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Approximation of the Incidence of Myocarditis by Systematic Screening With Cardiac Magnetic Resonance Imaging

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ABSTRACT

OBJECTIVES This study sought to obtain an approximation of the true incidence of myocarditis by systematic screening of patients at risk using cardiac magnetic resonance imaging (CMR) in a tertiary care center.

BACKGROUND Underdiagnosis of myocarditis and resulting uncertainty about its incidence remain a clinical dilemma. The authors hypothesized that systematic screening of patients presenting with angina-like symptoms, elevated troponin T, and no significant coronary artery disease using CMR will provide an approximation of the true incidence of myocarditis.

METHODS The authors performed a retrospective chart review of patients presenting with angina-like symptoms and elevated high-sensitivity troponin T (TnT-hs ≥14 ng/l) in 2015 and 2016. During the year 2015, only patients with elevated TnT-hs, no significant coronary artery disease, and moderate-to-high clinical likelihood of myocarditis underwent CMR. Starting in 2016, CMR was obtained in patients with similar presentation, but independent of clinical likelihood of myocarditis.

RESULTS A total of 1,788 patients (74% male, age 69 ± 14 years) qualified for our analysis. In 2015, 521 patients presented with angina-like symptoms and TnT-hs elevation. In 2016, the number increased to 1,267 patients. Although in the year 2015, a total of 4 of 88 (5%) CMRs were positive for myocarditis, the percentage of positive CMRs doubled (26 of 199; 13%; $p = 0.03$) in 2016.

CONCLUSIONS A novel diagnostic screening algorithm led to a 6.3-fold increase of the incidence of myocarditis in our hospital. Furthermore, the percentage of CMRs positive for myocarditis doubled, supporting the diagnostic value of this method. Considering the potentially lethal adverse events of myocarditis if left untreated, we recommend a low threshold for the use of CMR in patients with angina-like symptoms and elevated TnT-hs after exclusion of coronary artery disease. (J Am Coll Cardiol HF 2018;6:573–9) © 2018 by the American College of Cardiology Foundation.

Chest pain is currently 1 of the most common causes for patient visits in the emergency department (1). Although acute coronary syndrome remains the leading cause in mortality worldwide (2), approximately 3% to 13% of patients presenting with chest pain and suspected myocardial infarction (MI) have unobstructed coronaries (3–5). Remarkably, patients with unobstructed coronary artery disease or MI with nonobstructed coronary arteries (MINOCA) have poor prognosis with a 12-month all-cause mortality rate of 4.7% (4). The lack of guidelines for those "culprit free"-patients creates diagnostic and therapeutic challenges. Maddox et al. (6) showed that in contrast to patients with coronary artery disease, this population typically does not receive specific therapy to reduce risk for future cardiovascular events, suggesting potential for therapeutic improvement in this

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CMR = cardiac magnetic resonance imaging

CT = computed tomography

EMB = endomyocardial biopsy

HCM = hypertrophic obstructive cardiomyopathy

MI = myocardial infarction

MINOCA = myocardial infarction with nonobstructed coronary arteries

PCI = percutaneous coronary intervention

TnT-hs = high-sensitivity troponin T

population. Differential diagnoses in the setting of angina and unobstructed coronary arteries include microvascular disease, Takotsubo syndrome, spontaneous recanalization of thrombotic occlusion or embolisms, and acute myocarditis (4,7). Assomull et al. (8) found myocarditis to be the most frequent diagnosis in this population. Additionally, most cases of acute myocarditis in young men seem to mimic an MI (9). Moreover, studies in patients with angina-like symptoms, elevated high-sensitivity troponin T (TnT-hs), and unobstructed coronaries have estimated the prevalence of myocarditis to range from 16% to 56% (10–12). Postmortem data have revealed myocarditis in sudden cardiac death at a rate of 8.6% up to 42%, suggesting that a considerable number of cases remain undiagnosed and thus untreated (13–15).

