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ORIGINAL ARTICLE

Retrospective Study

Thirty-day readmission in patients with heart failure with preserved ejection fraction: Insights from the nationwide readmission database

Anil Kumar Jha, Chandra P Ojha, Anand M Krishnan, Timir K Paul

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Abstract

BACKGROUND

There are rising numbers of patients who have heart failure with preserved ejection fraction (HFpEF). Poorly understood pathophysiology of heart failure with preserved and reduced ejection fraction and due to a sparsity of studies, the management of HFpEF is challenging.

AIM

To determine the hospital readmission rate within 30 d of acute or acute on chronic heart failure with preserved ejection fraction and its effect on mortality and burden on health care in the United States.

METHODS

We performed a retrospective study using the Agency for Health-care Research and Quality Health-care Cost and Utilization Project, Nationwide Readmissions Database for the year 2017. We collected data on hospital readmissions of 60514 adults hospitalized for acute or acute on chronic HFpEF. The primary outcome was the rate of all-cause readmission within 30 d of discharge. Secondary outcomes were cause of readmission, mortality rate in readmitted and index patients, length of stay, total hospitalization costs and charges. Independent risk factors for readmission were identified using Cox regression analysis.

RESULTS

The thirty day readmission rate was 21%. Approximately 9.17% of readmissions were in the setting of acute on chronic diastolic heart failure. Hypertensive

chronic kidney disease with heart failure (1245; 9.7%) was the most common readmission diagnosis. Readmitted patients had higher in-hospital mortality (7.9% *vs* 2.9%, P = 0.000). Our study showed that Medicaid insurance, higher Charlson co-morbidity score, patient admitted to a teaching hospital and longer hospital stay were significant variables associated with higher readmission rates. Lower readmission rate was found in residents of small metropolitan or micropolitan areas, older age, female gender, and private insurance or no insurance were associated with lower risk of readmission.

CONCLUSION

We found that patients hospitalized for acute or acute on chronic HFpEF, the thirty day readmission rate was 21%. Readmission cases had a higher mortality rate and increased healthcare resource utilization. The most common cause of readmission was cardio-renal syndrome.

Key Words: Heart failure with preserved ejection fraction; Diastolic heart failure; Readmission; National readmission database; Health care resource utilization

Core Tip: Our study highlights the current trend in heart failure with preserved ejection fraction (HFpEF) readmissions, and important causes and predictors of readmissions. It also highlights that mortality in readmission is greater compared to index admissions. The economic burden of HFpEF is also highlighted.

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INTRODUCTION

The prevalence of heart failure (HF) is constantly increasing over time. Approximately 6.2 million adults ≥ 20 years of age were diagnosed with HF between 2013 and 2016 in the United States, which was lower than that in 2009 to 2012 with an estimated 5.7 million diagnosed with HF[1]. Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome with patients having signs and symptoms of HF with normal or near normal left ventricle (LV) ejection fraction as a result of high LV filling pressure [2,3]. Among HF hospitalizations, approximately half are characterized by HFpEF[4]. The prevalence of HFpEF compared to HF with reduced ejection fraction, seems to be going up due to the increasing elderly population.

The total cost associated with HF treatment for 2012 was $30.7 billion. According to Medicare, from 2009 to 2012 the median risk-standardized 30-d readmission rate for HF was 23.0%[1,5]. Readmissions receive greater attention from researchers and policy makers as they are recognized as being related to deficient medical care and a preventable cause of higher healthcare expenditure. The Affordable Care Act introduced a financial penalty for higher readmissions for hospitals that are capped at 3% of a hospital's total Medicare payments for 2015 and beyond. Previously, Medicare's diagnosis-related group payment system lacked a financial disincentive to reduce readmissions[6]. The Centers for Medicare and Medicaid Services' (CMS) Hospital Readmission Reduction Program currently only assesses risk-adjusted 30-d readmission rates for HF, acute myocardial infarctions, pneumonia, chronic obstructive pulmonary disease, and elective total knee and hip arthroplasty[7].

The objective of our study was to use the Healthcare Cost and Utilization Project (HCUP), Nationwide Readmission Database (NRD) 2017 to assess HFpEF readmission rate, compare mortality rate between the index hospitalization and readmissions, assess etiologies, and determine predictors of HFpEF readmissions to recognize areas of improvement and implement the targeted interventions.

MATERIALS AND METHODS

We performed a retrospective analysis of the NRD database of 2017. Our study populations were derived from the HCUP NRD database. The NRD database is sponsored by the agency for healthcare research and quality. It is an administrative database which records de-identified admission data to

acute care hospitals during that specific year. The NRD includes discharges for patients with and without repeat hospital visits in a year and those who have died in the hospital.

In 2017, approximately eighteen million discharges were recorded from 2454 participating hospitals. Variable "NRD_visitlink" was used to identify the patients and the time between the two admissions was obtained by subtracting the variable "NRD_DaysToEvent." Subtracting length of stay of index admissions from time between two admissions provided the interval time to readmission. Index hospitalizations were studied between January to November to facilitate identification of 30-d readmission rates for all discharged patients for the 2017 calendar year. During this specified period, index hospitalizations were defined as non-elective admission with a primary International Classification of Diseases and Related Health Problems (ICD)-10 diagnosis code of acute diastolic heart failure/HFpEF, (I5031) or acute on chronic HFpEF (I5033). Index hospitalizations were excluded if: (1) The patients were younger than 18 years; (2) the patient died during the index hospitalization; and (3) there was no information on the length of stay (LOS).

We extracted baseline patient characteristics such as age, discharge destination, sex, primary expected payer, and median household income from the NRD database. The Charlson comorbidity index was used to determine the effect of chronic comorbidities in patients on primary and secondary outcomes [8]. Hospital-level variables included bed size, rural/urban location, and teaching status. Discharge to a rehabilitation facility was also obtained.

The primary outcome was defined as any non-elective, non-traumatic readmission that occurred within the first 30 d of discharge from the index hospitalization. For index hospitalizations with more than one readmission within 30 d, only the first readmission was included.

Secondary outcomes were: (1) In-hospital mortality rate for index admissions; (2) 30-day mortality rate for index admissions; (3) ten most common principal diagnoses for readmission; (4) in-hospital mortality rate during readmissions; (5) resource utilization due to readmission: LOS, total hospitalizations cost and charges; and (6) independent risk factors for admissions.

For the in-patient mortality rate, we used the patient's recorded vitals at discharge which are directly coded in the NRD database. The thirty-day mortality was calculated by following the patient's vital status at discharge after any readmission within 30-d of index admission.

Total hospitalization charge is the amount that hospitals billed for the entire hospital stay but not equal to the actual cost of care. The HCUP provides hospital-specific cost to charge ratios based on all-payer inpatient cost. We used this information to calculate total cost of hospitalization by multiplying total hospitalization charges by the cost to charge ratio.

We obtained the ten most common reasons for readmission by tallying the principal diagnosis for each readmission. Independent risk factors for readmission were identified using Cox regression analysis. The statistical analyses were performed using STATA statistical software (StataCorp LLC, College Station, TX 77845, United States). P values < 0.005 was considered statistically significant.

RESULTS

The study included 60514 adult patients with acute and acute on chronic HFpEF admitted between January to November in 2017, of which 61.1% of patients were female. The mean age was 74.8 years. About 59.4% patients had a Charlson comorbidity index greater than three. The majority of patients came from large metropolitan areas [46%] and had Medicare insurance (82.4%). The number of patients discharged to rehabilitation facilities was minimal [0.098%]. Teaching hospitals had a comparatively higher admission rate of 58.9% compared to non-teaching hospitals. Table 1 summarizes details of patient and hospital level characteristics of index admission.

The 30-d rate of readmission was 21%. Only 1175 (9.17%) of readmissions were associated with an admitting diagnosis of acute on chronic HFpEF. Figure 1 shows the Kaplan-Meier survival curve, which showed the total time at risk was 850749 d, with the initial readmission occurring at day one and the last readmission at day twenty-eight. Hypertensive chronic kidney disease with HF (1245; 9.7%) was the most common diagnosis at readmission. Figure 2 shows the ten most common etiologies of readmission. Readmissions showed higher in-hospital mortality compared to index admissions (7.9% *vs* 2.9%, P = 0.000).

Readmission was associated with a total of 81997 hospital days. Total inpatient healthcare-related financial burden was $206 million in costs and $779 million in charges. Statistically significant predictors of higher rate of 30-d readmission were, higher Charlson comorbidity index (CCI) (1.08, 1.06–1.09, P = 0.000), Medicaid insurance (1.15, 1.05-1.27, P = 0.004), longer LOS in the hospital (1.01, 1.01-1.02, P = 0.000) and teaching hospital admissions (1.09, 1.04-1.15, P = 0.001). Lower readmission risk was associated with female gender (0.91, 0.86-0.95, P = 0.000), elderly patients (0.99, 0.993–0.997, P = 0.000), patients from a micropolitan area (0.83, 0.77-0.90, P = 0.000) or small metropolitan area (0.91, 0.86-0.97, P = 0.003), private insurance (0.85, 0.77-0.93, P = 0.000) or self-paying patients (0.70, 0.53-0.93, P = 0.015). Interestingly, discharges to rehabilitation did not have a significant effect on re-admission rate (0.67, 0.28-1.6, P = 0.381). Table 2 displays the independent predictors of 30-d readmission.

Table 1 Baseline characteristics of patients admitted with heart failure with preserved ejection fraction

Variable	*n* (%)
Total number of index admissions	60514
Female	37156 (61.4)
Mean age in year (Confidence interval)	74.8 (74.52-75.1)
Charlson comorbidity index score	
0	0
1	8956 (14.8)
2	15613 (25.8)
≥ 3	35945 (59.4)
Median income in patient zip code, US dollars	
1-43999	16823 (27.8)
44000-55999	18275 (30.2)
56000-73999	15007 (24.8)
74000+	10408 (17.2)
Patient residence	
Large metropolitan areas with at least 1 million residents	27836 (46.0)
Small metropolitan areas with less than 1 million residents	22753 (37.6)
Micropolitan areas 18493 (9.1)	7201 (11.9)
Not metropolitan or micropolitan (non-urban residents)	2723 (4.5)
Insurance type	
Medicare	49864 (82.4)
Medicaid	4054 (6.7)
Private	5809 (9.6)
Self-pay	726 (1.2)
Rehab transfer	59 (0.098)
Hospital teaching status	
Non-teaching	24871 (41.1)
Teaching	35643 (58.9)

Mean LOS during index admissions was 5.2 d and 6.4 d during readmission. Readmitted patients had higher LOS (Coefficient 1.15, 95%CI 0.99-1.31, P = 0.000). Total cost of hospitalization was higher for readmitted patients (USD 4831, 95%CI 4251-5410, P = 0.000). Table 3 shows the primary and secondary outcome details.

DISCUSSION

Heart failure readmission is one of the major outcomes measured by CMS. Several studies have analyzed the burden of HF to identify the predictors related to readmission[4,9,10]; however, most of these combined HF as a single entity, with only a few studies focusing on HFpEF specific readmission [10]. This study specifically evaluates HFpEF readmission rates and outcomes using the latest NRD database available at the time of study.

The patient population involved was primarily elderly, with a mean age of 74.8 years and predominantly female (61.4%) in line with previous studies[11-13]. Approximately 59.4% of patients had a CCI greater than three. A prior study had shown a mean CCI of 2.9[12]. Another study revealed a higher percentage of patients with CCI>3[14].

The 30-d rate of readmission was 21%, which is comparable to other studies[11,14,15]. A study by Arora *et al*[11] using the NRD database of 2013 and 2014 showed a readmission rate of 18.5% and this is

Table 2 Independent predictors of 30 d readmission

Variable	Adjusted OR (95%CI)	*P* value
Age	0.99 (0.99-0.99)	< 0.001
Female gender	0.91 (0.86-0.95)	< 0.001
Insurance provider (compared to medicare)		
Medicaid	1.15 (1.05-1.27)	0.004
Private	0.85 (0.77-0.93)	< 0.001
Self-pay	0.70 (0.53-0.93)	0.015
Charlson comorbidity index score	1.08 (1.06-1.09)	< 0.001
Patients admitted to teaching hospital	1.09 (1.04-1.15)	0.001
Length of stay	1.01 (1.01-1.01)	< 0.001
Geographic area (compared to large metropolitan area with at least 1 million residents)		
Small (area with < 1 million residents)	0.91 (0.86-0.97)	0.003
Micropolitan area	0.83 (0.77-0.90)	< 0.001
Patients admitted to teaching hospital	1.09 (1.04-1.15)	0.001
Length of stay	1.01 (1.01-1.01)	< 0.001
Geographic area (compared to large metropolitan area with at least 1 million residents)		
Small (area with < 1 million residents)	0.91 (0.86-0.97)	0.003
Micropolitan area	0.83 (0.77-0.90)	< 0.001

Table 3 Primary and secondary outcomes

Outcome measures	N (%), linearized standard error, 95%CI
Readmission rate	12812 (21%), 357.43, [12111-13513]
Mortality	
Index cases	1727 (2.9%), 76.98, [1576-1878]
Readmission	1012 (7.9%), 56.61, [901-1123]
Mean length of stay	
Index cases	5.2, 0.05, [5.15-5.32]
Readmission	6.4, 0.9, [6.21-6.56]
Total charges (in USD)	
Index cases	40570, 796.7, [39008-42132]
Readmission	60822, 1662.9, [57561-64083]
Total cost (in USD)	
Index cases	11234.2, 154.1, [10932-11536]
Readmission	16065, 349.7, [15379-16751]

likely due to the increasing prevalence of HFpEF among the elderly accounting for increased readmission rates.

About 1175 (9.17%) of readmissions were admitted with acute on chronic HFpEF. The most common readmission diagnosis was HF associated with hypertensive chronic kidney disease (1245; 9.7%). Combining all cardiac readmission reasons, our study found approximately 26.3% readmissions were due to cardiac etiologies. A previous study reported higher numbers (approximately 41%-50%) in this category[11]. A study carried out by Goyal *et al*[14] in 2018 showed a higher percentage of non-cardiac causes of readmission. This significant reduction in cardiac cause as the reason for readmission is encouraging, as it could be due to improvement in treatment modalities for HFpEF. This is despite the fact that there is no established goal directed medical therapy for this condition or use of monitoring

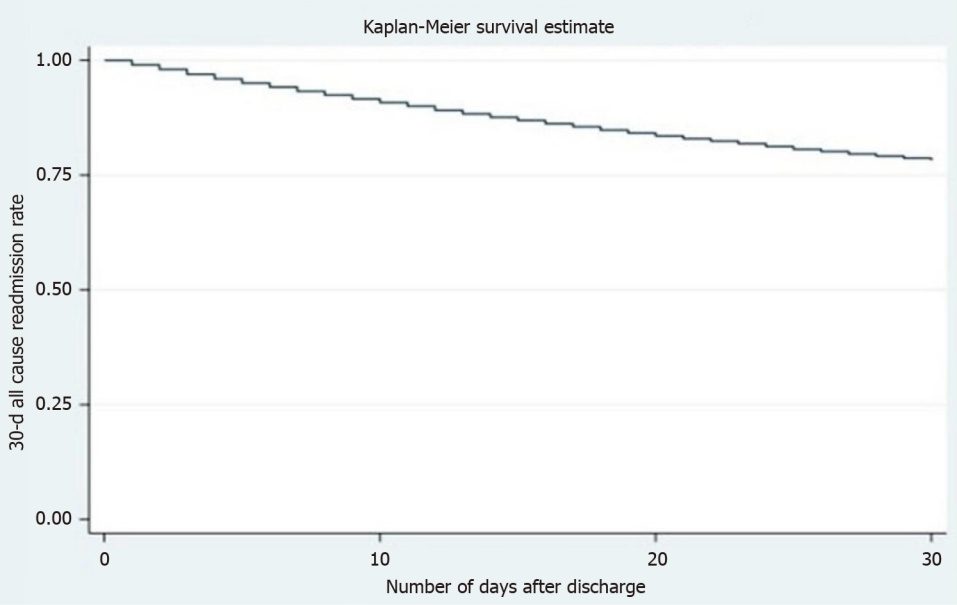

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Figure 1 Kaplan-Meier curve of 30-d all-cause readmission among patients with heart failure with preserved ejection fraction.

