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BRIEF REPORT

Cardiac involvement in idiopathic inflammatory myopathies detected by cardiac magnetic resonance imaging

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Abstract

Cardiac involvement in idiopathic inflammatory myopathies (IIM) adversely affects prognosis but is commonly sub-clinical. Cardiac magnetic resonance imaging (CMR) is an effective imaging modality for detecting myocardial inflammation and fibrosis but its use as a screening tool for cardiac disease in IIM has not been fully explored. Nineteen patients with IIM without cardiac symptoms underwent CMR using a specific cardiomyopathy protocol including specific sequences detecting focal and diffuse myocardial fibrosis. 9/19 patients demonstrated late gadolinium enhancement (LGE (3/9 right ventricular insertion, 1/9 sub-endocardial, 7/9 mid-wall/sub-epicardial)). T1 mapping was performed in 15 patients. In total, 7/15 had elevated native T1 values, of which four had detected LGE. Myocardial fibrosis was frequently detected in IIM patients without cardiac history. Detection of LGE and elevated T1 values may have negative prognostic implications. Longitudinal studies determining whether early or augmented treatment has a role in patients with sub-clinical cardiac involvement are needed.

Key Points
- *Cardiac involvement in myositis adversely affects prognosis.*
- *Cardiac magnetic resonance imaging is an effective tool for detecting cardiac involvement.*
- *T1 mapping is a technique which detects diffuse myocardial inflammation and fibrosis.*
- *In our study, focal and diffuse myocardial fibrosis was frequently found in myositis patients without cardiac symptoms.*

Keywords Cardiac magnetic resonance imaging · Cardiomyopathy · Heart failure · Idiopathic inflammatory myopathy · Myocardial fibrosis · Myocarditis

Introduction

Idiopathic inflammatory myopathies (IIM) are a group of systemic inflammatory diseases including the subsets polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM) and necrotising autoimmune myopathy (NAM). Although the dominant effects of these conditions are on skeletal muscle, the advent of more sensitive and less invasive diagnostic cardiac imaging [1] has led to growing interest in their effects on cardiac muscle.

Degrees of cardiac involvement vary considerably in IIM, with series reporting rates of 6–75% depending on case selection and investigations employed [2]. A 2011 systematic review reported frequent myocarditis (38%), focal fibrosis (22%) and arrhythmias (detected by ECG in 31%) in IIM patients [3]. Congestive cardiac failure was reported to contribute to 21% of mortality. Furthermore, sub-clinical cardiac involvement has been recognised in imaging studies and may

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occur in up to 50% of IIM patient [4]. It has been proposed that the effect of IIM on the heart is not only inflammatory via myocarditis [5] but also causes accelerated coronary atherosclerosis with increased risk of myocardial infarction, particularly in the first year after IIM diagnosis [6]. Danko et al. found that cardiac involvement (excluding other causes of cardiac pathology) was the main prognostic factor for death among patients with primary PM or DM [7].

Traditional screening for cardiac involvement in IIM includes a 12-lead ECG, troponin assays as markers of myocardial damage and echocardiography to assess cardiac structure and function [8]. The gold standard for detecting myocardial inflammation and fibrosis has been endomyocardial biopsy but this is invasive and limited in sensitivity by the localised and patchy nature of cardiac involvement [8].

Cardiac magnetic resonance (CMR) imaging is an imaging modality which assesses cardiac morphology, function, vasculature and metabolism at high resolution without ionising radiation [8]. Unlike echocardiography, CMR characterises myocardial tissue components and is not limited by obtainable acoustic window [9].

A number of small series (14–26 patients) have evaluated the role of CMR in detecting myocardial involvement in IIM [10–12]. No studies have compared echocardiography with CMR in IIM patients but in a viral myocarditis group, 91% had CMR evidence of cardiac inflammation compared with 35% with wall motion abnormalities on echocardiogram [13].