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Discrepancy in the published data about the incidence of myocarditis emphasizes the need for effective standardized diagnostic screening. Early accurate diagnosis is crucial to introduce therapy and lifestyle modifications in a timely manner (16,17). Whereas the gold standard for definitive diagnosis of myocarditis remains endomyocardial biopsy (EMB) (7,18,19), cardiac magnetic resonance imaging (CMR) has evolved as a valuable diagnostic alternative to EMB and helps stratifying the risk in patients with suspected myocarditis (20–24).

In the present study, we sought to test the hypothesis of whether systematic screening using CMR of patients presenting with angina-like symptoms, elevated TnT-hs (≥14 ng/l), and no significant coronary artery disease will improve detection of myocarditis and provide an approximation of its true incidence in a tertiary medical center.

METHODS

STUDY DESIGN. We performed a retrospective single-center registry study investigating the incidence of myocarditis. Our chart review included patients who presented during the years between 2015 and 2016 (from January 2015 to January 2017) to the University Hospital Zurich with angina-like symptoms and elevated levels of TnT-hs (normal range 0 to 14 ng/l), and who had significant coronary artery disease (>50% stenosis) excluded by coronary angiography or computed tomography (CT) coronary angiography. No patients were excluded.

OUTCOME MEASUREMENTS. The primary outcome measure was to obtain an approximation of the true incidence of myocarditis among patients with angina-like symptoms, elevated TnT-hs, and unobstructed coronary arteries by systematic CMR screening in our institution at the University of Zurich. To evaluate effectiveness of screening in 2016, results were compared with the previous year during which no systematic screening was performed. In addition, secondary outcome measures included: 1) number of patients presenting to our hospital with angina-like symptoms, elevated TnT-hs, and unobstructed coronary arteries per year; 2) number of CMRs performed in the years 2015 versus 2016, when the threshold for screening was lowered; 3) percentage of CMRs positive for myocarditis in 2015 versus 2016; and 4) incidence of other diagnoses in this patient population.

CLINICAL DATABASE. Clinical data was retrieved from the electronic medical records database of the University Hospital Zurich. All patients were de-identified and continuously numbered before analysis. Calculation and analysis were performed using IBM SPSS Statistics version 21 (Zurich, Switzerland). The study was approved by the regional ethics committee, and all patients provided their written informed consent.

DIAGNOSTIC SCREENING ALGORITHM. In patients presenting with angina-like symptoms and elevated TnT-hs, coronary artery disease was excluded by coronary angiography in the majority of patients. In cases of very low pretest probability for coronary artery disease, screening methods for coronary artery disease included CT coronary angiography or stress CMR with adenosine. In 2015, patients with moderate-to-high clinical suspicion for myocarditis underwent further diagnostic evaluation with CMR. Moderate-to-high clinical suspicion was raised in patients with classic symptoms of myocarditis such as chest pain, dyspnea, palpitations, syncope after viral prodrome (25,26) in the context of elevated TnT-hs, and unobstructed coronary arteries. In 2016, the threshold for obtaining CMRs was lowered and all patients with angina-like symptoms, elevated TnT-hs, and without obstructive coronary artery disease were screened with CMR unless another apparent etiology for their symptoms and TnT-hs elevation was identified (e.g., pulmonary embolism, severe hypertension, and so on). All CMRs were performed within 1 month of symptom onset.

CMR EXAMINATION. CMR examinations were performed either on a 1.5-T or 3.0-T scanner (SiemensSkyra, Erlangen, Germany, or Philips

Achieva, Best, the Netherlands) with the help of electrocardiography-gated breath-hold protocol under the oversight of the same reader in the time period from 2015 to 2016. A combination of T2-weighted black-blood imaging and T1-weighted late gadolinium enhanced imaging was used to diagnose myocarditis. These images were acquired 10 min after intravenous injection of gadolinium-based contrast agent. Although the threshold for CMR screening was lowered in 2016, the CMR protocol itself did not change between 2015 and 2016.

