European Review for Medical and Pharmacological Sciences 2020; 24: 12300-12305

Evaluation of the correlation between myocardial fibrosis and ejection fraction in dilated cardiomyopathy using magnetic resonance T1 mapping

X.-N. SHAO[1], Y.-N. JIN[1], Y.-J. SUN[2], W.-B. ZHANG[1], J.-L. CHENG[1]

[1]Department of Magnetic Resonance, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[2]Department of Radiology, The Second Affiliated Hospital of Luohe Medical College, Luohe, China

Abstract. – OBJECTIVE: The study aimed to evaluate the correlation between myocardial fibrosis and ejection fraction (EF) in dilated cardiomyopathy (DCM) by magnetic resonance T1 mapping.

PATIENTS AND METHODS: For this study, 48 patients with DCM and 24 healthy volunteers from 2015 to 2017 were included. All participants were examined by 3.0T cardiovascular magnetic resonance (CMR), and T1 mapping images were obtained using the MOLLI sequence. MATLAB software was used to extract the histogram parameters of the T1 mapping images, including five groups of percentiles, kurtosis coefficient, skewness coefficient, variance, and mean. The EF value was calculated based on short-axis cine cardiac images, and a Pearson's coefficient between T1 mapping parameters and the EF value was calculated.

RESULTS: The T1 mapping histogram parameters, such as the mean, variance, maximum, and 10, 25, 50, 75, and 90 percentiles of DCM patients were significantly higher than those of the controls. The differences were statistically significant ($p < 0.05$). The EF of DCM patients was significantly lower than that of the controls, and the difference was statistically significant ($p < 0.05$). The T1 mapping parameters, such as the mean, variance, maximum, and percentiles, were significantly negatively correlated with EF.

CONCLUSIONS: T1 mapping is helpful in diagnosing myocardial fibrosis, particularly diffuse myocardial fibrosis in DCM, and T1 mapping parameters are significantly negatively correlated with EF.

Key Words:
Dilated cardiomyopathy, Cardiovascular magnetic resonance, T1 mapping, Ejection fraction, Myocardial fibrosis.

Introduction

Dilated cardiomyopathy (DCM) is a type of cardiomyopathy characterized by cardiomyocyte degeneration and interstitial fibrosis. Its incidence in adults is higher in males than in females[1-4]. Myocardial fibrosis leads to changes in left and right ventricular myocardial stiffness and is associated with systolic and diastolic heart failure[5]. Histologic results have shown that diffuse myocardial fibrosis often occurs in DCM. At present, late gadolinium-enhanced (LGE) images are commonly used to display myocardial fibrosis[6]. However, LGE does not display a good image of diffuse myocardial fibrosis. T1 mapping is a new technique for evaluating myocardial fibrosis beyond delayed enhancement[7,8]. Some research has shown that T1 mapping is helpful in diagnosing diffuse myocardial fibrosis[9].

In this study, histograms of T1 mapping were analyzed, and the Pearson's correlation coefficient between the histogram parameters and EF value was calculated to investigate the clinical value of T1 mapping in the diagnosis of myocardial fibrosis in DCM, as well as the correlation between T1 mapping histogram parameters and EF.

Patients and Methods

Patients

From March 2015 to July 2017, 48 patients with DCM who underwent cardiovascular magnetic resonance (CMR) examination in our hospital were enrolled in the present study and included in the observation group (DCM group), and 24 healthy volunteers were recruited as the healthy

Corresponding Author: Jing-Liang Cheng, MD; e-mail: chengjingliang1868@163.com

control (HC) group. The volunteers had no medical history of chest distress, shortness of breath, fatigue, or other symptoms within six months prior to the start of the study, and no abnormalities were found in electrocardiogram (ECG) and color Doppler echocardiography. All participants underwent a routine 3.0T CMR examination. The present study met the Declaration of Helsinki requirements of the World Medical Association and was approved by the Ethics Committee of our Hospital, approval No. 2015-16. All patients provided signed informed consent.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) patients with a definite diagnosis of DCM, (2) patients aged >18 years, (3) the quotient of the minimum inner diameter of left ventricle divided by body surface area was more than 2.7 cm/m^2, and (4) the EF value was <45%. Exclusion criteria: (1) patients with coronary atherosclerotic heart disease, (2) patients with valvular heart disease, (3) patients with pulmonary heart disease, and (4) patients with incomplete case data.