There is a clinical need to assess the role of CMR as a screening modality for subclinical cardiac involvement in IIM patients without cardiac symptoms. Our current study uniquely utilises multiple modalities of CMR to this end, with a particular focus on detection of late gadolinium enhancement as well as T1 mapping for diffuse inflammation. Detection of cardiac involvement may prompt timely escalation in immunomodulatory therapies to prevent longer term consequences of untreated silent inflammation.

Methods

A cohort of patients with histologically confirmed IIM was identified from the Rheumatology Unit at the Royal Adelaide Hospital (RAH). Ethics approval was obtained from the RAH Human Ethics committee, protocol number 121020 (approved 9/5/13). The disease-features of these patients were well characterised including myositis-specific (MSA) and myositis-associated (MAA) antibody profiles, cardiac biomarkers and clinical features. All muscle biopsies were assessed in a single laboratory (SA Pathology) with accepted histopathological diagnostic criteria [14].

Patients were excluded if they had known cardiac involvement, coronary artery disease, hypertension, or myositis secondary to a precipitant (e.g. substance abuse, toxic myositis/rhabdomyolysis, or viral/infective myositis).

A specific CMR cardiomyopathy protocol was employed, including horizontal and vertical long-axis views and a volumetric stack. For tissue characterisation, the protocol included T2-STIR as well as early and late gadolinium sequences (taken 8–12 min post intravenous gadolinium). The modified look locker (MOLLI) sequence was performed for T1 mapping (where enabled by study quality), to allow measurement of a native T1 value taken from a region of interest within the myocardial septum (Fig. 1).

Results

Nineteen patients with IIM underwent screening CMR (12 female, 7 male; mean age 59 years ± 10.3 years). The distribution of histological diagnoses is shown in Table 1. Of note, 3 patients had myositis in the context of established systemic sclerosis, i.e. overlap disease. Disease duration was variable (mean duration 8.4 years, range 1–25 years).

A positivity of myositis-associated and myositis-specific antibodies was seen in 11/19 patients.

In this cohort of patients, 9 were found to have late gadolinium enhancement (LGE) on CMR. The locations of this LGE were 3 right ventricular insertion point, 1 subendocardial and 7 mid-wall or sub-epicardial fibrosis.

There was no difference in MSA/MAA among patients with demonstrable LGE (5/9) compared with those without LGE (6/10), $p = 1.00$. In total, 3/9 patients with LGE had concomitant diffuse systemic sclerosis, compared with 0/10 without LGE, $p = 0.09$.

Of the patients with documented smoking status, 3 had smoking exposure (1 current, 2 former) and 10 had never smoked. There was no difference in LGE positivity between these groups, $p = 0.56$.

T1 mapping with MOLLI (prior to intravenous contrast administration) was unable to be performed in 4 of the patients due to study quality. Of the 15 patients in whom it was measured, 7 had an elevated T1 value (47%) above a scanner-specific threshold of 980 msec (Fig. 2). Of these, 4/7 had concurrent LGE compared with 5/12 who did not have an elevated T1 value.

Discussion

In this study, we showed that in patients with a histological diagnosis of IIM, almost half had demonstrable cardiac involvement on CMR despite being asymptomatic.

In CMR, the distribution of late gadolinium enhancement (LGE) is of particular use in differentiating different causes of cardiac pathology. Myocardial inflammation, fibrosis or infiltration, on the other hand, can be patchy, sub-epicardial

