Cardiomyopathies

Cardiac Magnetic Resonance Reveals Signs of Subclinical Myocardial Inflammation in Asymptomatic HIV-Infected Patients

Julian A. Luetkens, MD*; Jonas Doerner, MD*; Carollynne Schwarze-Zander, MD; Jan-Christian Wasmuth, MD; Christoph Boesecke, MD; Alois M. Sprinkart, MSc; Frederic C. Schmeel, MD; Rami Homsi, MD; Juergen Gieseke, MSc; Hans H. Schild, MD; Jürgen K. Rockstroh, MD; Claas P. Naehle, MD

Background—People living with chronic HIV infection are at an increased risk for cardiovascular disease. With this study, we aimed to determine the extent of cardiovascular involvement in asymptomatic HIV-infected patients by a comprehensive cardiac magnetic resonance (CMR) approach.

Methods and Results—Asymptomatic patients with chronic HIV infection undergoing combination antiretroviral therapy (n=28) and control subjects (n=22) underwent CMR. HIV-infected patients were successfully controlled for the disease with a consistent plasma viremia of <200 copies/mL (mean CD4+-cell count, 475.1±307.9 cells/μL). CMR protocol allowed for the determination of cardiac function, myocardial inflammation, myocardial fibrosis, aortic stiffness, and pericardial fat volume. When compared with healthy controls, HIV-infected patients showed alterations in left ventricular function as demonstrated by a lower ejection fraction (60.9±7.1% versus 65.2±5.5%; P=0.023) and lower global peak systolic longitudinal and circumferential strain values (longitudinal strain, −17.7±3.4% versus −20.2±3.2%, circumferential strain, −21.2±4.6% versus −24.7±5.1%; P<0.001, respectively). CMR parameters indicating myocardial inflammation were elevated in HIV-infected patients (native T1 relaxation times, 1128.3±53.4 ms versus 1086.5±54.5 ms; P=0.009; relative T2 signal intensity ratio, 1.6±0.3 versus 1.4±0.3; P=0.046; early gadolinium enhancement ratio, 3.1±1.2 versus 2.1±0.6; P=0.003). Myocardial fibrosis, predominantly at the subepicardium of the midventricular and basal inferolateral wall, was prevalent in 82.1% of HIV-infected patients, but only in 27.3% of healthy controls (P<0.001).

Conclusions—Comprehensive CMR revealed a high burden of cardiovascular disease in asymptomatic HIV-infected patients.

Subclinical myocardial inflammation as detected by CMR may be a potential precursor of the increased cardiovascular morbidity and mortality observed in patients with chronic HIV infection. (Circ Cardiovasc Imaging. 2016;9:e004091. DOI: 10.1161/CIRCIMAGING.115.004091.)

Key Words: cardiovascular diseases ■ HIV infections ■ inflammation ■ magnetic resonance imaging ■ myocarditis

With a global prevalence of ≈35.3 million people, HIV infection represents a major public health concern. The introduction of antiretroviral therapy (ART) has distinctly reduced AIDS-related morbidity and mortality. However, because of the high prevalence of cardiovascular risk factors in HIV-infected patients and concurrent metabolic changes induced by ART, HIV-infected patients are at increased risk for cardiovascular disease. In addition, chronic inflammatory processes can accelerate the development of atherosclerosis, eventually aggravating the incidence of cardiovascular disease in HIV-infected patients. Besides the association of HIV and atherosclerosis, a high prevalence of myocardial disease, especially dilated cardiomyopathy and myocarditis, has been reported frequently in the pre-ART era. In HIV-infected patients with unrestricted access to ART, however, myocardial abnormalities were addressed by only few studies. Recently, cardiac steatosis and a high prevalence of myocardial fibrosis could be demonstrated in asymptomatic HIV-infected patients by the use of cardiac magnetic resonance (CMR). However, the pathogenic causality (inflammatory processes versus ART-induced effects) has not yet been determined and needs further clarification. Also, the type and degree of cardiovascular involvement in HIV-infected patients still remain indistinct.

Received September 3, 2015; accepted December 30, 2015.

