Eur Radiol (2011) 21:925–935
DOI 10.1007/s00330-010-1985-2

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Cardiac magnetic resonance imaging in dilated cardiomyopathy in adults—towards identification of myocardial inflammation

Antje Voigt · Thomas Elgeti · Tahir Durmus · Merve Ece Idiz · Craig Butler · Mark Beling · Rene Schilling · Karin Klingel · Reinhard Kandolf · Karl Stangl · Matthias Taupitz · Dietmar Kivelitz · Moritz Wagner

Received: 26 May 2010 / Revised: 30 August 2010 / Accepted: 10 September 2010 / Published online: 21 October 2010

Abstract
Objective To assess active myocardial inflammation by cardiovascular magnetic resonance (CMR) and endomyocardial biopsy (EMB) amongst adult patients with dilated cardiomyopathy (DCM).
Methods We evaluated 23 adults with chronic DCM, who had successfully undergone both CMR and EMB within 3.5± 2.6 days. EMB was considered the gold standard. CMR assessment of myocardial inflammation used the following parameters as recommended by the recently published "Lake Louise Criteria": global myocardial oedema, global relative enhancement (RE), and late gadolinium enhancement (LGE). According to "Lake Louise Criteria", myocardial inflammation was diagnosed if two or more of the three above-mentioned parameters were positive.
Results Myocardial inflammation was confirmed by immunohistology in 12 patients (52.2%). Sensitivity, specificity, and diagnostic accuracy of CMR to detect immunohistologically confirmed myocardial inflammation were 75.0%, 72.7%, and 73.9%, respectively. Sensitivity, specificity, and diagnostic accuracy of the individual CMR parameters to detect myocardial inflammation were as follows: global myocardial oedema, 91.7%, 81.8%, and 87.0%, respectively; global RE, 58.3%, 63.6%, and 60.9%, respectively; LGE, 58.3%, 45.4%, and 52.2%, respectively.
Conclusion Global myocardial oedema was identified as a promising CMR parameter for assessment of myocardial inflammation in patients with DCM. In these patients, global myocardial oedema yielded superior diagnostic performance compared to "Lake Louise Criteria".

Keywords Cardiomyopathy · Magnetic resonance · Inflammation · Myocarditis

A. Voigt · M. Beling · K. Stangl
Department of Cardiology, Campus Mitte,
Charité-Universitätsmedizin Berlin,
10117 Berlin, Germany

T. Elgeti · T. Durmus · M. E. Idiz · R. Schilling · M. Taupitz · M. Wagner (✉)
Department of Radiology, Campus Mitte,
Charité-Universitätsmedizin Berlin,
Charitéplatz 1,
10117 Berlin, Germany
e-mail: moritz.wagner@charite.de

C. Butler
Mazankowski Alberta Heart Institute, University of Alberta,
Edmonton, Canada

K. Klingel · R. Kandolf
Department of Molecular Pathology, University Hospital,
72076 Tübingen, Germany

D. Kivelitz
Department of Radiology, Asklepios Klinik St. Georg,
20099 Hamburg, Germany

Introduction

Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy worldwide [1]. DCM is characterised by left ventricular dilation and systolic dysfunction in the absence of coronary artery disease, hypertension and valvular disease [2, 3]. Myocardial inflammation mediated by acute or chronic viral infection, direct toxic injury, or autoimmune response is an important cause of DCM [4–6]. Immunomodulatory therapies have recently been shown to have clinical benefit in selected patients with DCM [7–9]. The accurate detection of myocardial inflammation may

identify a patient group that would benefit from immunomodulatory therapy and thereby change the clinical management of DCM.

Endomyocardial biopsy (EMB) is a widely accepted method for assessment of myocardial inflammation [10]. EMB can be safely performed by experienced operators, but life-threatening complications such as pericardial tamponade still occur in 0.1% to 0.5% of patients [10]. Cardiac magnetic resonance (CMR) has emerged as a powerful tool for non-invasive assessment of myocardial inflammation. Recently, the International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis developed recommendations for diagnosis of myocardial inflammation (i.e. "Lake Louise Criteria") [11]. The consensus statement proposed a comprehensive CMR protocol, which included assessment of global myocardial oedema, global relative enhancement (RE, e.g. myocardial hyperaemia), and late gadolinium enhancement (LGE, e.g. fibrosis, necrosis). For detection of global myocardial oedema, signal intensity of the entire myocardium is related to that of skeletal muscle on T2-weighted triple inversion-recovery spin-echo images [12]. Myocardial oedema is diagnosed if the myocardial/skeletal muscle signal intensity ratio is higher than a predefined cut-off value [13]. Assessment of global RE is based on measurement of myocardial and skeletal muscle signal enhancement on T1-weighted spin-echo sequences in the early phase after contrast agent administration [12]. Again, myocardial hyperaemia is diagnosed when global RE is higher than a predefined cut-off value [13]. In the delayed phase after contrast agent administration, inversion-recovery gradient-echo sequences are used to detect LGE, which represents myocardial fibrosis and necrosis [14]. According to the consensus diagnostic criteria ("Lake Louise Criteria"), myocardial inflammation can be predicted with a diagnostic accuracy of 78% in patients with suspected myocarditis if two or more of the three tissue-based criteria (global myocardial oedema, global RE, LGE with non-ischemic regional distribution) are positive [11]. The aim of the present study was to retrospectively assess the diagnostic performance of "Lake Louise Criteria", global myocardial oedema, global RE, and LGE to detect immunohistologically proven myocardial inflammation in adults with DCM.