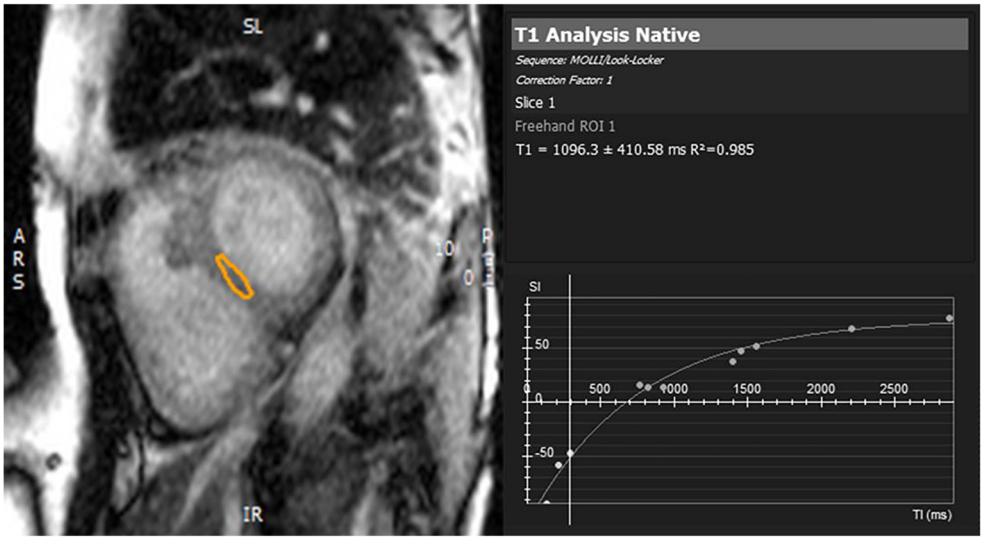

Fig. 1 Measurement of native T1 value using the MOLLI sequence with a region of interest drawn at the interventricular septum in a patient with IIM (this is tracked along the different phases of the cardiac cycle to derive the native T1 value)

Table 1 Patients with a histological diagnosis of idiopathic inflammatory myopathy who underwent cardiac magnetic resonance (CMR) imaging

Patient	Biopsy result	Myositis antibodies	Smoking status	Immunosuppression exposures	Disease duration (years)	Late gadolinium enhancement	Elevated native T1 value
1	DM	Negative	Unknown	MTX	25	No	No
2	PM	Negative	Former	MTX	18	No	No
3	IBM	Ro52	Unknown	Unknown	12	No	No
4	DM	SAE & HMGCR	Never	Aza, PNL, MTX	2	No	No
5	MNOS (DM clinically)	Jo1	Never	Aza, PNL	5	No	No
6	PM	Negative	Unknown	MTX, PNL	17	No	Yes
7	PM	PL7/Ro52	Never	HCQ, leflunomide, PNL, rituximab	8	Yes (insertion point)	NA
8	IBM	Jo1	Never	Aza, HCQ, MTX, PNL, rituximab	4	No	No
9	DM	Negative	Never	Aza, cyclophosphamide, MMF, PNL, tacrolimus	15	Yes (mid-wall)	NA
10	MNOS (with ANA 1:640)	Negative	Unknown	Adalimumab, infliximab, PNL, secukinumab, ustekinumab	1	Yes (mid-wall and sub-epicardial)	Yes
11	DM	Jo1/Ro52	Never	Cyclophosphamide, PNL	15	Yes (mid-wall and sub-epicardial)	No
12	NAM	PL7	Never	PNL, rituximab	7	No	No
13	PM	PMSCL, Ro52	Never	Aza, MTX, PNL	6	No	Yes
14	MNOS (DM clinically)	Negative	Never	Aza, HCQ, MTX, PNL, rituximab	4	No	Yes
15	DM/SSc overlap	Negative	Unknown	MTX, PNL	2	Yes (mid-wall and sub-epicardial)	NA
16	Diffuse SSc with myositis	Ro52	Current	Cyclophosphamide, HCQ, MMF, MTX	10	Yes (mid-wall and sub-epicardial and insertion point)	Yes
17	Diffuse SSc with myositis	PMCSL100 & SCL70	Unknown	MMF, PNL	2	Yes (mid-wall and sub-epicardial)	Yes
18	MNOS with some features DM	Ro52	Former	HCQ, MMF, PNL	6	Yes (mid-wall and sub-epicardal & insertion point)	NA
19	NAM	Negative	Never	MMF, PNL	1	Yes (sub-endocardial)	Yes

