and the uptake of Ca\textsuperscript{2+} by the sarcoplasmic reticulum (SR) with the onset of relaxation. For example, it has been shown in isolated canine LV wedge preparations near the LAD (same species and same site as in the in vivo studies of Ashikaga et al.) that whereas the onset of the epicardial and endocardial Ca\textsuperscript{2+} transients are almost synchronous, the epicardial decline of the Ca\textsuperscript{2+} transient (onset of relaxation) precedes the endocardial decline (3). Furthermore, the rate of Ca\textsuperscript{2+} uptake by the SR is faster in the epicardium compared with endocardium (3). These effects mimic the in vivo canine observations made by Ashikaga et al. (1). Because the dynamics of Ca\textsuperscript{2+} mirror that of contractility, changes in Ca\textsuperscript{2+} are considered to be surrogate of myocardial contractility (4). Consequently, we think that the combined tissue tethering and transmural cellular differences in Ca\textsuperscript{2+} handling need to be considered simultaneously as possible mechanisms for the in vivo observation of depth-dependent differences in myocardial mechanics in the canine mid–anterior LV.

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Reply

Our recent article (1) reported a new observation that there is discrepancy between cardiac electrical and mechanical behaviors by detecting relatively large mechanical dispersion with little electrical dispersion during both activation and relaxation in the canine mid–anterior left ventricle (LV). In his letter, Dr. Karagueuzian logically and correctly points out the potential contribution of transmural difference in intracellular calcium handling (2) to the transmural mechanical gradients that we had described in the article. Given a slower decay of intracellular calcium to diastolic levels at the endocardium, due in part to significantly lower levels of sarcoplasmic reticulum Ca\textsuperscript{2+} ATPase (SERCA2a) expression in endocardial cells than epicardial cells, the transmural differences in calcium handling likely contribute to the transmural dispersion of myofiber relaxation and should be added to the list of potential contributing factors, such as transmural dispersion of electrical repolarization, even if it is small at physiological heart rates, and tissue tethering. However, this does not seem to be the case with the transmural dispersion of myofiber shortening. Transmural differences in intracellular calcium during activation, where endocardial cells have a slower time to peak than epicardial cells, result in an earlier onset of myofiber shortening in the epicardium than in the endocardium by approximately 20 ms (3). This delay is close to the transmural conduction delay in the canine LV (1,4), thus allowing the impulse to traverse the LV wall to synchronize contraction across the ventricular myocardium; that is, the transmural differences in calcium handling do not contribute to but rather “negate” the transmural dispersion of myofiber shortening due to the delay in action potential propagation across the wall. Therefore, the transmural dispersion of myofiber shortening should be accounted for by other factors, including tethering.

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Immediate Coronary Imaging for Acute Chest Pain: Are We There Yet?

We read with great interest the elegant study by Goldstein et al. (1) suggesting the value of multislice coronary computed tomography (MSCT) in the evaluation of acute chest pain patients. The investigators should be commended for this landmark trial that constitutes one of the few studies assessing the value of an imaging diagnostic technique using a randomized design. As compared with patients managed in the emergency department with standard of care measures, those assigned to the MSCT arm not only had reduced diagnostic times and costs but also required less frequently repeated evaluations for recurrent chest pain (1). Considering the potential clinical implications of this provocative study, addressing some methodological issues would be appreciated.

First, in a randomized study defining the sample size calculation is critical. This is especially relevant considering the very-low-risk patient population included in the present study (none of the patients suffered an event after discharge). Likewise, the primary outcome measure of the study was not clearly stated. Therefore, the value and implications of the different study findings remain
difficult to establish. Second, the main study findings basically relate to the reduced diagnostic time found in the MSCT arm (3.4 vs. 15 h). However, precise data concerning the time required to access/perform/interpret MSCT versus the nuclear test studies were not provided. This information is of particular interest because improved logistics in the nuclear stress arm could have modified the results. It remains possible that a “fast tracked” access to the MSCT (driven by the investigators’ scientific interest) was not correlated with a similar enthusiasm in the nuclear arm. This is important considering that 95% of patients allocated to the nuclear arm were sent home after a negative scan, whereas 24% of patients randomized to MSCT eventually required a nuclear study before discharge as the result of either nondiagnostic results or intermediate lesions on MSCT. In fact, fewer patients in the MSCT arm could be discharged directly from the emergency department. Finally, it is likely that the use of alternative standard of care measures would have affected the results. In Europe, many patients evaluated in chest pain units are scheduled for an early conventional exercise test (2–4). This technique seems especially attractive for very-low-risk patients (such as those in the current study), avoids radiation exposure, is widely available and easily performed from a logistic perspective, and above all, is much cheaper.

We fully agree with the suggestion of Goldstein et al. (1) regarding the need of further studies to clarify how the impressive diagnostic capability of MSCT can be best implemented in clinical practice.

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To calculate the sample size of our single-center randomized trial, the primary outcome variable used was the time to diagnosis. As part of a previous study undertaken in 70 patients, we performed coronary computed tomographic angiography (CCTA) on 27 of these patients seen in the emergency department with chest pain (1). Based on information from that initial experience, we estimated that time from admission to the emergency department to definitive diagnosis would be: 5 h for patients with normal CCTA, 9 h for patients with severe stenosis who would undergo early catheterization after CCTA, and 20 h for patients who are evaluated by the standard diagnostic protocol. To detect a 25% reduction in emergency department length of stay (until definitive diagnosis), approximately 102 patients would be required to achieve a power of 80% and an alpha of 0.05. We increased the sample size to 200 to ensure adequate statistical strength.

Although time to diagnosis was the determinant of sample size, clinically a diagnostic test for triage of acute chest pain would be unacceptable for use if there were a significant occurrence of major adverse cardiac events (MACE) in those who were discharged as normal. Although this safety variable is of overriding importance, it could not be used to determine sample size because the low incidence of MACE in this low-risk patient group would require a much larger sample. Our view was that even a 3% occurrence of unanticipated MACE in this preliminary study would cast doubt on the use of CCTA for acute chest pain. As reported, there were no MACEs in either group (2). A larger multicenter trial is required to investigate the issue of safety in a statistically valid way, and such a trial is currently underway.

As pointed out in the Discussion section under Limitations, we agree that alternatives to our “standard” diagnostic evaluation exist, including electrocardiographic stress or stress echocardiography, which do not involve radiation exposure and may provide faster diagnostic time. Also, the article discusses at some length issues related to the need for a second diagnostic test in 24% of patients. Regarding whether CCTA patients were “fast tracked” through the system, there was a uniform notification method for nuclear medicine and CCTA interpreting physicians; both studies were performed and read emergently.

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