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Clinical Practice Variations in the Management of Stress-Induced Cardiomyopathy: A Canadian Perspective

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ABSTRACT

Despite increased recognition of stress-induced cardiomyopathy (SIC), there are no randomized controlled trials or established guidelines to direct therapeutic strategies and little is known about the local experience in Canada. The objective of this study was to better understand the clinical practice variations in the management of SIC across Canada. By using an online platform, a series of questions were distributed to practicing cardiologists between October and November 2018. In total, 172 cardiologists completed the survey. Although many cardiologists have managed patients with SIC, more than two-thirds do not adhere to any guidelines or references. Of those who do, the top referenced resources included expert consensus statements from the American College of Cardiology, the European Society of Cardiology,

RÉSUMÉ

Même si la cardiomyopathie de stress est de plus en plus reconnue, aucune étude contrôlée à répartition aléatoire n'a été réalisée ni aucune ligne directrice émise afin d'orienter la stratégie de traitement, et on en sait peu sur l'expérience à ce sujet au Canada. Cette étude visait à améliorer la compréhension des diverses pratiques cliniques pour la prise en charge de la cardiomyopathie de stress au Canada. Une série de questions a été distribuée à des cardiologues par le truchement d'une plate-forme en ligne entre octobre et novembre 2018. Au total, 172 cardiologues ont répondu au sondage. Même si de nombreux cardiologues avaient déjà traité des patients présentant une cardiomyopathie de stress, plus des deux tiers d'entre eux n'avaient consulté aucune ligne directrice ni aucune référence. Parmi ceux qui

First described in 1990, Takotsubo syndrome or stress-induced cardiomyopathy (SIC) is a condition characterized by left ventricular (LV) dysfunction in the absence of occlusive coronary artery disease (CAD), often preceded by a stressful event that can be an emotional or a physical trigger.[1] SIC was previously believed to be benign, but contemporary studies report increased rates of complications ranging from cardiogenic shock to long-term mortality exceeding that of ST-elevation myocardial infarctions.[2,3] Despite increased recognition, there are no randomized control trials or established guidelines to direct therapeutic strategies in the acute stage or to prevent recurrence.[4] As such, there exists clinical equipoise for the management of SIC, and little is known about the local experience in Canada. Therefore, the objective of this study is to better understand and define the clinical practice variations in the management of SIC across Canada.

Methods

This was a prospective study that used an online platform (Google Surveys, 2018) to distribute a series of 10 questions (Table 1) via email to practicing cardiologists throughout Canada between October and November 2018. Cardiology trainees and internists were excluded from the study population. Ethics approval was obtained by the local university research ethics board. To maximize the number of respondents, the program directors for Adult Cardiology Residency Training were contacted in each province to help distribute the survey link via email in their academic centers. We also reached out to the Canadian Cardiology Society by posting the link on the Members' Online Bulletin Board. Finally, the Association des Cardiologues du Quebec was contacted to help distribute the survey link to their members via email. The data were descriptively summarized and presented using IBM SPSS Statistics Version 25 (SPSS Inc., Chicago, IL).

Results

In total, 172 participants across Canada completed the survey, representing approximately 11% of the practicing cardiologists in the country per the latest Canadian Medical Association workforce profile from 2018 (https://www.cma.ca/sites/default/files/2019-01/cardiology-e.pdf). The highest

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general heart failure guidelines, and UpToDate. Regarding investigations, most participants routinely order TTEs and coronary angiograms, and a minority would order pheochromocytoma workup. Common medications prescribed for hemodynamically stable patients include β-blockers, angiotensin-converting enzyme inhibitors, antiplatelet agents, and anticoagulation. Some 3% of participants reported not prescribing any cardiac medications. Most respondents follow up with patients with SIC within a 3-month period. The risk factors most believed to be associated with SIC included female gender, anxiety, older age, ethnicity, and diabetes. No participants believed that male gender was a risk factor. Many participants believed there needs to be improvements made, such as a Canadian guideline, a Canadian registry, or dedicated workshops at the national cardiology conference. This study demonstrates ongoing variability in the clinical management of SIC across Canada and illustrates a potential area for further research.