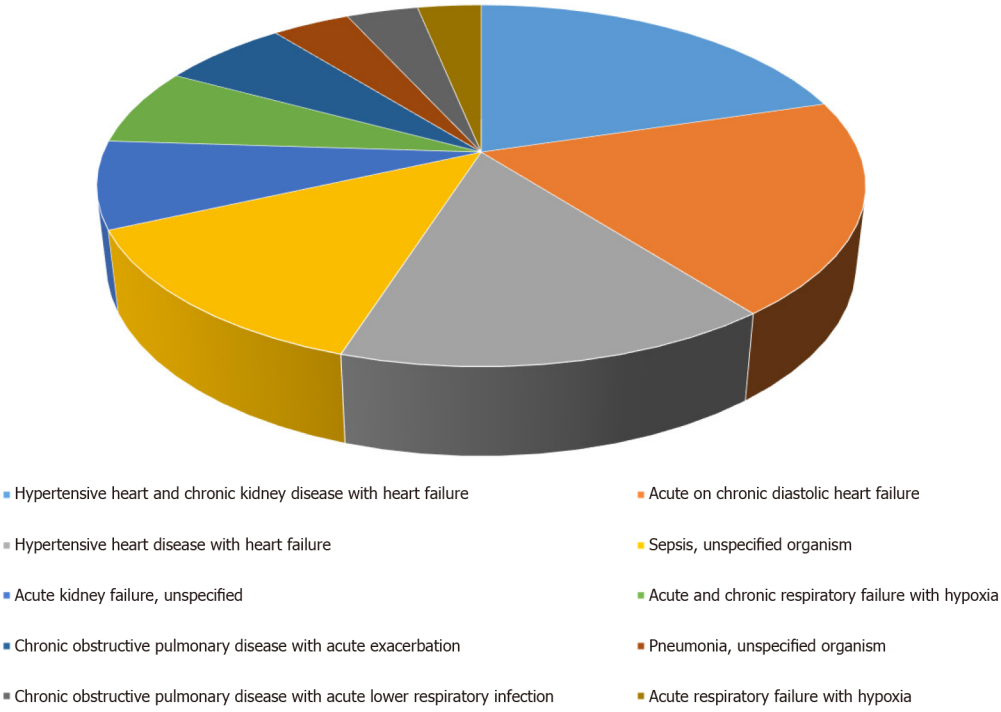

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Figure 2 Ten most common etiologies of heart failure with preserved ejection fraction readmission.

modalities such as Cardiomems, which have been proven to reduce readmission rate.

Significant predictors of increased 30-d readmission rate were Medicaid insurance, higher CCI, patient admitted to a teaching hospital and longer LOS in the hospital. Higher CCI is an obvious indicator of high readmission rate as multiple comorbidities are associated with frequent hospitalizations. Previous studies demonstrated that patients with HFpEF are also diagnosed with multiple comorbidities[16,17]. We did not further analyze individual medical conditions associated with HF readmission, although it would be interesting to see how these conditions affect frequent readmission. Teaching hospital patient populations are generally complex and that could explain higher readmissions. Similarly, longer LOS is explained during readmissions as this occurs with sicker patients, consistent with the study by Bergethon *et al*[18].

Residence in a small metropolitan (or micropolitan area), older age, female sex, and private or no insurance were associated with lower odds of readmission. López-Vilella *et al*[19] has shown that female gender is associated with a higher number of readmissions when compared to males, independent of the left ventricular ejection fraction (females = 33.5% *vs* males = 26.8%; P = 0.009). Our study showed lower odds of readmissions in females. The study by Manemann *et al*[20] revealed that the rural population with HF has an increased risk of death but reduced risk of emergency department visits as well as hospitalizations. Our study has shown residence in a small metropolitan or micropolitan area is a predictor of decreased risk of readmission. This might be due to the decreased or delayed access to health care facilities. Further study in this direction will help identify the gaps in healthcare access in these areas.

Private insurance and no insurance are two extreme ends of the spectrum, and our study showed a lower rate of readmissions with both. The lower rate of readmission could be explained by the fact that the patients with private insurance have good preventive and acute care along with good access to healthcare compared to patients with no insurance. Patients with no insurance may have delayed care and died before hospital readmission.

Interestingly, discharges to rehabilitation facilities had no effect on readmission. There are some contradicting results as per recent studies. Arora *et al*[4] showed an increased risk of readmission in patients discharged to rehabilitation facilities. The study by Gupta *et al*[21] showed no effect on readmission rate based on discharge to a hospital-based skilled nursing facility on chronic conditions like congestive heart failure, although this study showed lower readmission rate for acute conditions such as acute myocardial infarction and pneumonia. This study's results aligned to our study even though currently we do not see many hospital-based skilled nursing facilities compared to free standing skilled nursing facilities. This result could be due to a different patient population which requires discharge to a skilled nursing facility due to their complex medical history. Further research in this regard will certainly help to identify the associated factors.

Our study showed increased in-hospital mortality in readmitted patients when compared to index admission (7.9% *vs* 2.9%, P = 0.000). Multiple studies have shown readmission cases are associated with increased mortality[22-24]. This seems to be aligned to the predictors of readmissions, as these patients are generally sicker with multiple comorbidities. It would be helpful to analyze the basic characteristics of these patients, which could further highlight mortality related to cardiac *vs* non cardiac causes.

Mean LOS during index admissions was 5.2 d while it was 6.4 d for readmission. Several studies have shown that increased LOS has a negative effect on readmission rate, with longer index LOS correlating with a higher risk for readmission[24-26]. This finding is similar to our study result, which we hypothesize could be due to sicker patients and those with multiple comorbidities requiring a longer LOS, portending to higher readmission rates.

Total cost of hospitalization was higher for readmitted patients. 81997 hospital d were associated with readmissions. The total economic burden associated with readmissions was $206 million in costs and $779 million in charges. A study by Fingar *et al*[27] using NRD HCUP databases showed the total economic burden of readmissions for congestive HF patients was approximately $2728 million in 2013. This study did not further differentiate between the cost associated with heart failure with reduced ejection fraction and HFpEF. However, given the increasing prevalence of HFpEF, it is likely that HFpEF will soon, if not already, account for the majority of the economic burden of heart failure and targeted interventions are required to reduce the economic burden while improving patient care by identifying key variables involved.

CONCLUSION

For patients hospitalized for acute or acute on chronic HFpEF, 30-d readmission rate is comparable to recent studies, although readmissions were associated with higher mortality and resource utilization compared to index admission. Multiple comorbidities were associated with increased risk of readmission. Most readmissions were due to hypertensive chronic kidney disease with heart failure.

ARTICLE HIGHLIGHTS

Research background

Heart failure with preserved ejection fraction is a growing problem with a high risk for readmissions. Highlighting the cause and effect of this condition will further help in preparing guidelines to treat and prevent readmissions.

Research motivation

This study will help to understand important variables associated with readmission risks and burden on the American health care resource utilization.

Research objectives

The main research objective is to identify common hospital and patient related variables of increased or decreased risk of readmission in patients with heart failure with preserved ejection fraction. Identifying these variables can help clinicians as well as researchers to further modify these variables to improve the morbidity as well as financial burden.

Research methods

This study used the National Readmissions Dataset for 2017 to obtain patients with heart failure with preserved ejection fraction using International Classification of Diseases (ICD) codes-10. This was a retrospective study. Cox regression analysis was used to identify the significant variables on readmission rate.

Research results

This study clearly showed different hospital-related and patient-related variables which increased the risk of readmissions. Also, we found some interesting results showing the variables with decreased risk of readmissions. Some of these results align with recent study results but some others show different results which needs further research to identify new changes in the dynamics of this condition.

Research conclusions

Our results show that the rates of readmissions are similar to recent studies which indicate that we have to work harder to reduce this rate. We were able to provide different variables which are easy to modify which can reduce the risk of readmissions. Our study showed discharge to rehabilitation facility has no effect on the rate of readmissions.

Research perspectives

Further study on this important topic will be helpful to determine the ongoing change in managing this condition and decreasing its effect both on patients as well as the health care sector.

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SYSTEMATIC REVIEWS

Association of electrocardiographic markers with myocardial fibrosis as assessed by cardiac magnetic resonance in different clinical settings

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Abstract

BACKGROUND

Cardiac magnetic resonance (CMR) is a unique tool for non-invasive tissue characterization, especially for identifying fibrosis.

AIM

To present the existing data regarding the association of electrocardiographic (ECG) markers with myocardial fibrosis identified by CMR - late gadolinium enhancement (LGE).

METHODS

A systematic search was performed for identifying the relevant studies in Medline and Cochrane databases through February 2021. In addition, we conducted a relevant search by *Reference Citation Analysis* (RCA) (https://www.referencecitationanalysis.com).

RESULTS

A total of 32 studies were included. In hypertrophic cardiomyopathy (HCM), fragmented QRS (fQRS) is related to the presence and extent of myocardial fibrosis. fQRS and abnormal Q waves are associated with LGE in ischemic cardiomyopathy patients, while fQRS has also been related to fibrosis in myocarditis. Selvester score, abnormal Q waves, and notched QRS have also been associated with LGE. Repolarization abnormalities as reflected by increased Tp-Te, negative T-waves, and higher QT dispersion are related to myocardial fibrosis in HCM patients. In patients with Duchenne muscular dystrophy, a significant correlation between fQRS and the amount of myocardial fibrosis as assessed by LGE-CMR was observed. In atrial fibrillation patients, advanced inter-atrial block is defined as P-wave duration ≥ 120 ms, and biphasic morphology in inferior leads is related to left atrial fibrosis.

CONCLUSION

Myocardial fibrosis, a reliable marker of prognosis in a broad spectrum of cardiovascular diseases, can be easily understood with an easily applicable ECG. However, more data is needed on a specific disease basis to study the association of ECG markers and myocardial fibrosis as depicted by CMR.

Key Words: Myocardial fibrosis; Late gadolinium enhancement; Electrocardiogram; Cardiac magnetic resonance

Core Tip: Myocardial fibrosis, a reliable marker of prognosis in a broad spectrum of cardiovascular diseases, can be easily understood with an easily applicable electrocardiogram (ECG). However, more data is needed on a specific disease basis to study the association of ECG markers and myocardial fibrosis as depicted by cardiac magnetic resonance.

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INTRODUCTION

Cardiac magnetic resonance (CMR) is a useful non-invasive and radiation-free imaging modality that is the gold standard for estimating left ventricular volumes and ejection function[1]. Furthermore, CMR is a unique tool for non-invasive tissue characterization, especially for identifying edema, infarction, scar, and fibrosis. Tissue characterization can provide useful data not only for diagnostic purposes but also for the risk stratification of patients in different clinical settings[2-6]. In this setting, late gadolinium enhancement (LGE) is a commonly used CMR technique to identify myocardial fibrosis. However, CMR is not a widely available imaging modality, and also the high cost limits its widespread use in clinical practice.

On the other hand, electrocardiogram (ECG) is a well-established, easily obtained, low-cost diagnostic tool that is the cornerstone of cardiological evaluation. ECG markers have been associated with the presence of myocardial fibrosis, as depicted from CMR evaluation. This systematic review aimed to present the existing data regarding the association of ECG markers with myocardial fibrosis identified by CMR-LGE.

MATERIALS AND METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement; PROSPERO ID: CRD42021225119)[7].

Search strategy

This study aimed to identify all relevant studies that provided data about the association of ECG markers with myocardial fibrosis as depicted by CMR. Two independent investigators searched Medline and Cochrane databases systematically through February 2021. The reference lists of all included studies, relevant review studies, systematic reviews, and meta-analyses were manually searched. The following keywords were used in the search strategy: "(CMR OR cardiac magnetic resonance) AND (LGE OR late gadolinium enhancement) AND (ECG OR electroc*)" without any limitations. We first screened the titles and abstracts of each retrieved study, and in case of considering a study relevant, we studied the full text. In addition, we conducted a relevant search by *Reference Citation Analysis* (RCA) (https://www.referencecitationanalysis.com).

Inclusion/exclusion criteria

We included studies that provided data regarding the association of any ECG markers with myocardial fibrosis as depicted by CMR in different clinical settings. We excluded studies that did not provide data about the studied outcome, studies that provided data about the association of endocardial electrograms with fibrosis, or data about the association of atrial LGE with atrial fibrillation, as well as review studies, case reports/series, and experimental studies.

Data extraction

The data extraction was performed independently by two authors. The following data were extracted: First author, year of publication, journal, type of study (single or multicenter), number of patients, gender, age, clinical setting, ECG markers that were studied, as well as the major outcomes reported in each study. The Newcastle-Ottawa Quality Assessment Scale was used for the quality assessment of the observational studies[8].

RESULTS

Study search

Of the 616 studies initially retrieved, 534 were excluded at the title/abstract level, and 50 were excluded at the full-text level. Finally, 32 studies were included in the systematic review[9-40]. The search strategy is shown in Figure 1.

Study characteristics

The baseline characteristics and the main findings of the included studies are presented in Tables 1 and 2. Our search strategy identified 15 studies in hypertrophic cardiomyopathy patients[9-23], two with ventricular arrhythmias patients[24,25], two with non-ischemic cardiomyopathy patients[26,27], one with drug refractory AF patients[32], two with myotonic dystrophy patients[28,29], two with myocardial infarction patients[30,31], two about myocarditis[33,34], two including general population [35,36], one with arrhythmogenic cardiomyopathy patients[37], one with patients with preserved ejection fraction[38], one in cardiac sarcoidosis patients[39], and one in patients with left bundle branch block (LBBB)[40]. The quality assessment of the included studies is summarized in Supplementary Tables 1 and 2 (Supplementary material). Overall, the included studies were classified as high-quality studies.

Association of ECG markers with LGE in different clinical settings

Hypertrophic cardiomyopathy: Fragmented QRS (fQRS) is defined as additional notches in the QRS complex. FQRS has been found to be related to more extensive myocardial fibrosis in HCM patients (Figure 2A)[9]. A recent study showed that quantitative fQRS, defined as the total amount of deflections in the QRS complex in all 12 routine ECG leads together, was an independent predictor of myocardial fibrosis and showed a good performance in identifying patients with a higher fibrotic burden[9]. Dohy

Table 1 Baseline characteristics of the included studies

Ref.	Setting	Country of origin	Multicenter	*n*	Enrolment period	Mean age	Male (%)	LVEF (%)
Oebel *et al*[25], 2017	PVCs ablation	Germany	No	101	2015-2016	57	59	46
Sakamoto *et al*[24], 2015	VT/VF	Japan	No	34	-	60	71	45
Piers *et al*[26], 2016	NICM	Netherlands	No	40	2011-	57	83	30
Becker *et al*[27], 2020	DCM	Netherlands	No	165	2016-2018	59	62	36
Cho *et al*[29], 2017	Duchenne muscular dystrophy	Korea	No	37	-	16	-	55
Cardona *et al*[28], 2019	Myotonic dystrophy 1	United States	No	52	2012-2017	41	38	60
Nadour *et al*[30], 2014	MI	United States	No	235	2006-2009	62	82	33
Chew *et al*[31], 2018	MI	Canada	No	705	2011-2014	64	84	40
Ciuffo *et al*[32], 2020	AF	United States	No	152	2010-2015	60	76	57
Ferrero *et al*[33], 2020	Myocarditis	Italy	Yes	80	2008-2019	34	82	55
Fischer *et al*[34], 2020	Myocarditis	Switzerland	No	587	2002-2015	48	59	48
Inoue *et al*[35], 2017	General population	United States	Yes	1669	2000 - 2002	67	50	62
De Lazzari *et al*[37], 2018	AC	Italy	No	79	2006-2016	33	60	58
Mewton *et al*[38], 2016	HFpEF	United States	No	77	2009-2010	60	68	60
Sobue *et al*[39], 2015	Sarcoidosis	Japan	No	59	2006-2010		29	51
Wieslander *et al*[36], 2015	General population	United States	No	193	2011-2013	63	66	49
Wieslander *et al*[40], 2018	LBBB	United States	Yes	325	-	63	52	36
Bi *et al*[9], 2020	HCM	China	No	69	2015-2020	46	62	65
Chen *et al*[10], 2014	HCM	China	No	118	2005-2012	46	72	72
Chen *et al*[11], 2020	HCM	China	No	135	2012-2016	51	51	62
Riza-Demir *et al*[12], 2019	HCM	Turkey	No	74	2016-2018	51	65	66
Dohy *et al*[13], 2020	HCM	Hungary	No	181	-	49	57	63
Fronza *et al*[14], 2016	HCM	Italy	No	88	2004-2014	42	74	62
Grall *et al*[15], 2014	HCM	France	No	42	2008-2012	47	72	62
Guerrier *et al*[16], 2016	Pediatric HCM	United States	No	37	2006-2014	16	89	69
Kawasaki *et al*[17], 2015	HCM	Japan	No	60	2010-2013	66	76	64
Konno *et al*[18], 2015	HCM	Japan	No	108	2008 - 2014	62	65	-
Matsuki *et al*[19], 2020	HCM	Japan	No	41	-	62	76	65

Park *et al*[20], 2018	HCM	Korea	No	88	-	57	74	6
Sakamoto *et al*[21], 2015	HCM	Japan	No	42	2004-2014	59	79	58
Suwa *et al*[22], 2014	HCM	Japan	Yes	50	2004 - 2012	-	-	-
Tangwiwat *et al*[23], 2019	HCM	Thailand	No	144	2005 - 2015	66	60	73

LVEF: Left ventricular ejection fraction; PVC: Premature ventricular complex; VT/VF: Ventricular tachycardia/ fibrillation; NICM: Non-ischemic cardiomyopathy; DCM: Dilated cardiomyopathy; MI: Myocardial infarction; AF: Atrial fibrillation; AC: Arrhythmogenic cardiomyopathy; HFpEF: Heart failure with preserved ejection fraction; LBBB: Left bundle branch block; HCM: Hypertrophic cardiomyopathy.

