using quantitative magnetic resonance imaging. J Cardiovasc Magn Reson 2011;13 Suppl 1:P209.

4. Rowley AH, Orenstein JM. Clinical implications of a new model of Kawasaki disease arteriopathy. Pediatr Cardiol 2013;34:1290–1.

5. Hauser M, Bengel F, Kuehn A, et al. Myocardial blood flow and coronary flow reserve in children with "normal" epicardial coronary arteries after the onset of Kawasaki disease assessed by positron emission tomography. Pediatr Cardiol 2004;25:108–12.

Noninvasive Evaluation of Bone-Forming Activity Within the Calcified Atherosclerotic Lesions by Tc 99m HMDP Scintigraphy

The process of active calcium deposition as demonstrated by radiolabeled fluoride uptake has been

FIGURE 1 Bone-Forming Activity Within the Calcified Atherosclerotic Lesions by ^{99m}Tc-HMDP Scintigraphy

(A) Three- and 2-dimensional images of multislice computed tomography (CT) angiography demonstrated a calcified carotid atherosclerosis **(left: red arrow; right: yellow arrowheads). (B)** An intense uptake of technetium Tc 99m hydroxy-methylene-diphosphonate (^{99m}Tc-HMDP) was observed (^{99m}Tc-HMDP scintigraphy and fused images, **red arrows**) in the calcified carotid atherosclerosis (CT image, **yellow arrow**). **(C)** Immunohistochemical analysis revealed that expression levels of bone-specific alkaline phosphatase (ALP) were increased in the calcified lesion of atherosclerosis. Inset showed magnification of the marked area **(square)**.

recently proposed to be associated with high-risk plaques (1). Similarly, the computed tomography (CT)-verified spotty calcification is associated with the plaques that have resulted in recent acute coronary events (2). However, although coronary artery calcium score has been shown to positively correlate with cardiovascular disease risk, extensive vascular calcification, probably representing a burnt-out disease, may be more prominently associated with stable plaques (3). Because vascular calcification does not occur in a degenerative and passive process of calcium deposition, and may represent an active phenotypic change associated with bone mineralization (4), bone-forming activity within the atherosclerotic plaques rather than calcium volume and/or calcium density scores might be a better marker for predicting future cardiovascular events. Indeed, serum levels of alkaline phosphatase, a marker of osteoblastic activity, have been associated with all-cause or cardiovascular mortality among survivors of myocardial infarction and in a general population (5). Similar to the fluoride imaging of the active process of calcification, we measured the osteoblastic activity within the carotid atherosclerotic plaques by using a technetium Tc 99m hydroxy-methylene-diphosphonate (^{99m}Tc-HMDP) scintigraphy.

A 72-year-old man with a history of hyperuricemia, dyslipidemia, and hypertension had a bruit in his left neck. Although he had no symptoms associated with brain ischemia, carotid artery ultrasonography and CT angiography showed the calcified atherosclerotic lesions of the left internal carotid artery (**Figure 1A**). The peak systolic velocity in the left internal carotid artery was 255.8 cm/s (normal range <200 cm/s) in Doppler carotid artery ultrasonography, and a left post-bulbar internal carotid artery stenosis was 85% in a diagnostic angiography. In co-registration of enhanced CT and bone scintigraphy, an intense accumulation of ^{99m}Tc-HMDP was observed within the calcified carotid atherosclerotic lesions (**Figure 1B**). There was no measurable accumulation of ^{99m}Tc-HMDP in other atherosclerotic lesions without vascular calcification. Based on the NASCET (North American Symptomatic Carotid Endarterectomy Trial) guidelines, he was a very high-risk patient for cerebrovascular disease, and the carotid endarterectomy was performed. Immunohistochemical analysis revealed that bone-specific alkaline phosphatase was abundantly expressed in the excised calcified lesions of atherosclerosis (**Figure 1C**).

Because ^{99m}Tc-HMDP has a strong affinity for hydroxyapatite crystals in the mineral phase of bone, especially sites of new bone formation, the present report suggests that bone scintigraphy with ^{99m}Tc-HMDP might be a feasible and useful method to
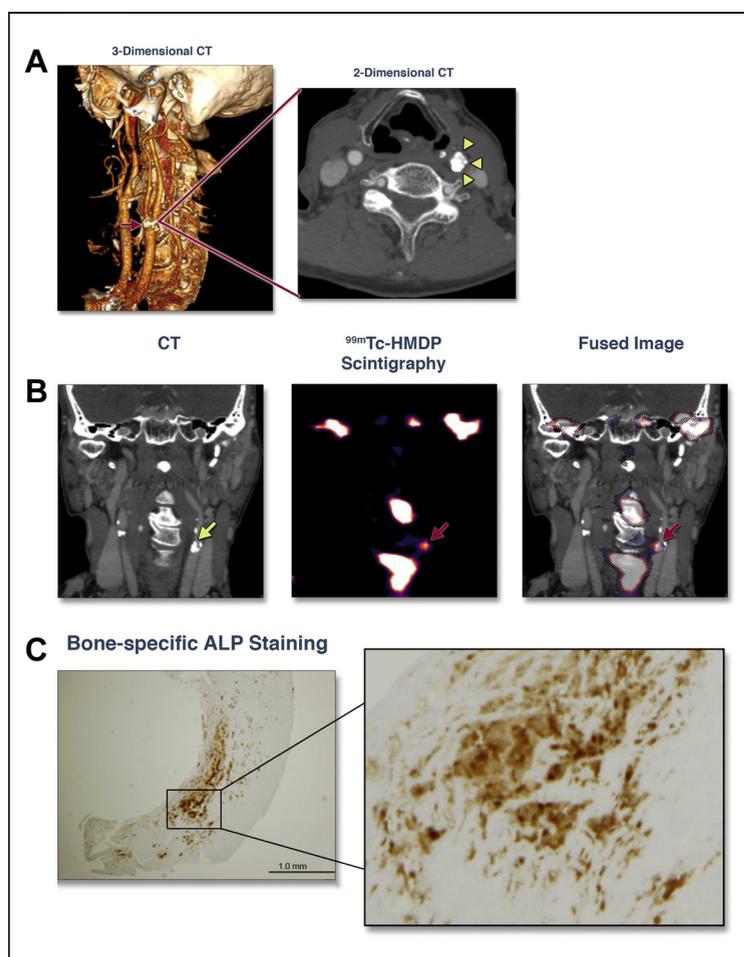
evaluate the osteoblastic activity within the calcified atherosclerotic lesions.

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REFERENCES

1. Joshi NV, Vesey AT, Williams MC, et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. Lancet 2014;383:705–13.

2. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol 2007;50:319–26.

3. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA 2014;311:271–8.

4. Suga T, Iso T, Shimizu T, et al. Activation of receptor for advanced glycation end products induces osteogenic differentiation of vascular smooth muscle cells. J Atheroscler Thromb 2011;18:670–83.

5. Tonelli M, Curhan G, Pfeffer M, et al. Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. Circulation 2009;120:1784–92.

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