l'avaient fait, les principales ressources utilisées comme référence comprenaient les énoncés consensuels d'experts de l'*American College of Cardiology* et de la Société européenne de cardiologie, les lignes directrices générales sur l'insuffisance cardiaque, et le système UpToDate. En ce qui concerne les examens, la plupart des répondants demandent systématiquement une échocardiographie transthoracique et une coronarographie, et une minorité demande la recherche d'un phéochromocytome. Les médicaments couramment prescrits aux patients dont l'hémodynamie est stable comprennent les bêtabloquants, les inhibiteurs de l'enzyme de conversion de l'angiotensine, les antiplaquettaires et les anticoagulants. Environ 3 % des répondants ont rapporté ne prescrire aucun médicament pour le cœur. La plupart des répondants effectuent un suivi auprès des patients présentant une cardiomyopathie de stress à l'intérieur de 3 mois. Les facteurs de risque qui sont le plus associés à la cardiomyopathie de stress selon les répondants sont le sexe féminin, l'anxiété, l'âge avancé, l'origine ethnique et le diabète. Aucun répondant ne considérait le sexe masculin comme un facteur de risque. De nombreux répondants estimaient que des améliorations devraient être apportées dans le domaine de la cardiomyopathie de stress, qu'il s'agisse de lignes directrices canadiennes, d'un registre canadien, ou d'ateliers consacrés à ce sujet offerts dans le cadre de conférences nationales sur la cardiologie. Cette étude montre la variabilité de la prise en charge clinique de la cardiomyopathie de stress au Canada à l'heure actuelle, et désigne un domaine dans lequel de plus amples recherches seraient nécessaires.

percent response rates were from the following provinces: Manitoba 71% (24/34), Quebec 14% (67/481), British Columbia 13% (19/150), Alberta 11% (18/165), and Ontario 7% (39/569). There were 4 respondents (2.3%) from Nova Scotia and Newfoundland/Labrador and 1 respondent (0.6%) from Saskatchewan. Most work primarily in an academic centre, specifically 44% in quaternary and 36% in tertiary hospitals. The remaining proportion reported working primarily in a community setting (33/172), either in a community hospital (16%) or outpatient clinics (3%).

Although most cardiologists have managed SIC in their practices (99%), more than two-thirds (68%) do not adhere to any guidelines or references. Of those who do, the top referenced resources included expert consensus statements from the American College of Cardiology, the European Society of Cardiology, general heart failure guidelines, and UpToDate. Regarding investigations, most participants routinely order transthoracic echocardiograms (TTEs) (96%), coronary angiograms (92%), and cardiac magnetic resonance imaging (34%), and 11% would order pheochromocytoma workup. Only 2% of respondents would order computed tomography of the head or other brain imaging, and 1% would not order any investigations. Among the top responding provinces, most would concurrently order a TTE and coronary angiogram (Alberta, 100%; British Columbia, 84%; Manitoba, 75%; Ontario, 97%; Quebec, 93%). Few participants (<1%) would order investigations on a case-by-case basis, including coronary computed tomography angiography or multigated acquisition scan.

Medications prescribed for hemodynamically stable patients included β-blockers (92%), angiotensin-converting enzyme (ACE) inhibitors (88%), aspirin (29%), diuretics (19%), oral or intravenous anticoagulation (13%), statins (9%), antiplatelet agents including clopidogrel or ticagrelor (5%), nitrates (4%), and calcium channel blockers (1%) (Fig. 1). Among the top responding provinces, most would prescribe both β-blockers and ACE inhibitors concurrently (Alberta, 89%; British Columbia, 79%; Manitoba, 79%; Ontario, 82%; Quebec, 88%). Likewise, among academic cardiologists, 83% would concurrently prescribe β-blockers and ACE inhibitors, compared with 91% of community cardiologists. Three percent of participants reported not prescribing any cardiac medications to patients with SIC.

More than 85% of respondents routinely follow up with patients with SIC, notably at 1 month (40%), 2 months (13%), and 3 months (33%). Often, LV function is reassessed at follow-up (97%).

