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Using coronary calcification to exclude an ischemic etiology for cardiomyopathy: A validation study and systematic review☆

Manuja Premaratne [a,b], Mohabbat Shamsaei [a], Jonathan D.H. Chow [a], Tony Haddad [a], Fernanda Erthal [a], Helen Curran [c], Yeung Yam [a], Agnieszka Szczotka [e], Lisa Mielniczuk [a], George A. Wells [d], Rob S. Beanlands [a], Alomgir Hossain [d], Benjamin J.W. Chow [a,*], On behalf of the IMAGE-HF investigators:

[a] University of Ottawa Heart Institute, Division of Cardiology, Canada
[b] Frankston Hospital, Department of Medicine, Frankston, Australia
[c] Dalhousie University and Queen Elizabeth II Health Sciences Center, Department of Medicine, Halifax, Canada
[d] University of Ottawa Heart Institute, Cardiovascular Research Methods Centre, Canada
[e] University of Ottawa, Health Sciences Library, Canada

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ABSTRACT

Background: Preliminary data suggests the absence of coronary artery calcification (CAC) excludes ischemic etiologies of cardiomyopathy. We prospectively validate and perform a systematic review to determine the utility of an Agatston score = 0 to exclude the diagnosis of ischemic cardiomyopathy.

Methods and results: Patients with newly diagnosed LV dysfunction were prospectively enrolled. Patients underwent CAC imaging and were followed until an etiologic diagnosis of cardiomyopathy was made. Eighty-two patients were enrolled in the study and underwent CAC imaging with 81.7% patients having non-ischemic cardiomyopathy. An Agatston score = 0 successfully excluded an ischemic etiology for cardiomyopathy with a specificity of 100% (CI: 74.7–100%) and a positive predictive value of 100% (CI: 85.0%–100%).

A systematic literature review was performed and studies were deemed suitable for inclusion if: 1) patients with CHF, cardiomyopathy or LV dysfunction were enrolled, 2) underwent CAC imaging and patients were assessed for an Agatston score = 0 or the absence of CAC, and 3) the final etiologic diagnosis (ischemic or non-ischemic) was provided. Eight studies provided sufficient information to calculate operating characteristics for an Agatston score = 0 and were combined with our validation cohort for a total of 754 patients. An Agatston score = 0 excluded ischemic cardiomyopathy with specificity and positive predictive values of 98.4% (CI: 95.6–99.5%), and 98.3% (CI: 95.5–99.5%), respectively.

Conclusions: In patients with cardiomyopathy of unknown etiology, an Agatston score = 0 appears to rule out an ischemic etiology. A screening CAC may be a simple and cost-effective method of triaging patients, identifying those who do and do not need additional CAD investigations.

1. Introduction

Invasive coronary angiography (ICA) is used to assess for coronary artery disease (CAD) in patients presenting with cardiomyopathy or congestive heart failure (CHF) [1,2]. Cardiac computed tomography is an accurate non-invasive modality and is often used for ruling out CAD [3–6]. Both coronary artery calcification (CAC) scans and coronary CT angiography (CCTA) have been proposed as alternatives to ICA in patients with CHF [5,7–11]. The widespread use of CCTA in CHF patients may be limited in individuals with renal insufficiency, arrhythmia, or contraindications to beta-blocker due to hypotension or pulmonary edema. Preliminary data suggests that the absence of CAC (Agatston score = 0) might effectively rule out ischemic cardiomyopathy, [7,12–18] and may be a reasonable cost-effective alternative to ICA in patients with newly diagnosed CHF.

The objective of this study is prospectively validate and perform a systematic review to determine the utility of an Agatston score = 0 to exclude the diagnosis of ischemic cardiomyopathy.

2. Methods

2.1. Prospective cohort

Between 2012 and 2014, 82 patients with newly diagnosed LV dysfunction of unknown etiology were prospectively enrolled. The study

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* Corresponding author at: University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, ON K1Y 4W7, Canada.
E-mail address: bchow@ottawaheart.ca (B.J.W. Chow).

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was approved by the Institutional Human Research Ethics Board and all patients provided informed consent.

2.1.1. Coronary artery calcification imaging and analysis

Patients were imaged irrespective of heart rate or rhythm. In the absence of contraindications, beta-blockers were administered to target ≤65 bpm. A non-contrast enhanced prospective ECG-triggered CT was performed using GE Volume CT with 64 × 0.625 mm slice collimation. Images were reconstructed using filtered backprojection with a 2.5 mm slice thickness [12,19]. Agatston scores were measured using a GE Advantage workstation or Aquarius iNtuition [12,19].

The etiology of LV dysfunction was made using Felker's definition [20].

2.2. Systematic literature review

A literature search was performed across six databases (MEDLINE, Pubmed, Embase, Health Technology Assessment, Cochrane Database of Systematic Review and Cochrane Central Register of Controlled Trials). The search terms are listed (supplemental 1) and the strategy was limited to articles after the publication of the Agatston score [21]. Studies that used CAC or CCTA and the Agatston score to differentiate between ischemic and non-ischemic cardiomyopathy were included. Two independent reviewers screened all titles and the abstracts of potential studies were reviewed. Discrepancies were resolved by consensus. Studies were deemed suitable for inclusion if: 1) patients with CHF, cardiomyopathy or LV dysfunction were enrolled, 2) underwent CAC imaging and patients were assessed for an Agatston score = 0 or the absence of CAC, and 3) the final etiologic diagnosis (ischemic or non-ischemic) was provided. Out of 6432 articles, a total of 21 CAC studies, 32 CCTA studies, and 32 review articles were reviewed in detail. The references for these articles and additional review articles were also searched to ensure that no others were missed. Eight studies provided sufficient information for inclusion [7,12–18]. Of the 710 patients in the systematic review, only the 672 patients with confirmed CHF etiology were included in the analysis. In the study that used >1 definition for ischemic cardiomyopathy, the Felker classification was used in our analysis [20].