Materials and methods

Patients

A total of 26 consecutive adult DCM patients, who underwent both CMR and EMB, were retrospectively analysed. EMB was performed prior to CMR in seven patients and after CMR in the remaining 19 patients. Retrospective patient selection was performed as follows: Firstly, we screened all patients undergoing EMB at our cardiology department between January 2006 and December 2009. Our inclusion criteria were as follows: 1) unexplained chronic heart failure (NYHA II-III) and disease duration of more than 3 months; 2) echocardiographic left ventricular end-diastolic diameter (LVEDD) >55 mm; 3) echocardiographic left ventricular ejection fraction (LVEF) ≤45%; 4) exclusion of relevant coronary artery disease by invasive coronary angiography; 5) exclusion of other primary disease like hypertension, valvular heart disease, congenital heart disease, and chronic alcohol excess that may eventually lead to chronic heart failure associated with left ventricular dilation; 6) no clinical suspicion of acute myocarditis or acute myocardial infarction, no recent symptoms of viral illness, no history of pericarditis type chest pain, no ECG-changes suggestive of pericarditis or acute myocardial injury, no positive biomarkers consistent with acute myocardial injury; and 7) no clinical suspicion of cardiac amyloidosis, sarcoidosis, or hemochromatosis. 37 patients met these inclusion criteria. In these patients, EMB was ordered at the discretion of the attending physician as part of the work-up for heart failure of unknown etiology. In this setting, EMB was typically used to detect myocardial inflammation and viral genomes. Moreover, EMB was considered to exclude cardiac sarcoidosis and cardiac hemochromatosis. Cardiac sarcoidosis and hemochromatosis were not detected in any of these patients. Secondly, we screened the database of our radiology department to determine which of these 37 patients underwent CMR as part of their routine diagnostic work-up for chronic heart failure. Patients were eligible for the study if: 1) CMR was performed within 2 weeks of EMB and 2) the CMR protocol complied with the recommendations published by the International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. 26 patients met these CMR inclusion criteria. Hence, the final study collective included 26 patients, who underwent both EMB and CMR. The study protocol complied with the Declaration of Helsinki and was approved by the local Ethics Committee.

Endomyocardial biopsy

Endomyocardial biopsy was performed in all patients. A minimum of 4 biopsy specimens with diameters of 1 to 3 mm were harvested under sterile conditions from the interventricular septum and/or left ventricular free wall: 2 to 3 biopsy specimens were fixed in 4% buffered formaldehyde for histology and immunohistology. The remaining 2 to 3 biopsy specimens were quick-frozen or fixed in RNAlater (Ambion Inc., Foster City, CA, USA) for detection of viral genomes by PCR. Biopsy specimens were investigated within 24 h, and acute myocarditis was excluded on the basis of the Dallas criteria [15]. According

to this classification, acute myocarditis was defined by lymphocytic infiltrates in association with myocyte necrosis. The immunhistological definition of myocardial inflammation was as follows: 1) ≥14 CD3-positive T-lymphocytes and/or CD68-positive macrophages per mm^2 detected by immunochemistry in a diffuse or focal pattern and 2) enhanced expression of HLA class II molecules [16]. Paraffin-embedded tissue sections were treated with an avidin-biotin-immunoperoxidase technique according to the manufacturer's protocol (Vectastain Elite ABC Kit, Vector, Burlingame, CA, USA). The following monoclonal antibodies were applied for identification, localisation, and characterisation of mononuclear cell infiltrates: CD3 for T-cells (Novocastra Laboratories, Newcastle upon Tyne, UK), PGM1 (CD68) for macrophages and natural killer cells (DAKO, Glostrup, Denmark), and HLA-DR (DAKO, Hamburg, Germany) for assessment of HLA class-II expression in professional antigen-presenting immune cells. Fibrosis was evaluated by Masson Trichrome staining. Amyloidosis was excluded on the basis of Congo staining. Nested polymerase chain reaction (PCR) and nested reverse transcription PCR was performed to detect enteroviruses (various coxsackie A viruses, coxsackie B viruses, and echoviruses), parvovirus B19 (PVB19), adenoviruses, human cytomegalovirus, Epstein-Barr virus, human herpes virus 6 (HHV6), and herpes simplex virus types 1 and 2 [16]. RNA of RNA viruses was transcribed into cDNA by reverse transcription according to the protocol of the manufacturer (AGS, Heidelberg, Germany). The enzymatic amplification of cDNA or viral DNA was performed as nested PCR in two 30-cycle programs on a Perkin-Elmer GeneAmp PCR System 9600 (Applied Biosystems, Weiterstadt, Germany). As an internal control for successful isolation of nucleic acids, the housekeeping gene GAPDH was detected by PCR. A biopsy was considered positive for viral infection if the viral genome was detected by PCR, and specificity was confirmed by automatic DNA sequencing of viral amplification products. Both pathologists (K. K., R. K.) involved in this study were blinded to CMR findings.

CMR

Cardiac magnetic resonance was performed on one of two clinical 1.5 Tesla MRI systems (Siemens Magnetom Avanto or Siemens Magnetom Sonata, Erlangen, Germany). The CMR protocol included the following sequences: 1) double-angulated left ventricular long-axis imaging using Cine steady-state free precession (SSFP) sequences (time of repetition (TR) 46.5 milliseconds, echo time (TE) 1.6 milliseconds, 6 mm slice thickness) and a left ventricular short-axis stack for the three-dimensional determination of left ventricular volume and function (TR 40.7 milliseconds, TE 1.3 milliseconds, 8 mm slice thickness, 2 mm inter-slice distance); 2) T2-weighted triple inversion-recovery spin-echo imaging (TR 2×RR-interval, TE 65 milliseconds, TI 150 milliseconds, 15-mm slice thickness, 5 mm inter-slice distance) in three short-axis positions of the left ventricle (basal, mid, and apical) [12, 17]; 3) T1-weighted spin-echo imaging (TR 1 RR-interval, TE 30 milliseconds, slice thickness 8 mm, 4 mm inter-slice distance) in three transverse sections of the left ventricle before and over 4 min after intravenous administration of 0.1 mmol Gd-DTPA/kg body weight (Magnevist®, BayerScheringPharma, Germany) [12, 18]; 4) 2D inversion-recovery gradient-echo imaging performed 10–15 min after injection of an additional dose of 0.1 mmol Gd-DTPA/kg body weight (TR 750 milliseconds, TE 4.3 milliseconds, slice thickness 8 mm, adapted inversion time) in short and long axis views. In patients who could not sufficiently hold their breath, 2D phase-sensitive inversion-recovery sequences (PSIR, TR 700 milliseconds, TE 1.1 milliseconds, slice thickness 8 mm, adapted inversion time) were performed. The optimal inversion time was determined using a modified look-locker sequence (TR 42.6 milliseconds, TE 1.1 milliseconds, slice thickness 8 mm) as described previously [19].