Table 1. Questions from the Canadian Stress-Induced Cardiomyopathy Survey

1. Where do you currently practice?
2. In what setting do you primarily carry out your practice?
3. Have you previously or currently manage patients with Takotsubo syndrome in your practice?
4. Are there guidelines or references you adhere to when managing these patients?
5. Which investigations do you routinely order for patients with Takotsubo syndrome?
6. Which of the following medications do you prescribe for hemodynamically stable patients with Takotsubo syndrome?
7. When do you follow up with these patients?
8. If you do follow up with these patients, do you routinely reassess LV function?
9. What improvements, if any, do you think are needed for this condition?
10. What risk factors do you think are associated with Takotsubo syndrome?

LV, left ventricular.

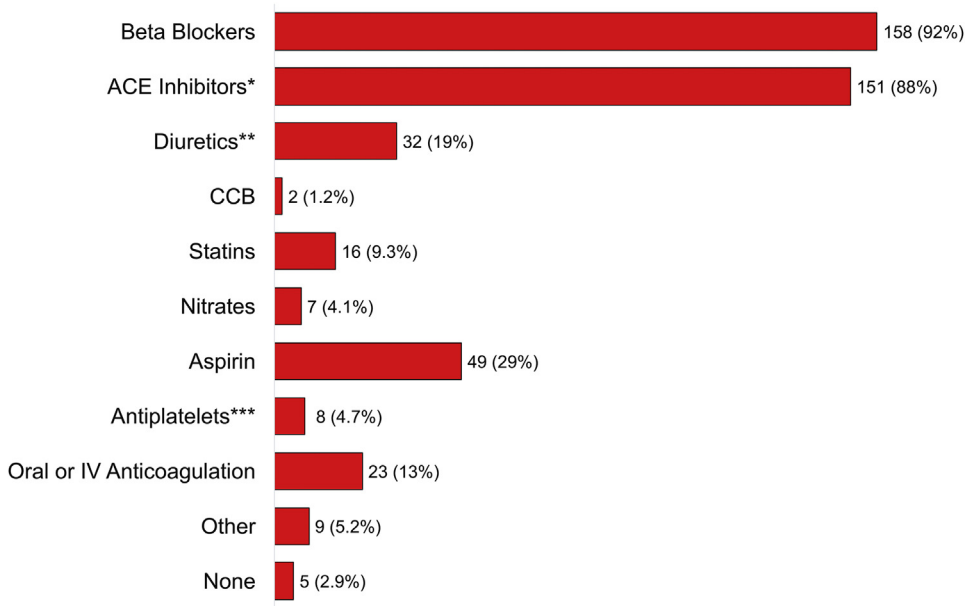

Figure 1. Medications prescribed for hemodynamically stable patients with stress-induced cardiomyopathy (SIC). ACE, angiotensin-converting enzyme; CCB, calcium channel blocker. *ACE inhibitors do not include angiotensin receptor blockers. **Diuretics may include all classes of relevant diuretics: loop diuretics, potassium-sparing diuretics, and thiazides. ***Antiplatelets specifically refer to clopidogrel or ticagrelor.

Risk factors most believed to be associated with SIC included female gender (95%), anxiety (67%), increased age (49%), hypertension (23%), smoking (18%), race or ethnicity (14%), diabetes (9%), dyslipidemia (9%), alcohol abuse (7%), and CAD (7%). No participants believed that male gender was a risk factor, and 3% of respondents believed there were no risk factors associated with SIC.

From the multiple choice options provided for improvements needed for SIC, 65% of respondents believed there needs to be a Canadian guideline or an expert consensus statement, 59% suggested more randomized control trials or high-quality systemic reviews/meta analyses, 26% preferred workshops or dedicated forums at the national cardiology conference, and 9% believed that no further improvements are needed. For those who answered "other," notable responses included a Canadian statement on myocardial infarction due to nonocclusive CAD, expert consensus White Paper, and more studies on the pathophysiology of SIC. A potential centralized Canadian Registry with supporting images was also suggested.

Discussion

To our knowledge, this is the first study to report the clinical practice variations in the management of SIC across Canada. The survey demonstrates areas of heterogeneity and illustrates a potential for future research to guide our treatment.

