J Biochem Tech (2018) Special Issue (2): 184-192
ISSN: 0974-2328

Comparison of Findings of Cardiac MRI (CMR) and Transthoracic Echocardiogram (TTE) in Patients Suspected of Myocarditis in Shaheed-Rajaaee Hospital in 2016 and 2017

Marzie Motevali and Sabrieh Zareie*

Received: 25 February 2018 / Received in revised form: 25 May 2018, Accepted: 29 May 2018, Published online: 05 September 2018

Abstract

Background and Objective: Despite numerous research studying the accuracy of various diagnostic methods used for the diagnosis of acute myocarditis, an ultimate method is yet to be found. Due to advances in terms of imaging and the development of modalities with high specificity and sensitivity, cardiac MRI (CMR), Transthoracic echocardiograms (TTE) and computerized tomography (CT) compete to help in the challenging diagnosis of diseases such as myocarditis that have diverse clinical presentations. This study compares the findings of CMR and TTE and their role in confirming the diagnosis of myocarditis in clinically diagnosed patients. Materials and Methods: This cross-sectional study was done in the imaging department of Shaheed-Rajaaee hospital in the years 2016 and 2017. Using a census procedure all patients with suspected myocarditis. (symptoms included chest pain, change in ECG and troponin levels) Acute coronary syndrome (ACS) was ruled out. After the completion of stabilizing procedures and acute coronary the patients underwent further assessment using CMR and TTE in order to study the diagnostic capabilities of CMR with more certainty. (n=100) The appearance of hyperenhancement in the myocardium in the post GD T1 phase, myocardial edema in STIR sequences and severe decrease of LVEF in cine images were considered as a confirmation of the myocarditis diagnosis. Moreover, the echocardiograms were obtained (using TTE), wall motion abnormality and pericardial effusion were also assessed in these patients. The results were compared using statistical analysis. Findings: 38 male patients and 62 female patients with the mean age of 37.16 ± 17.39 participated in the study. The estimated ejection fraction of the transthoracic echocardiograms was 36.15 ± 15.29 (domain 10-65) and 38.64 ± 14.10 for the cardiac MRI (domain 9-63) respectively. In 12% of the patients pericardial effusion was observed in the TTE. And 25% in the CMR regarding pericardial effusion. In 59% of the patients TTE showed wall motion abnormality and the majority of the involvement(13.5%) was global. In 36 % of the patients CMR revealed wall motion abnormality 13.8 % of which was regional and 86.1% global. STIR sequences were obtained to observe tissue edema and led to positive results in 71% of the patients. Myocard T2/Muscle T2 ratio was more than 1.9 in 29% of the patients and less than 1.9 in the remaining 32%. In the CMR investigations, 10% of the patients showed epicardial enhancement. moreover , delayed enhancement was observed in 66% of patients suspected of myocarditis. Discussion and Conclusion: The results of this investigation showed the imaging findings of CMR have more significant capabilities in detecting/confirming myocarditis compared to TTE.

Keywords: Myocarditis, Cardiac MRI, Transthoracic Echocardiogram.

Introduction

Acute myocarditis is acute edema of the myocardium. Although not common, since it is a possibly life-threatening disease it bares significance. Viral infections, particularly with the coxsackie B virus are the most common causes in developed countries. Other significant causes of myocarditis include autoimmune diseases, bacterial and parasitic infections and side-effects of drugs. (Woodruff, 1980; Feldman et al., 2000) Confirming a diagnosis of myocarditis is challenging. In 1-9% of the cases of routine autopsy myocarditis is observed and 5-12% of cases with sudden cardiac death are revealed to have had myocarditis after biopsy.(Skouri et al., 2006, Feldman et al., 2000) Acute myocarditis can masquerade as other diseases and manifest by flu-like symptoms and tiredness. It can cause life-threatening arrhythmias, cardiogenic shock and acute delayed cardiomyopathy and some cases are self-limited. (McCully et al., 2005, Feldman et al., 2000) In an epidemiologic investigation, 72% of patients had difficulty breathing, 32% chest pain and 18% cardiac arrhythmias. (Feldman et al., 2000)

In the active phase of the disease, proliferation of viruses is observed in the myocardial cells that results in the activation of humoral and

Marzie Motevali
Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.

Sabrieh Zareie*
MD; Department of Radiology and Cardiovascular Imaging, Shahid Rajaie Cardiovascular Medical and Research Center, Tehran, Iran.

