RFA is ever increasing (1,2,8,9).

Effective care for the growing RFA population in Canada is critical. A number of these patients have inadequate pain relief and revisit local hospital emergency departments and clinics in lieu of appropriate care (7-13). The potential cost implications are considerable. In the United Kingdom for example, the direct costs of persistent anginal pain in 2000, including prescriptions, repeated emergency department and other admissions, outpatient referrals and procedures, were estimated to be £669,000,000, accounting for 1.3% of the total National Health Service expenditure (12). A more recent (2008) Ontario-based study estimated the annualized cost of RFA-related disability from a societal perspective including direct, indirect and system costs, at $19,209 per patient (13); this cost estimate is likely conservative due to a reliance on self-report measures.

The neuropathophysiology of persistent cardiac pain arising from RFA is complex, posing unique management challenges to clinicians, patients and families. Effective RFA assessment and management requires an integrated knowledge of the specialized techniques that are effective for persistent pain and hyperalgesia, as well as ischemia. There is limited access to these resources within Canada. Underlying this problem are the lack of a definition of RFA commensurate with the current understanding of pain neuropathophysiology; a formalized, coordinated interprofessional strategy among the cardiovascular and pain science and clinical communities; and Canadian clinical practice guidelines providing clear direction for RFA assessment and management.

The Canadian Cardiovascular Society (CCS) executive (on behalf of the CCS council) appointed a multidisciplinary writing group of experienced clinicians and scientists from across Canada to develop a position statement to address these issues, raise greater awareness of RFA as a growing problem with significant patient, health care system and societal impacts, and present three primary recommendations for advancing the care of Canadians living with RFA.

Recommendation 1: Collect accurate Canadian data on the incidence and prevalence of RFA

Available estimates suggest that RFA affects between 600,000 and 1.8 million people in the United States (2), with as many as 50,000 new cases each year (14). Approximately 30,000 to 50,000 new cases per year are also estimated in continental Europe (1). Canadian Community Health Survey (2000/2001) data (www.statcan.gc.ca) suggest that approximately 500,000 Canadians are living with unresolved angina, but these data are limited by their reliance on self-report. The proportion of these patients living with true RFA is not known (8). Despite wide variation in methods used to derive population estimates, there is a general consensus that the incidence and prevalence of RFA will continue to rise across countries as CAD-related survival rates continue to increase and populations age (6,8,9). The European Society of Cardiology (ESC) Joint Study Group on the Treatment of Refractory Angina (1) has stressed the critical importance of systematic evaluation of the epidemiology of RFA to more accurately project disease burden and related health services demands. A Canadian Institutes of Health Research (CIHR)-funded pilot study designed to explore RFA prevalence six months after percutaneous coronary intervention at a large regional referral centre in southern Ontario is currently underway (unpublished). This study will yield preliminary estimates of RFA prevalence in a specific cardiac population and will provide direction for additional research and processes for collecting accurate data about RFA. We recommend that limitations in current angina surveillance systems be examined and recommendations be put forward regarding possible approaches to surveillance that will accurately determine the prevalence and incidence of RFA within Canada (eg, collaboration with the Canadian Insititute for Health Information and development of a registry). This work will be initiated as part of a recently funded CIHR project to develop joint CCS/Canadian Pain Society (CPS) clinical practice guidelines for RFA (see details under Recommendation 3).

Recommendation 2: Establish a CCS definition for RFA that reflects recent advancements in pain neuropathophysiology

The ESC Joint Study Group (1) defined refractory angina as:

> A chronic condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery. The presence of reversible myocardial ischaemia should be clinically established to be the cause of symptoms. Chronic is defined as a duration of more than 3 months.

The biochemical stimuli for pain related to RFA are multifactorial and analogous to the hypersensitivity seen in other forms of chronic tissue injury. Concentrations of bradykinin, adenosine, lactate and potassium from ischemic damage to the myocardium are released in the effluent of the coronary sinus (15). These algogenic ligands excite polymodal afferent cardiac sensory neurons. Substance P and calcitonin gene-related peptide are also synthesized and augment adenosine-provoked pain (15-17). Primary cardiac afferents transmitting this noxious input enter the upper thoracic spinal cord and synapse with second-order sensory neurons in the dorsal horn. The

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cardiac nociceptive information is amplified and ascends via multiple pathways including Lissauer's tract, the spinothalamic tract, and the spinoamygdaloid and spinohypothalamic pathways to cortical and subcortical areas of the brain with somatic receptive fields in the chest and arms (17). Cognitive appraisal of the stimulus occurs in the parietal cortex and anterior cingulate cortex (16,17). The noxious stimulus is assessed in these structures as threatening, causing activation of the bilateral prefrontal cortex and limbic system, leading to apprehension of further pain and fear for the future (16,17).