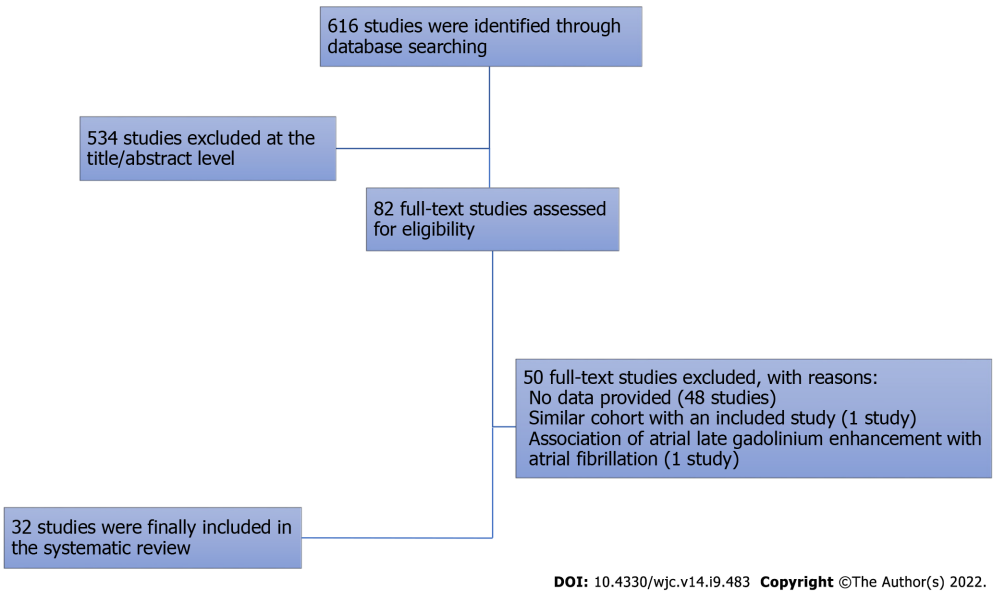

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Figure 1 Flow diagram of the search strategy.

et al[13] showed that fQRS and the strain pattern predicted more fibrosis, while the Cornell index was a negative predictor of myocardial fibrosis. The number of fQRS leads has been significantly correlated to %LGE, average ECV, and T2, while more than one lead with fQRS could predict > 5% of LGE mass with a 58% sensitivity and 63% specificity[20]. Suwa *et al*[22] showed that the presence of fQRS was associated with apical LGE. On the other hand, Tangwiwat *et al*[23] showed that fQRS was not associated with LGE. Chen *et al*[11] studied the role of Selvester QRS scoring criteria in diagnosing myocardial scar in HCM patients. The authors found that the Selvester score 1 showed a better performance in predicting LGE presence. Also, the same study showed a positive association between the Selvester score and the extent of LGE[11]. Abnormal Q waves are more prevalent in patients with LGE, but no correlation between the location of Q waves on ECG and territory of LGE on CMR was revealed (Figure 2B)[15]. Interestingly, quantitative analysis of LGE was not related to the presence of abnormal Q waves[15]. However, findings of another study showed that abnormal Q waves were associated with more ventricular segments with extensive LGE[10]. In a cohort study, LGE was associated with notched QRS, leftward QRS axis, and prolonged QRS duration, but not with abnormal Q waves, R-wave amplitude, or ST-T changes[17]. fQRS has been found to have higher diagnostic accuracy for detecting myocardial fibrosis compared to abnormal Q waves in HCM patients[18]. A cut-off of the number of leads with notched QRS ≥ 2 was found to predict the presence or absence of myocardial fibrosis, with a sensitivity of 70% and specificity of 81%[17]. Interestingly, the same study showed that the number of notched QRS leads was positively correlated with LGE volume, while a correlation between the lead distribution of notched QRS and the location of LGE was revealed[17]. Although giant negative T waves have been associated with apical HCM, no significant association was demonstrated with apical LGE[10]. On the other hand, in another observational study, repolarization disturbances, including negative T waves in lateral and anterior leads, have been correlated with "parietal" LGE scores, while QT dispersion has been associated with "global" LGE score[14]. Tp-Te has also been found to be an independent predictor of LGE, while a cut-off value of 99.4 ms can detect the LGE with a sensitivity of 64.3% and specificity of 84.2%[12]. In a small cohort of the pediatric population, the presence of LGE was associated with significantly decreased voltages in SV1, RV6, and

Table 2 Summary of the main findings of all included studies in the systematic review

Ref.	ECG markers studied	Main findings
Bi *et al*[9], 2020	fQRS, AF, bundle branch block	Quantitative fQRS was an independent predictor for myocardial fibrosis in HCOM
Chen *et al*[10], 2014	ST and T waves, LVH, Q waves, 1° AV block, 2° and 3° AV block, QRS duration	Abnormal Q waves were related to basal anteroseptal hypertrophy and extensive segmental LGE in HCM
Chen *et al*[11], 2020	QRS duration, QTc, LVH, RBBB, LAFB, LBBB, Selvester score	Selvester score showed a significant positive correlation with the extent of LGE enhancement in HCM
Riza Demir *et al*[12], 2019	QRS duration, QTc, TP-e interval, TP-e/QTc	Tp-e interval was an independent predictor of LGE in HCM
Dohy *et al*[13], 2020	fQRS, Q wave, ST deviation, Sokolow, Cornell, and Romhilt-Estes score	fQRS and ST deviation (strain pattern) predicts myocardial fibrosis in HCM
Fronza *et al*[14], 2016	Q waves, LBBB, signs of LV hypertrophy, negative T waves, ST depression	Negative T waves were correlated with LGE, whereas Q waves were associated with asymmetric hypertrophy in HCM
Grall *et al*[15], 2014	AF, QRS duration, ST deviation, negative T wave, Q wave, Sokolow, Cornell, Romhilt-Estes score	Q waves were more prevalent in the presence of LGE but didn´t correlate with LGE location and extent in HCM
Guerrier *et al*[16], 2016	QRS axis, QTc, PR interval, T wave inversion, ST depression, Q waves, LVH	Low left ventricle precordial voltages in ECG were associated with LGE in pediatric HCM patients
Kawasaki *et al*[17], 2016	QRS duration and axis, QTc, AF, LVH, Q wave, ST deviation, T wave inversion, notched QRS	Notched QRS was correlated with LGE in HCM without LBBB
Konno *et al*[18], 2015	Pathological Q waves and fQRS	fQRS was correlated with LGE in HCM, whereas Q waves were not correlated with LGE
Matsuki *et al*[19], 2020	QT interval, QRS duration, Sum of R-wave amplitude, ventricular late potentials	Ventricular late potentials were not correlated with LGE in HCM
Park *et al*[20], 2018	QRS, QTc, biphasic T wave, Q waves, sum S V1-3, Sokolow, Cornell, fQRS, AF, giant T wave inversion	The number of fQRS leads was significantly correlated to LGE in HCM
Sakamoto *et al*[21], 2015	24-hour ECG recordings and Time-domain T-wave alternans and QT dispersion	T-wave alternans and QT dispersion were associated with LGE in HCM
Suwa *et al*[22], 2014	QRS, QTc, Sokolov, max ST, max T waves, fQRS	fQRS was associated with impaired apical contraction and apical LGE in HCM
Tangwiwat *et al*[23], 2019	QRS duration, QTc, QRS axis, T-wave inversion, Sokolov, Cornell	fQRS in HCM was found to be associated with myocardial fibrosis in univariate analysis but not in the multivariate analysis
Sakamoto *et al*[24], 2015	HR, QT, QTc, QTe/RR slope, QTa/RR slope, day/night slope, VT/FV	QTe day/night and QTa day/night ratios were significantly greater in patients with Ventricular Arrhythmias and LGE
Oebel *et al*[25], 2017	PVC morphologies	RBBB, LBBB morphology and multiple PVC morphologies were associated with LGE in patients undergoing PVC ablation
Piers *et al*[26], 2016	Prolongation of the paced QRS duration after premature stimulation	QRS duration was associated with ventricular tachycardia but not with LGE in non-ischemic cardiomyopathy
Becker *et al*[27], 2020	HR, AV delay, 1° AV block, QRS duration, LBBB	QRS-prolongation was not correlated with LGE in non-ischemic dilated cardiomyopathy
Cardona *et al*[28], 2017	PR, QRS, QT, QTc, Frontal QRS-T angle, LVH Cornell	Surface conduction abnormality was not associated with LGE in myotonic muscular dystrophy type 1
Cho *et al*[29], 2019	fQRS	f-QRS was correlated with LGE in Duchenne muscular dystrophy with low statistical significance levels
Nadour *et al*[30], 2014	Q waves	Q waves in ECG have low value to detect a past myocardial infarction in the general population
Chew *et al*[31], 2018	QRS 120 ms, QRS fragmentation, Axis, AF	fQRS was associated with increased peri-infarct zone LGE and unfavorable left ventricle remodeling
Ferrero *et al*[33], 2020	fQRS	fQRS was correlated with LGE in patients with myocarditis
Fischer *et al*[34], 2020	QTc, QRS-T angle, fQRS, BBB, ST deviation, PR depression, low voltage, Q and T wave	fQRS, low voltage and QRS-T angle > 90° were independently correlated with LGE in myocarditis

Inoue *et al*[35], 2020	QRS duration, QTc, Sokolov and Cornell	QRS Cornell voltage, QRS duration, and QTc were significantly associated with LGE presence, while QRS Sokolow-Lyon voltage was not shown a significant correlation with LGE-CMR
Wieslander *et al*[36], 2015	LBBB, RBBB, LAFB, RBBB + LAFB and Selvester score	Selvester score was not accurate to detect myocardial scar and LGE in patients with conduction abnormalities and BBB
De Lazzari *et al*[37], 2018	Depolarization and repolarization abnormalities	Low QRS voltages in limb leads predicted LGE in Arrhythmogenic Cardiomyopathy
Mewton *et al*[38], 2016	QRS d, QTc, QRS-T angle, QRS score, T wave alternans	A significant association between T-wave alternans value and total scar. Patients with a myocardial ischemic scar had greater QRS duration. QRS-T angle was not associated with total myocardial scar size, core of scar, and gray zone size in grams by LGE-CMR
Sobue *et al*[39], 2015	QRS duration, atrioventricular block, LAFB, RBBB, Selvester QRS score	Selvester score was correlated with LGE in cardiac sarcoidosis
Wieslander *et al*[40], 2018	LBBB	Selvester score was not accurate to detect myocardial scar and LGE in patients with LBBB
Ciuffo *et al*[32], 2020	Inter-atrial block	Advanced IAB is associated with more fibrosis, while longer P-wave duration is also associated with more LA fibrosis.

fQRS: Fragmented QRS; AF: Atrial fibrillation; HCOM: Hypertrophic obstructive cardiomyopathy; HCM: Hypertrophic cardiomyopathy; AV: Atrioventricular; LGE: Late gadolinium enhancement; LVH: Left ventricular hypertrophy; RBBB: Right bundle branch block; LBBB: Left bundle branch block; LAFB: Left anterior fascicular block; PVC: Premature ventricular complexes; IAB: Inter-atrial block.

SV1 + RV6 despite increased septal dimensions[16]. Furthermore, the slopes of the QTe/RR and QTa/RR have been found to be significantly steeper in the LGE positive patients, while both slopes have been significantly correlated with the total LGE scores[24]. The association of late potentials with myocardial fibrosis has also been studied in HCM patients. However, ventricular late potentials were not found to be a reliable marker for the detection of myocardial fibrosis as assessed by LGE on CMR [19].

Ischemic and non-ischemic cardiomyopathy: Two studies were identified through the search strategy regarding the association of ECG markers with fibrosis as identified by CMR. Nadour W *et al*[30] studied the comparative efficacy of Q waves and CMR-LGE to predict prior myocardial infarction. Interestingly, the authors found that ECG-defined scars had a lower sensitivity compared to CMR-LGE-defined scars. Specifically, it was found that a significant number of pathological Q waves had absent infarct etiology, indicating high false positivity[30]. Chew *et al*[31] showed that in myocardial infarction patients, fQRS has been found to be significantly associated with the peri-infarct zone but not with core infarct volume. In the setting of non-ischemic cardiomyopathy, two studies were identified. Specifically, Piers *et al*[26] found that prolongation of the paced QRS duration after premature stimulation was related to long, thick strands of fibrosis but not to focal LGE-CMR. CMR has been reported to have a complementary role to ECG findings in dilated cardiomyopathy patients[27]. Specifically, it has been found that while QRS prolongation and septal mid-wall LGE are often co-existed, no significant correlation between these markers was revealed[27].

Myocarditis: Two studies that provided data about ECG markers with CMR fibrosis were identified. In myocarditis patients, fQRS has been correlated with the distribution of LGE (Figure 2C and D)[33]. Interestingly, fQRS was also associated with ongoing inflammation and poor prognosis in terms of ventricular function and fatal arrhythmias[33]. Fischer *et al*[34] studied the association of ECG parameters with LGE-CMR in patients with clinical suspicion of acute or subacute myocarditis. In this population, a wide QRS-T angle, low voltage, and fQRS were found to be significantly associated with LGE-CMR[34].

Myotonic dystrophy: Two studies were found to provide data about ECG markers and myocardial fibrosis in patients with muscular dystrophy. Specifically, in patients with Duchenne muscular dystrophy, a significant correlation between fQRS and the amount of myocardial fibrosis as assessed by LGE-CMR was observed[29]. On the other hand, in patients with myotonic muscular dystrophy type 1, PR, QRS, and QTc duration, frontal QRS-T angle, absolute Cornell voltage, LVH-Cornell, LBBB, right bundle branch block (RBBB), fascicular block, bifascicular block, AH interval, and HV interval were not significantly different between LGE positive and LGE negative patients[28].