From the Department of Radiology (J.A.L., J.D., A.M.S., F.C.S., R.H., J.G., H.H.S., C.P.N.) and Department of Internal Medicine I (C.S.-Z., J.-C.W., C.B., J.K.R.), University of Bonn, Bonn, Germany; Department of Radiology, University Hospital Cologne, Germany (J.D.); and Philips Healthcare, Clinical Science, Hamburg, Germany (J.G.).

*Dr Luetkens and Doerner contributed equally to this work.


Correspondence to Claas P. Naehle, MD, Department of Radiology, University of Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany. E-mail cp@naehle.net

© 2016 American Heart Association, Inc.

Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org

DOI: 10.1161/CIRCIMAGING.115.004091
Comprehensive CMR approaches not only provide anatomic, morphological, and functional cardiac information but also yield information on myocardial tissue composition including the degree of inflammation, edema, and fibrosis, and on concurrent vascular and metabolic changes.

The aim of this prospective study was, therefore, to investigate whether signs of cardiac involvement in HIV-infected patients without known cardiac disease receiving ART therapy can be detected by the use of a comprehensive CMR protocol.

**Methods**

The institutional review committee approved this study, and all subjects gave informed consent before CMR. This prospective study included subjects with HIV infection undergoing ART therapy and noninfected control subjects. HIV-infected patients were treated in accordance with national guidelines. Inclusion criteria were no medical history for cardiovascular disease, no contraindications to CMR, and age >18 years. Subjects who were incidentally found to have gross myocardial pathologies on CMR, eg, previous myocardial infarction, were excluded from analysis. The control group was recruited during routine clinical program. The control group consisted of outpatients referred for nonspecific thoracic pain and in which a detailed diagnostic workup and clinical follow-up was unremarkable and without signs of cardiac disease.

**Cardiac Magnetic Resonance**

All scans were performed on a 3 Tesla CMR system (Ingenia 3T; Philips Healthcare, Best, the Netherlands). CMR scans allowed for assessment of cardiac function, edema, early myocardial enhancement, T1 relaxation times, extracellular volume fraction (ECV), late gadolinium enhancement (LGE), aortic distensibility, and pericardial fat volumes. For functional analysis, ECG-gated steady-state free precession cine images were obtained including short axis (SA), vertical long-axis, and horizontal long-axis stacks. Edema-sensitive black blood T2-weighted short-tau inversion-recovery sequences were performed in SA, vertical long-axis, and transverse orientation. Early gadolinium enhancement was assessed using transverse free-breathing fast spin echo T1-weighted images, which were acquired in 3 identical slices both before and after intravenous injection of a double-dose bolus of 0.2 mmol/kg of body weight of gadobutrol (Gadovist; Bayer Healthcare, Leverkusen, Germany). For myocardial T1 mapping, a 3(3)3(3)5 MOLLI acquisition scheme was used. MOLLI sequences were performed in midventricular SA orientation before and 10 and 20 minutes after contrast administration. LGE imaging was performed in SA, vertical long-axis, and horizontal long-axis orientation using a segmented inversion-recovery gradient-echo sequence. Optimal inversion time was determined by using the Look–Locker technique. For aortic distensibility measurements, steady-state free precession cine images were acquired at the level of the pulmonary artery bifurcation to obtain cross sections through the ascending and the descending aorta. For assessment of pericardial fat volumes, a 3-dimensional (3D) transversal ECG and respiratory navigator gated mDixon sequence were acquired. Trigger delay was set to end diastole and optimized by means of cine CMR data. Detailed sequence parameters are given in the Table 1 in the Data Supplement.

**Image Analysis**

Two readers with 2 (J.A.L.) and 10 (C.P.N.) years of experience in CMR analyzed the data and performed the measurements. Readers were blinded to the clinical information. Cardiac functional analysis was performed offline using dedicated software (IntelliSpace Portal 6; Philips Healthcare).