STATISTICAL ANALYSIS. A retrospective chart review was performed including clinical parameters and angiographic and CMR findings. Descriptive statistics were used to characterize clinical data. To create a table of baseline parameters comparing the cohorts from 2015 and 2016, nominal variables were compared using the chi-square test, whereas metric scaled and normally distributed variables were reported as mean and analyzed with the Student's *t*-test. A p value of <0.05 was considered significant. To assess the incidence of myocarditis detected through aggressive screening in 2016 versus the less aggressive approach in 2015, we compared results from CMR screening of both years and evaluated level of significance using the chi-square test.

Coronary angiographies were counted once every 2 months per patient to exclude elective re-angiographies (e.g., for staged percutaneous coronary interventions [PCIs]) in our analysis.

Additionally, we listed all diagnostic results from CMR, including myocarditis, pericarditis, ischemia, scar tissue, hypertrophic obstructive cardiomyopathy (HCM), amyloidosis, idiopathic dilated cardiomyopathy, Takotsubo cardiomyopathy, and Fabry disease. Rare diagnoses were summarized under "others."

RESULTS

BASELINE CHARACTERISTICS. Our population consisted of 1,810 patients presenting from 2015 until the end of 2016. Twenty-two patients were lost to follow-up due to death or patients' refusal of further diagnostic workup (5 in the year 2015, and 17 in 2016). Therefore, the population included in this study consisted of 1,788 patients with a median age of 69 years of age (range 18 to 96 years) of whom 25.7% were women and 74.3% were men (Table 1).

Of the 1,788 patients, the majority (n = 1,661; 93%) underwent screening for coronary heart disease via coronary angiography. Seven patients (0.4%) underwent CT angiography and the remaining participants (n = 120; 7%) directly received CMR either because of contraindications to angiography or strong suspicion for myocarditis or structural heart disease. In patients who underwent coronary angiography, obstructive coronary heart disease was present in 57.7% (n = 963), leading to 82 cases of coronary artery bypass grafts (CABG) and 879 cases of PCIs performed during the period from 2015 to 2016. Seven hundred five patients (42.3%) were found to have unobstructed coronaries arteries (Figure 1).

TABLE 1 Comparison of Baseline Parameters and Performed Procedures in 2015 Vs. 2016

	2015 (n = 521)	2016 (n = 1,267)	Total (N = 1,788)
Mean age, yrs	71 ± 14	69 ± 14	69 ± 14
Male	404 (77.5)	924 (72.9)	1,328 (74.3)
Coronary angiography (%)	475 (91.2)	1,186 (94.0)	1,661 (92.9)
PCI	227 (43.6)	652 (51.5)	879 (49.1)
CABG	29 (5.6)	53 (4.3)	83 (4.6)
CMR	87 (16.7)	210 (16.6)	297 (16.5)

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance imaging; PCI = percutaneous coronary intervention.