***Email:** S-zarie@gmail.com

cellular systems. Lymphocyte T, inflammatory cytokines, TNF,... rush to the region and cause myocyte necrosis. (Kawai, 1999; Matsumori et al., 2007)

Some investigations show a meaningful (significant?) relationship between inflammation/cell destruction and symptoms of ventricular heart failure. The symptoms were resolved after the inflammation was resolved.

Common diagnostic modalities are not particularly effective in the diagnosis of myocarditis.

Serum cardiac enzyme levels and T-wave and ST-segment changes in the EKG are also common although they might not be observed in some patients. Additionally, these changes are non-specific and brief. Cardiac enzymes including TroponinT and creatnine kinase I increase in many patients (Morgera et al., 1992; Eckart et al., 2004). In many cases, patients presenting with heart failure (of unknown causes) and chest pain with unrevealing/normal coronary artery angiograms, acute myocarditis is probable/ a provisional diagnosis. Since both acute MI and myocarditis present with chest pain, elevated cardiac enzymes and changes in the EKG, differentiating the two may be challenging but it is necessary in order to choose the correct course of treatment. This diagnostic overlap can lead to unnecessary invasive diagnostic procedures such as coronary artery angiography or endomyocardial biopsy (Lieberman et al., 1991; Mason & O'Connell, 1989).

Traditionally, biopsy is the gold standard in the diagnosis of myocarditis which is both complicated and has low sensitivity. This low sensitivity is due to the spread-out nature of the myocardium which results in a possibility of performing biopsy on an unaffected region of the myocardium. Therefore, biopsy is not a highly sensitive diagnostic tool although it is entirely specific (Laissy et al., 2002; Frank & Globits, 1999).

Transthoracic echocardiogram (TTE) is the most common technique used to asses cases suspected of myocarditis. The most common findings in patients with acute myocarditis are localized wall motion abnormalities (WMAS) and include areas of hypokinesis, akinesis and dyskinesis (Pinamonti et al., 1988; Nieminen et al., 1984). These nonspecific changes cannot be used to differentiate between acute myocarditis and acute MI. In a study of 41 patients that had confirmed myocarditis with biopsy, 69% had left ventricular failure, 23% had right aortic insufficiency and 20% had left ventricular hypertrophy, 15% had thrombosis and 7% had restrictive ventricles (Pinamonti et al., 1988).

Similarly in some studies of cases with confirmed myocarditis ventricular wall thickening was observed which was due to interstitial edema brought on by inflammation. These findings are significant since cases of fulminant myocarditis don’t exhibit significant changes in cardiac wall thickness (Felker et al., 2000). Right atrial failure is the most important factor in determining the prognosis of the patient where cases with normal right atrial function perform much better and face less symptoms of the disease despite lower left ventricular ejection fraction (Mendes et al., 1994).

The use of nuclear medicine techniques has also been studied to some extent. For example, iimaging with Gallium-67 and 99mTC-MIBI SPECT is no longer used due to low specificity (Boccara et al., 1998; Sun et al., 2003). Imaging using Indium-111 antimyosin antibody in the diagnosis of myocarditis was common for two decades and had desirable specificity and sensitivity. However, due to difficult access and concerns about radiation use especially in youth has limited the use of this technique (Khaw et al., 1976; Skouri et al., 2006).

In the recent decade use of cardiac MRI has significantly increased because of its ability to precisely assess the size and function of various cardiovascular components as well as the characteristics of distal and proximal blood flow (Friedrich et al., 1998; Yilmaz et al., 2008; Feldman et al., 2000). T-weighted images, particularly after contrast with gadolinium (Gd-DTPA) shows global relative signal enhancement of the left ventricular myocardium in relation to the skeletal muscles in the acute phase of the disease (Friedrich et al., 1998). Tissue T2 relaxation time is also a valuable indicator to determine the presence of interstitial fluid and edema that increase in the inflammatory phases and cellular necrosis of acute myocarditis and MI (Abdel-Aty et al., 2005; Kellman et al., 2007). In more advanced modalities such as ? Higher quality images are produced and in some investigations desirable specificity has been observed. In a study of 44 patients with suspected myocarditis significant differences in the ratio of myocardial signal to other skeletal muscles was shown in comparison to the control group. Sensitivity and specificity of this technique was estimated as 77.8% and 90.5% respectively. The positive predictive value was reported as 93.3% (Jeserich et al., 2009).