Aza, azathioprine; *DM*, dermatomyositis; *HCQ*, hydroxychloroquine; *IBM*, inclusion body myositis; *MMF*, mycophenolate mofetil; *MNOS*, myositis not otherwise specified; *MTX*, methotrexate; *NAM*, necrotising autoimmune myopathy; *PM*, polymyositis; *PNL*, prednisolone; *SSc*, systemic sclerosis

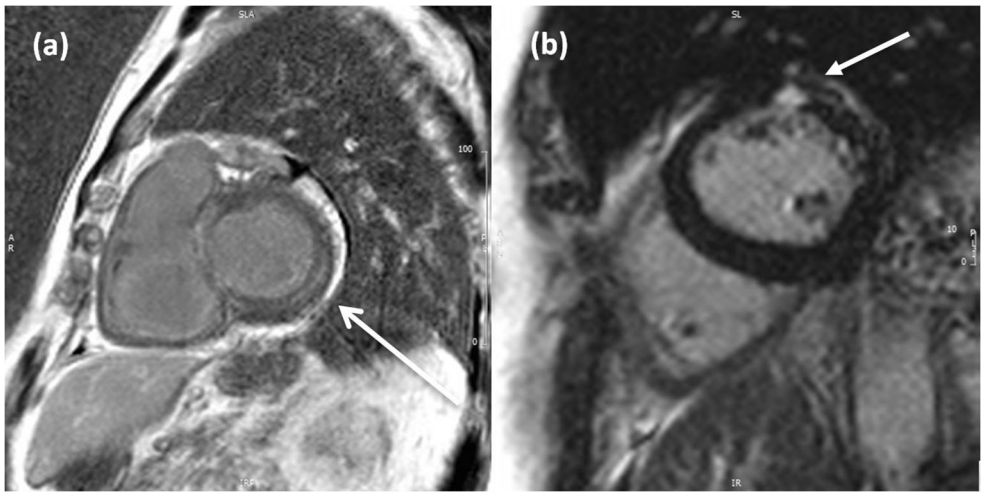

Fig. 2 Area of mid-wall fibrosis involving the basal inferolateral segment indicative of mid-wall myocardial fibrosis **a** and mid anterolateral wall **b**

(Fig. 2) or mid-myocardial (Fig. 3) [9]. Regardless of the aetiology of LGE, however, its presence and burden of myocardial involvement [15] carries important prognostic value and has been shown to be associated with all-cause mortality, hospitalisations and sudden cardiac death in patients with nonischaemic cardiomyopathies [16]. Myocardial fibrosis predisposes to malignant arrhythmias [17] and in a cohort of patients undergoing cardiac defibrillator insertion for advanced heart failure, LGE on CMR was found to correlate with a higher defibrillator discharge rate representing a greater arrhythmic burden [18].

The current study contributes to the evidence supporting sub-clinical cardiac involvement in IIM. Of the patients with LGE on CMR, only one had a pattern suggestive of ischaemic pathology whereas the others had variable degrees of both focal and diffuse fibrosis. These results are similar to those found by a previous study of 16 patients with PM/DM where 9 of 16 patients had LGE, none of which was sub-endocardial in distribution [19].

A CMR technique not used in this earlier study, however, is T1-mapping which is growing as a tool of assessment and quantification of diffuse myocardial fibrosis, by obtaining a native T1 value in the absence of an exogenous contrast agent. LGE relies on comparison of unaffected with diseased myocardium and while it is effective for focal lesions, diffuse fibrosis is more difficult to detect [20]. Our use of T1 mapping via the MOLLI sequence showed that almost half had an elevated T1 value suggestive of diffuse myocardial fibrosis. T1 mapping has an important prognostic role for all-cause mortality as well as heart failure both independently and in combination with LGE evaluation among patients with non-ischaemic dilated cardiomyopathies [21].

Overall, our findings indicate frequent detection of myocardial fibrosis in a group of patients with IIM without other clear cardiovascular pathology.