With the increasing recognition of SIC, worse outcomes are now reported and are not benign as previously believed. Compared with age- and gender-matched patients with ST-elevation myocardial infarction, long-term all-cause mortality was significantly higher for patients with SIC[2] and approximately 10% of patients with SIC were reported to experience cardiogenic shock during their hospital course, with increased mortality within the first 60 days and at 5-year follow-up.[3] Of note, established risk factors associated with the development of SIC, such as female gender and older age, do not necessarily portend worse outcomes in this population. Rather, independent predictors of mortality and adverse outcomes included male sex, physical stress factors (compared with emotional stressors), higher Killip class, and diabetes mellitus.[2] Patients with cardiogenic shock were more frequently male and younger, more often experienced physical triggers, were less frequently taking ACE inhibitors or angiotensin-receptor blockers on presentation, and had a higher prevalence of atrial fibrillation, diabetes, or smoking.[3] Although all respondents recognized that male gender is not a risk factor for the development of SIC,[1] it is a marker of poor prognosis, and further research is needed to better understand the gender differences related to SIC.

The current level of evidence for the medical management of SIC is Level C at best, based on clinical experience and expert consensus.[4] A review of the literature suggests that β-blockers are not beneficial for major adverse events during hospitalization, for mortality, or to prevent long-term recurrence.[4] However, expert consensus do suggest the acute use of β-blockers for treatment of SIC in patients with or without signs of heart failure and arrhythmias.[4] Few studies have reported the benefit of ACE inhibitors and angiotensin-receptor blockers for improving survival and preventing recurrence, and little is known about the role of antiplatelet agents, statins, and anticoagulation.[4] In our survey, the majority would concurrently prescribe β-blockers and ACE inhibitors, suggesting the prescribing pattern for both medications is high and consistent among cardiologists across Canada. Additionally, the role of anticoagulation in this population continues to remain largely unknown, with the incidence of thromboembolism ranging from 5% to as high as 14%.[5] Approximately 15% of respondents would prescribe anticoagulation to

patients with SIC, consistent with expert consensus recommending the consideration for anticoagulation in patients with LV ejection fraction $\leq$ 30% or evidence of large LV apical thrombus.[4] However, the indications, duration, and end point for treatment remain unknown, because this was not an intention of this survey.

Currently, there are multiple diagnostic criteria for SIC with lack of worldwide consensus regarding the role of concomitant CAD. The International Takotsubo Diagnostic Criteria explicitly state that significant CAD is not a contraindication. In these circumstances, although coronary angiography with left ventriculography may be the standard diagnostic tool,[1] a normal angiogram may not be sufficient and likely would require additional investigations. In keeping with this, a majority of respondents from our survey would concurrently order a TTE and coronary angiogram as part of the investigation for SIC.

We recognize that participants who completed the survey likely represented the most interested cardiologists in Canada. Therefore, although the majority believed that improvements are needed, there is an inherent volunteer bias. From a practical standpoint, it is difficult to execute meaningful clinical trials for a rare condition with limited patient recruitment. Likewise, instead of creating a set of Canadian guidelines, incorporation of our local data into the established international registry may be helpful,[1] because this would provide a means to better understand the epidemiology and unique environmental, social, and genetic variables contributing to SIC in the Canadian population.

Limitations

Multiple means were attempted to distribute the survey widely to nonacademic cardiologists, including contacting the Canadian Medical Association and the Ontario Cardiologist Association, but this was not within the scope of their mandate. As such, the survey was able to reach a small portion of mostly academic cardiologists, with few responses from the Maritime provinces. Therefore, the survey responses may not represent the viewpoints of the collective average. Second, responses were self-reported and may not reflect real-life practice patterns. The approach to management, for instance, may vary significantly on a case-by-case basis depending on the patient's presentation, and respondents may have been susceptible to recency bias.

Conclusion

Although there is increased recognition and understanding of the poor prognosis related to SIC, the management of the condition remains largely based on expert opinion and consensus, with varying clinical practice patterns in Canada. Our survey demonstrates a need for further research to help guide both the acute and the long-term treatment of SIC.

Disclosures

The authors have no conflicts of interest to disclose.

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