Other clinical settings: Ciuffo *et al*[32] studied the association between the interatrial block and atrial fibrosis using CMR imaging in patients with drug-refractory AF. It was found that advanced inter-atrial block, defined as P-wave duration ≥ 120 ms and biphasic morphology in inferior leads, was significantly associated with left atrial fibrosis[32]. Furthermore, P-wave duration was also independently associated with left atrial fibrosis in this clinical scenario[32]. Mewton *et al*[38] studied the association of ECG markers in patients with preserved ejection fraction. A significant independent and positive association

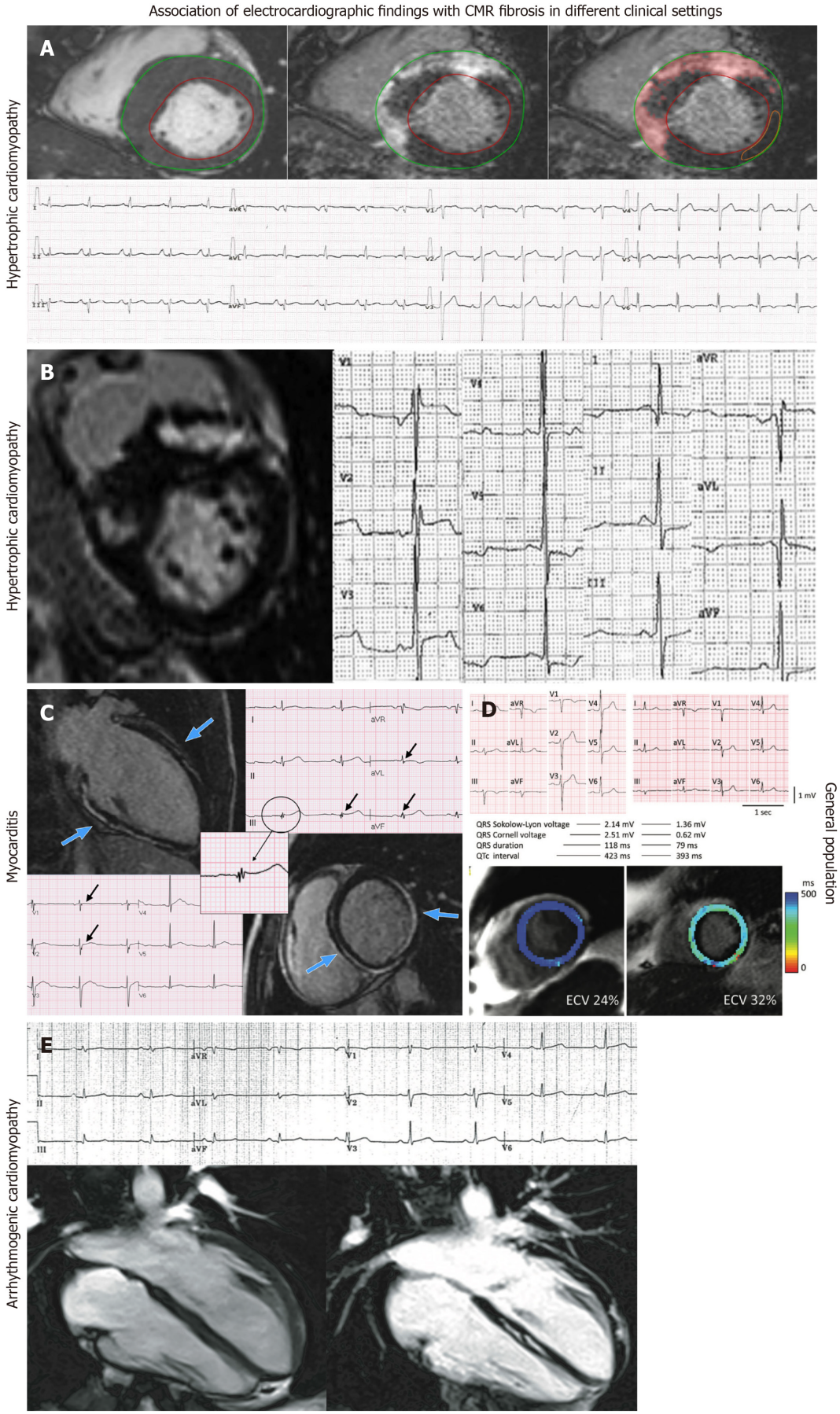

Figure 2 Association of electrocardiographic indices with cardiac magnetic resonance fibrosis in different clinical settings. A: Association of Fragmented QRS (fQRS) with myocardial fibrosis in hypertrophic cardiomyopathy patients (Adapted from Dohy Z *et al*[13], 2020-permission is not required for this

type of reuse); B: Association of Q wave with fibrosis in hypertrophic cardiomyopathy patients (adapted from Grall S *et al*[15], 2014-permission is not required for this type of reuse); C: Association of fQRS with fibrosis in myocarditis patients (adapted from Ferrero P *et al*[33], 2020-permission is not required for this type of reuse); D: Association of QRS voltage, QRS duration and QTc with fibrosis in the general population (adapted from Inoue YY *et al*[35], 2017-with permission from the Radiological Society of North America); E: Association of low QRS voltages with fibrosis in arrhythmogenic cardiomyopathy patients (adapted from De Lazzari M *et al*[37], 2018- permission is not required for this type of reuse).

between T-wave alternans value and total scar was revealed[38]. Furthermore, patients with a myocardial ischemic scar had significantly greater QRS duration as compared with patients with nonischemic scar and patients without a myocardial scar. On the other hand, QRS-T angle was not associated with total myocardial scar size, core of scar, and gray zone size in grams by LGE-CMR[38]. In the clinical setting of PVC, the presence of an RBBB pattern as the clinically dominant PVC morphology or the presence of multiple PVC morphologies were significantly correlated with the presence of LGE-defined fibrosis[25]. On the other hand, in patients with VT or VF, the slopes of the QTe/RR (QT measured at the apex of the T waves) and QTa/RR (QT measured at the end of T waves) were significantly steeper in the LGE positive patients while both slopes were significantly correlated with the total LGE scores[24]. Interestingly, the QTe day/night and QTa day/night ratios were significantly greater in LGE positive patients than in LGE negative patients, clearly demonstrating the correlation between fibrosis and QT dynamicity[24]. In the setting of cardiac sarcoidosis, QRS estimated scar using Selvester QRS score was significantly correlated with CMR-LGE scar while it was related with life-threatening arrhythmic events[39]. However, the Selvester QRS score intended for use in the presence of conduction abnormalities was not found to predict CMR-defined LV scar in a general population with suspected cardiovascular disease[36]. Similarly, the LBBB Selvester QRS score showed poor accuracy in the detection and quantification of myocardial scar in LBBB patients[40]. In ARVC patients, ε wave and terminal activation duration > 55 ms were not associated with either right or left ventricular LGE[37]. On the other hand, the presence of low QRS voltages in limb leads was associated with the presence of left ventricular LGE but not with right ventricular LGE (Figure 2E)[37]. In addition, the presence and extent of right precordial T-wave inversions were associated with the presence of right ventricular but not with left ventricular LGE[37]. Finally, in a prospective cross-sectional study that included individuals free of prior coronary heart disease, QRS Cornell voltage, QRS duration, and QTc were significantly associated with LGE presence, while QRS Sokolow-Lyon voltage was not shown to have a significant correlation with LGE-CMR (Figure 2D)[35].

DISCUSSION

In our systematic review, we examined in detail studies that have reported associations between ECG markers and CMR-reported myocardial fibrosis. In the literature, studies have reported controversial results regarding the association between pathological Q wave presence in ECG and LGE-CMR at first glance[10,17]. Moreover, another controversy on the association between fQRS and LGE in apical hypertrophic cardiomyopathy was reported[22,23]. These findings should be evaluated with caution because the study population, study design, ECG parameters used, and statistical approach have been heterogeneous among the included studies. Considering all included data, fQRS, QRS duration, Selvester QRS score, and ventricular repolarization variables have been detected to have great predictive value for myocardial fibrosis, which is validated by LGE-CMR in various cardiovascular diseases. The studies examining the association between ECG markers and CMR have been first evaluated in patients with HCM and ischemic cardiomyopathy. HCM has always been attracted attention due to its heterogenous electrocardiographic presentations, and it is rational to assess the fibrosis markers of ECG in HCM with the validation of CMR[41]. Since myocardial fibrosis has been associated with the arrhythmia burden in patients with HCM, early detection of myocardial fibrosis using 12-lead ECG has the potential to rapidly change management strategy in these patients[42,43]. LGE-CMR has been proposed as one of the predictors of clinical prognosis in patients with HCM[44]. Thus in the next step, ECG parameters correlated with LGE-CMR may be investigated in the risk scoring of HCM in addition to other well-known risk factors to provide more precise prediction in the follow-up of these patients. As the use of CMR is limited due to its high cost, ECG parameters found to represent myocardial fibrosis according to LGE-CMR may easily be used for the risk assessment.

In the evaluation of myocardial scar in patients with ischemic and non-ischemic cardiomyopathy, there appears to be a clear performance difference between CMR and ECG. The highly promising ECG parameters such as fQRS and pathological Q waves have not satisfied the expected performance compared to LGE-CMR[30]. The pathophysiological occurrence of myocardial scar in infarction may play an important role while explaining the poor performance of pathological Q waves in predicting myocardial fibrosis of LGE-CMR. Since Q waves symbolize a loss of electrical activity, not purely myocardial fibrosis, pathological Q waves without evident LGE-CMR may be explained for this reason

[45]. However, fQRS, which has not been correlated with core infarct volume, has been associated with peri-infarct volume[31]. In myocarditis, fQRS has been demonstrated to have a good LGE-CMR prediction performance, similar to its significance in patients with HCM[33,34]. Since ECG variables, including fQRS, change dynamically during the disease course of myocarditis, more investigations are warranted to determine the time of obtained ECG, which should be examined to correlate LGE-CMR. On the other hand, ECG parameters regarding atrial tissue fibrosis have been closely related to LGE-CMR because there have been several investigations defending the association between P-wave duration and morphology and left atrial fibrosis. Therefore, P-wave duration and inter-atrial block have a great potential to present left atrial fibrosis, which has been validated by CMR[32].

CONCLUSION

Myocardial fibrosis, which is a reliable marker of prognosis in a wide spectrum of cardiovascular diseases, can be easily understood with an easily applicable ECG. More investigations are needed on a specific disease basis to fill the gap of evidence regarding the association of ECG markers and CMR, which may practically change our daily clinical practice.

ARTICLE HIGHLIGHTS

Research background

Electrocardiogram (ECG) is a well-established, easily obtained, low-cost diagnostic tool that is the cornerstone of cardiological evaluation. ECG markers have been associated with the presence of myocardial fibrosis, as depicted from cardiac magnetic resonance (CMR) evaluation.

Research motivation

ECG can be a valuable tool for the risk stratification of sudden cardiac death in different clinical settings.

Research objectives

To elucidate the association of ECG markers with CMR-late gadolinium enhancement in different clinical settings.

Research methods

Methodology of Systematic reviews in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement).

Research results

Our results summarize the existing evidence about the association of ECG markers with fibrosis as identified by CMR. Existing data show that fragmented QRS, Q waves and repolarization abnormalities are some of the ECG indices that are associated with myocardial fibrosis.

Research conclusions

Myocardial fibrosis, a marker of prognosis in a wide spectrum of clinical settings, can be easily identified by ECG indices.

Research perspectives

Future research should be focused on the identification of ECG markers that are reliably associated with myocardial fibrosis in different clinical settings. Furthermore, the association of ECG markers with all-cause mortality and arrhythmic events is of great importance.

FOOTNOTES

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CASE REPORT

Intravascular lithotripsy for coronary calcium: A case report and review of the literature

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Abstract

BACKGROUND

Coronary calcium poses a challenge for the interventional cardiologist often leading to stent under-expansion and subsequent ischemic events. Aggressive balloon post-dilatation though helpful is usually inadequate. Multiple plaque ablation techniques are in vogue, but they are technically demanding and are not without complications. Shockwave intravascular lithotripsy (S-IVL) has emerged as a user-friendly and effective mechanism for calcium management with a high safety margin. A series of trials (DISRUPT CAD I-IV) have demonstrated both short-term and long-term safety and efficacy of the technique. As experience with the technique grows more and more, therapy areas like stent restenosis are being covered by the S-IVL.

CASE SUMMARY

We report a series of 2 cases successfully managed with S-IVL therapy at our center. The first case is of a 57-year-old smoker who presented with acute coronary syndrome. His left anterior descending coronary artery revealed calcified 90% stenosis on angiogram and a combination of superficial-deep calcium on intracoronary imaging. The calcium was treated with 20 pulses of S-IVL to create discontinuity and a sirolimus eluting drug-eluting stent was successfully implanted. The second case is that of an elderly lady who presented with stable angina and demonstrated diffuse calcified lesions in the left anterior descending artery on angiogram. She also demonstrated a mixture of superficial and deep seated calcium zones on imaging. S-IVL therapy was applied to generate fractures in calcium, and two overlapping drug-eluting stents were implanted successfully without any complications.

CONCLUSION

S-IVL is an emerging, efficient, user-friendly and safe therapy for managing intracoronary calcium in routine interventional practice.

Key Words: Coronary artery calcification; Acute coronary syndromes; DISRUPT-CAD; Shock wave; Premature ventricular contraction; Case report

Core Tip: The presence of severe calcification in coronary arteries poses a challenge for the interventional cardiologist. If inadequately addressed, it leads to inadequate stent expansion, difficulty in delivery of stent/balloon, balloon rupture, stent dislodgement, stent thrombosis and even perforation. Intravascular lithotripsy is a novel technique utilizing ultrasonic waves to disrupt the calcium in the vessel wall while retaining them in situ. With the accumulation of data and growing expertise of operators with intravascular lithotripsy, it is turning out to be an indispensable tool in catheterization laboratory. We present 2 cases in which intravascular lithotripsy was successfully utilized.

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INTRODUCTION

Calcified coronary artery lesions continue to be one of the pivotal challenges faced by interventional cardiologists. Stent under-expansion due to calcified lesions is a strong predictor of procedural failure and may lead to various acute complications, such as stent thrombosis and long-term stent restenosis [1]. Although aggressive balloon dilatation can sometimes achieve adequate room for stent deployment, the degree of final luminal gain is often limited. Furthermore, in eccentric lesions, high-pressure balloon dilatation can lead to overstretching of the noncalcified wall with minimal impact on the calcified lesion, which exacerbates the risk for coronary dissection and perforation[2].

Shockwave intravascular lithotripsy (S-IVL) or intravascular lithotripsy (IVL; Shockwave Medical Inc., Santa Clara, CA, United States) has recently been approved by the United States Food and Drug Administration for plaque modification in calcified coronary lesions. Contrary to rotational atherectomy, S-IVL uses ultrasonic waves to interrupt the calcium arc while retaining the residual chunks inside the vessel wall. Optical coherence tomography (OCT) sub-study of the DISRUPT-CAD trial revealed that circumferential lithotripsy fractures the superficial as well as deep layers of calcium, thereby enhancing the plaque compliance[3]. S-IVL is quite safe and easy to perform. Moreover, the traditional complications associated with rotational atherectomy, viz. distal microembolization, slow or no-flow, coronary perforation and bradycardia, necessitating temporary pacing lead insertion are not seen in lithotripsy. Herein, we share our experience with shockwave lithotripsy in two separate scenarios and a brief review of literature.

CASE PRESENTATION

Chief complaints

Case 1: Our patient was a 57-year-old man who smoked and was admitted with a diagnosis of acute coronary syndrome.

Case 2: A 58-year-old woman with chronic stable angina (CCS Class III) presented to a peripheral hospital where her coronary angiogram revealed triple vessel disease.

History of present illness

Case 1: He presented with intermittent retrosternal chest pain at rest with radiation to arm for the past 7 d.

Case 2: She had effort angina despite medical therapy for past 4 mo.

History of past illness

Cases 1 and 2: There was no past history of any specific illness.

Personal and family history

Case 1: He was a chronic smoker, and there was no family history of coronary artery disease (CAD).

Case 2: She was a nonsmoker, non-diabetic and had no family history of CAD.

Physical examination

Case 1: He was hemodynamically stable at admission with blood pressure of 134/70 mmHg and pulse rate of 80/min.

Case 2: She was hemodynamically stable at admission with blood pressure of 124/78 mmHg and pulse rate of 68/min.

Laboratory examinations

Case 1: A 12 lead electrocardiogram was normal except for a q wave and t wave inversion in lead III. His routine biochemistry and hemogram were within normal limits. His cardiac troponin value was 0.016 ng/mL (Normal < 0.014 ng/mL).

Case 2: A 12 lead electrocardiogram was unremarkable as was her routine biochemical and hematological profile.

Imaging examinations

Case 1: He exhibited normal left ventricular functions without any regional wall motion abnormality on echocardiography. Coronary angiography was performed with an intention to revascularize, which revealed calcific 90% stenosis in the proximal left anterior descending (LAD) coronary artery, 70%-80% stenosis in the major obtuse marginal artery and 80% stenosis in the distal left circumflex coronary artery (Figure 1A and B).

Case 2: The LAD showed severe calcified 90% stenosis in the proximal-mid part, whereas the left circumflex coronary artery exhibited 30%-50% disease in the distal part. There was mild disease in the left main coronary artery, whereas the non-dominant right coronary artery had severe stenosis. The patient was referred to our center for revascularization (Figure 2A-C). Her left ventricular ejection fraction was 62%.

MULTIDISCIPLINARY EXPERT CONSULTATION

Case 2: After the meeting of the cardiac team, she was given the options of coronary artery bypass graft surgery and percutaneous coronary intervention (PCI) to the LAD, and she opted for the latter.

FINAL DIAGNOSIS

Based on clinical, biochemical and angiographic features, a diagnosis of acute coronary syndrome-unstable angina with calcified double vessel disease was made in the first case. In the second case, chronic stable angina with calcified triple vessel disease was made.