CMRI with myocardial delayed sequences has been suggested as a non-invasive diagnostic method for myocarditis. In early post gadolinium enhancement increase in blood flow and vascular permeability is possible which the inflammatory immune response of the body is. Whereas late post enhancement gadolinium enhancement is an indicator of irreversible damage to the myocardium. In the process of cellular damage due to the dysfunction of the sarcolemma in removing the intracellular contrast agent as well as increase in the intracellular space and an increase in the amount of contrast agent in the damaged myocytes lead to hyper-enhancement of the necrotic region (Babu-Narayan et al., 2007). Similar mechanisms in terms of hyperenhancement are seen in inflammatory cardiac

diseases such as myocarditis and this is a sensitive method to assess myocardial fibrosis (Mahrholdt et al., 2004). in comparison to myocardial infarcts the involvements are more sporadic and smaller and are seen as cougar like. (Gutberlet et al.,2008; Yelgec et al., 2007) the most significant findings concerning the myocardium in MRI are patchy delayed enhancement form of the epicardium (Laissy et al., 2002; Mahrholdt et al., 2002; Gutberlet et al., 2008; Mahrholdt et al., 2006). that was estimated to be 91% in the Orly Goitein study (Goitein et al., 2009). moreover, lateral wall involvement in various studies has been reported as the most common region where delayed enhancement was observed (Abdel-Aty et al., 2005; Mahrholdt et al., 2002). In a study done by Marholdt, in 83 patients out of 87 with confirmed acute myocarditis, delayed gadolinium enhancement was observed (Mahrholdt et al., 2006). The sensitivity of LGE has been estimated within a range of 44-88% in various studies (Gutberlet et al., 2008; Rieker et al., 2002). Overall, it can be said that the advantages of CMRI compared to TTE and other modalities include

1. Better quality images
2. Large field of view
3. High spatial and temporal resolution
4. Excellent producibility of measured values (Kawai, 1999; Frank & Globits, 1999; Babu-Narayan et al., 2007)

With respect to the above, the purpose of this study is a comparative assessment of CMRI and TTE in the diagnosis of myocarditis.

Materials and Methods

During this study, done in the imaging department of shaheed-rajaee between the years of 2016 and 2017, using a census procedure all patients with suspected myocarditis. (Symptoms included chest pain, change in ECG and troponin levels) Acute coronary syndrome (ACS) was rejected. After the completion of stabilizing procedures and CPR the patients underwent further assessment using CMR and TTE in order to study the diagnostic capabilities of CMR with more certainty. (n=100)

The appearance of hyperenhancement in the myocard in the post GD T1 phase, myocardial edema in STIR sequences and severe decrease of LVEF in cine images were considered as a confirmation of the myocarditis diagnosis. Moreover, the echocardiograms were obtained (using TTE), wall motion abnormality and pericardial effusion were also assessed in these patients. The results of this study were collected and saved using the checklist in the database. The collection of findings were done by the physician in charge and analyzed using the SPSS18 software and qualitative statistical indicators such as frequency, percent frequency, mean value and standard deviation.

Demographic and anthropometric information of the patients

Subjects studies 62 males and 38 females. The mean age was (37.16 ± 17.39). The mean height and weight were as follows respectively (164.96 ± 15.96) & (17.53 ±13.30).

Mean LVEF in TTE findings were (36.15 ± 15.29) and (38.64 ±14.10) in CMR.
Mean RVEF in TTE is (36.15 ± 15.29) and (42.58 ± 11.98) in CMR

Fig. 1: Demographic and anthropometric information of the patients

MyocardT2/MuscleT2 ratio and relative enhancement findings

Mean MyocardT2/MuscleT2 ratio is (1.86 ± 0.42) and mean relative enhancement is (4.60 ± 3.76) in the patients.

Wall motion abnormality findings

In the TTE tests, 59 patients (59%) suffered from WMA, where 8 (13.5%) exhibited involvement in the form of akinesia and 51 (86.4%) exhibited hypokenisa.

