Diversity and Equality in Health and Care (2020) 17(5): 180-183
DOI: 10.36648/2049-5471.17.3.211

Research Article

Referral Bias in Coronary Micro vascular Dysfunction: a Retrospective Study

Mary McCarthy*, Olga Toleva, Karen Elliott, Chris Ardern, Steven Miner

Southlake Regional Health Center, Newmarket, ON, Canada

ABSTRACT

Obstructive coronary artery disease (CAD) is a well-defined condition and a significant cause of myocardial ischemia. Patients with angina typically undergo non-invasive cardiac investigations initially as a means of risk-stratifying. Coronary angiography is the diagnostic test of choice for patients with chest pain (angina) and signs of myocardial ischemia on non-invasive testing. Typically CAD is diagnosed based on the patency of the epicardial coronary arteries [1]. Approximately 30% of patients with angina have non-obstructive arteries on coronary angiogram and area diagnostic and management challenge for clinicians, contributing to significant social and economic burden [2]. They undergo multiple angiograms, experience a hospitalization rate 80% greater than patients with single vessel CAD and up to 50% have persistent symptoms leading to functional disability [3]. Historically, this population was given reassurance as long-term prognosis was believed to be benign [4]. We now know that a subset of these patients suffer from coronary micro vascular dysfunction (MVD) [1] and are at increased risk for adverse cardiac events including congestive heart failure (CHF), myocardial infarction (MI), left ventricular (LV) dysfunction, and death [1,5].

The Cardiovascular Integrated Physiology (CVIP) program at Southlake Regional Health Centre (SRHC) investigates and manages patients with MVD. CVIP has received referrals for only a small fraction of patients with angina and non-obstructive angiograms at SRHC. It is unclear what factors promote referral. We hypothesized that referrals were not random and that the clinical characteristics of the referred patients differed from the larger population of patients with angina and non-obstructive CAD. The primary objective of this study was to determine whether the patients referred to CVIP are an accurate representation of the overall population of patients with angina and non-obstructive coronary arteries.

Keywords: Obstructive coronary artery disease; Patients; Population

Methods and Procedures

The study was approved by the Research Ethics Board at SRHC.

Patient population

Two sub groups of patients were analyzed. The first included all patients referred for angiography with high-risk non-invasive testing to rule out CAD but with non-obstructive coronary angiograms at SRHC from 2016-2018 (n=1,816). The second included patients referred to CVIP for the assessment of possible MVD due to the presence of angina and non-obstructive CAD from 2017-2018 (n=281).

Data sources

Data was retrospectively obtained from two databases. The Cor Health database is a provincial administrative database that gathers patient information on various cardiac procedures for the measurement of quality and outcomes. Only data relating to SRHC was abstracted for this study. The TEAMWORKS© database gathers patient information relating to their clinic or procedural visit. It serves as both a research database and a reporting tool.

Cor Health data was collected from the patient's angiogram referral form and angiogram report and entered into the Cor Health database by data clerks. This information included age, sex, ethnicity, co-existing co morbidities, coronary risk factors, significant cardiac history, electrocardiogram, left ventricular (LV) function, non-invasive cardiac investigations and angiogram results.

Data from TEAMWORKS© was obtained during the patient's CVIP clinic visit. Patients completed a questionnaire consisting of questions about their race/ethnicity, social history, and medical history. Patients were assessed by a nurse practitioner who gathered the patient's past medical history, previous cardiac investigations and symptom history. Physical examination included blood pressure, heart rate, height, weight, and body mass index. Where appropriate, patients had a transthoracic echocardiogram and a symptom-limiting graded exercise stress test (GXT). Patients were also assessed by an interventional cardiologist who determined whether the patient was an appropriate candidate for an invasive coronary physiology study. Patient data collected from CVIP was electronically stored into TEAMWORKS©. Patient information was extracted from the database for the purpose of analysis.

Statistical analysis

Results of continuous (mean ± SD) and categorical (%) variables were compared using chi square and two-tailed independent t-tests, respectively. A P value of <0.05 was considered statistically significant.