CMR analysis

Cardiac magnetic resonance image analysis was performed in consensus by two radiologists with at least 4 years' experience in CMR (T. E., M. W.), who were blinded to the clinical data including EMB results. Left ventricular volumes and function were evaluated on Cine SSFP sequences using dedicated software (ARGUS, Version Siemens Medical Solutions, Erlangen, Germany). Calculation of global myocardial oedema and global RE was performed by encircling the entire left ventricular myocardium and a representative sample of skeletal muscle on T2-weighted triple-inversion-recovery spin-echo images and spin-echo T1-weighted images, respectively (Fig. 1)[12, 18]. For assessment of myocardial oedema, either the pectoralis muscle or the latissimus dorsi muscle was chosen as a representative sample of skeletal muscle. The mean signal intensity (SI) of the myocardium (SI_M) was correlated to the mean SI of the skeletal muscle (Si_S) using the following equation: Oedema ratio=SI_M/SI_S. A ratio of ≥1.8 was considered positive for myocardial oedema [13]. For assessment of global RE, the mean SI of the left ventricle myocardium and the erector spinae muscle on pre- and postcontrast T1-weighted images were used. Global RE was calculated using the following equation: global RE=$((postSI_M - preSI_M)/preSI_M)/((postSI_S - preSI_S)/preSI_S)$. Global RE of ≥5.0 was considered positive for detection of myocardial hyperaemia [13]. Assessment of LGE was performed visually, and LGE was classified as non-ischemic (typically subepicardial or mid-wall pattern) or ischemic (typically subendocardial pattern).

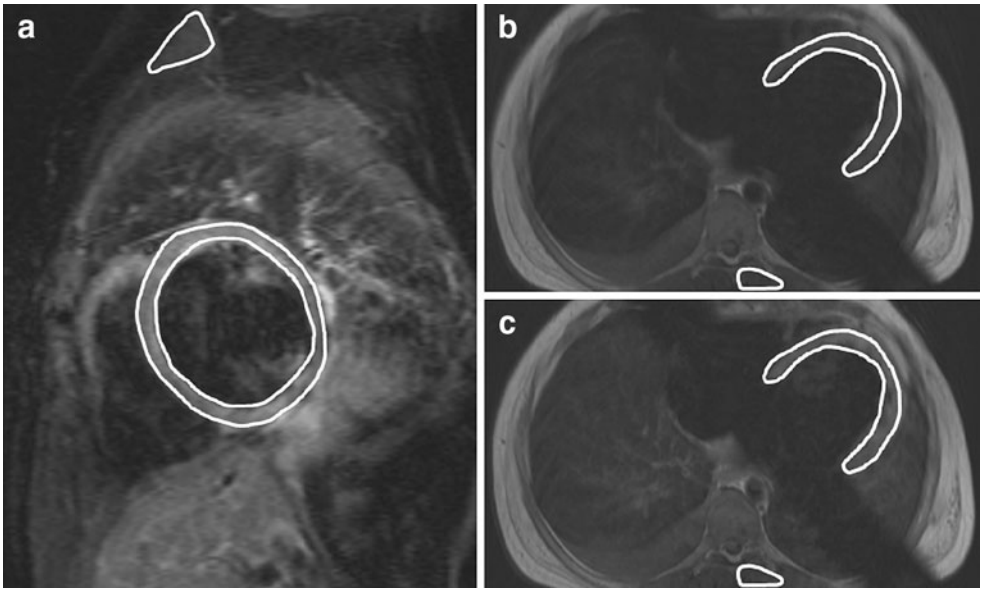

Fig. 1 Assessment of global myocardial oedema on T2-weighted triple inversion-recovery spin-echo images (**a**) and global relative enhancement (RE) on T1-weighted spin-echo images before (**b**) and after (**c**) contrast agent administration in a representative patient (A8). Global myocardial oedema and global RE were calculated based on signal intensity (SI) measurements in regions-of-interest manually drawn around the entire myocardium and a representative sample of skeletal muscle (A: pectoralis muscle; B and C: erector spinae muscle). Note: CMR and EMB results of patient A8 are illustrated in more detail in Fig. 3 and Table 2

Statistics

Continuous data are displayed as mean with standard error of the mean, categorical data as number of patients with the condition. The age, left ventricular ejection fraction, left ventricular end-diastolic volume, and left ventricular myocardial mass were analysed descriptively and tested for differences between patients with and without the event using two-sided Wilcoxon rank sum tests. Sensitivity, specificity and accuracy were calculated for the following parameters: global myocardial oedema, global RE, LGE and "Lake Louise Criteria". No confidence intervals are provided because of the limited overall sample size. Biopsy assessments were used as standard of reference. All statistical tests were performed two-sided, and p-values below 0.05 were regarded as statistically significant. Calculations were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and R software (version 2.7.1, R Development Core Team, Vienna, Austria).

Results

Patients and EMB findings

A total of 26 patients with DCM underwent both EMB and CMR. CMR was successfully performed in 23 patients (88.5%). In the remaining three patients, global myocardial oedema and/or global RE could not be assessed due to severe motion artefacts. The final study population included 23 patients, of whom 12 (52.2%) had evidence of myocardial inflammation by immunohistological analysis of EMB specimens. Myocardial fibrosis was found in 21 patients (91.3%) on EMB. Immunohistological findings and the presence of viral genomes in EMB specimens are presented in Table 1. The average duration between EMB and CMR was 3.5±2.6 days.

CMR findings

Ventricular volumes and function as assessed by CMR were not different between patients with and without proven inflammation on EMB. Specifically, there was no difference in left ventricular ejection fraction (22.8±4.0% versus 24.4±3.6%, respectively; p=0.661), left ventricular end-diastolic volume (292.3±31.7 ml versus 261.5±17.9 ml, respectively; p=0.661), and left ventricular myocardial mass (210.3±26.8 g versus 181.8±13.3 g, respectively; p=0.844). In patients with inflammation in EMB, global myocardial oedema was found in 11 patients (91.7%) and positive global RE in 7 patients (58.3%) (Table 2a). In patients without inflammation in EMB, positive global myocardial oedema was found in 2 patients (18.2%) and positive global RE in 4 patients (36.4%) (Table 2b). Non-ischaemic LGE was diagnosed in 7 patients (58.3%) with inflammation in EMB and in 6 patients (54.5%) without inflammation in EMB (Table 2). In three patients, small areas of subendocardial LGE (ischemic pattern) were detected without clinical or angiographic evidence of coronary artery disease (patient A12: basal and mid anterior (segment 1 and 7); patient B1: mid inferoseptal (segment 9) and apical lateral (segment 16); patient B10: basal anterior and anteroseptal (segment 1 and 2)). No difference in segmental distribution of LGE was found between patients with and without inflammation in EMB (Fig. 2). LGE was present in 15 of 21 patients with evidence of myocardial fibrosis on EMB. LGE was not found in the two patients without myocardial

Table 1 Results of EMB in patients with successfully completed CMR (n=23)