TREATMENT

Case 1: The lesion in the proximal LAD was predilated using a 2.5 mm × 10 mm semicompliant balloon. Subsequently, OCT was performed to evaluate the degree of calcium, which revealed both superficial and deep circumferential calcium (Figure 1C-E). An IVL balloon catheter (C2IVL from Shockwave Medical Inc., Santa Clara, CA) measuring 3 mm × 12 mm was then placed across the lesion and dilated at 4 atmospheric pressure (atm). Ten pulses of shock wave were then delivered followed by IVL balloon dilatation at 6 atm. The cycle was repeated twice, which resulted in calcium fractures as seen in OCT performed after IVL (Figure 3). Next, a 3.0 mm × 40 mm sirolimus-eluting stent was deployed at 10 atm. The lesion was then post dilated with 3.5 mm × 12 mm noncompliant balloon. The final angiographic run revealed thrombolysis in myocardial infarction (TIMI) 3 flow and well expanded without any residual dissection (Figure 4A). A corresponding OCT run revealed a well-expanded and opposed stent, with a minimum stent area of 6.2 cm^2.

Case 2: Because of severe calcification of the LAD, imaging-assisted PCI was planned. The lesion in the proximal LAD was predilated using a 2.5 mm × 12 mm noncompliant balloon to allow the passage of the OCT catheter, which revealed both superficial and deep circumferential calcium (Figure 2D-F). In view of the deep calcium, we selected S-IVL as the plaque modification strategy. An IVL balloon (C2IVL

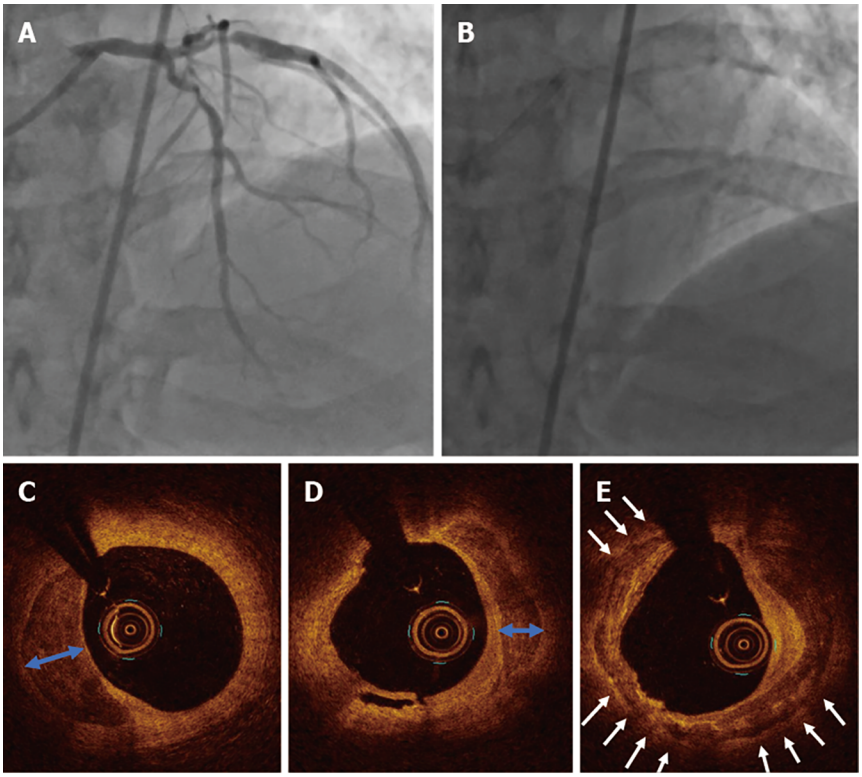

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Figure 1 Coronary angiogram of case 1. A and B: A severe calcific lesion in the left anterior descending coronary artery and proximal major obtuse marginal artery; C-E: An optical coherence tomography showed circumferential (white arrows) and deep calcium arc (blue arrow) prior to percutaneous coronary intervention.

from Shockwave Medical Inc., Santa Clara, CA) measuring 2.5 mm × 12 mm was then placed across the distal lesion and dilated at 4 atm. Subsequently, 10 pulses of shock waves were delivered, followed by dilatation at 6 atm. The cycle was repeated twice in the proximal lesions too. Subsequently, two overlapping sirolimus drug-eluting stents, 2.5 mm × 30 mm (distal) followed by 3 mm × 21 mm (proximal), were deployed at 10-12 atm. The lesions were then post dilated with a noncompliant balloon (sequentially 2.5 mm and 2.75 mm and subsequently 3.0 mm). Unfortunately, the OCT catheter could not be maneuvered into the LAD for final imaging as the patient became transiently unstable after post dilatation because of the slow-flow/no-reflow phenomenon. However, following intracoronary pharmacotherapy, the final angiography revealed TIMI 3 flow without residual dissection or stenosis (Figure 4B).

OUTCOME AND FOLLOW-UP

Both patients were doing well at the 30-d and 3-mo follow-up without any symptoms.

DISCUSSION

Coronary calcification is a part of the aging process and is exacerbated by concomitant cardiovascular risk factors and comorbidities[4,5]. Approximately 20% of the coronary interventions are complicated by severe calcific lesions, which are independent predictors of procedural failure and adverse cardiac events in the future[6,7]. Moreover, calcific lesions heighten the risk for procedural complications and increase the procedural time. Characteristics of calcific lesions, viz. location inside the coronary arteries (superficial *vs* deep) and calcium burden (thickness of the calcified plaque, arc angle subtended, and longitudinal extension), are the factors that determine plaque compliance, stent delivery, adequate stent expansion and finally procedural success and long-term outcomes[8].

Several techniques are available for plaque modification in severely calcified coronary lesions, including high pressure noncompliant balloons, scoring balloons, cutting balloons, rotational/orbital atherectomy and excimer laser. These devices cause plaque compression or plaque debulking and are not without complications, such as distal embolization, slow flow, coronary dissection and perforation. Moreover, they are less successful if the calcification is deep, thick or eccentric, and the tissue injury

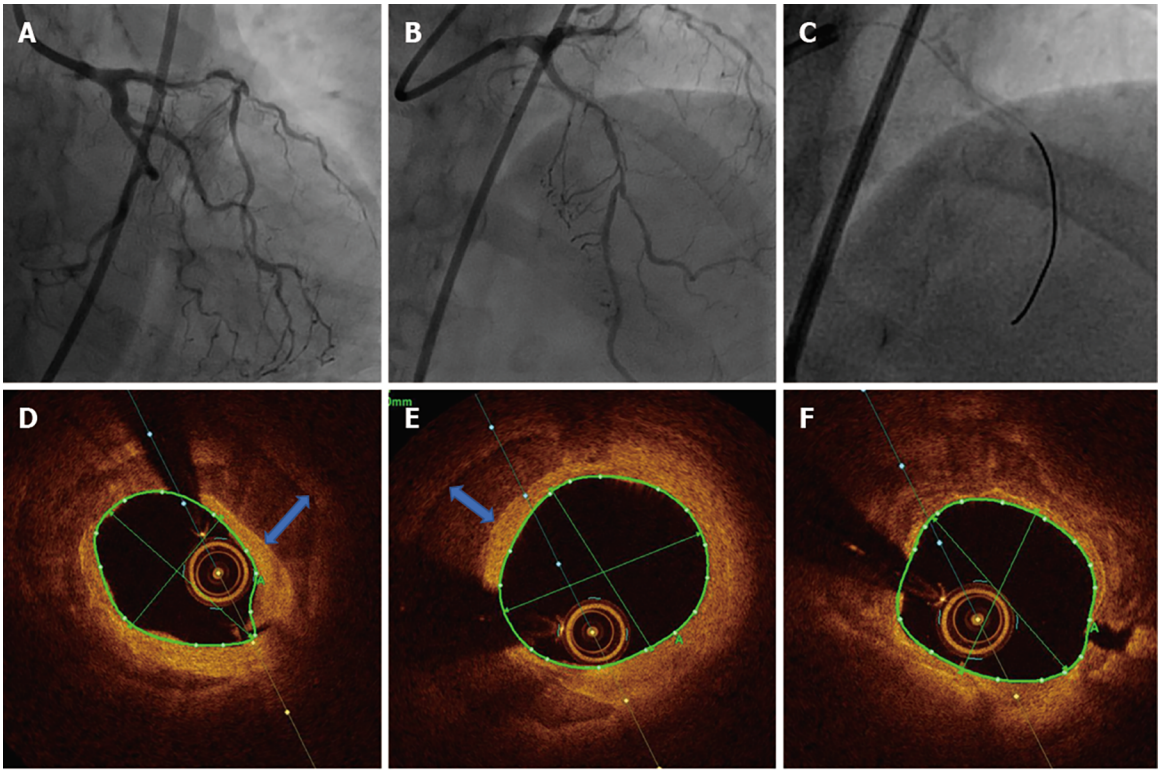

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Figure 2 Coronary angiogram of case 2. A-C: A severe calcific lesion in the left anterior descending coronary artery; D-F: Optical coherence tomography showed circumferential calcium and deep calcium (blue arrow) prior to percutaneous coronary intervention.

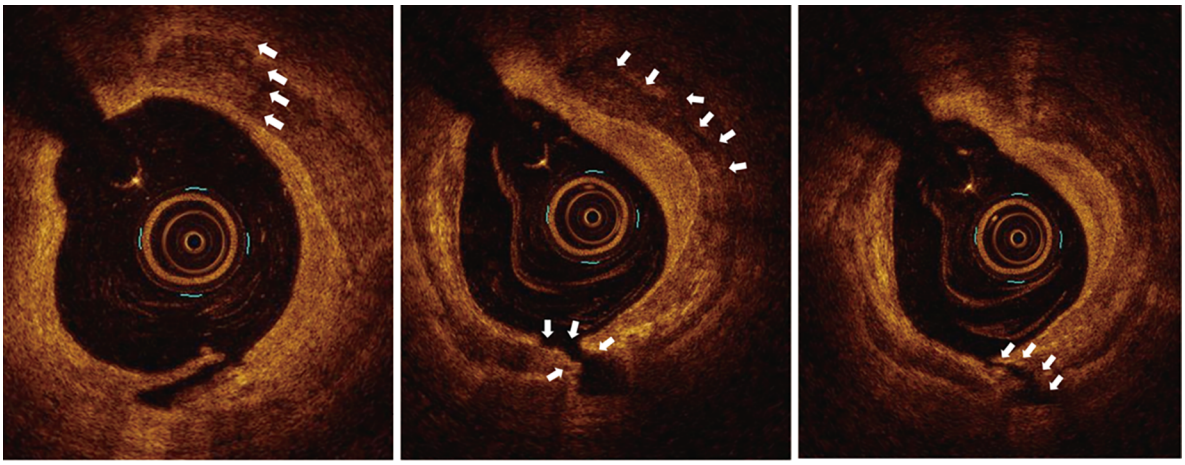

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Figure 3 Post intravascular lithotripsy optical coherence tomography images of left anterior descending coronary artery of case 1 depicting calcium fracture (white arrow).

occurring in the process may induce uncontrolled neointimal proliferation and restenosis[9].

IVL is a novel technique for bed preparation in severely calcified lesions in coronary as well as peripheral arteries. Calcium fractures are achieved with pulsatile mechanical energy delivered *via* lithotripsy emitters mounted inside a low-pressure balloon catheter (max 4-6 atm). The electrohydraulic-generated high-speed sonic pressure waves pass through the soft vessel wall tissue and selectively modify the subendothelial calcium, which disrupts the calcified plaque. IVL has been approved by the United States Food and Drug Administration for the treatment of calcified peripheral lesions and has obtained the CE mark for coronary lesions.

Mechanism of IVL

The mechanism of IVL is similar to the commonly utilized electrohydraulic lithotripsy or commonly

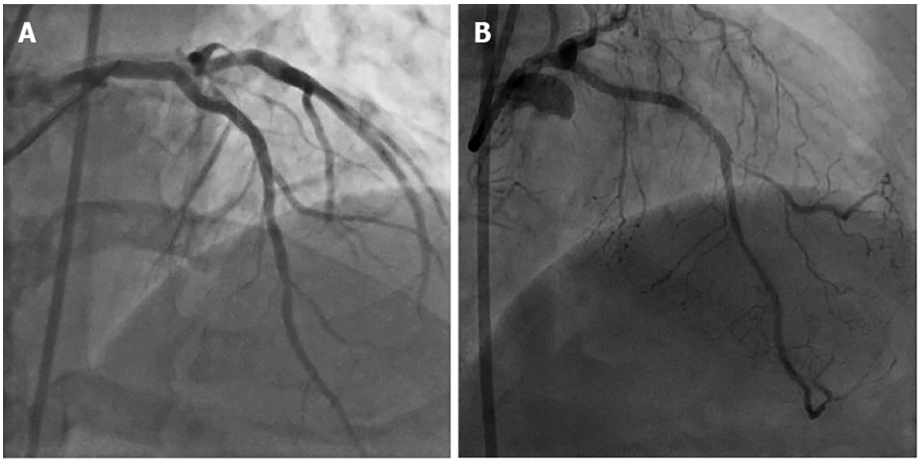

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Figure 4 Post percutaneous coronary intervention coronary angiogram. A: Post percutaneous coronary intervention coronary angiogram showed a well expanded left anterior descending coronary artery in case 1; B: Post percutaneous coronary intervention coronary angiogram showed fully expanded stent and thrombolysis in myocardial infarction 3 flow in case 2.

referred to as extracorporeal shockwave lithotripsy for fragmentation of urogenital tract stones[10]. IVL therapy uses the same technology with some modifications to address vascular calcium. The adaptations include the incorporation of lithotripsy emitters on the shaft of a balloon angioplasty catheter, which delivers localized pulsatile acoustic pressure waves circumferentially to modify vascular calcium.

In electrohydraulic lithotripsy, a spark gap discharge between two electrodes causes the formation of an acoustic pressure wave within the transmitting fluid medium. This pressure wave expands spherically outwards from the emitter. The energy discharged from the spark gap results in the formation of a plasma vapor bubble, and this immediately follows the initial acoustic shockwave. The rapid expansion and collapse of the vapor bubble, which is known as a cavitation bubble, and secondary shockwaves causes stone fracture on encountering differing acoustic impedances, such as the transition from soft tissue to calcified tissue.

Electrohydraulic lithotripsy spark gap technology was leveraged for use in IVL, but several modifications were done to ensure effective and safe intravascular treatment. Three key modifications were done for IVL: (1) IVL pressure waves deliver tissue-safe positive and minimal peak negative pressure pulses allowing sufficient compressive force to modify vascular calcium. This helps in mitigating soft tissue injury due to excessive cavitation or tensile stress; (2) Pressure wave emitters are enclosed within an inflated, fluid-filled balloon to prevent thermal injury; and (3) Multiple emitters are present in series along the shaft of the catheter for longitudinal treatment of the calcified vessel.

The IVL shockwaves are unfocused, which produces much lower energy flux density (the amount of acoustic energy per unit area) as compared to extracorporeal shockwave lithotripsy. Much less energy is required here as the IVL shockwaves are initiated in close proximity to the target vascular calcium. In addition, IVL integration of a semicompliant balloon with emitters on the shaft has several advantages. First, the mixture of contrast and saline in balloon dissipate heat generated during the formation of vapor bubbles and shields the emitters from direct contact with the vessel wall. Since the balloon is deflated in between two cycles, it helps in dissipating heat and residual gas bubbles allowing tissue perfusion and preventing ischemia. Second, it provides mechanical support, which minimizes any tissue deformation during IVL therapy. Last as the integrated balloon is thin and acoustically transparent, it provides efficient fluid to tissue transmission and effective coupling of IVL pressure pulse propagation from emitter to vascular wall. The appropriately sized IVL balloon catheter inflated at subnominal pressure (4 atm) produces efficient ring calcium fracture avoiding barotraumas.

Components of the IVL system

The IVL system comprises the following components: (1) *The IVL generator*: The IVL generator is a portable and rechargeable orthogonal "box" weighing 6.8 kg and measuring 28.0 cm × 15.2 cm × 29.2 cm, which delivers small electrical pulses of up to 3000 V of electrical energy. The discharge frequency is one pulse per second (1 Hz), and the maximum number of continuous pulses per cycle is fixed and depends on the type of the IVL catheter used. The machine is user friendly and comprises two buttons, one for power and the other one for delivering energy. There are no external connections, except from the IVL connector cable. There is a color-coding that depicts the number of pulses remaining after each cycle and the size of the IVL catheter being used[9,11-13]; (2) *The IVL connector cable:* The IVL connector cable is 1.53 m in length and contains two magnetic poles. One pole is connected to the IVL generator, and the other one is specially designed with a push button that triggers energy emission and is

connected directly to the proximal end of the IVL catheter. It forms the route and the gate for electrical energy transfer from the IVL generator to the IVL catheter[9,11-13]; and (3) *The IVL catheters:* The IVL catheters are balloon angioplasty catheters that possess a series of unfocused electrohydraulic lithotripsy emitters, which convert electrical energy into sonic pressure pulses. The sonic pressure waves travel circumferentially and create a spherical field at an effective pressure of approximately 50 atm. The waves selectively disrupt and fracture the calcium in situ and alter the vessel compliance while minimizing the injury and maintaining the integrity of the fibroelastic components of the vessel wall. The catheters are available in different sizes, internal design and maximum cycles and total pulses based on their use in coronary or peripheral vessels[9,11-13].