Results

From 2016-2018, 21% of patients undergoing angiography

Table 1: Comparison of patients referred to CVIP for suspected MVD versus those referred for angiography to rule out CAD but with non-obstructive angiograms (Cor Health).

Variable	CVIP MVD (n= 281)	CorHealth Non-obstructive, high risk non-invasive (n=1,816)	P Value
Sex (% female)	63	43	<0.0001
Age (years)	58 ± 11.8	63±11	<0.0001
White Ethnicity (%)	83	79	<0.0001
Weight (kg)	80 ± 20	88±21.6	<0.0001
Hypertension (%)	51	64	0.0001
Hyperlipidemia (%)	48	63	<0.0001
Smoking (%)			
Never	51	48	0.0001
Former	37	36	
Current	12	12	
Unknown	0	4	
Diabetes (%)	20	25	0.07
CHF (%)	2	3	0.13
LV Function (%)			
Normal	72	79	<0.0001
Mild Dysfunction	23	10	
Moderate Dysfunction	0.5	3	
Severe Dysfunction	0.5	0	
Unknown	4	8	

at SRH Crafter having a high-risk non-invasive cardiac test were found to have non-obstructive CAD (n=1,816). From 2017-2018, 281 patients were referred to CVIP for suspected MVD. The clinical characteristics of these patient populations were compared and are presented in Table 1 (Table 1). Comparing CVIP MVD patients with Cor Health non-obstructive patients revealed that patients referred to CVIP tended to be younger (58 ± 11.8 vs 63 ± 11, p<0.0001), more likely to be female (63% vs 43%, p<0.0001), of white ethnicity (83% vs 79%, p<0.0001), weighed less (80 ± 20 kg vs 88 ± 21 kg, p<0.0001), with less hypertension (51% vs 64%, p=0.0001), hyper lipidemia (48% vs 63%, p<0.0001), and no difference in diabetes (20% vs 25%, p=0.07). There were significant differences in smoking status: never smoked (51% vs 48%); former smoker (37% vs 36%); current smoker (12% vs 12%); unknown smoking history (0% vs 4%), p=0.0001. There were no significant differences in the prevalence of CHF (2% vs 3%, p=0.13), however there were differences between LV function: normal function (72% vs 79%); mild dysfunction (23% vs 10%); moderate dysfunction (0.5% vs 3%); severe dysfunction (0.5% vs 8%); unknown LV function (4% vs 8%), p<0.0001.

Discussion

This study revealed that patients referred for the investigation of possible MVD do not accurately reflect the larger population of patients with angina and non-obstructive CAD. A referral bias was demonstrated that favours younger, thinner, white females with fewer traditional CV risk factors, and better LV function.

An overarching theme in the current literature surrounding MVD is that a sex difference exists in those who are affected by MVD. As a result men have been underrepresented in studies [6]. One study found that MVD was common in both sexes and was associated with adverse events [7]. We found that patients referred to CVIP for suspected MVD were more likely to be female, yet the majority (57%) of patients with non-obstructive CAD found at the time of angiography were male. This referral bias suggests that clinicians believe that MVD typically affects females. Underrepresentation of men in research of MVD is problematic as it disregards the potential impact of MVD in the male population.

Ethnic differences in CV disease have also been extensively researched. Factors aside from geographic location may contribute to the development of CV disease such as genetic predisposition to various disease states [8]. South Asians living in the United States and African Americans are at a higher risk for developing ischemic heart disease due to many causes including higher prevalence of traditional CV risk factors [8,9]. Patients referred to CVIP were disproportionately of white ethnicity. It is unclear whether this is a result of the geographic homogeneity or the referring clinician's bias. This is of concern because the WISE study found that women of non-white race had higher rates of mortality [10]. Non-white ethnic groups have higher rates of CV risk factors which have been associated with the development of MVD [11]. There may be other ethnic factors relating to the development of MVD and this hypothesis will be difficult to determine if non-white patients are disproportionately excluded from advanced testing.