	Inflammatory lesions absent (n=11)	Inflammatory lesions present[a] (n=12)
Age[b] (years)	48.0±4.2	47.2±5.2
Gender male/female (n)	10/1	10/2
Virus positive (n)	6	3
Parvovirus B19 (PVB19)	1	2
Human Herpesvirus 6 (HHV6)	2	1
Human Herpesvirus 7 (HHV7)	1	0
Epstein-Barr virus (EBV)	1	0
PVB19+HHV6	1	0
Fibrosis in EMB	10	11

[a] Focal/and or diffuse mononuclear infiltrates with ≥14 CD3-positive T-lymphocytes and/or CD68-positive macrophages per mm^2, in addition to enhanced expression of HLA class II molecules

[b] Mean±standard error of mean

fibrosis on EMB (patient A9 and B11). In seven patients, EMB was performed prior to CMR which could theoretically impact features of inflammation seen on CMR including global myocardial oedema, global RE, and LGE (Table 2). However, no obvious impact of EMB on these CMR parameters was observed in our study group

Diagnostic performance of CMR

According to the "Lake Louise Criteria", CMR correctly identified myocardial inflammation in 9 out of 12 patients, yielding a sensitivity of 75.0% (Table 3, Fig. 3), and correctly excluded myocardial inflammation in 8 out of 11 patients, yielding a specificity of 72.7% (Table 3, Fig. 4). Using the "Lake Louise Criteria", CMR diagnosed myocardial inflammation in three patients, in whom EMB was negative for myocardial inflammation. Overall diagnostic accuracy of CMR using the "Lake Louise Criteria" was 73.9%. Diagnostic performance of CMR was inferior when global RE or LGE were used individually for detecting myocardial inflammation (Table 3). In contrast, global myocardial oedema revealed high sensitivity, specificity, and diagnostic accuracy to detect myocardial inflammation in patients with DCM (91.7%, 81.8%, and 87.0%, respectively).

Discussion

The present study evaluated the diagnostic performance of a comprehensive CMR protocol to detect immunohistologically proven myocardial inflammation in patients with DCM. The CMR protocol complied with the recommendations of the International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis [11]. Our data indicate that a CMR examination which includes assessment of global myocardial oedema is a promising diagnostic tool for detection of myocardial inflammation in DCM.

The unique myocardial tissue characterisation offered by CMR has proven value in the work-up of heart failure [20]. In particular, assessment of LGE is a well established CMR parameter in the evaluation of heart failure in the setting of coronary artery disease, myocarditis, and various cardiomyopathies [21–27, 35]. It is important to recognize that LGE is not specific but can reflect myocardial necrosis, non-ischemic fibrosis, and ischemic scars. The underlining mechanism proposed for LGE is an increase of interstitial space within areas of myocardial damage [28]. Unspecific gadolinium contrast agents diffuse into pathologically enlarged interstitial space, which results in hyperintensity on inversion-recovery-prepared gradient-echo images (e.g. LGE). Hereby, local distribution of LGE differs substantially between ischemic and non-ischemic myocardial damage [14, 29]. In a study of McCrohn et al., all patients with heart failure related to coronary artery disease presented with subendocardial or transmural LGE [29]. In contrast, LGE is found less frequently in patients with heart failure due to DCM (35%–42%) or chronic myocarditis (up to 70%) [30–32]. In these patients, LGE has mostly epicardial or mid-wall distribution. In our study, we detected LGE in several DCM patients with myocardial inflammation on EMB. This result is in accordance with the data of De Corbelli et al. on patients with heart failure in the setting of chronic myocarditis [32]. However, LGE was also frequently found in DCM patients without immunohistologically proven myocardial inflammation. Hence, diagnostic performance of LGE was insufficient for reliable diagnosis of myocardial inflammation in patients with DCM. Our results are in good accordance with a recently published study of Gutberlet et al. which reported low diagnostic accuracy of LGE for detection of myocardial inflammation in patients with chronic myocarditis [18]. Moreover, diffuse myocardial damage including diffuse

Table 2 Results of endomyocardial biopsy (EMB) and cardiovascular magnetic resonance (CMR)

Pat. ID	Age	Gender	EMB Virus	EMB Fibrosis	CMR Oedema	CMR RE	CMR LGE	Lake Louise Criteria
2a Patients with inflammation in EMB								
A1	44	m	–	+	1.96	16.10	–	+
A2	73	m	–	+	2.70	5.90	+	+
A3[a]	76	m	–	+	2.29	5.05	+	+
A4[a]	49	m	–	+	1.29	6.97	–	–
A5	33	f	PVB19	+	2.11	4.03	–	–
A6	44	m	–	+	2.24	4.05	+	+
A7	46	m	–	+	2.08	5.82	+	+
A8	25	m	PVB19	+	2.70	5.28	+	+
A9[a]	42	m	–	–	2.04	11.00	–	+
A10	76	m	HHV6	+	1.95	4.68	+	+
A11[a]	18	f	–	+	1.92	2.44	+	+
A12	43	m	–	+	2.03	1.94	–	–
2b Patients without inflammation in EMB								
B1	49	m	HHV6	+	1.26	15.70	+	+
B2	49	m	–	+	2.18	3.96	+	+
B3	35	f	–	+	1.53	8.50	–	–
B4	23	m	–	+	1.71	8.33	+	+
B5	66	m	HHV6	+	1.60	5.88	–	–
B6	43	m	EBV	+	1.66	2.77	+	–
B7	65	m	HHV7	+	1.56	4.65	+	–
B8[a]	44	m	PVB19	+	1.80	1.43	–	–
B9	72	m	PVB19+HHV6	+	1.67	4.02	+	–
B10[a]	38	m	–	+	1.77	3.10	–	–
B11[a]	44	m	–	–	1.50	4.87	–	–

[a] EMB was performed prior to CMR

RE relative myocardial enhancement; *LGE* late gadolinium enhancement with non-ischemic pattern; *PVB19* Parvovirus B19; *HHV* human herpes virus; *EBV* Epstein-Barr virus