There are some salient limitations to our study. No comparison was made between CMR and echocardiography and we were unable to assess superiority of one imaging technique

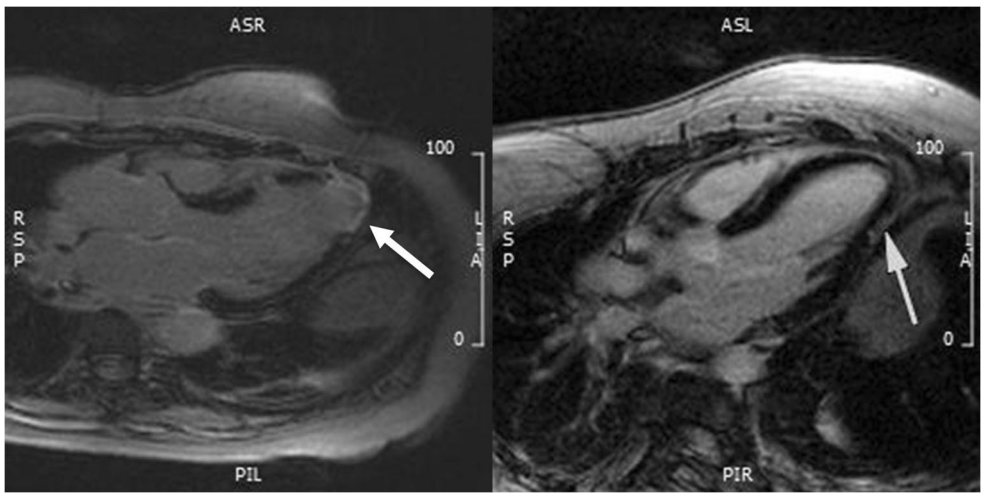

Fig. 3 Transmural late gadolinium enhancement (LGE) of the apex in a patient with myocardial infarction (left) compared with sub-epicardial LGE in a patient with myocarditis (right)

over the other. Our study would benefit from a larger sample size as well as comparison with control groups, though LGE/abnormal T1 mapping is rarely detected in healthy normal individuals and is associated with poor prognosis in other disease groups. Larger cohorts would also allow comparison between the histological subtypes of IIM to investigate any differences in cardiac involvement as detected on CMR. Although we did demonstrate that there are signs of myocardial inflammation in these patients with IIM, we do not have the long-term data to assess prognosis or the development of future cardiac events. Additionally, it remains unknown whether there is benefit to early intervention such as augmented immunosuppression or early heart failure therapy.

In our study group, there was a variable treatment duration with immunosuppressants between biopsy diagnosis and CMR. Despite this, however, we demonstrate that a significant proportion of patients have ongoing myocardial inflammation in the absence of symptoms. It can be theorised that despite sufficient immunosuppression to render them asymptomatic from a peripheral and cardiac muscle perspective, there is an ongoing low level myocardial inflammation. Evaluation of patients with newly diagnosed IIM who are immunosuppression-naive using CMR with serial imaging as part of long-term follow-up could elucidate if LGE/abnormal T1 mapping predicts poorer clinical outcomes.

It should also be noted that hypertension and ischaemic heart disease have been found to be more prevalent in IIM patients prior to diagnosis compared with background population prevalence [22]. Differentiating between patients who already have the substrate for developing cardiovascular disease from those who develop cardiac complications secondary to IIM can be challenging [23].

Continuing advances in CMR imaging techniques for characterising myocardial tissue may also increase the ability to detect myocardial involvement in IIM. The T2-STIR sequence is the original sequence for the detection of myocardial oedema. More recently, T2 mapping is an evolving technique that has the ability to quantify the burden of myocardial oedema. In the suspected acute phase of cardiac inflammation, both of these may have an important role.

Conclusion

Focal and diffuse fibroses were frequently present in this cohort of patients with IIM. Long-term studies including cardiac and inflammatory serum biomarkers are required to evaluate the long-term prognostic impact of these CMR findings in IIM and to assess the role of augmented immunosuppression in the treatment of sub-clinical cardiac disease in IIM.

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Compliance with ethical standards

Disclosures None.