The referral patterns to CVIP also revealed a bias away from most traditional CV risk factors. Patients referred to CVIP had less hypertension and hyper lipidemia compared to Cor Health patients with non-obstructive CAD. Traditional CV risk factors have been associated with the development of MVD [11] and were independent predictors of all-cause mortality in the WISE study [12]. The current data suggests a referral bias in the opposite direction for reasons which are unclear.

Numerous studies have found a link between aging and MVD, thought to be from the effects of vascular remodelling that comes with the aging process [1,5]. Older women with MVD had an increased risk of CV mortality compared to younger women [12]. CVIP receives referrals for women who are younger than the overall population of patients with angina and non-obstructive coronary arteries. The reason for this bias is unclear and would tend to exclude those at highest risk of adverse cardiovascular events.

Progressive LV dysfunction has been implicated in MVD [5]. A growing body of research suggests a link between heart failure with preserved ejection fraction (HFpEF) and MVD [13]. Patients referred to CVIP for suspected MVD had better LV function and lower incidence of CHF which is particularly counterintuitive given the association between MVD and HFpEF [13-20].

This study has multiple limitations. The Cor Health data does not give a thorough understanding of the patient's symptom burden, which may be a driver for referral. TEAMWORKS© is a clinical database and as such captures more detailed data than Cor Health. This may lead to overrepresentation of some disease states in the CVIP data. Since our concern relates to lower prevalence of CV risk factors, this limitation does not seem to affect our conclusions. Comparing body mass index would have been superior to using weight, especially given the differences in sex, however the Cor Health database did not collect BMI. This dataset does not include definitive diagnoses for the CVIP patients, thus we cannot conclude that patients were referred inappropriately [21-27].

Conclusion

MVD is a poorly understood, but emerging condition that plays a significant role in a subset of patients with angina and non-obstructive coronary arteries. Our data suggests a significant referral bias that may not reflect our current understanding of MVD and potentially limits future research. Efforts to educate clinicians on potential risk factors for development of MVD should be utilized in order to reduce bias in the referrals and capture a broader population of patients who may be affected by MVD.

Conflict of Interest

The authors declare that there is no conflict of interest.

Funding

Mary McCarthy received funding for this research from the Registered Nurses Association of Ontario Advanced Clinical Nursing Fellowship.