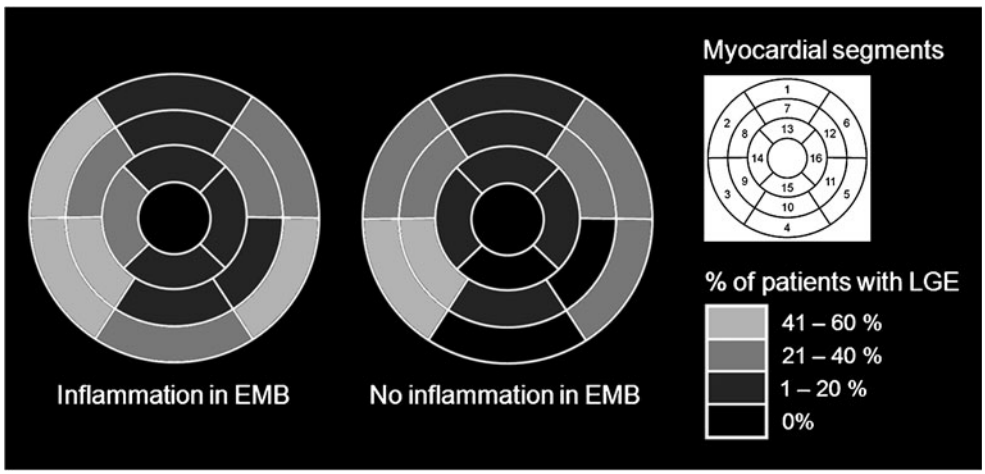

Fig. 2 Distribution of late gadolinium enhancement (LGE) in patients with dilated cardiomyopathy (DCM). Segmental distribution of LGE is shown separately for patients with and without inflammation in endomyocardial biopsy. The left ventricular segmentation is illustrated using a 16-segment model (1: basal anterior; 2: basal anteroseptal; 3: basal inferoseptal; 4: basal inferior; 5: basal inferolateral; 6: basal anterolateral; 7: mid-anterior; 8: mid-anteroseptal; 9: mid-inferoseptal; 10: mid-inferior; 11: mid-inferolateral; 12: mid-anterolateral; 13: apical anterior; 14: apical septal; 15: apical inferior; 16: apical lateral). The percentage of patients with LGE in the corresponding myocardial segment is represented on a grey scale

Table 3 Diagnostic performance of global myocardial oedema, global relative myocardial enhancement (RE), late gadolinium enhancement (LGE), and "Lake Louise Criteria"

	Oedema	RE	LGE	Lake Louise Criteria
Sensitivity	91.7%	58.3%	58.3%	75.0%
Specificity	81.8%	63.6%	45.4%	72.7%
Accuracy	87.0%	60.9%	52.2%	73.9%

myocardial fibrosis might not be detected by LGE [33]. Indeed, in 6 of the 21 patients with fibrosis on EMB, LGE was absent on inversion recovery gradient-echo images. Advanced techniques such as T1-mapping could substantially improve the diagnostic performance of contrast-enhanced MR imaging in the future [33, 34]. However, these techniques are currently not broadly available. Nevertheless, assessment of LGE yields valuable clinical information for patients with heart failure. In particular, detection of mid-wall LGE was