Magnetic Resonance Inspection

A Siemens Skyra (3.0T) magnetic resonance imaging system with body coils (16-channel) was used for CMR imaging. During the imaging process, four MRI-compatible electrodes were pasted between the right first and second and the left fifth and sixth ribs of the subjects. ECG signals were collected to trigger the scanning at a specific time. Scan sequences included the following: 1) half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence; 2) true-FISP sequence; and 3) cine sequence: repetition time (TR) = 45.64 ms, echo delay time (TE) = 1.43 ms, Flip angle = 80°, slice thickness = 8 mm, the scan scope included long-axis two-chamber heart, three-chamber heart, four-chamber heart and 8-10 short-axis layers; 4) modified Look-Locker inversion recovery (MOLLI) sequence: TR = 324.96 ms, TE = 1.12 ms, Flip angle = 35°, slice thickness = 8 mm, T1 mapping image covered two-chamber heart, three-chamber heart, and four-chamber heart layers, and three short-axis layers of the base, middle part, and apex of the heart; 5) LGE scanning, using phase-sensitive inversion recovery sequence: TR = 643 ms, TE = 2 ms, Flip angle = 20°, slice thickness = 8 mm, TI = 300 ms. The contrast agent used was gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) at a dose of 0.2 mmol/kg. At ten minutes after injection of the contrast medium, image data of long-axis and short-axis layers were collected layer by layer. Healthy volunteers were not injected with the contrast agent and did not undergo LGE scanning. Only scanning of the first four items was conducted.

Histogram Analysis

Histogram analysis is an effective texture analysis method. Through programming (using MATLAB software), the endocardium and epicardium of the myocardium were outlined, and the T1 value of each pixel in the myocardium was extracted. Following this, 11 histogram parameters were calculated according to the distribution of the T1 value, including five percentiles (10, 25, 50, 75, and 90 percentiles), the minimum value, mean value, maximum value, skewness coefficient, kurtosis coefficient, and variance.

Statistical Analysis

Data were analyzed using statistical software SPSS 20.0 (IBM, Armonk, NY, USA). Measurement data were expressed as mean ± standard deviation (x ± SD), and count data were expressed as a percentage (%). The normality of variables was tested using a W-test. The homogeneity of variance was tested using an F-test. The gender distribution was compared between the DCM group and the HC group using an independent sample t-test. Continuous features and histogram parameters were compared between the DCM group and the HC group. Means were compared among multi-groups using a one-way analysis of variance (ANOVA), and a post-hoc test was conducted using the least significant difference (LSD). A Pearson's correlation analysis was conducted to evaluate the correlation between T1 mapping histogram parameters and EF in the DCM group. Non-normally distributed means or normally distributed means with heterogeneity of multiple samples were evaluated using a non-parametric test. Count data were evaluated using a Chi-square test, and $p < 0.05$ was considered statistically significant.

Results

General Data

A total of 72 subjects were included in this study, including 48 DCM patients and 24 healthy volunteers. The patients in the DCM group included 38 males and ten females, and the average

Table I. The general data of the two groups.

	DCM group	HC group	χ^2/t	p
N	48	24		
Age (Year)	47.40 ± 13.83	47.67 ± 13.15	0.08	0.94
Gender (Male/Female)	38/10	14/10	3.46	0.06
Height (m)	1.69 ± 0.08	1.67 ± 0.09	-0.95	0.35
Weight (kg)	75.51 ± 22.58	69.21 ± 12.49	-1.52	0.13
EF	21.75±9.31	55.22±7.39	15.34	< 0.01

Note: DCM: dilated cardiomyopathy; HC: healthy control; EF: ejection fraction.

age was 47.40 ± 13.83 years. The volunteers in the HC group included 38 males and ten females, and the average age was 47.67 ± 13.15 years. The differences in age and gender between the two groups were not statistically significant ($p > 0.05$). The EF was 21.75 ± 9.31 in the DCM group and 55.22 ± 7.39 in the HC group. The EF value was significantly lower in the DCM group than in the HC group, and the difference was statistically significant ($p < 0.05$; Table I and Figure 1).