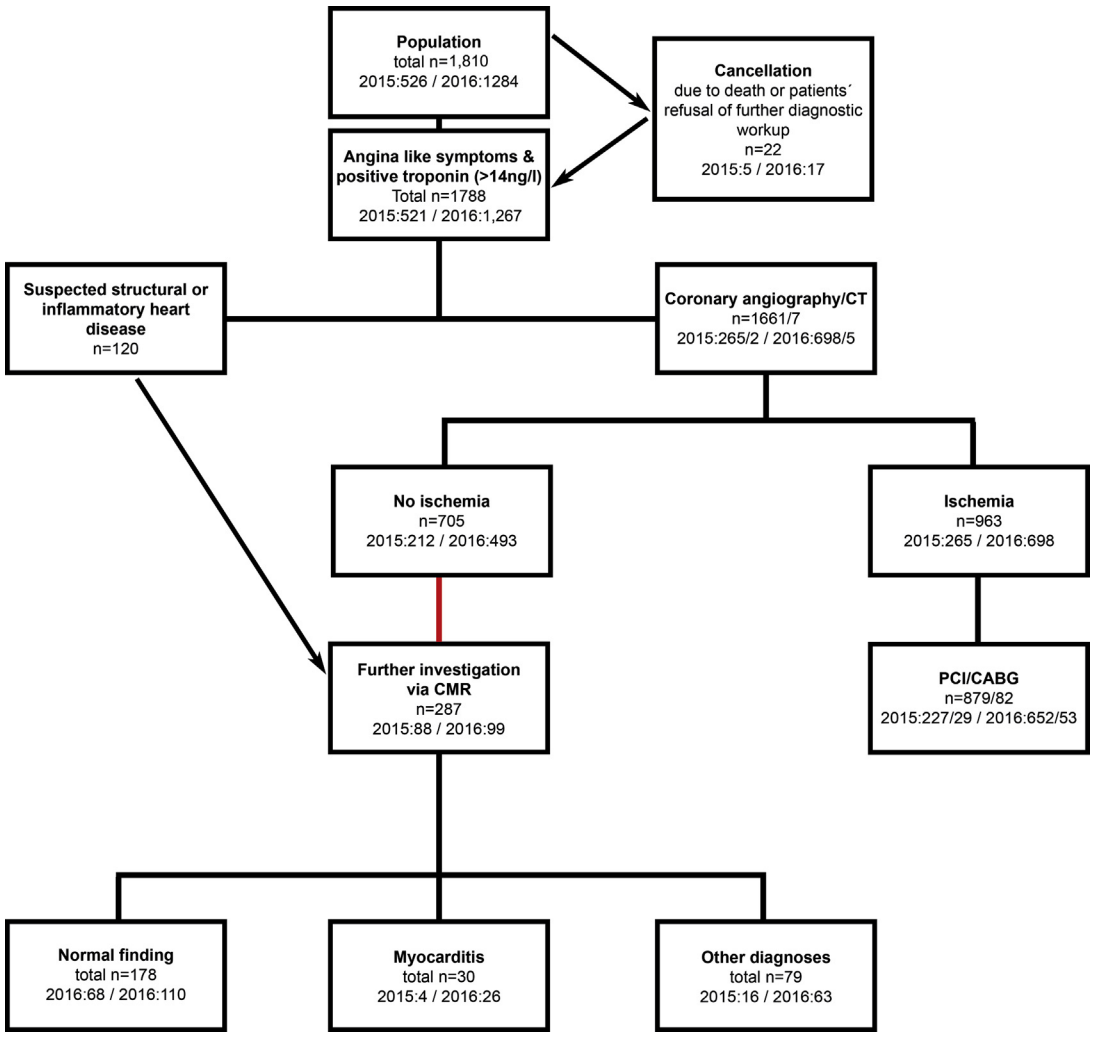
In total, 287 CMR scans were obtained from 2015 to 2016. The most common underlying etiology was ischemia (n = 34, 11.9%) followed by myocarditis (n = 30, 10.5%), HCM (n = 11, 3.8%), pericarditis (n = 4, 1.4%), Takotsubo cardiomyopathy (n = 4, 1.4%), amyloidosis (n = 2, 1%), sarcoidosis (n = 2, 0.7%), Fabry disease (n = 2, 0.7%), and idiopathic dilated cardiomyopathy (n = 1, 0.3%). Rare diagnoses included scleroderma and eosinophilic granulomatosis with polyangiitis (n = 18, 6.3%). In 178 of all cases (62%), the etiology of troponin elevation could not be identified with CMR (Table 2).

In summary, we identified a total of 30 cases of myocarditis (4.2%) among patients with angina-like symptoms, elevated TnT-hs, and unobstructed coronary arteries in the years 2015 and 2016. Patients with myocarditis were mostly men (73.3%) with an average age of 49 ± 16 years.

INCIDENCE OF MYOCARDITIS SINCE INTRODUCTION OF A NOVEL SCREENING ALGORITHM IN 2016. Of the 1,788 patients with angina-like symptoms and elevated TnT-hs, 521 presented in 2015 versus 1,267 who presented in 2016. There was no significant difference in baseline parameters (Table 1).