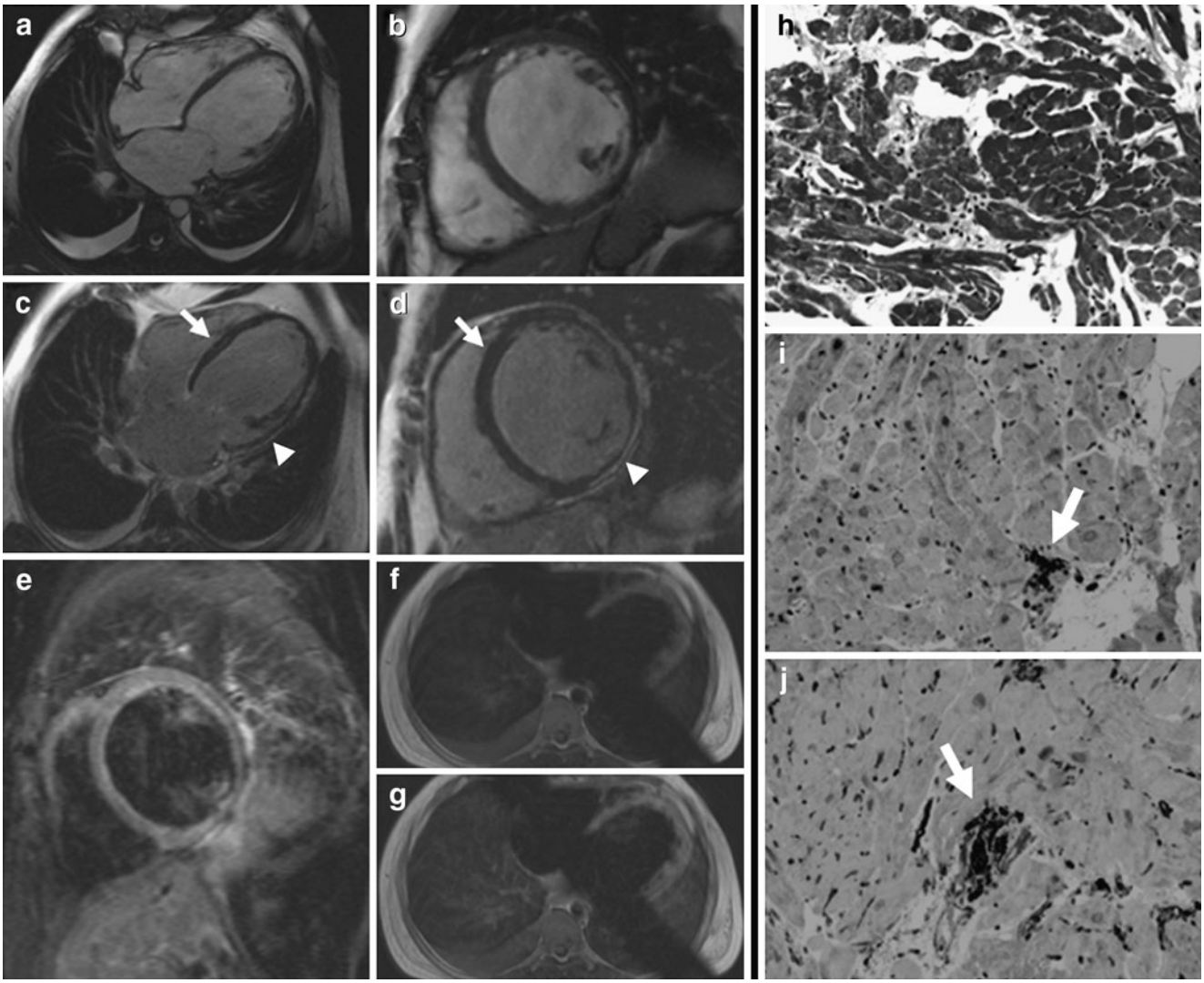

Fig. 3 Patient (A8) with diagnosis of myocardial inflammation both by cardiovascular magnetic resonance imaging (CMR, **a**–**g**) and endomyocardial biopsy (EMB, **h**–**j**). Steady state free precession (SSFP) images were acquired in the long (**a**) and the short axis (**b**). Corresponding inversion-recovery gradient-echo imaging (**c**, **d**) detected late gadolinium enhancement (LGE) anteroseptal (arrow; mid-wall LGE) and inferolateral (arrow-head; subepicardial LGE). T2-weighted triple inversion-recovery spin-echo imaging in the short axis (**e**) demonstrated global myocardial oedema (value=2.7). Global RE, which was assessed on pre- and post-contrast axial T1-weighted spin echo imaging (**f**, **g**), was also positive (value=5.28). EMB showed typical histopathological and immunohistochemical findings in inflammatory cardiomyopathy (**h**–**j**). Masson's trichrome staining (**h**) revealed chronic myocardial lesions that are characterised by interstitial fibrosis and the concomitant presence of hypertrophic and degenerated myocytes. In addition, focal areas with T-lymphocytes (**i**, indicated by the arrow) and increased expression of HLA class II (**j**, indicated by arrow) were detected

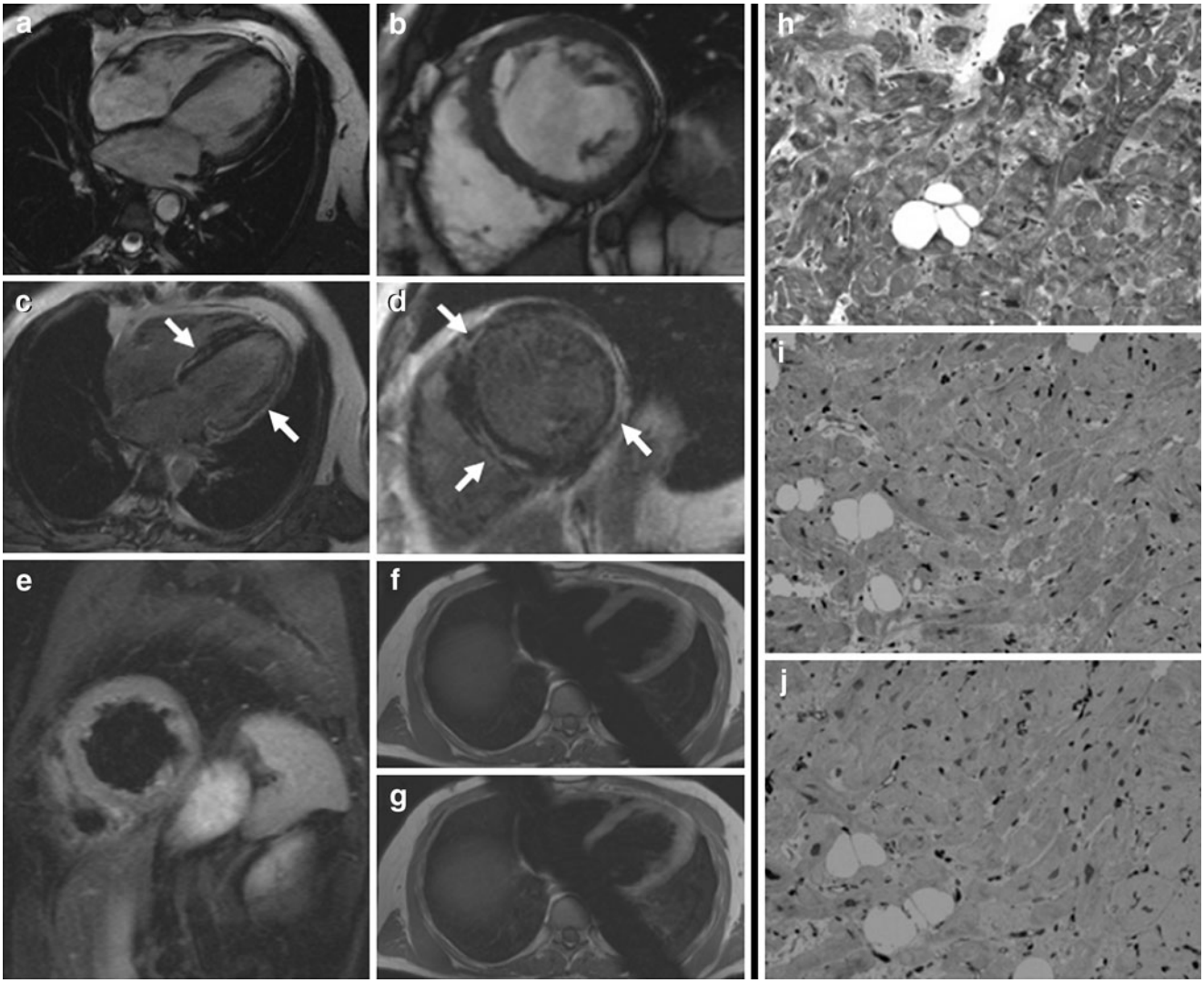

Fig. 4 Patient (B6) without evidence of myocardial inflammation both on cardiovascular magnetic resonance imaging (CMR, **a**–**g**) and endomyocardial biopsy (EMB, **h**–**j**). Steady state free precession (SSFP) images were acquired in the long (**a**) and short axis (**b**). Inversion-recovery gradient-echo imaging in the corresponding axes (**c**, **d**) detected mid-wall and subepicardial late gadolinium enhancement (LGE, indicated by arrows). T2-weighted triple inversion-recovery spin-echo imaging in the short axis (**e**) showed no global myocardial oedema (value=1.66). Global RE, which was assessed on pre- and post-contrast axial T1-weighted spin-echo imaging (**f**, **g**), was also negative (value=2.77). EMB revealed typical histopathological and immunohistochemical findings in uninflamed dilated cardiomyopathy. Masson's trichrome staining (**h**) showed chronic myocardial lesions characterised by interstitial fibrosis and concomitant presence of hypertrophic and degenerated myocytes. Immunohistological staining for T-lymphocytes (**i**) and HLA class II (**j**) was negative

identified as predictor of ventricular tachycardia and sudden cardiac death in patients with DCM [30, 31].