**T2 Short-Tau Inversion-Recovery Images**

The presence of focal myocardial edema on T2 short-tau inversion-recovery images was visually assessed by consensus agreement between the 2 readers. Quantitative relative T2 signal intensity (SI) ratio was calculated by relating the SI of myocardium to the SI of skeletal muscle in the same slice, as previously described. In short, regions of interest were manually drawn in the left ventricular myocardium and the skeletal muscle of a precontrast image and copied to the corresponding postcontrast images to calculate EGEr.

**Fast Spin Echo T1-Weighted Images**

Early gadolinium enhancement ratio (EGEr) was calculated as previously described. In short, regions of interest were manually revealing cross-sectional areas throughout the cardiac cycle. Blood pressure was measured from the left arm during distensibility measurements using an electronic sphygmomanometer.

**Pericardial Fat Measurement**

In-phase, opposed-phase, water-only, and fat-only images were reconstructed online at the scanner. Pericardial fat volume was extracted from fat-only mDixon images using a dedicated volumetric tool (IntelliSpace Portal 6; Philips Healthcare).

**Myocardial T1 Mapping and ECV**

T1 maps were reconstructed offline using a dedicated plugin for the OsiriX DICOM viewer software (Pixmeo, Geneva, Switzerland). For motion correction, the endocardial and epicardial contours were manually defined via polygon regions of interest and carefully realigned throughout the MOLLI relaxometry data. Then, an exponential fitting with a maximum likelihood estimator was used to calculate the T1 maps. The following fit model was used for the magnitude data: \[ A + B \times \exp(-T1/ T1^*)]\.

A Rician noise distribution was assumed because of the magnitude operation. A Look–Locker correction was performed to calculate T1 based on the fit parameters T1^* A, and B. Myocardial T1 relaxation times were extracted from the relaxation maps by using freely available software (Segment, version 1.9; http://www.segment.heilberg.se). Endocardial and epicardial borders were carefully contoured to exclude epicardial fat, blood pool, and pericardial effusion from analysis. Hematocrit-corrected segmental ECV values were calculated from pre- and postcontrast MOLLI T1 values as previously described.

**Myocardial Strain Assessment**

Strain measurements were obtained with a feature tracking technique as previously described using a dedicated CMR feature tracking software (Image-Arena 4.6; TomTec Imaging Systems, Unterschleissheim, Germany). Horizontal long-axis and vertical long-axis cine data sets were tracked to measure systolic longitudinal strain and strain rate. SA cine data sets were tracked to measure circumferential and longitudinal strain and strain rate. Peak segmental values of circumferential and longitudinal strain and strain rate were averaged resulting in global peak systolic longitudinal and circumferential strain and global peak systolic longitudinal and circumferential strain rate.
of SA LGE images. Enhanced areas were defined as those with SI ≥ 3 SD above the mean SI of normal myocardium. Enhanced volume percentage was calculated from enhanced and nonenhanced myocardial volumes.

Statistical Analysis
Statistical analysis was performed using SPSS (IBM SPSS Statistics 22.0, Armonk, NY). Patient characteristics are given as mean±SD or as absolute frequency. Continuous variables were tested for normal distribution. The independent 2-sample Student t test (for normally distributed variables) or the Mann–Whitney U test (for not normally distributed variables) was used for comparison of continuous variables between 2 different groups. Dichotomous variables were compared using the χ² test (with a cell count > 5) or Fisher exact test (with a cell count ≤ 5). A P<0.05 was considered indicative of a significant difference.