In the year 2015, 88 CMRs were performed versus 199 in 2016. Overall, we found significantly less CMR reports that were negative for any pathology in 2016 versus 2015 (p = 0.00037). An underlying diagnosis was found in 89 patients (44.7%) in 2016, whereas in 2015 the etiology of symptoms and troponin elevation was identified in only 20 patients (22.7%). There were

FIGURE 1 Diagnostic Algorithm



In 2016 the threshold for further investigation via CMR was lowered in patients with angina-like symptoms, elevated troponin (>14 ng/l), and unobstructed coronaries. CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance imaging; CT = computed tomography; PCI = percutaneous coronary intervention.

6.5 times more cases of myocarditis diagnosed by CMR in 2016 versus 2015 (4 in 2015 vs. 26 in 2016) ($p = 0.03$). We counted 39,694 hospitalized patients in 2015 and 41,121 in 2016 at the University Hospital Zurich. Therefore, the incidence was 0.1 per 1,000 admissions in 2015 and 0.63 per 1,000 admissions in 2016 resulting in a 6.3-fold increase between the 2 years. Patients were diagnosed only once per year with myocarditis.

No significant difference in the number of diagnoses of pericarditis, HCM, sarcoidosis, amyloidosis, Takotsubo cardiomyopathy, or Fabry disease was identified between the 2 years (Table 2).

DISCUSSION

This study shows for the first time a significant increase in detection rate of myocarditis through systematic CMR screening of patients with angina-like symptoms, elevated TnT-hs, and unobstructed coronary arteries. Whereas the number of patients admitted to our hospital in 2016 with angina-like symptoms and elevated TnT-hs increased 2-fold due to a partnership with a new referring hospital, the incidence of myocarditis at the University Hospital Zurich increased 6.3-fold after introducing a novel systematic screening algorithm.

TABLE 2 Comparison of Diagnoses Based on Cardiac Magnetic Resonance Imaging Between 2015 and 2016*

Diagnosis	2015 (n = 88)	2016 (n = 199)	2015 and 2016 (n = 287)
Normal heart	68 (77.3)	110 (55.3)	178 (62)
Coronary ischemia	8 (9.1)	26 (13.1)	34 (11.9)
Pericarditis	0 (0)	4 (2)	4 (1.4)
Amyloidosis	1 (1.1)	2 (1)	3 (1)
Sarcoidosis	1 (1.1)	1 (0.5)	2 (0.7)
Fabry disease	1 (1.1)	1 (0.5)	2 (0.7)
Takotsubo cardiomyopathy	0 (0)	4 (2)	4 (1.4)
Dilated cardiomyopathy	0 (0)	1 (0.5)	1 (0.3)
HCM	2 (2.3)	9 (4.5)	11 (3.8)
Myocarditis	4 (4.6)	26 (13.1)	30 (10.5)
Others	3 (3.4)	15 (7.5)	18 (6.3)

Values are n (%). *Number of total CMRs performed per year is listed in columns; resulting diagnoses per year are listed in rows. Although the total number of diagnoses increased for most cardiomyopathies in 2016 (e.g., for HCM), the percentage of CMRs positive for a specific diagnosis increased only for myocarditis significantly (p = 0.03). Importantly, at the same time, the percentage of CMRs without a specific disease identified decreased from 77% to 55% (p = 0.00037).

HCM = hypertrophic cardiomyopathy; NS = not significant; other abbreviation as in Table 1.

This suggests myocarditis had been underdiagnosed when the indication for CMR was primarily based on clinical symptoms.

Up to this point, numerous studies evaluated the incidence of myocarditis based on CMR data. However, due to discrepancy in the results and a lack of a shared standardized diagnostic approach the true incidence of myocarditis has remained uncertain (5,8,9,11,14–16). In that regard Pitts et al. (1) and Karjalainen and Heikkilä (9) showed that clinically diagnosed myocarditis in young men was present in 99 patients of 672,672 Finnish military conscripts over a period of 20 years with an incidence rate of 0.17 per 1,000 man-years. Data of the global burden study described 156,300 cases of acute myocarditis worldwide in 2015. The combined prevalence of dilated cardiomyopathy and myocarditis has been shown to be approximately 2,380,400 cases in 2015 worldwide (27). In 2005, Kühl et al. (28) described a high prevalence of viral infection in patients who had been initially diagnosed with dilated cardiomyopathy based on histology. Although there is still an ongoing discussion concerning whether viruses are causative or bystanders in the pathophysiology of myocarditis, at least for some viruses a pathogenic effect on cardiomyocytes has been shown (29–31).