Poor diagnostic performance of LGE in DCM and chronic myocarditis reinforces the need for additional diagnostic targets to detect an inflammatory process in the myocardium. Regional vasodilatation and increased capillary permeability is an important hallmark of tissue inflammation. The increased blood volume and the capillary leak in inflamed myocardium is believed to cause an increase in RE during the early phase of contrast agent administration on T1-weighted spin-echo images [36]. In patients with acute and chronic myocarditis, global RE yields moderate diagnostic accuracy of approximately 70% [12, 18]. Our study, however, reports substantially lower diagnostic accuracy (58.3%) for global RE to detect myocardial inflammation in DCM. Tissue oedema is another integral feature of both inflammatory and ischaemic myocardial injury. T2-weighted imaging that assesses myocardial oedema has improved significantly during the last few years [37]. In particular, the introduction of triple inversion-recovery spin-echo sequences with inversion pulses for blood and fat suppression have increased robustness and image quality. Assessment of myocardial inflammation using T2-weighted imaging was introduced by Gagliardi et al. in 1991 [38]. In their initial study, SI of the myocardium was compared with

that of skeletal muscle to identify myocardial inflammation in patients with suspected acute myocarditis. The results of Gagliardi et al. demonstrated for the first time that increased myocardial/skeletal muscle SI ratio on T2-weighted images identifies patients with acute myocarditis [38]. Two recently published studies also confirm the value of T2-weighted imaging for assessment of myocardial inflammation [12, 18]. In patients with suspected acute myocarditis, T2-weighted imaging identified myocarditis with a diagnostic accuracy of 79% [12]. In patients with chronic myocarditis, T2-weighted imaging yielded somewhat lower diagnostic accuracy (67%) for detection of myocardial inflammation [18]. Our study indicates that T2-weighted imaging might be a powerful diagnostic tool for assessment of myocardial inflammation in patients with DCM, as detection of global myocardial oedema on T2-weighted triple inversion-recovery spin-echo images yielded high sensitivity, specificity, and diagnostic accuracy. The high diagnostic accuracy of global myocardial oedema in our study is in apparent contradiction to the study of De Cobelli et al., which reported evidence of myocardial oedema only in 5 of 23 with chronic myocarditis [32]. However, De Cobelli et al. assessed myocardial oedema only visually whereas myocardial oedema was assessed in our study based on signal intensity measurement in the entire myocardium.

Currently, it is recommended to use comprehensive CMR protocols including all the above-mentioned sequences to exploit the full potential of CMR. According to the International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis, a comprehensive CMR protocol should assess myocardial oedema, myocardial hyperaemia (e.g. RE), as well as myocardial necrosis and fibrosis (e.g. LGE) [11]. Moreover, the International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis published diagnostic criteria ("Lake Louise Criteria") for diagnosis of myocardial inflammation [11]. According to the "Lake Louise Criteria", myocardial inflammation can be diagnosed if two or more of the three tissue-based criteria are positive. Based on published clinical controlled studies, a diagnostic accuracy of 78% was predicted. Of note, the "Lake Louise Criteria" were developed for diagnosis of myocardial inflammation in patients with suspected myocarditis. Nevertheless, the comprehensive CMR approach might be used in other cardiac pathological conditions to provide insights into underlying pathophysiological mechanisms [39]. Our study, however, indicates that the "Lake Louise Criteria" provide only moderate diagnostic accuracy (73.9%) in patients with chronic DCM. Moreover, our data suggest that one could shorten CMR examinations in DCM patients by focusing exclusively on T2-weighted imaging for assessment of myocardial inflammation. LGE may provide additional prognostic information for identification of patients at risk of sudden cardiac death [30, 31]. Shorter CMR imaging times are particularly important in patients who may not tolerate prolonged MR examinations because of possible heart failure.

Several limitations of the present study deserve mention. Major limitations of the study are the retrospective design and the limited number of patients. The small sample size allowed only for descriptive comparison of the diagnostic values of global myocardial oedema, global RE, LGE, and the "Lake Louise Criteria". In the present study, we evaluated a comprehensive CMR protocol which was initially designed to detect myocardial inflammation in patients with myocarditis. We assessed only global myocardial edema and global RE, whereas focal hyperintensities on T2-weighted triple-inversion-recovery spin-echo images and T1-weighted spin-echo images were not considered for the diagnosis of myocardial inflammation. We focused on assessment of global myocardial edema and global RE as our CMR protocol was not optimized for detection of small areas of myocardial oedema and circumscribed pathologic RE due to acquisition of only three T2-wheighted images in short-axis and three T1-wheighted images in transverse position. Another limitation of the study is the fact that we adopted cut-off values for global myocardial oedema and global RE that were previously established in patients with myocarditis [13]. Prospective studies in larger numbers of DCM patients are needed to establish optimal cut-off values for CMR assessment of myocardial inflammation in this patient group, to evaluate the prognostic significance of myocardial inflammation, and to assess the response of myocardial inflammation to contemporary heart failure therapy.

Conclusion

A comprehensive CMR protocol including assessment of myocardial oedema is a promising diagnostic tool for detection of myocardial inflammation. In adult DCM patients, assessment of myocardial oedema yielded superior diagnostic performance compared to "Lake Louise Criteria". Prospective studies in a large number of DCM patients are warranted to confirm this initial finding.

Acknowledgements The study was supported by DFG SFB TR19 B3 to Antje Voigt. A. V. and T. E. contributed equally to this study.

References

1. Jefferies JL, Towbin JA (2010) Dilated cardiomyopathy. Lancet 375:752–762
2. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kühl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A (2008) Classification of the cardiomyopathies: a position statement from