References

1. Rosenbohm A, Buckert D, Gerischer N, Walcher T, Kassubek J, Rottbauer W, Ludolph AC, Bernhardt P (2015) Early diagnosis of cardiac involvement in idiopathic inflammatory myopathy by cardiac magnetic resonance tomography. J Neurol 262(4):949–956. https://doi.org/10.1007/s00415-014-7623-1
2. Danieli MG, Gelardi C, Guerra F, Cardinaletti P, Pedini V, Gabrielli A (2016) Cardiac involvement in polymyositis and dermatomyositis. Autoimmun Rev 15(5):462–465. https://doi.org/10.1016/j.autrev.2016.01.015
3. Gupta R, Wayangankar SA, Targoff IN, Hennebry TA (2011) Clinical cardiac involvement in idiopathic inflammatory myopathies: a systematic review. Int J Cardiol 148(3):261–270. https://doi.org/10.1016/j.ijcard.2010.08.013
4. Guerra F, Gelardi C, Capucci A, Gabrielli A, Danieli MG (2017) Subclinical cardiac dysfunction in polymyositis and dermatomyositis: a speckle-tracking case-control study. J Rheumatol 44(6):815–821. https://doi.org/10.3899/jrheum.161311
5. Toong C, Puranik R, Adelstein S (2012) Use of cardiac MR imaging to evaluate the presence of myocarditis in autoimmune myositis: three cases. Rheumatol Int 32(3):779–782. https://doi.org/10.1007/s00296-009-1324-6
6. Rai SK, Choi HK, Sayre EC, Avina-Zubieta JA (2016) Risk of myocardial infarction and ischaemic stroke in adults with polymyositis and dermatomyositis: a general population-based study. Rheumatology (Oxford) 55(3):461–469. https://doi.org/10.1093/rheumatology/kev336
7. Danko K, Ponyi A, Constantin T, Borgulya G, Szegedi G (2004) Long-term survival of patients with idiopathic inflammatory myopathies according to clinical features: a longitudinal study of 162 cases. Medicine (Baltimore) 83(1):35–42. https://doi.org/10.1097/01.md.0000109755.65914.5e
8. Pohost GM (2008) The history of cardiovascular magnetic resonance. JACC Cardiovasc Imaging 1(5):672–678. https://doi.org/10.1016/j.jcmg.2008.07.009
9. Mavrogeni SI, Kitas GD, Dimitroulas T, Sfikakis PP, Seo P, Gabriel S, Patel AR, Gargani L, Bombardieri S, Matucci-Cerinic M, Lombardi M, Pepe A, Aletras AH, Kolovou G, Miszalski T, van Riel P, Semb A, Gonzalez-Gay MA, Dessein P, Karpouzas G, Puntmann V, Nagel E, Bratis K, Karabela G, Stavropoulos E, Katsifis G, Koutsogeorgopoulou L, van Rossum A, Rademakers F, Pohost G, Lima JA (2016) Cardiovascular magnetic resonance in rheumatology: current status and recommendations for use. Int J Cardiol 217:135–148. https://doi.org/10.1016/j.ijcard.2016.04.158
10. Diederichsen LP, Simonsen JA, Diederichsen AC, Kim WY, Hvidsten S, Hougaard M, Junker P, Lundberg IE, Petersen H, Hansen ES, Eskerud KS, Kay SD, Jacobsen S (2015) Cardiac abnormalities assessed by non-invasive techniques in patients with newly diagnosed idiopathic inflammatory myopathies. Clin Exp Rheumatol 33(5):706–714