Histogram Parameters

In the present study, the 11 histogram parameters measured included the following: five percentiles (10, 25, 50, 75, and 90) and the minimum, mean, maximum, skewness coefficient, kurtosis coefficient, and variance. The differences in the five percentiles, mean, maximum, and variance between the DCM group and HC group were statistically significant ($p < 0.05$).

After enhancing the LGE images, the DCM group was divided into two subgroups: LGE (+) subgroup (n = 33) and LGE (−) subgroup (n = 15). The differences in the mean, variance, maximum, and five percentiles between the LGE (+) subgroup and the HC group, as well as between the LGE (−) subgroup and the HC group, were statistically significant ($p < 0.05$). The differences in the minimum, kurtosis coefficient, and skewness coefficient were not statistically sig-

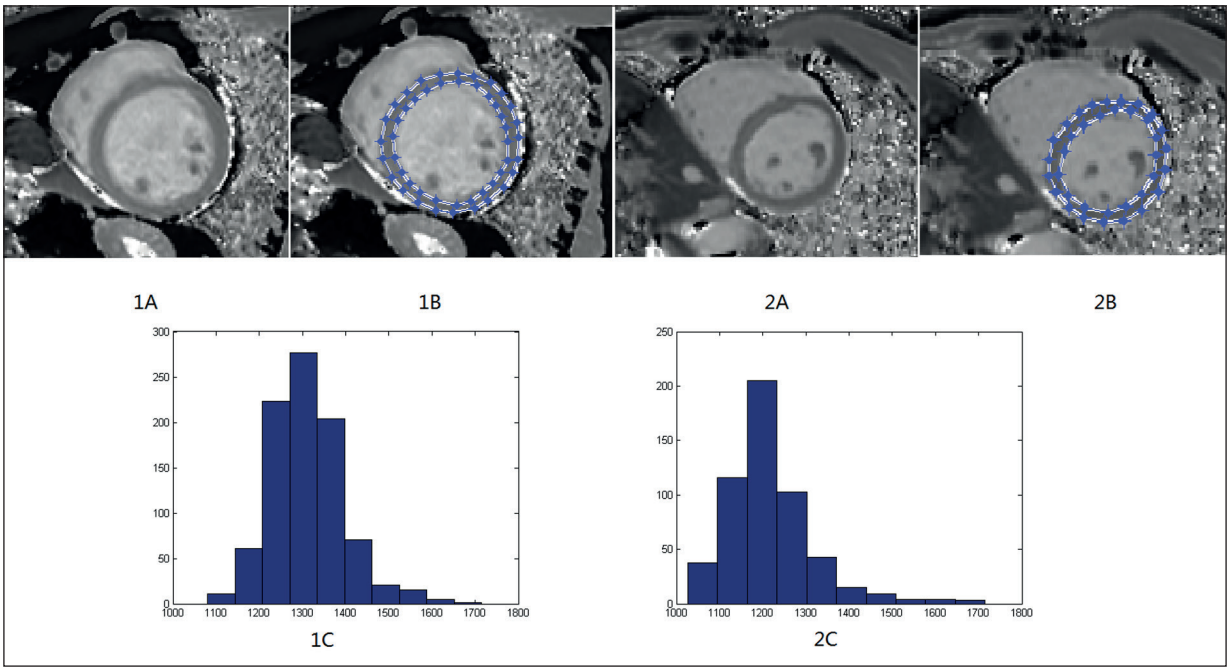

Figure 1. 1A, 1B, and 1C indicate patients with DCM. 1A shows the T1 mapping image of the middle ventricle, 1B shows the endocardium and epicardium, and 1C shows the myocardial histogram. 2A, 2B, and 2C refer to the healthy volunteers. 2A shows the T1 mapping image of the middle ventricle, 2B shows the endocardium and epicardium, and 2C shows the myocardial histogram.

nificant ($p > 0.05$). The difference in the maximum between the LGE (+) subgroup and LGE (−) subgroup was statistically significant ($p < 0.05$), though the differences in other parameters were not statistically significant ($p > 0.05$). Compared with the control group, the EF values of the LGE (+) and LGE (−) subgroups were significantly lower, and the difference was statistically significant ($p < 0.05$). The difference in the EF value between the LGE (+) subgroup and LGE (−) subgroup was not statistically significant ($p > 0.05$; Table II).