References

1. Chen C, Wei J, AlBadri A, Zarrini P, Bairey Merz CN (2016) Coronary Micro vascular Dysfunction - Epidemiology, Pathogenesis, Prognosis, Diagnosis, Risk Factors and Therapy. Circ J 81(1): 3-11.
2. Marinescu MA, Löffler AI, Ouellette M, Smith L, Kramer CM, et al. (2015) Coronary micro vascular dysfunction, micro vascular angina, and treatment strategies. JACC Cardiovasc Imaging 8(2): 210-20.
3. Jones E, Eteiba W, Merz NB (2012) Cardiac Syndrome X and Micro vascular Coronary Dysfunction. Trends Cardiovasc Med 22(6): 161-8.
4. Kaski JC, Rosano GMC, Collins P, Nihoyannopoulos P, Maseri A, et al. (1995) Cardiac syndrome X: Clinical characteristics and left ventricular function: Long-term follow-up study. J Am Coll Cardiol 25(4): 807-14.
5. Mittal SR (2015) Diagnosis of coronary micro vascular dysfunction - Present status. Indian Heart J 67(6): 552-60.
6. Petersen JW, Pepine CJ (2014) The prevalence of micro vascular dysfunction, its role among men, and links with adverse outcomes: Non invasive imaging reveals the tip of the iceberg. Circulation 129(24):2497-9.
7. Davies (2008) Genetic changes NIH Public Access. Bone 23(1):1-7.
8. Volgman AS, Palaniappan LS, Aggarwal NT, Gupta M, Khandelwal A, et al. (2018) Atherosclerotic Cardiovascular Disease in South Asians in the United States: Epidemiology, Risk Factors, and Treatments: A Scientific Statement From the American Heart Association. Circulation. 138: 1-34.
9. Saab KR, Kendrick J, Yracheta JM, Lanaspa MA, Pollard M, et al. (2015) New insights on the risk for cardiovascular disease in African Americans: The role of added sugars. J Am Soc Nephrol 26(2): 247-57.
10. Pauly DF, Johnson BD, Anderson RD, Handberg EM, Smith KM, et al. (2011) In women with symptoms of cardiac ischemia, non obstructive coronary arteries, and micro vascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved micro vascular function: A double-blind randomized study from the National Hea. Am Heart J 162(4): 678-84.
11. Lanza GA, Crea F (2010) Primary coronary micro vascular dysfunction: Clinical presentation, pathophysiology, and management. Circulation 121(21): 2317-25.
12. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, et al. (2010) Coronary Micro vascular Reactivity to Adenosine Predicts Adverse Outcome in Women Evaluated for Suspected Ischemia. Results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) Study. J Am Coll Cardiol 55(25): 2825-32.
13. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, et al. (2018) Prevalence and correlates of coronary micro vascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J 39(37): 3439-50.
14. Fioranelli M, Bottaccioli AG, Bottaccioli F, Bianchi M, Rovesti M, et al. (2018) Stress and inflammation in coronary artery disease: A review psycho neuro endocrine immunology-based. Front Immunol.
15. Recio-Mayoral A, Mason JC, Kaski JC, Rubens MB, Harari OA, et al. (2009) Chronic inflammation and coronary micro vascular dysfunction in patients without risk factors for coronary artery disease. Eur Heart J 30(15): 1837-43.
16. Vogelzangs N, Beekman ATF, De Jonge P, Penninx BWJH (2013) Anxiety disorders and inflammation in a large adult cohort. Transl Psychiatry 3(4): e249-8.
17. Harada M, Van Wagoner DR, Nattel S (2015) Role of inflammation in Atrial fibrillation pathophysiology and management. Circ J 79(3): 495-502.
18. Sokolove J, Lepus CM (2013) Role of inflammation in the pathogenesis of osteoarthritis: Latest findings and interpretations. Ther Adv Musculoskelet Dis 5(2): 77-94.
19. Yoshida N (2007) Oxidative Stress in Digestive Disease Guest Editor: Yuji Naito Inflammation and Oxidative Stress in Gastroesophageal Reflux Disease. J Clin Biochem Nutr 40(1): 13-23.
20. Amodeo G, Allegra Trusso M, Fagiolini A (2018) Depression and Inflammation: Disentangling a Clear Yet Complex and Multifaceted Link. Neuropsychiatry (London) 7(4): 448-57.
21. Garvey JF, Taylor CT, McNicholas WT (2009) Cardiovascular disease in obstructive sleep apnoea syndrome: The role of intermittent hypoxia and inflammation. Eur Respir J 33(5): 1195-205.
22. Hayward C (1995) Psychiatric Illness and Cardiovascular Disease Risk. Epidemiol Rev 17(1): 129-38.
23. Chaddha A, Robinson EA, Kline-Rogers E, Alexandris-Souphis T, Rubenfire M (2016) Mental Health and Cardiovascular Disease. Am J Med 129(11): 1145-8.

24. Vural M, Satiroğlu O, Akbas B, Goksel I, Karabay O (2009) Coronary Artery Disease in Association with Depression or Anxiety. Texas Hear Inst J 36(1): 17-23.

25. Stiermaier T, Thiele H, Eitel I (2016) Prognosis in Patients with Takotsubo Cardiomyopathy. JACC Hear Fail 4(6): 519-20.

26. Konstantinos G, El-Battrawy I, Schramm K, Uzair A, Hoffmann U, et al. (2017) Comparison and outcome analysis of patients with takotsubo cardiomyopathy triggered by emotional stress or physical stress. Front Psychol 8: 527.

27. Brody DJ, Pratt LA, Hughes JP (2018) Prevalence of Depression among Adults Aged 20 and Over: United States, 2013-2016. NCHS Data Brief 303: 1-8.

Address of Correspondence: Mary McCarthy, Southlake Regional Health Centre, 596 Davis Dr, Newmarket, ON, L3Y 2P9, Tel: +19058302605; Email: mmccarthy@southlakeregional.org

Submitted: July 10, 2020; Accepted: August 18, 2020; Published: August 25, 2020