Results

General Characteristics
A total of 50 subjects were included in this study (28 asymptomatic HIV-infected patients and 22 healthy controls). Mean age of HIV-infected patients was 49.0±9.3 years (range, 28–68 years). Mean age of healthy controls was 45.4±15.8 years (range, 20–71 years). Age (P=0.321), sex (P=0.084), and body mass index (P=0.672) did not differ significantly between both groups (Table). About cardiac risk factors, hyperlipidemia was present in 6 of 28 (21.4%) HIV patients and in 3 of 22 (13.6%) control subjects (P=0.713), who were all treated with statins. No differences in other cardiac risk factors (hypertension, 3/28 [10.7%] versus 5/22 [22.7%]; tobacco use, 7/28 [25.0%] versus 6/22 [27.2%]; diabetes mellitus, 0/28 [0.0%] versus 0/22 [0.0%]; family history, 3/28 [10.7%] versus 3/22 [13.6%]) were present between the 2 groups (P>0.05). Patients with chronic HIV infection had diagnosed infection for a mean of 9.7±6.9 years. About the Centers for Disease Control and Prevention staging system, severity of HIV disease was categorized as follows: category A2: 5 of 28 (17.9%), category A3: 2 of 28 (7.1%), category B2: 4 of 28 (14.3%), category B3: 7 of 28 (25.0%), and category C3: 10 of 28 (35.7%). Mean CD4+ nadir before initiation of ART was 129.0±126.7 cells/μL. Of 28, 11 (39.3%) patients received protease inhibitor–, 10 (35.7%) received nonnucleoside reverse transcriptase inhibitor–, 2 (7.1%) received integrase inhibitor–, 4 (14.3%) received protease inhibitor/integrase inhibitor–, and 1 (3.6%) received protease inhibitor/nonnucleoside reverse transcriptase inhibitor–based ART regimen. Under therapy, plasma viremia was consistently suppressed to <40 copies/mL in 27 of 28 (96.4%) patients. Of 28, 1 (3.6%) patient had a HIV-RNA count of 80 copies/mL. Mean CD4+ cell count in HIV-infected patients at enrollment was 475.1±307.9 cells/μL.

Measurements of Cardiac Function and Aortic Distensibility
Left ventricular ejection fraction was significantly lower in HIV-infected patients than in healthy controls, but still within normal range (60.9±7.1% versus 65.2±5.5%; P=0.023). Left ventricular endsystolic volume index showed no differences between both groups (65.8±11.9 mL/m² versus 63.5±10.7 mL/m²; P=0.480). Global peak systolic longitudinal and circumferential strain values were reduced in HIV-infected patients when compared with healthy controls (longitudinal strain, −17.7±3.4% versus −20.2±3.2%; circumferential strain, −21.2±4.6% versus −24.7±5.1%; P<0.011, respectively; Figure 1). Aortic distensibility of the descending aorta was significantly reduced in HIV patients (5.6±4.3 versus 10.3±10.0; P=0.036), whereas distensibility of the ascending aorta did not reach the level of statistical significance (4.6±4.1 versus 7.7±8.3; P=0.101). Pericardial fat volume was evenly distributed between both groups (140.9±51.6 138.8±89.3 mL; P=0.923).

Measurements of Myocardial Fibrosis
Myocardial native T1 relaxation times were increased in HIV-infected patients when compared with healthy controls (1128.3±53.4 versus 1086.5±54.5 ms; P=0.009; Figures 1 and 2). T1-derived ECV measures showed no differences between both groups at 10 minutes (27.4±4.1% versus 26.5±3.7%; P=0.43) and 20 minutes (28.1±5.1% versus 26.1±2.8%; P=0.123) after contrast injection. LGE imaging demonstrated that 23 of 28 (82.1%) HIV-infected patients, but only 6 of 22 (27.3%) healthy controls, had evidence of patchy or linear myocardial fibrosis on visual assessment (P<0.001). Visible signs of myocardial fibrosis were present in a total of 37 of 448 (8.3%) myocardial segments in the HIV, but only 12 of 352 (3.4%) segments in the control group. Enhanced areas were mostly visible at the subepicardium of the midventricular and basal inferolateral wall (in 64.3% of HIV-infected patients; Figure 3). This qualitative impression was confirmed in quantitative LGE analysis, where enhanced areas were also more pronounced in HIV-infected patients (7.0±7.1% versus 3.6±2.7%; P=0.043).

Discussion
In this prospective study, we evaluated whether signs of cardiovascular involvement in asymptomatic HIV-infected patients can be detected by a comprehensive CMR approach. The novel key finding of this study is that in HIV-infected patients, CMR markers of myocardial inflammation are elevated indicating subclinical myocardial inflammation. Subclinical myocardial inflammation in HIV-infected patients, who are controlled for the disease, has not been previously reported. Other main findings of the study on HIV-infected patients are that (1) myocardial fibrosis occurs more frequently and at specific locations, and (2) left ventricular myocardial function is altered and reduced when compared with healthy controls.