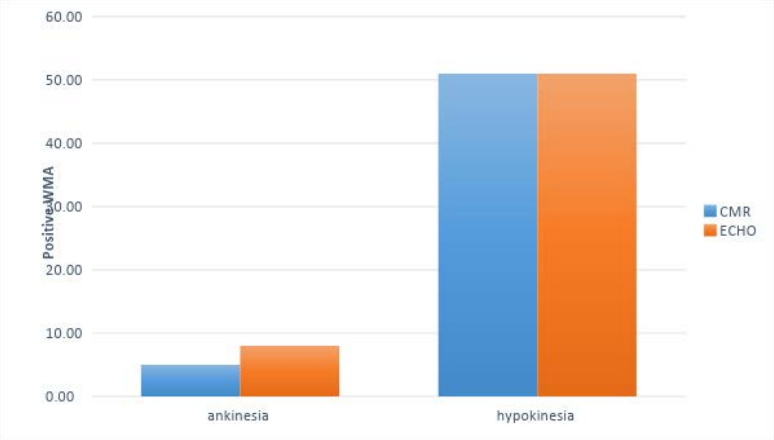

Fig. 2: Wall motion abnormality findings

In CMR studies, 36 patients suffered from WMA where 5 (13.8%) had akinesia and 51 (86.1%) showed involvement in the form of hypokinesia.

Pericardial effusion findings

TTE results were positive for 12 (12%) and negative for 88 (88%) of the patients. Out of the 12 patients with positive results, 11 (91.6%) it was mild and moderate to mild in 1 (8.4%).

Cardiac MRI results were 25 normal (25%) and 75 (75%) negative . out of the normal patients, 19 (76%) were mild, 2(8%) were moderate to mild and 3 were not specified.

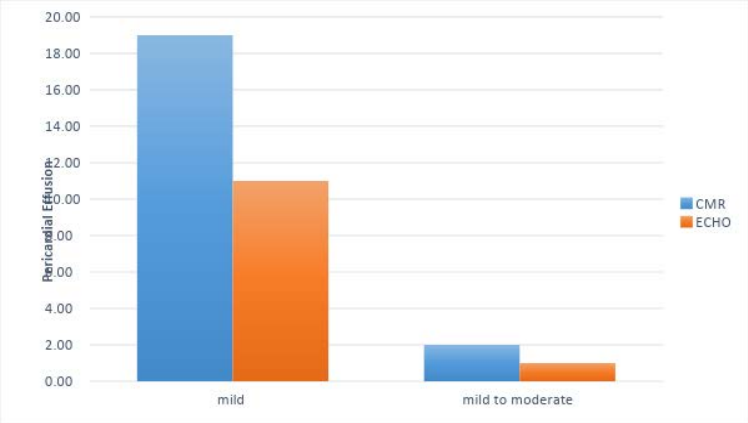

Fig. 3: Pericardial effusion findings

EF Echo findings

Among patients with suspected myocarditis, 34 (34%) were normal and 66 (66%) had abnormal results.

Myocardial changes

Among patients with suspected myocarditis, 5 (5%) were positive for myocardial changes, 71 (71%) were negative and 24 (24%) were uncertain. Also, the level of these changes among the 5 people with a positive change was mild.

Myocarditis

In TTE, 63 patients (63%) had positive results. In the MRI, 91 (91%) of the patients were positive.

Delayed enhancement

Among the 66 patients studied, the results for Delayed Enhancement were negative and in 34 cases it was positive.

Epicardial Enhancement

Among the 99 patients studied, the results for Epicardial Enhancement was negative and positive in 10 patients.

STIR edema

Among the patients studied, the results were negative for STIR edema in 29 and it was positive in 71 patients.

Relative enhancement

Out of patients suspected of myocardium dysfunction, 23 (23%) were normal, 32 (32%) were abnormal and 45 (45%) had uncertain results.

T2Myo 1.9

Out of patients suspected of myocardium dysfunction, 26 (26%) were normal, 29 (29%) were abnormal and 45 (45%) had uncertain results.

Qualitative results

In this section, we examine the agreement rate of two methods of MRI and echo in patients with suspected myocarditis using Kappa statistical index.

Table 1: MRI and echo in patients

MRI			
Positive	Negative		
31	6	Negative	Echo
60	3	Positive	
053/0=p-value	14/0=kappa	Agreement Coefficient	

Among 37 healthy individuals (assessed with Echo), 6 were healthy and 31 were positive for MRI diagnosis. Moreover, out of the 63 patients diagnosed with Echo, 3 patients were diagnosed normal with MRI, and 60 were diagnosed affected. Also, the correlation coefficient for diagnosis by Echo and MRI methods was 0.14, which showed a poor agreement rate (p-vlaue <0.05)

Evaluation of the agreement between the diagnosis using WMA involvement and the two diagnostic methods (MRI and Echo)

Table 2: Evaluation of the agreement between the diagnosis using WMA involvement and the two diagnostic methods (MRI and Echo)