11. Mavrogeni S, Douskou M, Manoussakis MN (2011) Contrast-enhanced CMR imaging reveals myocardial involvement in idiopathic inflammatory myopathy without cardiac manifestations. JACC Cardiovasc Imaging 4(12):1324–1325. https://doi.org/10.1016/j.jcmg.2011.05.009
12. Zhang L, Wang GC, Ma L, Zu N (2012) Cardiac involvement in adult polymyositis or dermatomyositis: a systematic review. Clin Cardiol 35(11):686–691. https://doi.org/10.1002/clc.22026
13. Goitein O, Matetzky S, Beinart R, Di Segni E, Hod H, Bentancur A, Konen E (2009) Acute myocarditis: noninvasive evaluation with cardiac MRI and transthoracic echocardiography. AJR Am J Roentgenol 192(1):254–258. https://doi.org/10.2214/AJR.08.1281
14. Holton JL, Wedderburn LR, Hanna MG (2013) Polymyositis, Dermatomyositis, and Inclusion Body Myositis. In: H. H. Goebel, C. Sewry, R. Weller (ed) Muscle Disease. First edn. Wiley Blackwell, pp 298–312 https://doi.org/10.1002/9781118635469.ch33
15. Poyhonen P, Kivisto S, Holmstrom M, Hanninen H (2014) Quantifying late gadolinium enhancement on CMR provides additional prognostic information in early risk-stratification of nonischemic cardiomyopathy: a cohort study. BMC Cardiovasc Disord 14:110. https://doi.org/10.1186/1471-2261-14-110
16. Kuruvilla S, Adenaw N, Katwal AB, Lipinski MJ, Kramer CM, Salerno M (2014) Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in nonischemic cardiomyopathy: a systematic review and meta-analysis. Circ Cardiovasc Imaging 7(2):250–258. https://doi.org/10.1161/circimaging.113.001144
17. Perazzolo Marra M, De Lazzari M, Zorzi A, Migliore F, Zilio F, Calore C, Vettor G, Tona F, Tarantini G, Cacciavillani L, Corbetti F, Giorgi B, Miotto D, Thiene G, Basso C, Iliceto S, Corrado D (2014) Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. Heart Rhythm 11(5):856–863. https://doi.org/10.1016/j.hrthm.2014.01.014
18. Iles L, Pfluger H, Lefkovits L, Butler MJ, Kistler PM, Kaye DM, Taylor AJ (2011) Myocardial fibrosis predicts appropriate device therapy in patients with implantable cardioverter-defibrillators for primary prevention of sudden cardiac death. J Am Coll Cardiol 57(7):821–828. https://doi.org/10.1016/j.jacc.2010.06.062
19. Mavrogeni S, Sfikakis PP, Dimitroulas T, Kolovou G, Kitas GD (2014) Cardiac and muscular involvement in idiopathic inflammatory myopathies: noninvasive diagnostic assessment and the role of cardiovascular and skeletal magnetic resonance imaging. Inflamm Allergy Drug Targets 13(3):206–216. https://doi.org/10.2174/1871528113666140526162640
20. Everett RJ, Stirrat CG, Semple SI, Newby DE, Dweck MR, Mirsadraee S (2016) Assessment of myocardial fibrosis with T1 mapping MRI. Clin Radiol 71(8):768–778. https://doi.org/10.1016/j.crad.2016.02.013
21. Puntmann VO, Carr-White G, Jabbour A, Yu CY, Gebker R, Kelle S, Hinojar R, Doltra A, Varma N, Child N, Rogers T, Suna G, Arroyo Ucar E, Goodman B, Khan S, Dabir D, Herrmann E, Zeiher AM, Nagel E, International TMCMROS (2016) T1-mapping and outcome in nonischemic cardiomyopathy: all-cause mortality and heart failure. JACC Cardiovasc Imaging 9(1):40–50. https://doi.org/10.1016/j.jcmg.2015.12.001
22. Limaye VS, Lester S, Blumbergs P, Roberts-Thomson PJ (2010) Idiopathic inflammatory myositis is associated with a high incidence of hypertension and diabetes mellitus. Int J Rheum Dis 13(2):132–137. https://doi.org/10.1111/j.1756-185X.2010.01470.x
23. Diederichsen LP (2017) Cardiovascular involvement in myositis. Curr Opin Rheumatol 29(6):598–603. https://doi.org/10.1097/BOR.0000000000000442