2.3. Statistical analysis

Statistical analyses were performed using SAS. Continuous variables were presented as means and standard deviations, and categorical variables were presented as frequencies with percentages. Patient characteristics were compared using the Wilcoxon rank sum test and the Fisher's exact test. Operating characteristics of Agatston score = 0 for detecting non-ischemic cardiomyopathy were calculated. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Prospective cohort

Over an enrolment period of 17 months, 109 patients were prospectively screened. Twenty-seven patients were excluded because they did not have heart failure, did not undergo CAC imaging or CAC images were not available for analysis. The final cohort was comprised of 82 CHF patients with 67 (81.7%) patients having non-ischemic cardiomyopathy (Table 1). The most common causes of non-ischemic cardiomyopathy were idiopathic/unknown etiology (46.3%), arrhythmia (16.4%) and toxic exposure (14.9%).

All patients without coronary calcification had non-ischemic cardiomyopathy (Table 2). An Agatston score = 0 was able to successfully exclude ischemic etiology for cardiomyopathy with a specificity of 100% and a positive predictive value of 100% (Table 2). Conversely, Agatston > 0 was not a good discriminator for an ischemic etiology, with 39 of 54 patients with Agatston score > 0 having non-ischemic cardiomyopathy.

3.2. Systematic review

We combined our data with those of others for a total of 754 patients (Table 2). An Agatston score = 0 excluded CAD with a sensitivity, specificity, positive and negative predictive values of 46.4%, 98.4%, 98.3%, and 46.9%, respectively (Table 3) and had an area under the receiver operator curve of 0.943 (Figs. 1 and 2). The weighted positive and negative likelihood ratios were 59.0 and 1.13, respectively (Fig. 3). A subanalysis, using studies published after Felker's definition of ischemic cardiomyopathy, yielded similar results (Table 4).

Table 1
Patient characteristics.

	All patients (n = 82)	Agatston score = 0 (n = 28)	Agatston score > 0 (n = 54)	p	Ischemic (n = 15)	Non-ischemic (n = 67)	p
Age	56.2 ± 12.0	50.0 ± 11.5	59.4 ± 11.1	0.001	65.6 ± 8.7	54.0 ± 11.7	0.001
Men	53 (64.6%)	14 (50.0%)	39 (72.2%)	0.055	13 (86.7%)	40 (59.7%)	0.072
Body mass index (kg/m^2)	28.9 ± 6.0	29.2 ± 6.0	28.8 ± 6.1	0.749	29.8 ± 6.3	28.7 ± 6.0	0.526
Diabetes	7 (8.5%)	1 (3.6%)	6 (11.1%)	0.413	3 (20.0%)	4 (6.0%)	0.111
Smoker/ex-smoker	41 (50.0%)	10 (35.7%)	31 (57.4%)	0.102	9 (60.0%)	32 (47.8%)	0.569
Hypertension	41 (50.0%)	16 (57.1%)	25 (46.3%)	0.485	8 (53.3%)	33 (49.3%)	1.000
Hyperlipidemia	31 (37.8%)	5 (17.9%)	26 (48.1%)	0.009	11 (73.3%)	20 (29.9%)	0.003
Family history of CAD	29 (35.4%)	9 (32.1%)	20 (37.0%)	0.808	7 (46.7%)	22 (32.8%)	0.375
HR (bpm)	69.7 ± 12.5	72.1 ± 12.6	68.4 ± 12.4	0.197	69.9 ± 10.8	69.6 ± 12.9	0.926
Systolic BP (mmHg)	130.9 ± 22.0	127.1 ± 19.9	132.8 ± 22.9	0.274	135.9 ± 23.3	129.7 ± 21.7	0.325
Diastolic BP (mmHg)	75.6 ± 11.8	74.1 ± 13.5	76.4 ± 10.9	0.395	74.6 ± 11.3	75.9 ± 12.0	0.705
Creatinine (μmol/l)	89.2 ± 92.1	72.6 ± 16.8	97.9 ± 112.2	0.240	92.3 ± 17.6	88.6 ± 101.7	0.889
GFR (ml/min)	113.0 ± 44.4	128.6 ± 45.7	104.9 ± 41.9	0.021	89.5 ± 24.8	118.3 ± 46.3	0.022
Left ventricular ejection fraction (%)[a]							
Mean	34.1 ± 9.9	35.3 ± 10.2	34.4 ± 9.8	0.463	33.0 ± 9.0	34.3 ± 10.2	0.665
Median (interquartile range)	34.0 (25.0.42.0)	32.0 (30.0.45.0)	36.0 (25.0.40.0)		35.0 (25.0.41.5)	33.0 (26.5.42.0)	
Radiation dose							
Dose length product (mGy * cm)	143.1 ± 27.1	144.2 ± 29.8	140.8 ± 21.0	0.591	151.7 ± 24.1	141.1 ± 27.5	0.172
Effective dose (mSv)	2.4 ± 0.5	2.5 ± 0.5	2.4 ± 0.4	0.591	2.6 ± 0.4	2.4 ± 0.5	0.172

CAD: coronary artery disease.
[a] n = 67.

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