MRI				
Hypokinesia	Akinesa	No WMA		
9	0	32	No WMA	Echo
2	4	2	Akinesia	
20	1	30	Hypokinesia	
002/0=p-value	24/0=kappa	Agreement Coefficient		

Among 41 healthy individuals (diagnosed with Echo), MRI revealed 32 as healthy, and 32 were diagnosed with acineia, and 9 were diagnosed with Hypokinesia. Of the 8 people diagnosed with akinesia,(using Echo) MRI diagnosed 2 were as healthy,, and 4 were diagnosed as akinesia and 2 were diagnosed with Hypokinesia. Of the 51 people diagnosed with hypokinesia through Echo, 30 were diagnosed in MRI, and 1 diagnosed with acinesia and 20 were diagnosed with Hypokinesia. Also, the agreement coefficient for diagnosis by Echo and MRI was 0.24, indicating a moderate agreement that is significant (p-vlaue <0.05)

Evaluating the agreement between the diagnosis obtained from WMA from both MRI and Echo diagnostic methods

Among 37 healthy individuals (assessed with Echo), 6 were healthy and 31 were positive for MRI diagnosis. Moreover, out of the 63 patients diagnosed with Echo, 3 patients were diagnosed normal with MRI, and 60 were diagnosed affected. Also, the correlation coefficient for diagnosis by Echo and MRI methods was 0.14, which showed a poor agreement rate (p-vlaue <0.05)

Table 3: Evaluating the agreement between the diagnosis obtained from WMA from both MRI and Echo diagnostic methods

MRI			
Positive	Negative		
9	32	Negative	Echo
27	32	Positive	
015/0=p-value	22/0=kappa	Agreement Coefficient	

Among 41 healthy individuals (assesed with Echo), 32 were healthy and 9 were positive using MRI diagnosis. Moreover, out of the 60 patients diagnosed with Echo, 32 patients were diagnosed normal with MRI, and 27 were diagnosed affected. Also, the correlation coefficient for diagnosis by Echo and MRI methods was 14.0, which showed a poor agreement rate that was non-significant (p-vlaue <0.05)

Evaluation of the agreement between the diagnosis of Pericardial Effusion from two diagnostic methods of MRI and Echo

Table 4: Evaluation of the agreement between the diagnosis of Pericardial Effusion from two diagnostic methods of MRI and Echo

MRI				
Mild to mod	Mild	No Pericardial Effusion		
0	16	70	No Pericardial Effusion	Echo
1	3	6	Mild	
1	0	0	Mild to mod	
13/0=p-value	13/0=kappa	Agreement Coefficient		

Among 86 healthy individuals (diagnosed with Echo), using MRI, 70 were diagnosed as normal, and 16 were diagnosed as mild and 0 were mild to mod. Of the 10 people diagnosed as Mild by Echo, MRI results showed that 6 were diagnosed as normal, 3 were mild and 1 were mild to mod. Of the 1 people diagnosed with mild to mod through Echo, MRI showed normal results in 0 patients, and 0 with a mild diagnosis and 1 with a mild to moderate. Also, the agreement coefficient for diagnosis by Echo and MRI was 0.13, which showed a poor agreement rate (p-vlaue <0.05).

Correlation between Ejection Fraction between Echo and MRI

Table 5: Correlation between Ejection Fraction between Echo and MRI

RVEF	LVEF	Variable
58/0	79/0	Correlation Coefficient
01/0>p	01/0>p	p-value

The correlation coefficient between LVEF in both ECHO and MRI methods was 0.79 (p <0.01), which showed a significant, direct and very strong correlation.

Correlation coefficient between RVEF in ECHO and MRI methods was 0.58 and significant (P <0.01), which showed a significant and direct correlation.

Findings

Discussion and Conclusion

By definition, myocarditis is an infiltration of inflammatory cells in the myocardium of the heart, which has important clinical significance. It is responsible for death in young people and counts as significant risk-factor for dilated and arrhythmogenic cardiomyopathy. Despite its importance, a diagnostic modality with desirable sensitivity and specificity is yet to be found. This has let to discrepancies in the guidelines of treatments for myocarditis. Although endomyocardial biopsy and immunochemical imaging are considered gold standards in the diagnosis of myocarditis, the invasiveness of this diagnostic method has rendered it as a non-desirable method. With advancement in cardiac magnetic resonance imaging modalities, it has become easier to study changes on the cellular level.

CMR is a valuable technique for studying the myocardial tissue particularly in the inflammatory cases. The STIR T2 modality and increase in enhancement The close relationship between an increase in T2W signal and acute myocardial damage or acute myocarditis resulting from increase in fluid in the myocardium.