Correlation Between Histogram Parameters and EF

The results revealed that the mean, variance, maximum, and 10, 25, 50, 75, and 90 percentiles were negatively correlated with the EF. The correlation coefficients were −0.546 ($p < 0.05$), −0.380 ($p < 0.05$), −0.580 ($p < 0.05$), −0.387 ($p < 0.05$), −0.502 ($p < 0.05$), −0.564 ($p < 0.05$), −0.583 ($p < 0.05$), and −0.562 ($p < 0.05$). The minimum, kurtosis coefficient, and skewness coefficient were not significantly correlated with EF.

Discussion

Impaired heart function is an important clinical index of DCM. CMR is increasingly being used in the diagnosis of heart disease and has gradually developed into the gold standard for EF measurements. It has been shown to aid in the differential diagnosis of myocardial diseases[10-12]. As the most representative index of cardiac function, EF plays an important role in the diagnosis of DCM. MRI T1 mapping technology has been widely used in the examination of heart disease. A large amount of research suggests that T1 mapping is helpful in the diagnosis of diffuse myocardial fibrosis[13,14]. Medical images tend to have an irregular texture that cannot be readily observed by the human visual system[15]. As a common method of texture analysis, histogram analysis can reflect the rule of distribution of different gray levels in the image, and as such, plays an important role in medical image analysis. Choi et al. revealed that ADC histogram analysis could be used in chemotherapy evaluation of rectal cancer[16]. In the past two years, scholars have conducted texture analyses of T1 mapping and T2 mapping. Yu et al[17] showed that numerous texture feature parameters could be used to identify liver fibrosis of varying degrees; therefore, texture analysis based on T1 mapping and T2 mapping has the potential to assess liver fibrosis noninvasively. Joseph et al[18] revealed that T2 values were significantly higher in the high-risk group than in the control group, and T2 mapping texture feature parameters were correlated with histomorphology. T1 mapping histogram analysis is used in DCM for the first time. The present study provides novel results in this regard. This study discussed the diagnostic value of T1 mapping in DCM myocardial fibrosis and evaluated the correlation between T1 mapping histogram parameters and EF.

Diffuse myocardial fibrosis is common in patients with DCM. Fibrosis can cause an increase in the myocardial T1 value. In this study,

Table II. The histogram parameters and EF value of the two groups.

Index	HC group	DCM group		*F*	*p*
		LGE (+)	LGE (-)		
Mean	1281.28 ± 50.15	1285.12 ± 61.08	1211.39 ± 41.32	16.25	< 0.01
Maximum	1563.29 ± 83.74	1618.83 ± 102.15	1439.88 ± 62.74	26.11	< 0.01
Minimum	1006.03 ± 135.41	974.79 ± 92.57	1007.09 ± 73.76	0.50	0.61
SD	81.93 ± 21.43	92.62 ± 20.88	70.00 ± 14.61	6.59	< 0.01
Kurtosis	4.48 ± 1.48	4.62 ± 1.91	4.01 ± 1.78	0.77	0.47
Skewness	0.06 ± 0.50	0.05 ± 0.36	0.02 ± 0.47	0.32	0.73
P10	1179.71 ± 59.08	1167.92 ± 56.78	1121.72 ± 47.87	8.00	< 0.01
P25	1231.04 ± 50.30	1231.34 ± 58.69	1168.44 ± 42.56	12.70	< 0.01
P50	1282.18 ± 48.37	1289.01 ± 62.75	1213.51 ± 39.42	16.80	< 0.01
P75	1331.54 ± 52.77	1341.82 ± 68.00	1254.12 ± 41.69	18.71	< 0.01
P90	1379.43 ± 60.17	1393.68 ± 76.02	1296.12 ± 47.20	17.44	< 0.01
EF	21.80 ± 9.52	21.62 ± 9.18	55.22 ± 7.39	116.02	< 0.01

Note: DCM: dilated cardiomyopathy; HC: healthy control; LGE: late gadolinium-enhanced; EF: ejection fraction.