the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 29:270–276
3. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB (2006) Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 113:1807–1816
4. Kawai C (1999) From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future. Circulation 99:1091–1100
5. Kuhl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D, Poller W, Kandolf R, Schultheiss HP (2005) High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. Circulation 111:887–893
6. Kuhl U, Pauschinger M, Seeberg B, Lassner D, Noutsias M, Poller W, Schultheiss HP (2005) Viral persistence in the myocardium is associated with progressive cardiac dysfunction. Circulation 112:1965–1970
7. Frustaci A, Chimenti C, Calabrese F, Pieroni M, Thiene G, Maseri A (2003) Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. Circulation 107:857–863
8. Frustaci A, Russo MA, Chimenti C (2009) Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. Eur Heart J 30:1995–2002
9. Staudt A, Hummel A, Ruppert J, Dorr M, Trimpert C, Birkenmeier K, Krieg T, Staudt Y, Felix SB (2006) Immunoadsorption in dilated cardiomyopathy: 6-month results from a randomized study. Am Heart J 152(712):e711–716
10. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R (2007) The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 50:1914–1931
11. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, Aletras A, Laissy JP, Paterson I, Filipchuk NG, Kumar A, Pauschinger M, Liu P (2009) Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol 53:1475–1487
12. Abdel-Aty H, Boye P, Zagrosek A, Wassmuth R, Kumar A, Messroghli D, Bock P, Dietz R, Friedrich MG, Schulz-Menger J (2005) Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. J Am Coll Cardiol 45:1815–1822
13. Zagrosek A, Abdel-Aty H, Boye P, Wassmuth R, Messroghli D, Utz W, Rudolph A, Bohl S, Dietz R, Schulz-Menger J (2009) Cardiac magnetic resonance monitors reversible and irreversible myocardial injury in myocarditis. JACC Cardiovasc Imaging 2:131–138
14. Bohl S, Wassmuth R, Abdel-Aty H, Rudolph A, Messroghli D, Dietz R, Schulz-Menger J (2008) Delayed enhancement cardiac magnetic resonance imaging reveals typical patterns of myocardial injury in patients with various forms of non-ischemic heart disease. Int J Cardiovasc Imaging 24:597–607
15. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, Olsen EG, Schoen FJ (1987) Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol 1:3–14
16. Kindermann I, Kindermann M, Kandolf R, Klingel K, Bultmann B, Muller T, Lindinger A, Bohm M (2008) Predictors of outcome in patients with suspected myocarditis. Circulation 118:639–648
17. Abdel-Aty H, Zagrosek A, Schulz-Menger J, Taylor AJ, Messroghli D, Kumar A, Gross M, Dietz R, Friedrich MG (2004) Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. Circulation 109:2411–2416
18. Gutberlet M, Spors B, Thoma T, Bertram H, Denecke T, Felix R, Noutsias M, Schultheiss HP, Kuhl U (2008) Suspected chronic myocarditis at cardiac MR: diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. Radiology 246:401–409
19. Elgeti T, Abdel-Aty H, Wagner M, Busjahn A, Schulz-Menger J, Kivelitz D, Dietz R, Hamm B (2007) Assessment of late gadolinium enhancement in nonischemic cardiomyopathy: comparison of a fast Phase-Sensitive Inversion Recovery Sequence (PSIR) and a conventional segmented 2D gradient echo recall (GRE) sequence—preliminary finding. Invest Radiol 42:671–675
20. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S (2009) The role of cardiovascular magnetic resonance imaging in heart failure. J Am Coll Cardiol 54:1407–1424
21. Cummings KW, Bhalla S, Javidan-Nejad C, Bierhals AJ, Gutierrez FR, Woodard PK (2009) A pattern-based approach to assessment of delayed enhancement in nonischemic cardiomyopathy at MR imaging. Radiographics 29:89–103
22. Gahide G, Bertrand D, Roubille F, Tron C, Skaik S, Piot C, Leclerq F, Cribier A, Vernhet H, Dacher JN (2010) MR delayed enhancement imaging findings in suspected acute myocarditis. Eur Radiol 20:65–72
23. Korkusuz H, Esters P, Naguib N, Nour Eldin NE, Lindemayr S, Huebner F, Koujan A, Bug R, Ackermann H, Vogl TJ (2009) Acute myocarditis in a rat model: late gadolinium enhancement with histopathological correlation. Eur Radiol 19:2672–2678
24. Mouquet F, Lions C, de Groote P, Bouabdallaoui N, Willoteaux S, Dagorn J, Deruelle P, Lamblin N, Bauters C, Beregi JP (2008) Characterisation of peripartum cardiomyopathy by cardiac magnetic resonance imaging. Eur Radiol 18:2765–2769
25. Rodriguez E, Soler R (2008) New MR insights of cardiomyopathy. Eur J Radiol 67:392–400
26. Sparrow P, Merchant N, Provost Y, Doyle D, Nguyen E, Paul N (2009) Cardiac MRI and CT features of inheritable and congenital conditions associated with sudden cardiac death. Eur Radiol 19:259–270
27. Yelgec NS, Dymarkowski S, Ganame J, Bogaert J (2007) Value of MRI in patients with a clinical suspicion of acute myocarditis. Eur Radiol 17:2211–2217
28. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ (2005) Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J 26:1461–1474
29. McCrohon JA, Moon JC, Prasad SK, McKenna WJ, Lorenz CH, Coats AJ, Pennell DJ (2003) Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. Circulation 108:54–59
30. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, Sheppard MN, Poole-Wilson PA, Pennell DJ (2006) Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. J Am Coll Cardiol 48:1977–1985
31. Wu KC, Weiss RG, Thiemann DR, Kitagawa K, Schmidt A, Dalal D, Lai S, Bluemke DA, Gerstenblith G, Marban E, Tomaselli GF, Lima JA (2008) Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. J Am Coll Cardiol 51:2414–2421

32. De Cobelli F, Pieroni M, Esposito A, Chimenti C, Belloni E, Mellone R, Canu T, Perseghin G, Gaudio C, Maseri A, Frustaci A, Del Maschio A (2006) Delayed gadolinium-enhanced cardiac magnetic resonance in patients with chronic myocarditis presenting with heart failure or recurrent arrhythmias. J Am Coll Cardiol 47:1649–1654
33. Iles L, Pfluger H, Phrommintikul A, Cherayath J, Aksit P, Gupta SN, Kaye DM, Taylor AJ (2008) Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol 52:1574–1580
34. Messroghli DR, Greiser A, Frohlich M, Dietz R, Schulz-Menger J (2007) Optimization and validation of a fully-integrated pulse sequence for modified look-locker inversion-recovery (MOLLI) T1 mapping of the heart. J Magn Reson Imaging 26:1081–1086
35. Mahrholdt H, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, Fritz P, Klingel K, Kandolf R, Sechtem U (2004) Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation 109:1250–1258
36. Friedrich MG, Strohm O, Schulz-Menger J, Marciniak H, Luft FC, Dietz R (1998) Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. Circulation 97:1802–1809
37. Abdel-Aty H, Simonetti O, Friedrich MG (2007) T2-weighted cardiovascular magnetic resonance imaging. J Magn Reson Imaging 26:452–459
38. Gagliardi MG, Bevilacqua M, Di Renzi P, Picardo S, Passariello R, Marcelletti C (1991) Usefulness of magnetic resonance imaging for diagnosis of acute myocarditis in infants and children, and comparison with endomyocardial biopsy. Am J Cardiol 68:1089–1091
39. Eitel I, Lucke C, Grothoff M, Sareban M, Schuler G, Thiele H, Gutberlet M (2009) Inflammation in takotsubo cardiomyopathy: insights from cardiovascular magnetic resonance imaging. Eur Radiol 20:422–431