Technical aspects of IVL

In general, the coronary IVL balloon is sized 1:1 to the reference artery diameter and is inflated to low pressure (4 atm). One cycle of ultrasound energy, *i.e.* 10 pulses over 10 s, is delivered. This process is followed by IVL balloon dilatation to the size of the reference vessel according to the balloon compliance chart. The procedure should be repeated to provide a minimum of 20 pulses in the target lesion, with a period of deflation in between the pulses to allow for distal perfusion. The required number of cycles depends upon the lesion resistance; however, a maximum of 80 pulses (8 cycles) can be emitted by a single catheter. If the lesion length exceeds the balloon length (12 mm), then the balloon can be repositioned and the lithotripsy repeated. Although the currently available IVL balloon is relatively bulky, contemporary rapid exchange guide extension catheters can accommodate it easily and aid in its smooth delivery.

Clinical studies on IVL

Clinical studies on IVL are shown in Table 1.

Randomized trial data: (1) DISRUPT CAD I Trial. This trial was a prospective multicenter study designed to evaluate the safety of IVL in 60 patients with heavily calcified coronary lesions. The incidence of major adverse cardiac events (MACE), defined by cardiac death, myocardial infarction and target vessel revascularization, was low (5.0% at 30 d and 8.6% at 6 mo). Clinical success rate (defined by a residual stenosis of < 50% and no in-hospital MACE) and device success rate (defined by successful device delivery and IVL treatment at target lesion) were high (95.0% and 98.3%, respectively). The major mechanism for calcium modification was fracture, as evidenced on OCT, and it was independent of the depth[14].

(2) DISRUPT CAD II Trial. This trial was also a prospective multicenter study involving 120 patients with severe coronary artery calcium and an indication for revascularization. The primary endpoint was in-hospital MACE (cardiac death, myocardial infarction and target vessel revascularization). Furthermore, an OCT substudy was performed to elucidate the mechanism of calcium modification. The incidence of primary endpoint was 5.8%, and there was no evidence of abrupt closure, slow flow-no reflow or perforation. Post PCI OCT showed calcium fracture in 78.7% of the lesions[15].

(3) DISRUPT CAD III Trial. This trial was a larger multicenter international study that enrolled 431 patients with severely calcified de novo lesions undergoing PCI. The primary safety endpoint was freedom from MACE at 30 d, and the primary efficacy endpoint was procedural success. The overall primary safety endpoint achieved was 92.2%, whereas the procedural success rate was 92.4%. The study also noted that the procedure was well tolerated, with a low rate of periprocedural complications. An OCT substudy showed calcium fracture in 67.4% of the lesions[16].

(4) DISRUPT CAD IV Trial. This trial was a prospective multicenter study designed for Japanese regulatory approval for coronary interventions. Again, the primary safety endpoint was freedom from MACE at 30 d, and the primary efficacy endpoint was procedural success (residual stenosis < 50%). A propensity-matched historical control group was used for the comparison. The primary endpoints were noninferiority for freedom from MACE at 30 d (CAD IV 93.8% *vs* control 91.2%, P = 0.008) and procedural success (CAD IV 93.8% *vs* control 91.6%, P = 0.007). There were no complications in the form of perforations, abrupt closure or slow-flow/no-reflow during the procedure[17].

(5) Pooled Analysis of the DISRUPT Trials. A pooled analysis of the four above mentioned studies comprising 628 patients enrolled at 72 sites spread across 12 countries was performed[18]. Severe calcium was seen in almost all patients, with an average calcium segment size of 41.5 mm. The efficacy and safety outcomes were achieved in approximately 92% of the patients, whereas the 30-d cardiac death and stent thrombosis rates were < 1% each. Perforation, abrupt closure and slow flow were characteristically absent.

(6) Long-term follow-up. Long-term (1 year) follow-up data were published recently[19]. The MACE rate at 1 year was low at 13.8% (*vs* 7.8% at day 30 *vide supra*). The cardiac death and stent thrombosis rates were low at 1.1% each. Repeat revascularization (ischemia-driven) rates were also low at 4.3% for the target lesion and 6% for the target vessel.

Registry experience: A total of 71 patients from three centers who were eligible for IVL were taken into a prospective registry. Three patient groups participated, namely primary IVL therapy (Group A) with calcified de novo lesions (n = 39 lesions), secondary IVL therapy (Group B) for patients with failed

Table 1 Major clinical studies with intracoronary intravascular lithotripsy

Trial	Year	No. of patients	Severe calcification at baseline	Calcified segment length in mm	Primary endpoints	Outcome	Luminal gain post IVL	Luminal gain post stenting	Residual stenoses	Calcium fracture on OCT
DISRUPT CAD I	2019	60	100%	22.3 ± 12.3	30 d MACE	5% MACE observed		1.7 mm	< 50% in 100 lesions; < 30% in 92% lesions; < 20% in 73% lesions	78%
DISRUPT CAD II	2019	120	94.3%	25.7 ± 12.4	In-hospital MACE	MACE occurred 5.8% patients	0.83 ± 0.47 mm		7.8 ± 7.1%	78.7%
DISRUPT CAD III	2020	431	100%	47.9 ± 18.8	Freedom from in-hospital MACE, procedural success	Freedom from in-hospital MACE occurred in 92.2%; Procedural success in 92.4%		1.7 mm	11.9%	67.4%
DISRUPT CAD IV	2021	64	100%	49.8 ± 15.5	Freedom from in-hospital MACE, procedural success	Freedom from in-hospital MACE occurred in 93.8%, Procedural success in 93.8%	1.42 ± 0.42 mm	1.67 ± 0.37 mm	Residual diameter stenosis < 50% and < 30% in all	53.5%

MACE: Major adverse cardiovascular events; IVL: Intravascular lithotripsy; OCT: Optical coherence tomography.

dilatation of lesion with noncompliant balloon (n = 22 lesions) and tertiary IVL therapy (Group C) for patients with stent under-expansion after previous stenting (n = 17 lesions). The primary endpoints were procedural success (< 20% residual stenosis) and safety outcomes. The mean diameter of the pre-IVL stenosis was 71.8% ± 13.1%, which reduced to 45.1% ± 17.4% after IVL and 17.5% ± 15.2% after the stenting. Similarly, the mean minimal lumen diameter increased from 1.01 ± 0.49 mm at baseline to 1.90 ± 0.61mm after IVL and 2.88 ± 0.56 mm after the stenting. The procedural success rates were 84.6% (Group A), 77.3% (Group B) and 64.7% (Group C). There was no in-hospital MACE[20].

In another registry, patients treated with IVL were studied retrospectively to assess the clinical and angiographic outcomes of coronary IVL use in all-comers with moderate to severe calcified coronary lesions. The primary endpoint was in-hospital MACE (cardiac death, myocardial infarction and target vessel revascularization), and the secondary endpoints were clinical success [stent expansion with < 30% in-stent restenosis (ISR) and no in-hospital MACE] and angiographic success. A total of 50 calcified lesions were treated with IVL in 45 patients divided into three subgroups, similar to the above registry: primary IVL therapy (n = 23 lesions), secondary IVL (n = 15 lesions) and tertiary IVL (n = 12 lesions). The mean diameter of the stenosis decreased from 63.2% ± 10.2% at baseline to 33.5% ± 10.9% post IVL (P < 0.001) and 15.0% ± 7.1% post stenting (P < 0.001). The mean minimal lumen diameter increased from 1.1 ± 0.3 mm at baseline to 1.90 ± 0.5 mm post IVL and 2.80 ± 0.50 mm post stenting. The overall clinical success and angiographic success rates were 90% and 94%, respectively[21].

Systemic reviews and meta-analyses: In a meta-analysis performed by Sattar *et al*[22] involving 282 patients from four studies, IVL significantly improved the size of the vessel lumen to facilitate coronary stent delivery and deployment in severely calcified plaques. The mean pre-IVL diameter was 1.01 mm,

whereas the post-IVL mean diameter was 2.70 mm. The post-IVL lumen diameter was significantly higher than the pre-IVL mean diameter, with a mean difference of -4.16 (95% confidence interval: from -5.08 to -3.24, $P = 0.000001$).

In another meta-analysis performed by Sattar *et al*[23] involving 24 patients from case reports and series, a success rate of 100% was achieved for stent implantation, with minimal complications. No significant differences were observed in the mortality rates of patients undergoing IVL for LAD, left circumflex coronary and left main coronary artery. The mortality rate was higher in patients who had prior comorbidities or required more than three cycles of IVL. Kaul *et al*[24] compared IVL with traditional rotational atherectomy in severely calcified coronary stenosis. Trials on rotablation and IVL revealed that the latter was safer than the former primarily because it reduced the risk for atheromatous embolization. The studies also revealed that IVL yielded better results for parameters such as acute lumen gain and residual stenosis; however, in-hospital MACE was better with rotablation.

Limitations

One of the limitations of IVL is that it is contraindicated in angulated and tortuous coronary lesions because of its bulky design. The presence of uncrossable lesions may preclude its application; however, the use of hybrid techniques, such as "RotaTripsy," can overcome this shortcoming.

RotaTripsy: When the balloon cannot cross

RotaTripsy refers to the hybrid and tandem utilization of rotablation followed by IVL for lesions with extremely severe calcification in which a balloon cannot cross the lesion or fails to expand. The initial use of rotablation allows the passage of the IVL balloon while debulking the superficial calcium. The subsequent use of IVL fractures the deep calcium, thus leading to extraluminal gain. The technique aims to achieve the best of both contemporary avenues for managing calcium, *i.e.* combining the advantages of the balloon-based procedure and the ablation-based procedure. In an observational study of 34 patients in a real-world setting, the technique attained 100% procedural success without any in-hospital MACE[25]. Another case series also demonstrated the safety and feasibility of the "RotaTripsy" technique underscoring the frequent coexistence of superficial and deep calcium on intracoronary imaging[26].

IVL in ISR

Although not approved for use in ISR, there are many emerging reports on the successful use of IVL in calcific ISR with drug-eluting stents where the use of noncompliant balloons and rotablation failed to produce satisfactory luminal gain[27,28]. Recently, a report has been published on the use of IVL for treating neointimal hyperplasia after bare metal stent implantation where cutting balloon and nonslip element balloon had failed[29]. A single center retrospective study found that angiographic success was achieved in all but 1 patient with an IVL-guided management strategy for moderate to severe ISR (65%-88% stenosis)[30]. In the multicenter SMILE registry for ISR, IVL was utilized after the failure of noncompliant balloons. The use of IVL led to significant improvements in minimal stent area and minimal stent diameter in 87% of the patients[31]. There were no cases of death or stent thrombosis at 30 d.

The recently published IVL-DRAGON registry ($n = 62$) has also explored the role of S-IVL in stent under-expansion[32]. The primary end point (stent expansion > 80% as seen by qualitative coronary angiography) was seen in 72.5% cases. Significant increase in stent expansion following application of IVL was confirmed by contemporary imaging techniques: OCT (37.5 % to 86%) and intravascular ultrasound (57% to 89%). Device oriented composite end point was seen in only 1.6%. Furthermore, there is a report on the combined use of IVL and brachytherapy in such cases[33]. Hence, the use of IVL in cases of ISR appears promising.

Complications

Serious angiographic complications were witnessed in up to 2.1% of the patients in the pooled analysis of DISRUPT trials[18]. These complications were dominated by dissections and slow flow. Perforations, no reflow and abrupt closure were not reported. The data in the registries mirrored similar findings, with minimal complications and a predominance of dissections[20-21]. Premature ventricular ectopic beats or "shocktopics" and asynchronous ventricular pacing were observed in some subjects on electrocardiogram but were not associated with clinical consequences[34]. Bradycardia at baseline (heartrate < 65 bpm) was the most powerful predictor of ventricular capture although it also tended to occur in younger patients, those with higher creatinine levels and those with previous infarction. A few case reports on transient atrial arrhythmias have emerged, but the course was benign[35,36]. The use of S-IVL in proximal coronary arteries has been associated with supraventricular tachyarrhythmias because of the anatomical proximity. Synchronization of the shock waves with R waves on the electrocardiogram has been suggested as a precautionary measure to ameliorate these arrhythmic effects.

Indications for S-IVL

Currently, S-IVL is approved for severely calcified coronary lesions with clinical indications for revascularization. Intravascular imaging (especially OCT) can help identify severe lesions that will benefit from this novel technology thereby allowing judicious usage of this costly therapy. Calcium arc more than 180 degrees, calcium length more than 5 mm and thickness more than 0.5 mm indicate increased calcium burden that will necessitate specialized lesion modifying therapies[37]. Being a balloon based technology, this eliminated any specialized training and hence almost no learning curve. However, this makes balloon uncrossable lesions a contraindication for S-IVL. As previously described a combined approach with rotablation first followed by IVL - "Rotatripsy" can be applied for such cases. In addition, rotational or orbital atherectomy can be followed by S-IVL to address deeper and stubborn calcific lesions. A simplified algorithm by De Maria *et al*[1] for heavily calcified coronary lesions places S-IVL into context.

S-IVL vis-a vis contemporary calcium therapies

Current techniques for calcium modification can be broadly divided into "atherectomy" type and "balloon" based. S-IVL offers many advantages over many of these techniques[1,9,24]. It obviates the need for any proprietary wire like Rota wire (rotablation) or Viper Wire (orbital atherectomy), and the procedure is carried on a routine workhorse wire. This makes it cost and time effective. Again being a balloon-based technology, it does not require any additional equipment like an advancer, foot pedal and saline infusion as needed for atherectomy devices. The technique is also similar to the "run of the mill" monorail balloons used in daily interventional practice making it easy to master even for the beginners recusing the need for special training. It also offers uniform and circumferential calcium modification as the balloon emits acoustic waves all round compared to other local atherectomy techniques that might be subject to wire bias. There is also amelioration of any distal embolization as with atherectomy techniques like rotablation and orbital atherectomy making it a safe procedure.

The balloon inflation is done at low pressures compared to other balloon based methods (with some utilizing ultrahigh pressures), which has the potential to minimize vascular trauma and increase safety. There is no data of any reported case of perforation with S-IVL so far. There also is no need to remove additional wires in the vessel lumen like side branch wire or buddy wire as with other atherectomy techniques. Temporary pacemaker insertion again is not needed as with rotablation. Both superficial and deep calcium are taken care of by S-IVL, whereas all the contemporary calcium modification techniques target only superficial calcium due to their localization at the luminal surface of the vessel. Very severe lesions where a balloon cannot cross remains the Achilles' heel for S-IVL therapy.

CONCLUSION

Calcific coronary stenosis is one of the biggest challenges for interventional cardiologists. If not treated properly, then the condition can lead to inadequate stent expansion and result in stent thrombosis and restenosis. Techniques such as rotablation, orbital atherectomy and excimer laser are commonly used to modify the coronary calcium; however, they are associated with high procedural complications and are less successful in cases of deep and eccentric calcium. S-IVL is a novel technique that selectively modifies the subendothelial calcium and is easy to perform. Based on the short-term and long-term success demonstrated in the DISRUPT-CAD trial series, S-IVL is being employed in hitherto unexplored areas, such as ISR, vein graft and balloon uncrossable lesions (coupled with rotablation). S-IVL is gradually becoming an indispensable tool for managing calcified lesions in the cardiac catheterization laboratory.

FOOTNOTES

Author contributions: Pradhan A and Bhandari M devised the project, performed the literature search, wrote the first draft and prepared the final manuscript; Vishwakarma P and Bhandari M collected the data; Vishwakarma P and Sethi R critically reviewed and suggested changes; Vishwakarma P created all the images; Sethi R revised the entire manuscript and prepared the final version; Pradhan A, Bhandari M and Vishwakarma P submitted the revised version.

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CASE REPORT

Rare case of chronic Q fever myocarditis in end stage heart failure patient: A case report

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Abstract

BACKGROUND

Q fever myocarditis is a rare disease manifestation of Q fever infection caused by *Coxiella burnetii*. It is associated with significant morbidity and mortality if left untreated. Prior studies have reported myocarditis in patients with acute Q fever. We present the first case of chronic myocarditis in an end-stage heart failure patient with chronic Q fever infection.