For patient assessment and management, it is important to recognize that there is no clear relationship between the severity of one's anginal pain and the degree of ischemia (18), as indicated by changes in the electrocardiogram or serum levels of cardiac enzymes. As the ESC group (1) and others (15-19) have argued, RFA, similar to other types of pain, is not simply the end product of the linear transmission of a noxious stimulus. Increasing basic science and clinical evidence obtained using electrocardiogram holter monitoring, angiography, positron emission tomography and wall motion imaging demonstrates the variability of cardiac pain, wherein significant pain occurs for those with CAD with minimal myocardial ischemia and, conversely, the majority of ischemic episodes are silent (16-19). To date, no clear association has been found between the magnitude and location of the ischemic region and those ischemic episodes experienced as painful. Moreover, there are no specific central nervous system (CNS) pain projections associated with sites of myocardial ischemia (16-19). Procacci et al (19) have therefore argued that with no clear mechanistic link, the association between severity and duration of myocardial ischemia and the experience of pain is, at best, probabilistic.

Melzack and Wall's seminal gate control theory (20) led to the understanding that tissue insults, such as myocardial ischemia, produce neural signals that enter an already active nervous system that reflects the cumulative and combined effects of past experience, cultural background, context, emotion and perceived psychological and social well-being. Nociceptive processes arising in the periphery are modulated in the CNS by mechanisms that actively participate in the selection, abstraction and synthesis of information from the total peripheral sensory input. The amount, quality and nature of pain experienced is therefore a dynamic and multidimensional product of sensory-discriminative, cognitive-evaluative and affective-motivational components. Each of these is a function of modulation of noxious stimuli at several CNS levels, and each is unique to the context and experience of the individual.

More recent discoveries related to the plasticity of the nervous system support neuronal modifiability as fundamental to, and chiefly responsible for, the experience of persistent pain (21,22). Pain mechanisms in the periphery and CNS undergo pathological changes in response to continued noxious stimulation. These processes are collectively known as sensitization. Repeated exposure to the algogenic products of tissue insult acts directly on peripheral sensory neurons to generate spontaneous discharges and respond at lowered thresholds to noxious stimuli. This is referred to as hyperalgesia (21). Centrally, second-order sensory neurons terminating in the dorsal horn of the spinal cord and third-order neurons projecting to higher centres, can – in tandem with peripheral changes – respond excessively to inputs from the periphery. This phenomenon is known as central sensitization. Central sensitization is characterized by potentiation of synaptic transfer in the dorsal horn augmenting the normal duration (hyperpathia) and amplitude of pain, and/or the creation of spontaneous pain (allodynia) (22).

Understanding nociceptive processes and related nervous system plasticity is critical to comprehensive and effective pain assessment and management for RFA patients. The determinants of pain arising from chronic tissue injuries such as RFA are complex. RFA pain is an unpleasant experience beyond the conveyance and perception of an ischemic stimulus; it has sensory-discriminative, cognitive-evaluative and affective-motivational components. While anti-ischemic treatments are paramount, there are also well-established and emerging pain-oriented interventions with compelling evidence of effectiveness. A comprehensive approach to treatment includes strategies that target mechanisms of ischemic as well as persistent pain mechanisms and factors related to individual responses to the pain.

A definition of RFA commensurate with current advancements in pain neuropathophysiology is required to raise greater awareness of RFA as a condition involving persistent pain as well as ischemic mechanisms, and to provide continued direction to clinical treatment and research. We therefore recommend that the CCS adopt the following amended version of the definition of RFA put forth by the ESC Joint Study Group in 2002:

> Refractory angina is a persistent, painful condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery. While the presence of reversible myocardial ischaemia must be clinically established to be the root cause, the pain experienced may arise or persist with or without this ischaemia. Chronic is defined as persisting for more than 3 months.

Correct diagnosis of RFA requires ongoing, thorough assessment to ensure that revascularization is unfeasible, medical therapy is optimal and all noncardiac-originating sources of chest pain have been ruled out (eg, costochondritis, intercostal neuralgia, anemia, thyrotoxicosis, reflux esophagitis, esophageal spasm) (1).

