evaluate the osteoblastic activity within the calcified atherosclerotic lesions.

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Diagnostic Value of Quantitative CMR in Patients Suspected of Having Myocarditis: A Question of Timing

With interest we read the article by Radunski et al. (1) reporting on cardiac magnetic resonance (CMR) using quantitative tissue parameters in patients suspected of having severe myocarditis. However, several aspects of this study differ from previous studies (2,3) and therefore require careful discussion.

First, viral clearance usually is completed within the first days after infection during the natural course of myocarditis, and mean duration of disease activity lasts between 2 and 4 weeks (4). In the present study (1), median interval between onset of symptoms and CMR was 2 weeks, indicating that approximately 25% of the patients underwent CMR after more than 7 weeks (interquartile range: 1 to 7 weeks).

Second, no information is given on what the definition of severe myocarditis was based on, and no comparison group of patients with "less severe" myocarditis is presented. In addition, disease severity is not listed as an inclusion criterion (1), also suggesting that patient inclusion in the study was retrospective and not prospective. Therefore, it remains unclear to what degree the results were influenced by disease severity and by the time interval between disease onset and date of CMR. All factors cause an inhomogeneity of the patient population, which may be responsible for the relatively low diagnostic accuracy for native T1 mapping of 69%, compared with 2 previous studies (2,3). In these studies, native T1 mapping yielded a diagnostic accuracy of 91%, respectively, and showed a superior diagnostic performance compared with single conventional CMR parameters (Lake Louise Criteria) (2,3).

Third, quantitative T2 relaxation times yielded a lower diagnostic accuracy compared with edema-sensitive black-blood T2-weighted ratio (63% vs. 70%) (1). Here, 2 more factors may have hampered the diagnostic performance of T2 mapping: 1) the accuracy of the T2 mapping sequence has not been validated with appropriate phantom studies; and 2) T2 mapping was performed with free breathing, making it more susceptible to motion artifacts compared with breath-hold sequences.

Fourth, diagnostic accuracy is reported to be significantly higher compared with classic Lake Louise Criteria when using extracellular volume (ECV) quantification in combination with late gadolinium enhancement (90% vs. 79%, $p = 0.0053$) (1). Increased ECV has also been reported in patients with several cardiac risk factors, for example, diabetes (5). Interestingly, the diagnostic value of ECV was less favorable in another recent study on patients with acute myocarditis with an area under the curve of only 0.71 (2) compared with 0.86 in this study. Unfortunately, no detailed information is provided on the distribution of comorbidities in the study population (1), because an unequal distribution of comorbidities between patients and controls might have falsely influenced the diagnostic performance to the advantage of ECV.

We believe that in a setting of acute myocardial injury and inflammation, quantitative CMR (using native T1 and T2 mapping) may improve diagnostic performance of CMR as reported previously (2,3). However, carefully defined patient populations with

well-defined disease stages are necessary to obtain reliable results that allow for introduction of these diagnostic techniques into clinical routine.

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REPLY: Diagnostic Value of Quantitative CMR in Patients Suspected of Having Myocarditis: A Question of Timing

We thank Dr. Luetkens and colleagues for their interest in our work (1). We agree that all novel diagnostic techniques require careful evaluation before clinical implementation, but some aspects of Luetkens et al. require clarification.

In particular, we disagree that our inhomogeneous patient population represents a major limitation. Dr. Luetkens and colleagues outlined in their letter an idealized course of myocarditis, which is not reflecting clinical reality. It is essential to appreciate that myocarditis is a complex disease with variable presentations and courses (2,3). Importantly, the subacute phase of myocarditis can last with persisting inflammation for several months (3). Thus, there is no uniform "natural course" of myocarditis as suggested by Luetkens et al. Real-life patients present at various stages and with various intervals between onset of symptoms and presentation for diagnostic evaluation. We therefore think that the heterogeneity of our large, consecutive, and unselected study population is a strength rather than a limitation, because this population is fully representative for patients with clinically defined myocarditis in our tertiary center (1).

Luetkens et al. also questioned the performance of T2 mapping in our study. However, global myocardial T2 values in our patients and control subjects agree well with previously reported T2 values in normal and inflamed myocardium (4). We therefore assume the inclusion of more chronic myocarditis stages as the main explanation for the modest performance of T2 mapping in our study. Indeed, there may be a role for T2 mapping to assess disease activity in myocarditis. However, this aspect was not the focus of our study, but could be an interesting topic for a future, biopsy-controlled study.

Finally, we did not address the potential confounding effect of diabetes mellitus on the performance of extracellular volume. However, the same problem also applies to other quantitative cardiac magnetic resonance parameters, such as native T1 values, which are affected by myocardial fibrosis. The relevance of this aspect should be addressed in future studies including a significant number of patients with myocarditis *and* potential confounders such as diabetes mellitus, to provide meaningful conclusions on this issue.

In summary, we do not see that the issues raised by Dr. Luetkens and colleagues substantially challenge the major findings and implications of our study.

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