smaller than 1.0 cm; the stage was IA in 5 patients and IIIA in 1 patient. For the entire 16 patients with ground-glass opacities, the stage was IA in 13, IB in 1, and IIIA in 2. Our report, however, only examined those patients who underwent surgical intervention, so it does not represent a complete description of all patients in our CT screening trial with ground-glass opacities. We eagerly await continued reporting from the radiology literature about the entire spectrum of patients found to have ground-glass opacity on a screening CT.

The question regarding computer-aided diagnosis for enlargement of small nodules is provocative. Three-dimensional computer-aided diagnosis is clearly superior to 2-dimensional human measurement. This would be the preferred technique only when it can be smoothly automated for efficient use in day-to-day practice.¹

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Why clopidogrel failed to inhibit platelet function early after coronary artery bypass surgery: To load or not to load, and is it a question of resistance?

To the Editor:

Antiplatelet therapy remains a topic of much-deserved attention and debate. We read with interest the recent article by Lim and associates¹ in which they found that clopidogrel after coronary artery bypass grafting failed to inhibit platelet function, on the basis of the percentage platelet aggregation on day 5. Patients were randomized to receive 100 or 325 mg of aspirin daily or 75 mg of clopidogrel daily for 5 days after coronary artery bypass grafting.

It is not clear whether patients in the clopidogrel arm received a loading dose before the daily maintenance dose. Several similar studies assessing platelet inhibition, albeit in the context of percutaneous coronary intervention, have demonstrated the importance of appropriate loading of 300 to 600 mg if steady-state levels of platelet aggregation are to be achieved within the first 24 hours.²⁻⁴ Daily maintenance dosing with 75 mg of clopidogrel without preloading, as in this study, has been shown to result in steady-state levels of platelet inhibition only after 3 to 7 days.⁵

The second observation with regard to this study is that the investigators did not state whether a baseline pretreatment sample was taken before surgery or before administration of the antiplatelet therapy. Whether this would have added much to the final analysis remains unclear, but evidence, again drawn from studies in the percutaneous coronary intervention setting, have suggested pretreatment platelet reactivity to be an important determinant of posttreatment reactivity.⁶

The final comment is the most elusive, namely, the issue of "clopidogrel resistance." Although it was not directly mentioned by the authors, we can assume that it was alluded to in their discussion. It is likely that a correlation exists between a laboratory measure of clinical clopidogrel nonresponsiveness and the clinical outcome. However, until such time as there is greater understanding of the likely mechanisms of clopidogrel responsiveness and the individual heterogeneity that is apparent, can we totally dismiss the efficacy of clopidogrel in the early postoperative period?

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Reply to the Editor:

In our reply to Raja, we have addressed a similar query with regard to the dosing regimen of clopidogrel. It is vitally important to appreciate that the study in which Hunt and associates quote the time to the onset of the effects of clopidogrel (4 to 7 days) is from a sample of healthy subjects.¹ Nonrandomized studies after coronary artery bypass surgery suggest that it takes 9 to 28 days.² Our results are consistent with the latter.

In our article, you will note that we reported all measurements as the percentage change compared with baseline.³ The baseline sample was taken on the day before surgery.

We respectfully disagree with the final comment of Hunt. A previous observational study and our randomized data are consistent regarding the inefficacy of clopidogrel early after coronary surgery assessed on aggregometry. At present, we are unaware of any evidence to the contrary; therefore, the onus should be to prove that an effect exists before prescribing clopidogrel (as the sole antiplatelet in this time frame), rather than subjecting patients to the possibility of ineffective treatment while awaiting a "greater understanding of the likely mechanisms of clopidogrel responsiveness."

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Aortic dissection and ankylosing spondylitis in hypocystinemia

To the Editor:

The first author and past associates recently described aortic dissection without Marfan syndrome in ankylosing spondylitis,¹ and coexistent ankylosing spondylitis and Marfan syndrome without aortic dissection has been reported in the literature.² Reduced fibrillin deposition into the extracellular matrix is found in not only Marfan syndrome but also in a range of connective tissue disorders collectively termed fibrillinopathies, such as isolated ascending aortic aneurysm and dissection.³ The defective fibrillin of Marfan microfibrils and the inflammation-targeted fibrillin of ankylosing spondylitis might each lead to comparable structural phenotypes of failure.⁴ On the other hand, fibrillin-1 is rich in cysteine, and its deposition into the extracellular matrix is greatly diminished under conditions of cysteine deficiency.⁵ We here add another case, with hypocystinemia, of coexistent aortic dissection and ankylosing spondylitis, and discuss possible roles of cyst(e)ine and fibrillin-1 in these 2 disorders.

A 68-year-old woman with back pain was referred to our department. Computed tomographic scanning disclosed Stanford type A (DeBakey type I) acute aortic dissection (Figure 1, A), but she presented with no traits of Marfan syndrome on physical examination. Urgent replacement of the ascending aorta was successfully performed, and the pathologic examination of the aortic wall revealed neither aortitis nor cystic medial necrosis. Plasma total homocysteine concentration was normal (4.7 nmol/mL [range, 3.0-14 nmol/mL]), and cystine concentration was decreased to

Figure 1. Computed tomographic scanning disclosed Stanford type A (DeBakey type I) acute aortic dissection (A). Abdominal radiography revealed the characteristic deformation of the lumbar vertebrae, so-called bamboo spine (B).

14.5 nmol/mL (range, 29-49 nmol/mL). There was a past history of ankylosing spondylitis without medication, including steroids, and abdominal radiography disclosed the characteristic deformation of the lumbar vertebrae, so-called bamboo spine (Figure 1, B). The patient had negative results for human leukocyte antigen B27 but met the European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy: inflammatory spinal pain, alternate buttock pain, and sacroiliitis.

Reduced fibrillin deposition into the extracellular matrix causes thoracic aortic aneurysm or dissection in patients without Marfan syndrome.³ Most sites of inflammation in patients with ankylosing spondylitis involve

fibrocartilage, and fibrillin-1, a major component of the microfibrils in fibrocartilage, might be the target of this response in the aorta and the eye, as well as in bones and joints.⁴ It has been hypothesized that spondylitic inflammation might include release and activation of latent transforming growth factor β from binding sites on fibrillin-1. The hypothesis is supported by some reported cases, including the present one, of coexistent ankylosing spondylitis and Marfan syndrome without aortic dissection² or coexistent aortic dissection without Marfan syndrome and ankylosing spondylitis.¹ On the other hand, it has been demonstrated that fibrillin-1 deposition into the extracellular matrix was greatly diminished, as revealed by means of immunocytochemistry, when arterial smooth muscle cells were cultured under conditions of cysteine deficiency.⁵ When cysteine concentrations were returned to normal, the smooth muscle cells began to accumulate a matrix rich in fibrillin-1. These results indicate that a deficiency of cysteine impairs the accumulation of fibrillin-1 in the extracellular matrix and could contribute to the pathologic changes of connective tissue. Although the cause of hypocystinemia in the present case is unclear, a possible role of fibrillin-1 affected by decreased cyst(e)ine is suggested in coexistent aortic dissection and ankylosing spondylitis.

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