CASE SUMMARY

A 69-year-old male was admitted with dyspnea on exertion, hypotension and bilateral lower extremity edema for a few months. He has a past medical history of ischemic cardiomyopathy with left ventricular ejection fraction of 25%, implantable cardioverter defibrillator in place, bioprosthetic aortic valve and mitral valve replacement. He continued to have shortness of breath despite diuresis along with low grade fevers. Initial infectious work up came back negative. On further questioning, the patient was found to have close contact with farm animals and the recurrent fevers prompted the work-up for Q fever. Q fever serologies and cardiac positron emission tomography confirmed the diagnosis of chronic Q fever myocarditis. He was then successfully treated with doxycycline and hydroxychloroquine for 18 mo.

CONCLUSION

Chronic Q fever myocarditis, if left untreated, carries a poor prognosis. It should be kept in differentials, especially in patients with recurrent fevers and contact with farm animals.

Key Words: Chronic Q fever; Myocarditis; *Coxiella burnetii*; Heart failure; Farm animals; Case report

Core Tip: Q fever myocarditis is a rare disease (< 1% of cases) caused by infection with *Coxiella burnetii* (gram-negative proteobacteria). Q fever normally has a pleomorphic and non-specific clinical presentation which leads to delayed diagnosis and treatment, which can lead to worse outcomes. Q fever myocarditis should be kept in differentials not only in patients with acute Q fever but also with chronic Q fever infection, like in our case. Q fever serologies help in making a diagnosis of acute and chronic Q fever. Cardiac positron emission tomography and magnetic resonance imaging can be utilized to diagnose myocarditis in the setting of Q fever. Hydroxychloroquine and doxycycline, in combination, are used for treatment of Q fever myocarditis.

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INTRODUCTION

Q fever is caused by infection with gram-negative proteobacteria, *Coxiella burnetii*[1]. *Coxiella burnetii* is found in many domestic animals like deer, rabbits, rodents, birds, horses and even in arthropods like ticks[2]. Q fever is a zoonosis and is transmitted to humans *via* inhalation of contaminated aerosols[1]. *C. burnetii* can survive for extended periods of time and can be carried long distances *via* wind, hence direct animal contact may not be required for transmission[3]. Disease presentation is variable, ranging from asymptomatic, flu like symptoms to intensive care admission. The variability is mostly due to host factors, bacterial virulence factors and extent of exposure[1]. Myocarditis is a rare disease manifestation of acute Q fever (< 1% of cases)[1]. To the best of our knowledge, less than 30-35 isolated cases of myocarditis with Coxiella have been reported in the literature. However, no case of chronic myocarditis in Chronic Q fever infection has been reported. We present an interesting and rare case of chronic Q fever leading to chronic myocarditis in a patient with a prior history of ischemic cardiomyopathy and valvular heart disease.

CASE PRESENTATION

Chief complaints

A 69-year-old male presented with chief complaints of shortness of breath, fatigue, and intermittent fevers for the last 6 mo which were treated with antibiotics twice.

History of present illness

The patient's symptoms of dyspnea and fatigue had been ongoing for the last few months with severe hypotension, bilateral lower extremity edema and dyspnea on exertion. He denied any chest pain or pressure.

History of past illness

The patient had several comorbidities including ischemic cardiomyopathy with left ventricular ejection fraction (LVEF) of 25%, prior ST-elevation myocardial infarction status post (s/p) stent to proximal left anterior descending artery, s/p implantable cardioverter defibrillator (ICD) in 2018 for primary prevention, bicuspid aortic valve s/p aortic valve replacement with 25 mm Carpentier-Edwards bioprosthetic prosthesis in October 2012 followed by transcatheter aortic bioprosthetic valve in valve (26 mm Sapien S3) in April 2019, mitral valve repair with 32 mm seguin ring repair in October 2012 and subsequent transcatheter bioprosthetic mitral valve replacement with 29 mm Sapien 3 bioprosthetic valve for mitral regurgitation in June 2019, hyperlipidemia, chronic kidney disease stage III and atrial fibrillation.

Personal and family history

The patient denied pertinent family history.

Physical examination

On physical examination, the vital signs were as follows: T max of 100.04 degrees Fahrenheit, blood pressure of 91/61 mmHg, heart rate of 80/minute and oxygen saturation of 96% on room air. The patient's jugular venous pressure was elevated, and a diastolic murmur was heard at the aortic area, bilateral bibasilar crackles at the lung bases, and minimal bilateral lower extremity edema was present.

Laboratory examinations

Troponin-I level was 0.01 ng/mL (normal) and BNP was 1562 pg/mL. WBC count was normal and multiple blood cultures were negative.

Imaging examinations

ECG on admission showed atrial paced rhythm with left bundle branch block. Transthoracic echocardiogram (TTE) on admission showed LVEF of 20%-25% with global hypokinesis, mild to moderate aortic regurgitation, mitral valve mean gradient of 10 mmHg (@ HR of 72 bpm) with normal right ventricle size and function and no vegetation. His most recent TTE prior to admission was done at an outside facility on July 2019 and showed LVEF of 30%, no aortic valve or mitral prosthetic valve regurgitation, mean mitral valve gradient of 7 mmHg (@ HR of 67 bpm), and normal RV function. The chest X-ray on admission showed moderate cardiomegaly with central venous congestion and interstitial edema.

Further diagnostic work-up

To determine his cardiac hemodynamics, shock profile, and whether escalation to temporary mechanical support device is needed, an urgent right heart catheterization was done on admission that showed right atrial pressure 12 mmHg, right ventricular oressure 54/6 mmHg, pulmonary artery pressure 54/25 mmHg, mean pulmonary artery pressure 35 mmHg, pulmonary capillary wedge pressure 24 mmHg and cardiac index by Fick of 2 L/min/m^2 with pulmonary artery saturation of 57%. An infectious disease specialist was consulted. He underwent trans-esophageal echocardiogram to look for endocarditis. It showed a moderate paravalvular aortic valve regurgitation, the replaced mitral valve was functioning normally with no stenosis or regurgitation, and no definitive vegetation was noted on defibrillator leads and prosthetic material.

On further discussion with the patient's wife, his functional status decline was associated with intermittent fevers for the last 6 mo that were treated with antibiotics twice, but no source was identified. On further questioning, the patient reported that he raised horses for the last 30 years and has been in close contact with dogs and cats his whole life. Due to close animal contact, Q fever was suspected. Q fever titers were significantly high: Phase I IgG (1:16384), Phase II IgG (>1:32768), Phase I IgM (1:>2048), and Phase II IgM (>1:2048). 18-Flourine fluorodeoxyglucose (FDG) cardiac positron emission tomography (PET) was preferred over magnetic resonance imaging (MRI) due to the presence of ICD. It revealed heterogenous areas of increased 18-F FDG uptake in the left ventricle raising the concern for myocarditis. The heterogenous uptake was identified in septal, lateral, and anterior walls of the left ventricle (Figure 1A). The basal anterolateral wall demonstrated maximum SUV of 6.9 and basal anteroseptal demonstrated maximum SUV of 5.3. No increased uptake around the valvular structures was noted.

FINAL DIAGNOSIS

Based on the history above, physical examination, laboratory findings, and discussions with our infectious disease colleagues, the most likely etiology of the patient's presentation was chronic myocarditis secondary to chronic Q fever infection. Patient met criteria of both chronic Q fever and chronic myocarditis[4,5].

TREATMENT

The patient was started on milrinone 0.125 mcg/kg/min and intravenous diuresis for his acute presentation of acute on chronic heart failure; however, it was stopped after a few days due to ventricular ectopies. Moreover, he did not feel any improvement in symptoms with milrinone. For the Q fever myocarditis, treatment with doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times daily was initiated for an 18-mo course. Prolonged treatment course was utilized due to his history of prosthetic valves. Due to the patient's significant underlying comorbidities, our advanced heart failure therapy committee meeting deemed him an unsuitable candidate for advanced heart failure therapies at the time of admission. Due to his hypotension, he could not be discharged on guideline directed medical management.

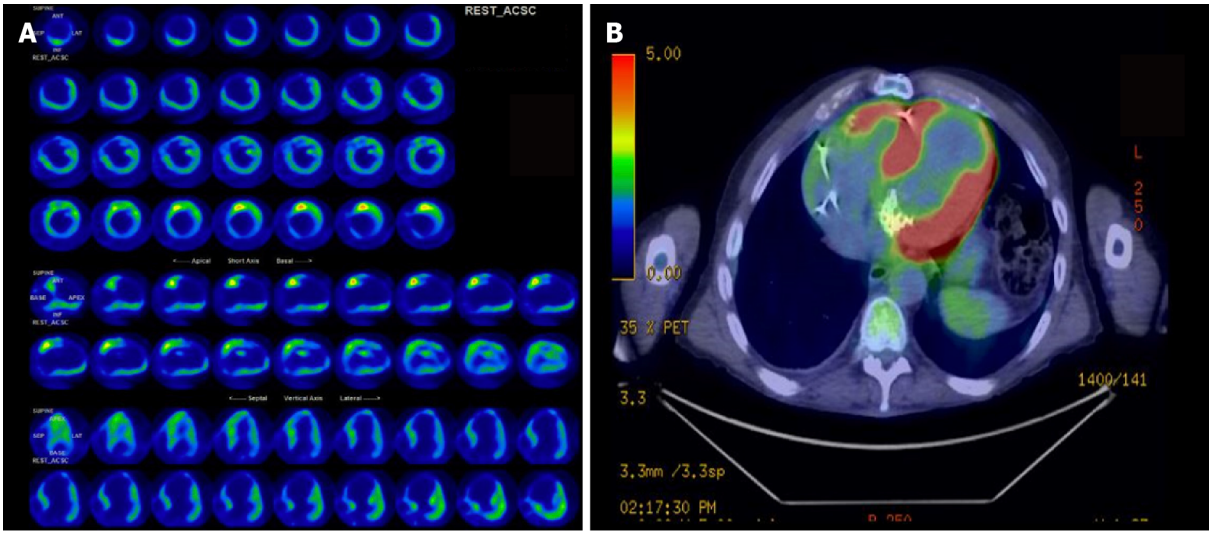

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Figure 1 18-Flourine fluorodeoxyglucose positron emission tomography scan. A: Heterogenous areas of increased uptake involving septal, lateral as well as basal and anterior wall of left ventricle suggestive of myocarditis; B: Whole body positron emission tomography obtained after 1 mo with focus on cardiac structure showing no evidence of residual myocarditis.

OUTCOME AND FOLLOW-UP

On subsequent follow up clinic visits, the patient was noted to have significant improvement in his heart failure symptoms and his fevers resolved. Repeat Cardiac PET after 1 mo showed complete resolution (Figure 1B). The patient was doing better at 1 wk post discharge follow-up and his blood pressure improved. He was started on dapagliflozin 10 mg daily, losartan 25 mg daily and metoprolol XL 100 mg daily. At the patient's 6-month routine follow up, he was doing well and repeat phase I and phase II titers were significantly down: Phase I IgG (1:16384), Phase II IgG (1:16384), Phase I IgM (1:256), and Phase II IgM (1:16) (Table 1). Repeat echocardiogram at 6 mo showed no change in the LVEF, no aortic regurgitation and no stenosis or regurgitation of the mitral valve. He will continue doxycycline and hydroxychloroquine for 18 mo.

DISCUSSION

To the best of our knowledge, this is the first case of chronic myocarditis in a patient with chronic Q fever. Our patient suffered from chronic Q fever infection which ultimately led to chronic myocarditis. Certain conditions like immunosuppression, pregnancy, vascular abnormalities and heart valve conditions predispose individuals to chronic Q fever infection[1]. Our patient had significant valvular heart disease which may have been a predisposing factor for this chronic infection. Myocarditis secondary to *Coxiella burnetii* is a rare manifestation (< 1%)[6,7]. Chronic Q fever diagnosis can often be delayed for months due to nonspecific symptoms and pleomorphic presentation. Endocarditis is the most commonly reported cardiac pathology in chronic Q fever cases[5]. Myocarditis has been almost always reported in the setting of acute Q fever[8,9].

Myocarditis is most likely underestimated in this population due to non-specific signs and symptoms, and a high index of suspicion is required for diagnosis. The diagnosis of Q fever myocarditis is challenging as *C. burnetii* does not grow in routine cultures. Thus, serology is used in most cases for diagnosis[3,10]. *C. burnetii* displays a two-phase antigenic variation due to changes in lipopolysaccharide C antigens: Phase I (often seen in chronic Q fever) and phase II (often seen in acute Q fever). Indirect immunofluorescent assay is used for serological detection. Cut-off for serological titers varies between countries, but the screening test is generally considered positive for acute disease when anti-phase II IgG anti-immunoglobulins return active at a dilution of ≥1:200 or IgM ≥1:50[8]. These positive tests are then diluted and tested for presence of anti-phase I IgG and IgM. Chronic Q fever is found when phase I IgG ≥1:800, usually in the presence of anti-phase II antibodies[3,11]. Cardiac MRI and ^{18}FDG-PET scan have been used before to diagnose Q fever myocarditis[12]. Another point worth mentioning is the negative troponin-I in our patient. Prior studies have shown negative troponin-I with biopsy proven myocarditis. The lack of troponin-I release does not rule out myocarditis[13]. There have been a few cases in the past showing Q fever infection leading to valvulitis[14], and this may explain the aortic regurgitation in our patient which got better with treatment of Q fever.

Table 1 Q fever serology

Variables	Reference range	Admission	3 months	6 months
Phase I IgG	<1:16	1:16384	1:32768	1:16384
Phase II IgG	<1:16	>1:32768	1:131072	1:16384
Phase I IgM	<1:16	>1:2048	1:1024	1:256
Phase II IgM	<1:16	>1:2048	1:2048	1:16

IgG: Immunoglobulin G; IgM: Immunoglobulin M.

The prognosis of Q fever myocarditis is uncertain, but it has worse prognosis compared to other forms of Q fever diseases. In some studies, mortality with Q fever myocarditis has been reported to be up to 30%[8,15]. Patients with chronic *C. burnetii* are usually unable to eradicate the infection without utilizing antibiotics[1]. Center for Disease Control and Prevention recommends doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times a day for ≥ 18-24 mo as the treatment of choice for Q fever myocarditis, endocarditis or vascular infection[16,17]. Hydroxychloroquine is used mainly to increase the efficacy of doxycycline and prevents the development of chronic Q fever endocarditis. Although this regimen seems long, the addition of hydroxychloroquine has reduced the treatment time from 5 years to 18-24 mo[17]. Our patient was started on the long course of antibiotics to prevent endocarditis due to significant valvular abnormalities. Both doxycycline and hydroxychloroquine can cause photosensitivity, and patients should be warned to avoid excessive sun exposure. Regular heart and eye examinations are needed due to the risk of hydroxychloroquine induced retinopathy[16].

CONCLUSION

Q fever myocarditis is a rare disease, and a high index of suspicion is required for diagnosis. Given the poor prognosis of Q fever myocarditis and the presence of reliable therapy, it should be kept in differentials for patients with fevers and cardiomyopathy, especially in patients with a history of animal exposure. Multimodality imaging like echocardiogram, cardiac MRI and cardiac PET can be utilized in diagnosing myocarditis in patients with Q fever.

FOOTNOTES

Author contributions: Goyal A and Dalia T have contributed equally to the manuscript writing, editing, and data collection; Bhyan P and Farhoud H have assisted with writing and edits; Shah Z and Vidic A have contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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CASE REPORT

Intra-atrial course of right coronary artery: A case report

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Abstract

BACKGROUND

Intra-atrial right coronary artery (RCA) is a rare and generally asymptomatic anomaly of development of the coronary arteries. This malformation could potentially expose the patient to a catastrophic outcome in the case of injury during interventional or surgical procedures. Currently, only a few case reports and no systematic reviews are available in the literature.

CASE SUMMARY

We report the case of a 54-year-old man with atypical chest pain who underwent multi-detector computed tomography angiography (MDCTA). The exam revealed no significant coronary artery stenoses; however, an intra-atrial course of mid RCA was evident. Medical therapy was administered, and the patient was discharged to home without undergoing a conventional angiography. Previously reported autoptic and clinical cases were retrieved from the PubMed literature database to compare the clinicopathological features of this case.

CONCLUSION

MDCTA depicted the abnormal course of the coronary artery in this patient as an intra-atrial course of the mid RCA. Finding this abnormality was crucial to avoid an inadvertent injury during interventional or surgical procedures.