- In a study done by Mavrogeni and colleagues in 2011 done on 20 greek children suspected of myocarditis (between the ages of 8 and 16) comparing them to 20 healthy children, the subjects were investigated using various diagnostic modalities such as CMR, STIR, LGE and EGE. 8 patients of the control and 16 of the group met the endomyocardial biopsy criteria and were biopsied. The results showed an increase in the STIR signal in 2.35±0.5 in the and 1.57±0.13 in the control group that showed statistical significance. Moreover, in the case of EGE, 3±8.5 and 3.59±0.08 in the control group was observed. Despite these findings, LGE was only 10 and 16 of the case and control group respectively. The results of the biopsy showed that positive immunochemistry in two of the case group and 6 of the control group and viral genome in 6 of the case and 8 of the control. Also, ejection fraction was estimated to be 49.6±4.8 and 64±0.2. This decrease was significant. A 6 month follow up revealed normal EGE, STIR, LGE and reduction of differences between the ejection fractions of both groups. In the current study, the ejection fractions in the TTE were estimated to be 15.93 ±33.69 (domain 65-10, range of 9-63) and 15.52 ±39.33 in CMR. These differences can be explained due to the age differences between the examined group in this study and the Magroveni study.
- In another investigation done by Jeserich and and colleagues in 2013, studying the relationship between viral genome in peripheral blood and CMR findings in patients with recent viral infections, 21 out of 55 patients tested positive for viral genomes in local leukocytes and 18 (86%) of them also showed generalized CMR findings associated with myocarditis. (Jeserich et al., 2013) Despite these results, no significant correlation was found between viral genome in peripheral blood and myocardial scarring or necrosis.The results of this study showed a 84% agreement between reporting of edema in CMR and the probability of finding viral genomes in patients that were suspected of myocarditis.
- Stensaeth and colleagues investigated 42 patients with a confirmed diagnosis of myocarditis and performed a follow-up over a 12 month period. In the acute phase of the disease, T2 ratio in 57%, overall signal increase in 31%, and LGE in 64% of the patients was observed. After the 12-month follow-up, LGE and T2 ratio had significantly decreased where LGE had reached 1.7±0.28 to 2.04±0.32 and overall cardiac signal was 3.11±1.22 from 4.07±1.63. This study was particularly valid because of its distinction between acute and chronic myocarditis.
- Rottgen and colleagues investigated 131 patients suspected of myocarditis and then confirmed the diagnosis using immunochemistry. (Rottgen et al., 2011) out of the subjects, the diagnosis was confirmed in 82 and disproved in 49. Sensitivity, specificity and accuracy of CMR was estimated as 48.8%, 73.8% and 53.7% respectively. As for relative signal increase, the results were 58.3%, 57.1% and 59.1%. As for relative signal increase, the values were 58.3%, 57.1% and 57.9% for relative fluid levels,30.6%, 88.1% for T2 and 49.6% for LGE. Overall, CMR has a sensitivity of 39.3%, specificity of of 91.3% and precision of 62.7%. In this study STIR sequences were obtained to study tissue edema for which 25% of the subjects tested positive. Myocard T2/Muscle T2 ratio was more than 2.8 in 24.1% of the patients and less than 2.8 in the remaining 25.9%. Cardiac MRI studies showed epicardial enhancement in 29.4% and delayed enhancement in 34.3% of the subjects suspected of myocarditis. These findings are in-line with the results of previous studies.
- Goitein and colleagues performed an investigation on 32 patients, clinically suspected of myocarditis to compare the precision of CMR and TTE. The results of their investigation showed patchy pericardial enhancement in the MRI of 91% of the patients.(Goitein et al., 2009) Abnormal wall motion is observed in 35% of the patients. A significant finding of this study was that regional involvement was mostly observed in the infero-lateral part of the heart. Similarly, the results of TTE in the current study showed pericardial effusion in 11.1% of the subjects. This indicator was also seen in the CMR to the same extent. Moreover, in 44.4% of the patients TTE showed wall motion abnormality and the majority of the involvement(36.1%) was global. 8.3% of the patients exhibited regional wall motion abnormality. Although the number of abnormal TTE findings is higher in the current study than the Goitein study, the number of positive confirmations by MRI is still higher than TTE

confirmations. Therefore, it seems as if in line with the other published studies, CMR has superior abilities in comparison to TTE in diagnosing acute myocarditis and has better precision in terms of showing the extent and the region of involvement.