A meta-analysis by Pasupathy et al. (4) shows the importance of myocarditis as a differential diagnosis in patients presenting with angina-like symptoms, elevated TnT-hs, and unobstructed coronary arteries. Leurent et al. (5) evaluated a population with similar characteristics prospectively by CMR. A total of 107 patients were screened, of which 59.9% were positive for myocarditis. In contrast, a similar study conducted by Assomull et al. (8) found myocarditis to be present in 50% of patients with angina-like symptoms, elevated TnT-hs, and unobstructed coronary arteries. We identified myocarditis in only 10.5% of all CMR studies. However, in our cohort myocarditis remained by far the most common diagnosis after coronary ischemia similar to what other investigators have found (4,5,8). A potential explanation for this difference could be the fact that in 2016, we performed very comprehensive CMR screening in patients with signs and symptoms of myocarditis. Although Assomull et al. (8), as well as Leurent et al. (5) excluded patients with history of cardiac disease (5,8), we investigated all patients with angina-like symptoms and elevated TnT-hs in the years 2015 and 2016, regardless of whether patients had prior cardiac problems. This difference among cohorts may explain the higher percentage of cases with myocarditis in the studies from Assomull et al. (8) and Leurent et al. (5) compared to ours.

In agreement with other studies, we showed that CMR is a helpful tool for establishing the underlying diagnosis in patients presenting with angina-like symptoms, elevated TnT-hs (≥14 ng/l), and no significant coronary artery disease (8,11,12,20,32). Indeed, a more inclusive clinical diagnostic algorithm regarding patients with MINOCA increased the percentage of CMRs positive for myocarditis within 1 year from 5% to 13%. Whereas the detection rate of other potential diseases causing MINOCA such as amyloidosis, HCM, or Takotsubo did not increase significantly between 2015 and 2016, the overall incidence of such nonischemic cardiomyopathies increased, suggesting a potential benefit in detection for all nonischemic cardiomyopathies. In comparison to the previously-mentioned studies, we found overall a substantially higher number of patients with unobstructed coronary arteries experiencing angina-like symptoms and elevated TnT-hs. Hence, in the present high-volume tertiary care center, the threshold for coronary angiographies seems to be lower due to better availability of emergency physicians and a 24-h interventional service.

Given the fact that age and male sex are known risk factors for developing arteriosclerosis and coronary heart disease, our population consists mostly of elderly male patients (33). Similar to prior investigations, patients with myocarditis in our study were mostly men and considerably younger than those with obstructive coronary artery disease (4,5,8,32).

In summary, in 2016 we successfully implemented a systematic diagnostic algorithm for the screening of

patients with angina-like symptoms, elevated TnT-hs, and unobstructed coronary arteries to detect myocarditis with CMR and to obtain an approximation of the true incidence of myocarditis at a tertiary heart center with 24-h primary PCI service. Within 1 year after introduction of the new algorithm at our hospital, the incidence of myocarditis among all admissions increased 6.3-fold from 0.1 per 1,000 in 2015 to 0.63 per 1,000 in 2016 at our hospital. Although EMB remains the gold standard for definitive diagnosis of myocarditis, CMR is 1 of the best noninvasive screening tools we have currently available for the diagnosis of myocarditis. Our data is critical for raising the awareness that myocarditis continues to be underdiagnosed and that systematic screening with CMR may be a valuable diagnostic tool in the population with angina-like symptoms, elevated TnT-hs, and unobstructed coronary arteries. The high diagnostic sensitivity of this algorithm has important clinical implications because early therapy and cessation of exercise during the acute phase of myocarditis are interventions that are crucial for treatment success. With regards to physical activity, it has been shown that during the initial phases of myocarditis exercise may lead to increased viral replication and inflammation resulting in cytolysis, necrosis, and potentially arrhythmias (17,25,33–35).