Key Words: Coronary artery anomaly; Anomalous course of right coronary artery; Intra-atrial right coronary artery; Intracavitary right coronary artery; Multi-detector computed tomography angiography; Case report

Core Tip: We present a rare case of an intra-atrial course of the mid right coronary artery (commonly referred to as right coronary artery) detected by multi-detector computed tomography angiography (MDCTA). We performed a systematic review of the few cases in the literature. Since this anomaly could potentially expose the patient to catastrophic outcome in case of injury during interventional or surgical procedures, its recognition *via* MDCTA is crucial before such interventions.

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INTRODUCTION

Intra-atrial or intra-cavitary course of the right coronary artery (RCA) is defined as a segment of the RCA that courses through the right atrial (RA) chamber[1,2]. It is a relatively rare vascular anomaly, with a reported incidence of 0.09%-0.1%[1,2].

Historically, this anomaly of development was most often identified by accident, during coronary surgery or autopsy, due to its benign outcome; however, in the era of multi-detector computed tomography angiography (MDCTA), it is now detected more frequently, and its incidence rate has risen to 1.8%[1]. From a radiological point of view, it was defined as a segment of RCA entirely surrounded by intra-atrial contrast in all phases of the cardiac cycle, unlike the myocardial bridge, in which a segment of the coronary artery appears as entirely surrounded by myocardial muscle[1,2]. Its recognition is very important before cardiac surgery or endocavitary procedures (*i.e.* ablation for arrhythmias, catheterization of the RA, and pacemaker implantation) since it carries a concerning potential for injury to the intra-atrial RCA, which could have a catastrophic outcome[1].

Herein, we report the case of a patient with an anomalous course of the RCA through the RA which was identified using MDCTA. Furthermore, to the best of our knowledge, we provide, for the first time, a discussion based on a review of all cases of intra-atrial course of RCA in the literature. The review was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Padua.

CASE PRESENTATION

Chief complaints

A 54-year-old Caucasian male with moderate cardiovascular risk factors (*i.e.*, obesity, hyperlipidemia, and hypertension) presented to the cardiologic clinic with atypical angina presenting without dyspnea.

History of present illness

The patient reported that the symptoms had started 2 h before presentation, describing atypical chest pain without dyspnea.

History of past illness

The past history of the patient was unremarkable.

Personal and family history

The patient denied any personal history relevant to atypical angina, dyspnea, or other cardiovascular symptoms and any family history of cardiovascular disease.

Physical examination

On physical examination, the significant vital signs were as follows: body mass index of 28.7 kg/m^2; heart rate at regular pulse of 80 beats per min; and blood pressure of 163/92 mmHg. Dyspnea, heart murmurs, and other signs of heart failure were absent.

Laboratory examination

Levels of myocardial injury enzymes (*i.e.*, troponin T and creatine kinase) were normal. Electrocardiography demonstrated a sinus rhythm of 77 beats per min and absence of ST depression with minimal alterations in lateral repolarization.

Imaging examination

The patient underwent MDCTA (Aquilion ONE; Toshiba Medical Systems, Otawara, Japan) using the following scan parameters: prospective protocol; gantry rotation time of 350 ms; 512 × 512 matrix; slice thickness of 0.5 mm with 0.25 mm increments using kernel FC03; automatic exposure control (SURE bExposure 3D; Toshiba Medical Systems) (SD 110 for contrast-enhanced images); and iterative reconstruction.

An intravenous contrast (60 mL Iomeron® 400 mg iodine/mL; Bracco Imaging Italy s.r.l., Milan, Italy) was administrated at 5 mL/s flow. Heart rate was set between 50 and 60 beats per min with intravenous administration of metoprolol. The data were transferred to an external workstation (Vitrea2 FX version 6.3; Vital Images, Plymouth, MN, United States) providing multiplanar reformation (commonly referred to as MPR) and volume rendering technique (commonly referred to as VRT).

From the scans, mild coronary calcification (Agatston calcium score of 34) of the left anterior descending (LAD) coronary artery, without significant stenoses (> 70%) of all segments, was detected. Additionally, an abnormal course of the mid RCA was identified. As demonstrated by axial images and CT multiplanar reconstruction, the origin and the proximal tract of the RCA were normal, with an epicardial course in the right atrio-ventricular groove; however, the artery penetrated the anterior RA wall and then exhibited an intracavitary course of 25 mm (Figure 1). After the exit from RA, the RCA passed normally in the atrio-ventricular groove and then continued normally at the level of the diaphragmatic crux.

FINAL DIAGNOSIS

Considering the patient's medical history along with the MDCTA imaging findings, the final diagnosis was an intra-atrial course of the mid RCA without significant coronary atherosclerosis.

TREATMENT

The patient responded well to standard medical therapy (*i.e.*, rosuvastatin, administered at 5 mg per day) and was discharged home on postoperative day 2 without having to undergo a conventional angiography study.

OUTCOME AND FOLLOW-UP

At the last follow-up (5 mo postoperatively), the patient was still alive.

DISCUSSION

RCA anomalies are rare and abnormal courses of the RCA are even more rare, with an incidence of 0.1% [2]. In the literature, an intra-atrial course of the RCA was reported only in 9 autoptic cases[3,4] and in about 80 clinical cases[1,2,5-26] (Table 1). Most clinical cases were case reports, but a few case series were reported[1,2,5,9,10,16,21].

An intra-atrial course of RCA was first described in 1975 by McAlpine[27]. The prevalence of this variant was initially reported to be between 0.09% and 0.1%[5-7], but these rates probably represented underestimations because the conventional angiographic luminographic 2D assessment may not be able to recognize this abnormal variant. The most recent studies – involving cases that are being diagnosed by the new advanced imaging techniques – have reported a prevalence of 1.3%[2] and 1.8%[4]; certainly, the increasing use of MDCTA of the coronary arteries will lead to an even greater increase in identification of this anomaly[8].

Reportedly, the segments of the RCA most frequently involving an intra-atrial course were segments 3 (47%) and 2 (40%)[9], with mean length ranging from 14 mm to 53 mm[9]. In our perusal of the literature, the most frequent intra-atrial segment of the RCA reported was the mid segment (Table 1), with a length of intra-atrial RCA ranging from 13.2 mm[10] to 55 mm[5]. Rarely, the intra-atrial course of the RCA involved segments 1 and 4 (13%)[9] or has lengths shorter (as low as 13 mm) or longer (up to 55 mm)[10-12].

In our review of the literature, most cases were female, and the patient's ages ranged from 45 years [20] to 78 years[13]. In none of the cases was there presence of significant coronary artery stenoses nor were mild atherosclerotic plaques indicated[9]. A possible explanation could be the absence of mechanical stress on the segment of the coronary artery when it coursed intra-atrially or intra-myocardially rather than in the epicardial fat, although this conclusion is not definitive[9].

Table 1 Literature summary of intra-atrial course of the right coronary artery

Ref.	Patients, *n*	Type	Sex	Age in yr	Risk factors	Symptoms	Imaging	Segment of RCA	Intra-atrial course length in mm	Stenosis, %	Outcome
Kolodziej *et al*[3], 1994	3	Autoptic series	UNK	UNK	UNK	UNK	Postmortem examination	Mid	15; 20; 30	No	Mortem
Rosamond *et al* [14], 2007	1	Case report	M	54	NR	Palpitation, atrial fibrillation	MDCTA 64	Distal	35	No	No atrial fibrillation
Scheffel *et al*[11], 2007	1	Case report	F	77	Hypertension, hyperlipidemia, family history	Atypical chest pain	MDCTA	Mid	55	No	NR
Zalamea *et al*[5], 2009	2	Series	F; F	70; 54	Atrial fibrillation; Smoker	Dyspnea on exertionChest pain, nausea, diaphoresis	MDCTA	Mid-distal; Mid-distal	40-50; 55	No; No	No ablation; NR
Andrade *et al*[6], 2010	1	Case report	M	46	Strong family history	No	MDCTA	Mid	25	No	NR
Lee *et al*[8], 2010	1	Case report	F	57	Hypertension, hyperlipidemia	Atypical chest pain	MDCTA	Mid	38	No	Discharged
Renapurkar *et al* [12], 2010	1	Case report	F	49	Family history	Atypical chest pain	MDCTA 64 DS	Mid	10	No	NR
Chou *et al*[19], 2011	1	Case report	M	56	Diabetes, hypertension	Chest tightness	MDCTA	PL	NS	No	Symptoms persistence
Christopher and Duraikannu[7], 2011	1	Case report	F	48	No	Chest pain, dyspnea, palpitation	MDCTA	Mid	15	No	NR
Bansal *et al*[10], 2011	2	Series	NS	NS	NS	NS	MDCTA	Segment 3; Segment 2	13.2; 15.6	NS	NS
Zeina[17], 2011	1	Case report	M	59	Multiple	Chest pain	MDCTA 64	Distal	40	No	NR
Waniewska *et al* [24], 2012	1	Case report	F	62	NR	Atrial flutter, atrial fibrillation, fainting, hypotension	MDCTA	Distal	50	No	RFA
Opolski *et al*[9], 2014	14	Series	M:F = 2:12	54 (mean)	Diabetes, hypertension, hyperlipidemia, smoker, family history	Atypical chest pain, stable angina pectoris, syncope, dyspnea, palpitations, arrhythmia	MDCTA	Segment 3 (47%); Segment 2 (40%); Segment 1 and 4 (13%)	29 (mean)	No	Conservative approach
Bunkiewicz *et al* [13], 2015	1	Case report	F	78	Hypertension, previous acute coronary syndrome	Not specific chest pain, low tolerance of physical effort, dry cough	MDCTA	Mid	20	No	UNK
Buckley *et al*[16],	17	Series	NS	NS	NS	NS	MDCTA	NS	NS	NS	NS

2017											
Krishnan *et al*[4], 2017	6	Autoptic series	M	69 (mean)	NS	UNK	Postmortem examination	Type I: Mid; Type II: Mid; Type III: Anterior branch	Type I: 22 (mean); Type II: 36; Type III: UNK	No	Mortem
Ganga *et al*[20], 2019	1	Case report	M	45	NR	Atypical chest pain	MDCTA	Mid	45	No	NR
Bouhuijzen *et al* [18], 2019	1	Case report	F	64	NR	Atypical chest pain	MDCTA	NS	40	No	
Hossain *et al*[2], 2019	7	Series	M:F = 71.4:28.6	67.3(mean)	Chest pain (25%), shortness of breath (33%)	Pre-TAVR	MDCTA	NS	33.4 (mean)	No	No coronary intervention
Mahmoud *et al* [22], 2020	1	Case report	F	61	NS	Chest pain	MDCTA	Mid	39	NS	NR
Junco-Vicente *et al* [21], 2020	3	Series	1M; 2F	NS	NS	Chest pain	MDCTA	Mid	27.7 (mean)	No	UNK
Marrone *et al*[26], 2020	1	Case report	F	48	Aortic valve disease	NR	MDCTA	Distal	49	No	NR
Ganga *et al*[1], 2021	21	Series	M:F = 1.3:1	53.7 (mean)	NR	NR	MDCTA	Mid (16/21); Distal (5/21)	14.85 (mean)	No	NR
Frey *et al*[23], 2022	1	Case report	M	55	Hypertension, hypercholesterolemia, smoker, obesity	Atypical angina, dyspnea	MDCTA	Mid (posterior)	40	No	Conservative approach
Borges *et al*[25], 2022	1	Case report	M	66	NS	Palpitation, tachycardia, dyspnea	MDCTA	Mid	30	No	NR
Barbiero *et al*	1	Case report	M	54	Hypertension, hyperlipidemia, smoker	Atypical chest pain	MDCTA	Mid	25	No	Medical treatment

F: Female; M: Male; MDCTA: Multi-detector computed tomography angiography; NR: Not reported; NS: Not specified; PL: Posterior lateral; RFA: Radiofrequency ablation; TAVR: Transcatheter aortic valve replacement; UNK: Unknown; DS: Dual source.

Association between the intra-cavitary course of the RCA and other coronary anomalies have been described, such as with the intramuscular course of the LAD coronary artery or with the anomalous origin of the left circumflex (commonly known as LCX) coronary artery from the right aortic sinus[9]. Patients with intra-cavitary course of the RCA were usually asymptomatic, and its discovery was incidentally encountered during an MDCTA coronary study conducted for other reasons (*i.e.*, atypical chest pain, chest tightness, dyspnea, palpitation, atrial flutter or fibrillation, arrhythmia, fainting, hypotension, or syncope) (Table 1).

An intracavitary course of the RCA has a higher probability of iatrogenic damage than myocardial bridging because of the risk of direct injury at the abnormal vessel segment during surgical manipulation or endoatrial procedures (*i.e.*, ablation, catheterization, or electrode implantation). Therefore, although it is usually considered an asymptomatic variant, its early recognition is crucial to avoid vessel

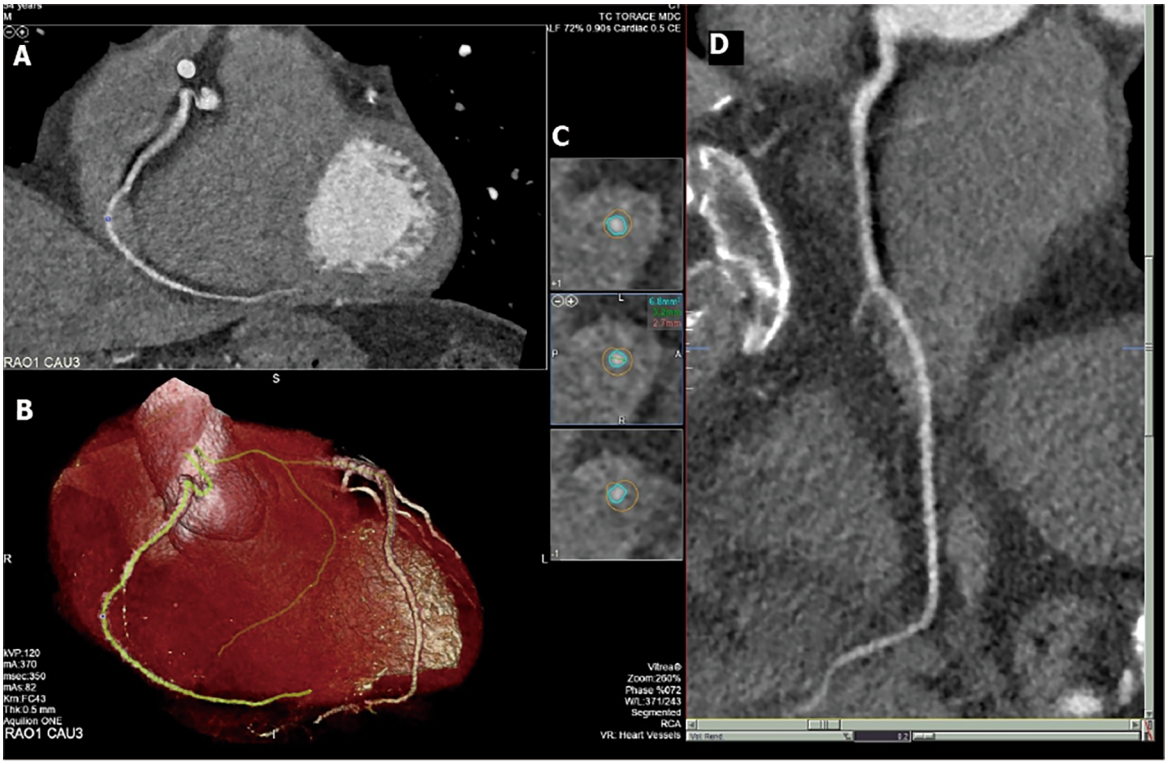

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Figure 1 Multi-detector computed tomography angiography showed the anomalous intra-atrial course of the mid right coronary artery. A: Curved planar reformatting showed the entire course of the right coronary artery (RCA) with a mid-segment with an intra-atrial course; B: Volume rendering technique showed the entire course (green line) of the RCA; C: Cross-sectional images showed the intra-atrial segment of the RCA, which was completely surrounded by blood in the right atrium; D: Curved planar reformatting showed the entire course of the RCA with a mid-intra-atrial course of the artery.

catastrophic lesions during such procedures[2].

CONCLUSION

MDCTA is a less invasive and less user-dependent method than conventional angiography and can accurately depict the coronary vasculature and its variants of origin, termination, or course[2]. The recognition of an intra-atrial course of the RCA by MDCTA could facilitate avoidance of potential hazards during surgical and/or interventional procedures.

FOOTNOTES

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