Myocardial Inflammation and Fibrosis
The widespread availability of ART has resulted in a distinct reduction of AIDS-related complications and deaths. In the pre-ART era, histopathologic signs of myocarditis were found in >50% of necropsy studies in patients, who died from...
The mechanisms of HIV-associated myocardial dysfunction are still unclear, but the pathogenesis is likely multifactorial: first, subclinical coronary atherosclerosis, as well as an increased arterial stiffness, has been frequently reported in HIV-infected patients. In our study cohort, aortic distensibility of the descending aorta, a sensitive marker of aortic elasticity, was also significantly reduced in the HIV group. As CMR can characterize inflammatory myocardial tissue changes, it is nowadays increasingly used in patients with clinically suspected myocarditis. Typical signs of myocardial inflammation are an increase of semiquantitative T2 ratio (representing myocardial edema) and EGEr (representing myocardial hyperemia). A recent developed and generally accepted new parameter is native T1 relaxation time, which showed to have high diagnostic accuracies for the diagnosis of acute myocarditis. In the present study, besides nonscischemic, patchy lesions on LGE imaging, all 3 markers of myocardial inflammation were significantly elevated in HIV-infected patients when compared with the control group. In this regard, the elevated CMR parameters of active myocardial inflammation (T2 ratio, EGEr, and native T1 relaxation times) might be assumed to represent subclinical myocarditis. Remarkably, myocardial inflammation seems to prevail despite effective therapy, as all patients with HIV infection in our study received ART. In this regard, ART side effects should be recognized as a possible confounding factor (see Cardiac Function section of this article).

We found a higher prevalence of myocardial fibrosis in HIV-infected patients than in healthy controls (82.1% versus 27.3%), the differences in percentage of LGE extent, however, was only 3.4% between both groups. This finding is in concordance with a previous study on HIV-infected patients and suggests that although nonscischemic scars can be observed more frequently in patients with HIV infection, the total volume of fibrosis is relatively low. This corollary is supported by a nonsignificant difference of ECV values between both patient groups, which are known to represent an indirect measure of diffuse interstitial myocardial fibrosis. The LGE pattern of myocardial fibrosis observed in our study might, therefore, represent irreversible myocardial injury as a part of a healing response to the aforementioned subclinical myocarditis as previously described also for the noninfected population.

### Cardiac Function

Both infection with HIV and ART may affect the function of the heart. In our study, left ventricular ejection fraction, global peak systolic longitudinal strain, and global peak systolic circumferential strain were lower in HIV-infected patients than in uninfected controls. These findings are consistent with previous echocardiography and CMR studies. The mechanisms of HIV-associated myocardial dysfunction are still unclear, but the pathogenesis is likely multifactorial: first, subclinical coronary atherosclerosis, as well as an increased arterial stiffness, has been frequently reported in HIV-infected patients. In our study cohort, aortic distensibility of the descending aorta, a sensitive marker of aortic elasticity, was also significantly reduced in the HIV group. Therefore, underlying ischemic heart disease and increased arterial stiffness might be a possible mechanism of myocardial dysfunction.
dysfunction. Second, subclinical myocardial inflammation as revealed by CMR further predisposes to left myocardial dysfunction. Studies in the noninfected population could show that especially biopsy-proven myocarditis is associated with a high long-term mortality. Although direct HIV infection of myocytes is rare, it is possible that HIV itself or other cardiotropic viral infection leads to myocarditis, which might be important in the pathogenesis of otherwise unexplained left ventricular dysfunction in symptomatic HIV patients. Up to 50% of HIV-infected patients have resting ECG abnormalities, which may also be indicative of myocardial involvement. Third, as a possible sequel of ART-induced hyperlipidemia, HIV patients are known to have a high prevalence of cardiac steatosis, which, together with myocardial fibrosis, might stimulate cardiac dysfunction. In this regard, it is noteworthy that myocardial T1 relaxation times were elevated in our study although intramyocardial fat is known to decrease T1 values. This further supports the hypothesis that T1 relaxation time prolongation as observed in our study resulted from an ongoing inflammatory process and myocardial fibrosis. Finally, HIV therapy may also play a role in development of impaired cardiovascular function. Animal models indicate that exposure to nucleoside analog reverse-transcriptase inhibitors (zidovudine and stavudine) may have marked adverse effects on myocardial structure, which is mediated by mitochondrial destruction. Moreover, some ART drugs (especially the protease inhibitors indinavir and lopinavir) seem to be associated with an increased risk for cardiovascular disease in humans.