STUDY LIMITATIONS. The gold standard for definitive diagnosis of myocarditis is EMB. Therefore, our attempt to evaluate the incidence of myocarditis through CMR remains an approximation as no histopathologic confirmation for myocarditis had been performed in this population.

Additionally, it is conceivable that a raised awareness of myocarditis during the implementation of the new screening algorithm in 2016 contributed to some degree to the increased number of cases of myocarditis in 2016.

CONCLUSIONS

This is the first study assessing the incidence of myocarditis by systematic screening through CMR in patients with angina-like symptoms, elevated TnT-hs, and nonobstructed coronary arteries. Our data support the hypothesis that myocarditis continues to be an underdiagnosed disease. Given the potentially severe adverse outcomes if patients with myocarditis are left untreated, we recommend a low threshold for the use of CMR in diagnostic workup.

Our study suggests that myocarditis continues to be underdiagnosed with standard clinical testing and raises awareness of a considerable incidence of myocarditis among patients with angina-like symptoms, elevated TnT-hs, and unobstructed coronary arteries. Accurate diagnosis in myocarditis is important for 3 main reasons. 1) Early therapy of specific subtypes of myocarditis has been shown to be crucial for treatment success (25,35,36). 2) Exercise during acute myocarditis increases the risk for malignant arrhythmias and potentially sudden cardiac death. Therefore, 3- to 6-month cessation of exercise after diagnosis is recommended (17,25,35). 3) Accurate diagnosis of a disease is crucial to learn about treatment response in affected patients and to improve therapies in the future. Identifying those patients early through broad noninvasive screening by CMR has great potential to improve clinical outcomes overall in this patient population. Although EMB will still be required to initiate therapies such as immunosuppression in specific cases, lowering the threshold for CMR will hopefully reduce the number of cases underdiagnosed in the future and provide us with a better understanding of the clinical trajectory of myocarditis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Myocarditis continues to be underdiagnosed and estimates of its incidence vary greatly in literature. In our study we applied a systematic diagnostic screening algorithm for myocarditis to improve diagnostic sensitivity and to obtain an approximation of the true incidence of myocarditis.

TRANSLATIONAL OUTLOOK: CMR has been established as an important pillar in the diagnostic workup of myocarditis. Given its non-invasive nature as well as minimal side effects, this technology is an excellent screening tool. In our study, we investigated a population at risk that has been described in literature as clinically challenging. We hope that future studies will evolve from our data and use this comprehensive algorithm to obtain a better understanding of myocarditis globally.

REFERENCES

1. Pitts SR, Niska RW, Xu J, Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 Emergency Department Summary. Available at: https://www.cdc.gov/nchs/data/nhsr/nhsr007.pdf. Accessed April 11, 2017.

2. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J 2016;37(42):3232–45.

3. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303(16):897–902.

4. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation 2015; 131:861–70. Available at: http://circ.ahajournals.org/content/131/10/861.long. Accessed April 11, 2017.

5. Leurent G, Langella B, Fougerou C, et al. Diagnostic contributions of cardiac magnetic resonance imaging in patients presenting with elevated troponin, acute chest pain syndrome and unobstructed coronary arteries. Arch Cardiovasc Dis 2011;104:161–70.

6. Maddox TM, Ho PM, Roe M, Dai D, Tsai TT, Rumsfeld JS. Utilization of secondary prevention therapies in patients with nonobstructive coronary artery disease identified during cardiac catheterization. Circ Cardiovasc Qual Outcomes 2010;3: 632–41.

7. Dastidar AG, Rodrigues JCL, Ahmed N, Baritussio A, Bucciarelli-Ducci C. The role of cardiac MRI in patients with troponin-positive chest pain and unobstructed coronary arteries. Curr Cardiovasc Imaging Rep 2015;8:28.

8. Assomull RG, Lyne JC, Keenan N, et al. The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. Eur Heart J 2007; 28(10):1242–9.