the mean of the T1 value in the DCM group increased significantly with myocardial fibrosis. The increase in the T1 value was related to the degree of fibrosis. The statistically significant differences in the 10 and 25 percentiles indicate that histogram analysis can potentially be used to detect mild fibrosis. The standard deviation (SD) reflects the dispersion of data. In this study, due to the irregular distribution of myocardial fibrosis, the distribution of T1 in the DCM group was more scattered; therefore, the SD in the DCM group increased significantly. The mean, maximum, variance, and 10, 25, 50, 75, and 90 percentiles were significantly higher in the LGE (+) and LGE (−) subgroups than in the HC group. The difference in maximum between the LGE (+) subgroup and LGE (−) subgroup was statistically significant ($p = 0.03$), and there was no statistical difference in other parameters. Despite the enhancement in the LGE images, some T1 mapping histogram parameters of the DCM group differed significantly from those of the HC group. The results suggest that the T1 mapping technique is more sensitive to myocardial fibrosis and represents a novel diagnosis method for patients who cannot be injected with a contrast agent.

The degree of myocardial fibrosis is related to the systolic and diastolic motility[19,20]. The results of the present study revealed that the differences in EF between the LGE (+) subgroup and HC group, as well as between the LGE (−) subgroup and HC group were statistically significant, while the difference in EF between the LGE (+) and LGE (−) subgroups was not statistically significant. These results are consistent with the results reported by Neilan et al[21]. The mean, variance, maximum, 10, 25, 50, 75, and 90 percentiles were negatively correlated with EF. The present study findings suggest that diffuse myocardial fibrosis mainly causes a decrease in EF in DCM patients, and is less affected by focal fibrosis.

This study had the following limitations: first, this study was a single-center clinical trial, and the included sample size was small. Therefore, multi-center clinical trials with larger sample sizes are needed. Second, the T1 value of myocardial tissue changes significantly before and after injection of a contrast agent, and the changes in T1 and the difference between the DCM group and HC group were not analyzed after injection of the contrast agent in this study. Last, DCM has different manifestations in different periods and has similar characteristics to other heart diseases. However, this study did not conduct a comparative identification. Further research on this subject is needed in the future.

Conclusions

We showed that T1 mapping technique is helpful in diagnosing myocardial fibrosis, particularly diffuse myocardial fibrosis in DCM, and T1 mapping parameters are significantly negatively correlated with EF.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of our hospital. All participants had signed the informed consent.

References

1) Begic E, Begic Z, Naser N. Clinical course and treatment of dilated cardiomyopathy during twenty years of follow-up. Med Arch 2018; 72: 68-70.
2) Yu J, Zeng C, Wang Y. Epigenetics in dilated cardiomyopathy. Curr Opin Cardiol 2019; 34: 260-269.
3) Zhao L, Yang XC. [Research progress on genetic mechanisms and pathogenic genes screening of dilated cardiomyopathy]. Zhonghua Xin Xue Guan Bing Za Zhi 2018; 46: 499-501. Chinese.
4) Halliday BP, Gulati A, Ali A, Newsome S, Lota A, Tayal U, Vassiliou VS, Arzanauskaite M, Izgi C, Krishnathasan K, Singhal A, Chiew K, Gregson J, Frenneaux MP, Cook SA, Pennell DJ, Collins P, Cleland JGF, Prasad SK. Sex- and age-based differences in the natural history and outcome of dilated cardiomyopathy. Version 2. Eur J Heart Fail 2018; 20: 1392-1400.
5) Choi EY, Choi BW, Kim SA, Rhee SJ, Shim CY, Kim YJ, Kang SM, Ha JW, Chung N. Patterns of late gadolinium enhancement are associated with ventricular stiffness in patients with advanced non-ischaemic dilated cardiomyopathy. Eur J Heart Fail 2009; 11: 573-580.
6) Ordovas KG, Higgins CB. Delayed contrast enhancement on MR images of myocardium: past, present, future. Radiology 2011; 261: 358-374.
7) aus dem Siepen F, Buss SJ, Messroghli D, Andre F, Lossnitzer D, Seitz S, Keller M, Schnabel PA, Giannitsis E, Korosoglou G, Katus HA, Steen H. T1 mapping in dilated cardiomyopathy with cardiac mag-

netic resonance: quantification of diffuse myocardial fibrosis and comparison with endomyocardial biopsy. Eur Heart J Cardiovasc Imaging 2015; 16: 210-216.

8) Aus dem Siepen F, Seitz SA, Giannitsis E, Katus HA, Steen H, Abdel-Aty H. Non-invasive measurement of myocardial extracellular volume using T1 mapping as a novel biomarker of diffuse fibrosis in dilated cardiomyopathy. J Cardiovasc Magn Reson 2013; 15: E113.