Recommendation 3: Joint CCS/CPS clinical practice guidelines are needed

Over the past two decades, intervention research in North America and continental Europe has led to the development of multiple treatment approaches for RFA, including spinal cord stimulation (SCS), enhanced external counterpulsation (EECP), stellate and paravertebral ganglion blockade, transmyocardial laser revascularization (with or without autologous bone marrow), intrathecal anesthesia and high thoracic epidural, heart rate modulating agents, oral opioids, shockwave therapy, physical exercise and rehabilitation, and self-management training interventions. Among the more well established of these interventions are SCS (23,24) and EECP (24,25). These techniques generate anginal pain relief secondary to reducing ischemia. The anti-ischemic effect of SCS is most likely produced by decreasing myocardial oxygen consumption and a probable amelioration of coronary blood flow via neurohormonal mechanisms (23). EECP is a pneumatic therapy used to augment diastolic and coronary perfusion pressure, and decrease systemic vascular resistance; available evidence supports improvement of endothelial function as a key mechanism of beneficial effect (25). Among the less well-known interventions, self-management training programs target symptom self-management, fear and perceived self-efficacy to reduce pain and improve functional status (26).

It has not been within the mandate or scope per se of most practice guidelines for the management of CAD and myocardial ischemia to review RFA interventions in any detail. While efforts have been made (in several countries) to improve this knowledge gap through review papers and guidelines, most are narrative-based and largely unsystematic, differing and/or contradictory in their recommendations, and devoid of context, multidisciplinary input or patient perspectives. To date, there are no resources for RFA assessment and management that meet the complete requirements of the Appraisal of Guidelines, Research and Evaluation (AGREE) Collaboration (27), an international organization dedicated to improving the quality and effectiveness of clinical practice guidelines by establishing a shared framework for their development, reporting and assessment. Perhaps the greatest weakness of most existing reviews is the lack of recommendations related to comprehensive pain assessment and collaboration among cardiovascular and pain experts.

Given the underlying disease complexity, RFA patients are at risk for misdiagnosis and inappropriate treatment. In Canada, expert knowledge of RFA assessment and management is limited to a small group of scientists and clinicians practicing in pain and neurosurgery, cardiovascular anesthesia and surgery, and a limited number of cardiologists specializing in specific interventions. There is a critical need in Canada to increase awareness of RFA diagnosis and assessment, and provide the broader

clinical community with evidence-informed recommendations about the available therapeutic options for safe and optimal pain management. It was our recommendation to the CCS that these aims be met through the development and implementation of joint CCS/CPS clinical practice guidelines for the assessment and management of RFA. These guidelines should follow AGREE criteria (27) to ensure that all relevant stakeholder groups (ie, decision makers, scientists, clinicians, patients and family members) are represented to produce guidelines that take into account the requisite assessment skills and criteria for making a correct diagnosis (including the characterization of RFA and related symptomatic equivalents); and the feasibility of treatment options and barriers to access. These guidelines should fit with current clinical acumen; the context and resources of the Canadian health care system; future research and capacity building needs for RFA care; and use appropriate language, media and knowledge translation strategies known to maximize end-user uptake.

By virtue of a joint effort between the CCS and CPS, these guidelines would also integrate pain and cardiovascular perspectives, both of which are critical to effective RFA-related care. We have secured funding from the CIHR to convene a CCS/CPS guidelines team with scientific, clinical, decision-maker, patient and family representation from across Canada. This position statement will be retired by the CCS once the AGREE-compliant clinical practice guidelines for RFA assessment and management are released.

CONCLUSION

RFA is a debilitating, chronic disease characterized by severe, unremitting cardiac pain. The pain of RFA severely impairs health-related quality of life and is of growing global concern; the impending burden of this condition to the health of Canadians has not been adequately addressed. RFA is resistant to all conventional treatments for CAD and there is a critical need to raise awareness of the pain and cardiovascular mechanisms involved that have implications for appropriate assessment and treatment. In the present position statement, we have made three initial recommendations for advancing the care of Canadians living with RFA pertaining to assessment of disease burden, adoption of an updated definition of RFA to guide future clinical practice and research, and development of a formal, strategic collaboration of the CCS and CPS to address the problem of RFA.

SECONDARY PANELISTS: Paul W Armstrong MD FRCPC, Joan Tranmer RN PhD, Martin Juneau MD FRCPC, Sammy Chan MD FRCPC and Anthony Graham MD FRCPC.

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