9. Karjalainen J, Heikkilä J. Incidence of three presentations of acute myocarditis in young men in military service: a 20-year experience. Eur Heart J 1999;20:1120–5.

10. Panovský R, Borová J, Pleva M, et al. The unique value of cardiovascular magnetic resonance in patients with suspected acute coronary syndrome and culprit-free coronary angiograms. BMC Cardiovasc Disord 2017;17:170.

11. Mahmoudi M, Harden S, Abid N, et al. Troponin-positive chest pain with unobstructed coronary arteries: definitive differential diagnosis using cardiac MRI. Br J Radiol 2012;85(1016): e461–6.

12. Gerbaud E, Harcaut E, Coste P, et al. Cardiac magnetic resonance imaging for the diagnosis of patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. Int J Cardiovasc Imaging 2012;28:783–94.

13. Fabre A. Sudden adult death syndrome and other non-ischaemic causes of sudden cardiac death. Heart 2005;92:316–20.

14. Phillips M, Robinowitz M, Higgins JR, Boran KJ, Reed T, Virmani R. Sudden cardiac death in Air Force recruits. JAMA 1986;256:2696.

15. Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. Ann Intern Med 2004;141:829–34.

16. Basso C, Carturan E, Corrado D, Thiene G. Myocarditis and dilated cardiomyopathy in athletes: diagnosis, management, and recommendations for sport activity. Cardiol Clin 2007;25: 423–9.

17. Pelliccia A, Fagard R, Bjørnstad HH, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur Heart J 2005;26:1422–45.

18. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease. J Am Coll Cardiol 2007;50:1914–31.

19. Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. Circulation 2016;134:e579–646.

20. Baccouche H, Mahrholdt H, Meinhardt G, et al. Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy in troponin-positive patients without coronary artery disease. Eur Heart J 2009;30:2869–79.

21. Gräni C, Eichhorn C, Bière L, et al. Prognostic value of cardiac magnetic resonance tissue characterization in risk stratifying patients with suspected myocarditis. J Am Coll Cardiol 2017;70: 1964–76.

22. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. J Am Coll Cardiol 2009;53:1475–87.

23. Bohnen S, Radunski UK, Lund GK, et al. Performance of t1 and t2 mapping cardiovascular magnetic resonance to detect active myocarditis in patients with recent-onset heart failure. Circ Cardiovasc Imaging 2015;8:e003073.

24. Lurz P, Luecke C, Eitel I, et al. Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: the MyoRacer-Trial. J Am Coll Cardiol 2016;67:1800–11.

25. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636–48.

26. Hufnagel G, Pankuweit S, Richter A, Schönian U, Maisch B. The European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID). Herz 2000;25: 279–85.

27. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388: 1545-602.

28. Kühl U, Pauschinger M, Noutsias M, et al. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. Circulation 2005;111:887–93.

29. Fairweather D, Stafford KA, Sung YK. Update on coxsackievirus B3 myocarditis. Curr Opin Rheumatol 2012;24:401–7.

30. Klingel K, Sauter M, Bock CT, Szalay G, Schnorr J-J, Kandolf R. Molecular pathology of inflammatory cardiomyopathy. Med Microbiol Immunol 2004;193:101–7.

31. Rose NR. Myocarditis: infection versus autoimmunity. J Clin Immunol 2009;29:730–7.

32. Collste O, Sörensson P, Frick M, et al. Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study. J Intern Med 2013;273:189–96.

33. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.

34. Gatmaitan BG, Chason JL, Lerner AM. Augmentation of the virulence of murine coxsackievirus B-3 myocardiopathy by exercise. J Exp Med 1970:131. Available at: http://jem.rupress.org/content/131/6/1121.long. Accessed January 28, 2018.

35. Bozkurt B, Kribbs SB, Clubb FJ, et al. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. Circulation 1998;97:1382–91.

36. Kuhl U, Pauschinger M, Schwimmbeck PL, et al. Interferon-beta treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction. Circulation 2003;107:2793–8.

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