Unfortunately, conducting the study as a case-control using patients with low suspension of myocarditis was not possible. Another limitation was inability to perform endomyocardial biopsy to confirm the clinical diagnosis. Removing these limitations can lead to further investigations, where the sensitivity and specificity of CMR is estimated.

Conclusion

The findings of this study showed that CMR provides more valuable findings in the diagnosis of acute myocarditis compared to TTE. CMR and TTE have similar accuracy in terms of comparable indicators. However, CMR provides information about indicators such as epicardial, delayed enhancement and tissue edema that can not be obtained using TTE and this information can be valuable in the diagnosis of myocarditis.

References

Skouri HN, Dec GW, Friedrich MG, Cooper LT. Noninvasive imaging in myocarditis. J Am Coll Cardiol. 2006 Nov 21;48(10):2085-93.

McCully RB, Cooper LT, Schreiter S. Coronary artery spasm in lymphocytic myocarditis: a rare cause of acute myocardial infarction. Heart. 2005 Feb;91(2):202.

Kawai C. From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future. Circulation. 1999 Mar 2;99(8):1091-100.

Matsumori A. Treatment options in myocarditis: what we know from experimental data and how it translates to clinical trials. Herz. 2007 Sep;32(6):452-6.

Kuhl U, Pauschinger M, Seeberg B, Lassner D, Noutsias M, Poller W, et al. Viral persistence in the myocardium is associated with progressive cardiac dysfunction. Circulation. 2005 Sep 27;112(13):1965-70.

Morgera T, Di Lenarda A, Dreas L, Pinamonti B, Humar F, Bussani R, et al. Electrocardiography of myocarditis revisited: clinical and prognostic significance of electrocardiographic changes. Am Heart J. 1992 Aug;124(2):455-67.

Lauer B, Niederau C, Kuhl U, Schannwell M, Pauschinger M, Strauer BE, et al. Cardiac troponin T in patients with clinically suspected myocarditis. J Am Coll Cardiol. 1997 Nov 1;30(5):1354-9.

Eckart RE, Love SS, Atwood JE, Arness MK, Cassimatis DC, Campbell CL, et al. Incidence and follow-up of inflammatory cardiac complications after smallpox vaccination. J Am Coll Cardiol. 2004 Jul 7;44(1):201-5.

Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL. Clinicopathologic description of myocarditis. J Am Coll Cardiol. 1991 Dec;18(7):1617-26.

Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ, Jr., et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987 Jan;1(1):3-14.

Mason JW, O'Connell JB. Clinical merit of endomyocardial biopsy. Circulation. 1989 May;79(5):971-9.

Laissy JP, Messin B, Varenne O, Iung B, Karila-Cohen D, Schouman-Claeys E, et al. MRI of acute myocarditis: a comprehensive approach based on various imaging sequences. Chest. 2002 Nov;122(5):1638-48.

Frank H, Globits S. Magnetic resonance imaging evaluation of myocardial and pericardial disease. J Magn Reson Imaging. 1999 Nov;10(5):617-26.

Pinamonti B, Alberti E, Cigalotto A, Dreas L, Salvi A, Silvestri F, et al. Echocardiographic findings in myocarditis. Am J Cardiol. 1988 Aug 1;62(4):285-91.

Nieminen MS, Heikkila J, Karjalainen J. Echocardiography in acute infectious myocarditis: relation to clinical and electrocardiographic findings. Am J Cardiol. 1984 May 1;53(9):1331-7.

Felker GM, Boehmer JP, Hruban RH, Hutchins GM, Kasper EK, Baughman KL, et al. Echocardiographic findings in fulminant and acute myocarditis. J Am Coll Cardiol. 2000 Jul;36(1):227-32.

Mendes LA, Dec GW, Picard MH, Palacios IF, Newell J, Davidoff R. Right ventricular dysfunction: an independent predictor of adverse outcome in patients with myocarditis. Am Heart J. 1994 Aug;128(2):301-7.

Boccara F, Blanchard-Lemoine B, Sarda L, Bardet J, Le Guludec D, Cohen A. [Diagnostic strategy in acute myocarditis]. Arch Mal Coeur Vaiss. 1998 Sep;91(9):1151-8.

Sun Y, Ma P, Bax JJ, Blom N, Yu Y, Wang Y, et al. 99mTc-MIBI myocardial perfusion imaging in myocarditis. Nucl Med Commun. 2003 Jul;24(7):779-83.