9) Noya-Rabelo MM, Macedo CT, Larocca T, Machado A, Pacheco T, Torreão J, Souza BSF, Soares MBP, Ribeiro-Dos-Santos R, Correia LCL. The presence and extension of myocardial fibrosis in the undetermined form of chagas' disease: a study using magnetic resonance. Arq Bras Cardiol 2018; 110: 124-131.

10) White SK, Sado DM, Fontana M, Banypersad SM, Maestrini V, Flett AS, Piechnik SK, Robson MD, Hausenloy DJ, Sheikh AM, Hawkins PN, Moon JC. T1 mapping for myocardial extracellular volume measurement by CMR: bolus only versus primed infusion technique. JACC Cardiovasc Imaging 2013; 6: 955-962.

11) van der Wall EE. Myocardial perfusion imaging in coronary artery disease: SPECT, PET or CMR? Neth Heart J 2012; 20: 297-298.

12) Ohyama Y, Volpe GJ, Lima JA. Subclinical myocardial disease in heart failure detected by CMR. Curr Cardiovasc Imaging Rep 2014; 7: 9269.

13) Bull S, White SK, Piechnik SK, Flett AS, Ferreira VM, Loudon M, Francis JM, Karamitsos TD, Prendergast BD, Robson MD, Neubauer S, Moon JC, Myerson SG. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. Heart 2013; 99: 932-937.

14) Teraoka K, Suzuki Y, Komori Y. The study about the difference of extra cellular volume calculated with T1mapping in dilated cardiomyopathy with and without late gadolinium enhancement. J Cardiovasc Magn Reson 2015; 17: P306.

15) Holli KK, Harrison L, Dastidar P, Wäljas M, Liimatainen S, Luukkaala T, Ohman J, Soimakallio S, Eskola H. Texture analysis of MR images of patients with mild traumatic brain injury. BMC Med Imaging 2010; 10: 8.

16) Choi MH, Oh SN, Rha SE, Choi JI, Lee SH, Jang HS, Kim JG, Grimm R, Son Y. Diffusion-weighted imaging: Apparent diffusion coefficient histogram analysis for detecting pathologic complete response to chemoradiotherapy in locally advanced rectal cancer. J Magn Reson Imaging 2016; 44: 212-220.

17) Yu H, Touret AS, Li B, O'Brien M, Qureshi MM, Soto JA, Jara H, Anderson SW. Application of texture analysis on parametric T1 and T2 maps for detection of hepatic fibrosis. J Magn Reson Imaging 2017; 45: 250-259.

18) Joseph GB, Baum T, Carballido-Gamio J, Nardo L, Virayavanich W, Alizai H, Lynch JA, McCulloch CE, Majumdar S, Link TM. Texture analysis of cartilage T2 maps: individuals with risk factors for OA have higher and more heterogeneous knee cartilage MR T2 compared to normal controls--data from the osteoarthritis initiative. Arthritis Res Ther 2011; 13: R153.

19) Rajic D, Jeremic I, Stankovic S, Djuric O, Zivanovic-Radnic T, Mrdovic I, Mitrovic P, Matic D, Vasiljevic Z, Matic M, Asanin M. Oxidative stress markers predict early left ventricular systolic dysfunction after acute myocardial infarction treated with primary percutaneous coronary intervention. Adv Clin Exp Med 2018; 27: 185-191.

20) Ladouceur M, Baron S, Nivet-Antoine V, Maruani G, Soulat G, Pereira H, Blanchard A, Boutouyrie P, Paul JL, Mousseaux E. Role of myocardial collagen degradation and fibrosis in right ventricle dysfunction in transposition of the great arteries after atrial switch. Int J Cardiol 2018; 258: 76-82.

21) Neilan TG, Coelho-Filho OR, Danik SB, Shah RV, Dodson JA, Verdini DJ, Tokuda M, Daly CA, Tedrow UB, Stevenson WG, Jerosch-Herold M, Ghoshhajra BB, Kwong RY. CMR quantification of myocardial scar provides additive prognostic information in nonischemic cardiomyopathy. JACC Cardiovasc Imaging 2013; 6: 944-954.