Implications for Clinical Management

The findings of this study, especially the finding of subclinical myocardial inflammation, may have many clinical implications for affected patients. About the clinical management of asymptomatic HIV-infected patients, the following clinical implications may be inferred from our study results: first, for patients with pathological findings at CMR, it should be ensured that the respective HIV therapy does not include drugs with a known potential for increasing cardiovascular risk such as abacavir or boosted lopinavir. Second, the role and clinical benefit of additional anti-inflammatory therapy in HIV-infected individuals should be evaluated. To date, no benefit of adjunct anti-inflammatory medication on top of HIV therapy has yet been proven to significantly improve clinical end points, but this is currently under investigation in numerous clinical trials (additional information is available in [https://clinicaltrials.gov](https://clinicaltrials.gov)). Third, strict control of HIV replication seems warranted.
not only for the treatment HIV-related immunosuppression per se but also to control HIV-associated inflammation. However, the latter must carefully be counterbalanced against the cardiovascular toxicity of certain HIV drug regimens. Fourth, especially in affected patients, a careful evaluation and optimization of individual cardiovascular risk profile should be ensured.

Limitations
Because of the observational and explorative study design, our study has several limitations. The exact causality or pathogenesis for the described findings cannot be determined with absolute certainty. Endomyocardial biopsy as a diagnostic reference standard for myocardial inflammation was not performed, and therefore no immunohistochemical or molecular biological analysis can be provided. Because HIV-infected patients represent a heterogeneous group with comorbidities playing an important role in the development of cardiovascular disease, we included a control group with a comparable frequency of cardiac risk factors. This might also have led to abnormal measurements for some parameters in the control group (eg, LGE and aortic distensibility) because the control group was not completely free of disease. Finally, the statistical evaluation was mainly descriptive, and no additional regression analysis was performed because of the limited sample size. Because the study was conceived as exploratory no correction for multiple testing was performed, possibly leading to inflated type I errors. However, the reported pattern of fibrosis and inflammation in the HIV-infected group was consistent over several different variables underlining the validity of the findings described. Nonetheless, additional studies with larger cohorts are needed to confirm these finding before the study results may be generalized.

Conclusions
In asymptomatic HIV-infected patients, a comprehensive CMR approach revealed a high burden of subclinical cardiovascular disease, including structural and functional myocardial alterations. CMR parameters indicating myocardial inflammation were elevated in HIV-infected patients, which leads to the hypothesis that these findings are consistent with a subclinical myocardial inflammation in HIV-infected patients. Myocardial functional alteration might be a sequel of this higher inflammatory burden. Our findings, therefore, may
help to explain the increased cardiac morbidity and mortality observed in patients with chronic HIV infection.

Acknowledgments
We thank Dr Christian Stehning for the provision of the MOLLI patch and the OsiriX plugin as well as for his support and invaluable advice.

Disclosures
J. Gieseke is an employee of Philips Healthcare (Hamburg, Germany). The other authors report no conflicts.

