resection of the involved layers of the popliteal wall was performed (Fig 2). She had an uneventful recovery, without walking impairment afterwards.

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Reply

We read with interest the letter to the editor regarding our article "High spatial resolution magnetic resonance imaging of cystic adventitial disease of the popliteal artery."[1] As the title implies, we reported the (never before published) use of a novel magnetic resonance (MR) technique, high spatial resolution magnetic resonance imaging (MRI) in three patients with cystic adventitial disease (CAD).

The MR technique used in our cases provides a far higher spatial resolution than MR techniques reported in previous MRI publications on CAD. The voxel size of 0.4 × 0.4 × 0.7 mm achieved in our work allowed us to detect even very small communications between the adventitial cysts and the joint space, such as the one shown in our Fig 1, *E*. By our estimates, the spatial resolution of our technique is 10 to 30 times higher than the one achieved in the Crolla and Chiche reports.[2,3]

The focus of our article was not the description of the MRI features of CAD, something that indeed has been described previously. Rather, we report the use of a novel, high spatial resolution MRI technique that enabled us to detect these communications in all our patients. We are therefore somewhat surprised that the authors "doubt the value" of our study. We do congratulate them however on the successful surgical treatment and ultrasonographic diagnosis of their CAD patient. We believe that high spatial resolution MRI reliably allows the detection of connections between adventitial cysts and adjacent joints in CAD patients and thus has the potential to diminish postsurgical CAD recurrence rates.

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Regarding "Serum carboxymethyllysine concentrations are reduced in diabetic men with abdominal aortic aneurysms: Health In Men Study"

We have read with great interest the article of Norman et al[1] in the *Journal of Vascular Surgery* dealing with serum carboxymethyllysine (CML) concentrations in diabetic men with abdominal aortic aneurysms. CML belongs to the group of advanced glycation end products (AGEs) and has been associated with the development of atherosclerosis. AGE concentrations are increased in diabetes and are related to arterial stiffness. Tissue accumulation of AGEs leads to cross-linking of proteins, for example, within the vessel wall, which may lead to increased arterial stiffness. Norman et al hypothesize that AGEs may be partly responsible for the observed inverse association between abdominal aortic aneurysm and diabetes. Indeed, they observed lower serum CML concentration in diabetic men with AAA than in those without. Several questions remain after reading this article, however.

AGEs form a heterogeneous group in which some show cross-linking properties, whereas others do not.[2] In their study, Norman et al only measured serum concentrations of the non-cross-linking AGE CML. They did not measure concentrations of cross-linking AGEs, such as pentosidine. Assessing concentrations of cross-linking AGEs, such as pentosidine, seems more appropriate to test their hypothesis that protein cross-linking reduces the risk for developing AAAs. Furthermore, the authors cannot exclude the possibility that other AGEs are related to the development of AAAs. Zhang et al[3] recently observed a 2.7-fold higher accumulation of AGEs in human AAA tissue than in normal aortic tissues. The expression of the multiligand receptor for AGEs (RAGE) was also highly elevated in human AAA tissue. Increased RAGE expression was associated with higher levels of matrix metalloproteinases, an important mediator for aneurysmal development.[3]

Tissue AGE concentrations are strongly related to the severity of cardiovascular disease, whereas serum concentrations are often not. High serum AGE levels, for example, were associated with a better survival in hemodialysis patients.[4] High tissue AGE concentrations in these patients, however, were strong predictors of death and cardiac failure.[5,6] Higher serum AGE levels were probably a measure of a better nutritional support, associated with improved survival. Serum AGE levels are strongly influenced by renal function, absorption from food, smoking, and medication use, such as statins. It seems therefore appropriate to prefer assays of tissue AGE accumulation rather than serum samples. In our opinion, even after the elegant study from Norman et al, it remains unclear whether AGEs play a role in causing or preventing aneurysmal disease.

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Reply

The points made in the letter do not contradict our data. Advanced glycation end products (AGEs) are a heterogeneous group. Non-carboxymethyllysine (CML) AGEs may influence the development of abdominal aortic aneurysms (AAAs), and assessing concentrations of cross-linking AGEs like pentosidine will be important. We did not claim that our study provided conclusive evidence—merely that the data suggested that accelerated advanced glycation might explain the inverse association between diabetes and AAA. We had also acknowledged that other markers of the glycation pathway would need to be examined in future studies.

The assessment of any putative biomarker at tissue level is always desirable, and sometimes preferable. However, this is not without problems in AAA, because only tissue samples from end-stage disease (ie, large AAAs) with secondary degenerative changes are available. Furthermore, such samples are becoming scarce due to the increasing role of endoluminal stenting. We are also unsure about whether the findings in the three cited studies in hemodialysis patients are generalizable to the vast majority of patients with normal or mildly impaired renal function.

Despite the acknowledged limitations of our study, CML is used as a general and reproducible measure of glycation, and our data are consistent with evidence that glycation of the extracellular matrix inhibits degradation both by deactivating macrophages and increasing the resistance of the extracellular matrix to degradation.[1]

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Regarding "Statins, heme oxygenase-1, iron, and atherosclerosis"

DePalma et al[1] described interactions of serum ferritin with statin use in a substudy of the iron (Fe) and atherosclerosis study (FeAST). At baseline, 53 participants on statins had slightly lower mean entry-level ferritin values (114.06 ng/mL) vs the 47 off statins (127.62 ng/mL). Longitudinal analysis of follow-up data, after adjusting for the phlebotomy treatment effect, showed that statin use was associated with significantly lower ferritin levels (−29.78 ng/mL; Cohen effect size, −0.47 [tdf, 134 = 2.33, $P = .02$]).

Statins induce heme oxygenase-1 (HO1)[2,3] the rate limiting enzyme involved in heme catabolism. Heme catabolism is a key process in mobilizing macrophage iron derived from ingested erythrocytes. Alterations in the activity of HO1 influence the rate of clearance of hemoglobin-derived iron from macrophages. Pharmacologic inhibition of HO1 is associated with marked elevation in serum ferritin without significant changes in several other acute phase reactants.[4] In normal subjects, serum ferritin rose by approximately fourfold within 2 days of administration of Sn mesoporphyrin, an HO1 inhibitor.[4]

In the HO1 deficient mouse (HO1−/−), conspicuous iron loading is seen in Kupffer cells, hepatocytes, hepatic vascular tissue, and renal cortical tubules.[5] In another study of HO1−/− mice, increased levels of reactive oxygen species production in macrophages and increased atherosclerotic plaque were thought to be a result of relatively decreased intracellular levels of biliverdin or bilirubin, or increased intracellular levels of iron stores.[6]

In diabetic humans, HO1 promoter polymorphisms causing weaker upregulation of the enzyme are associated with both increased cardiovascular disease and significantly increased serum ferritin.[7,8] It has been proposed that statins may stabilize atherosclerotic plaques in part by inducing intralesional HO1, facilitating iron mobilization, and lowering plaque iron levels.[9,10] The findings of DePalma et al[1] are compatible with this proposed mechanism.

Statins have also been reported to lower interleukin-6 (IL-6) concentrations.[11] IL-6 is a potent inducer of hepcidin which favors iron retention in the macrophage. This effect of statins is another potential mechanism for lowering iron levels in plaque macrophages, a process proposed to inhibit atherogenesis.[10]

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