Khaw BA, Beller GA, Haber E, Smith TW. Localization of cardiac myosin-specific antibody in myocardial infarction. J Clin Invest. 1976 Aug;58(2):439-46.

Friedrich MG, Strohm O, Schulz-Menger J, Marciniak H, Luft FC, Dietz R. Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. Circulation. 1998 May 12;97(18):1802-9.

Yilmaz A, Mahrholdt H, Athanasiadis A, Vogelsberg H, Meinhardt G, Voehringer M, et al. Coronary vasospasm as the underlying cause for chest pain in patients with PVB19 myocarditis. Heart. 2008 Nov;94(11):1456-63.

Abdel-Aty H, Boye P, Zagrosek A, Wassmuth R, Kumar A, Messroghli D, et al. Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. J Am Coll Cardiol. 2005 Jun 7;45(11):1815-22.

Kellman P, Aletras AH, Mancini C, McVeigh ER, Arai AE. T2-prepared SSFP improves diagnostic confidence in edema imaging in acute myocardial infarction compared to turbo spin echo. Magn Reson Med. 2007 May;57(5):891-7.

Jeserich M, Olschewski M, Bley T, Merkle N, Kirchberger J, Pavlik G, et al. Cardiac involvement after respiratory tract viral infection--detection by cardiac magnetic resonance. J Comput Assist Tomogr. 2009 Jan-Feb;33(1):15-9.

Mahrholdt H, Wagner A, Judd RM, Sechtem U. Assessment of myocardial viability by cardiovascular magnetic resonance imaging. Eur Heart J. 2002 Apr;23(8):602-19.

Babu-Narayan SV, McCarthy KP, Ho SY, Magee AG, Kilner PJ, Sheppard MN. Images in cardiovascular medicine. Myocarditis and sudden cardiac death in the young: extensive fibrosis suggested by cardiovascular magnetic resonance in vivo and confirmed post mortem. Circulation. 2007 Aug 7;116(6):e122-5.

Mahrholdt H, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, et al. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation. 2004 Mar 16;109(10):1250-8.

Gutberlet M, Spors B, Thoma T, Bertram H, Denecke T, Felix R, et al. Suspected chronic myocarditis at cardiac MR: diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. Radiology. 2008 Feb;246(2):401-9.

Yelgec NS, Dymarkowski S, Ganame J, Bogaert J. Value of MRI in patients with a clinical suspicion of acute myocarditis. Eur Radiol. 2007 Sep;17(9):2211-7.

Mahrholdt H, Wagner A, Deluigi CC, Kispert E, Hager S, Meinhardt G, et al. Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. Circulation. 2006 Oct 10;114(15):1581-90.

Goitein O, Matetzky S, Beinart R, Di Segni E, Hod H, Bentancur A, et al. Acute myocarditis: noninvasive evaluation with cardiac MRI and transthoracic echocardiography. AJR Am J Roentgenol. 2009 Jan;192(1):254-8.

Rieker O, Mohrs O, Oberholzer K, Kreitner KF, Thelen M. [Cardiac MRI in suspected myocarditis]. Rofo. 2002 Dec;174(12):1530-6.

Mavrogeni S, Bratis K, Georgakopoulos D, Karanasios E, Kolovou G, Pavlides G, et al. Evaluation of myocarditis in a pediatric population using cardiovascular magnetic resonance and endomyocardial biopsy. Int J Cardiol. 2012 Oct 18;160(3):192-5.

Jeserich M, Brunner E, Kandolf R, Olschewski M, Kimmel S, Friedrich MG, et al. Diagnosis of viral myocarditis by cardiac magnetic resonance and viral genome detection in peripheral blood. Int J Cardiovasc Imaging. 2013 Jan;29(1):121-9.

Stensaeth KH, Hoffmann P, Fossum E, Mangschau A, Sandvik L, Klow NE. Cardiac magnetic resonance visualizes acute and chronic myocardial injuries in myocarditis. Int J Cardiovasc Imaging. 2012 Feb;28(2):327-35.

Rottgen R, Christiani R, Freyhardt P, Gutberlet M, Schultheiss HP, Hamm B, et al. Magnetic resonance imaging findings in acute myocarditis and correlation with immunohistological parameters. Eur Radiol. 2011 Jun;21(6):1259-66.

Woodruff JF. Viral myocarditis. A review. Am J Pathol. 1980 Nov;101(2):425-84.

Feldman AM, McNamara D. Myocarditis. N Engl J Med. 2000 Nov 9;343(19):1388-98.