References
Clinical Perspective

People living with chronic HIV infection are at an increased risk for cardiovascular disease. After the introduction and widespread use of combination antiretroviral therapy, the prevalence of myocardial dysfunction in HIV-positive patients—as shown in echocardiographic studies—was markedly reduced. Furthermore, overall life expectancy for HIV-positive patients was significantly improved. In the present study, we investigated HIV-infected patients, which were controlled for the disease, using state-of-the-art cardiovascular magnetic resonance techniques including myocardial T1 mapping. With this multiparametric cardiovascular magnetic resonance approach, we could demonstrate that HIV-infected patients without cardiac symptoms not only have subtle evidence of impaired myocardial function but also elevated markers of myocardial inflammation (hyperemia and edema) and increased myocardial fibrosis. These findings indicate subclinical myocardial inflammation in HIV-infected patients despite effective antiretroviral therapy and, therefore, may contribute to the persistently increased cardiovascular morbidity and mortality observed in these patients. To detect subclinical myocardial involvement in HIV-infected patients, a comprehensive cardiovascular magnetic resonance evaluation maybe warranted (1) to allow for early optimization of classic cardiovascular risk factors and (2) to evaluate possible new anti-inflammatory treatment options in cases of persistent myocardial inflammation.
Cardiac Magnetic Resonance Reveals Signs of Subclinical Myocardial Inflammation in Asymptomatic HIV-Infected Patients

_Circ Cardiovasc Imaging_. 2016;9:e004091
doi: 10.1161/CIRCIMAGING.115.004091

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/9/3/e004091

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2016/03/07/CIRCIMAGING.115.004091.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Imaging_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Imaging_ is online at:
http://circimaging.ahajournals.org//subscriptions/
Supplemental Material

Supplemental Table. CMR imaging protocol.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SA SSFP cine</th>
<th>SA black-blood T2 STIR</th>
<th>EGE</th>
<th>SA LGE</th>
<th>SA MOLLI</th>
<th>SSFP cine distensibility</th>
<th>3D mDixon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field of view [mm]</td>
<td>320 x 320</td>
<td>320 x 320</td>
<td>320 x 320</td>
<td>360 x 287</td>
<td>330 x 354</td>
<td>300 x 279</td>
<td>350 x 302</td>
</tr>
<tr>
<td>TR [ms]</td>
<td>2.9</td>
<td>1.44</td>
<td>2 RR intervals</td>
<td>1 RR interval</td>
<td>15</td>
<td>4.4</td>
<td>1.3</td>
</tr>
<tr>
<td>TE [ms]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angle of excitation (flip angle) [°]</td>
<td>45</td>
<td>90</td>
<td>90</td>
<td>15</td>
<td>35</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Voxel size [mm]</td>
<td>2 x 2.22 x 8</td>
<td>1.57 x 2.32 x 10</td>
<td>1.4 x 1.75 x 8</td>
<td>1.41 x 2.81 x 12</td>
<td>2 x 2.45 x 10</td>
<td>1.29 x 1.42 x 8</td>
<td>0.78 x 0.78 x 8</td>
</tr>
<tr>
<td>acquired/reconstructed</td>
<td>1.25 x 1.25 x 8</td>
<td>0.95 x 0.95 x 10</td>
<td>0.83 x 0.83 x 8</td>
<td>1.41 x 1.41 x 6</td>
<td>1 x 1.11 x 10</td>
<td>0.78 x 0.78 x 8</td>
<td>0.99 x 0.99 x 1.50</td>
</tr>
<tr>
<td>Parallel Imaging (SENSE)</td>
<td>Yes, SENSE factor 2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes, SENSE factor 2</td>
<td>Yes, SENSE factor 1.1</td>
<td>Yes, SENSE factor 2</td>
</tr>
<tr>
<td>Scan duration [mm:ss]</td>
<td>01:24</td>
<td>01:52</td>
<td>07:37</td>
<td>00:34</td>
<td>00:45</td>
<td>00:12</td>
<td>02:07</td>
</tr>
<tr>
<td>Scan time/breath-hold [s]</td>
<td>00:07</td>
<td>00:14</td>
<td>-</td>
<td>00:17</td>
<td>00:15</td>
<td>00:12</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac phases per RR interval</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Shot duration [ms]</td>
<td>-</td>
<td>116</td>
<td>20</td>
<td>148</td>
<td>200</td>
<td>-</td>
<td>157</td>
</tr>
</tbody>
</table>

SA=short axis, SSFP=Steady-state free precession, MOLLI=Modified Look-Locker-Inversion recovery, STIR=Short-tau inversion recovery, EGE=Early gadolinium enhancement, LGE=Late gadolinium enhancement, TR=Time of repetition, TE=Time to echo, SENSE=Sensitivity encoding.