REPLY: ^{18}F-FDG Imaging in Patients With "Suspected," But Not "Proven," Sarcoidosis

We thank Drs. Njeim, Bogun, and Crawford for their interest in our study (1). We agree that in the absence of histological confirmation of sarcoidosis, it is possible that there may be other chronic inflammatory processes that could have a similar presentation, hence, our designation in the title "suspected cardiac sarcoidosis." Patients with this constellation of findings who lack a histological diagnosis are as common as those with a histological diagnosis and raise difficult management issues. We would note the following: 1) the vast majority of events in patients with abnormal positron emission tomography (PET) studies occurred in patients with known or a high likelihood of cardiac sarcoidosis (see the Online Appendix in our original paper [1]); 2) none of the patients in our study had known acute myocarditis (e.g., elevated cardiac enzymes), and although scar from prior episodes of myocarditis may cause arrhythmias, this would not result in increased FDG uptake; and 3) none of the patients with increased FDG had other potential alternative reasons for such findings such as coronary artery disease or any known systemic inflammatory or rheumatologic disease. Even in the absence of a histological diagnosis (which cannot always be obtained in cardiac sarcoidosis), abnormal PET findings were associated with a substantial increase in the rate of death/ventricular tachycardia.

The high event rate observed in our study is in part due to referral bias, because our center is a quaternary care center for advanced heart failure and arrhythmias. As expected, our study therefore included patients with a prior history of arrhythmias. It is also noteworthy that the high event rate observed in our study is in keeping with data from Schuller et al. (2), who reported that appropriate implantable cardioverter-defibrillator (ICD) therapies occurred in 36 (32%) of 112 patients with cardiac sarcoidosis over a mean of 29 months, and from Betensky et al. (3), who reported ICD therapies in 17 (38%) of 45 patients with cardiac sarcoidosis followed over a median of 2 years. In regard to events in patients with normal PET, we would point out that we used PET only to evaluate for inflammation or scar, and that it does not exclude nonischemic cardiomyopathy. In fact, all of the 6 patients with a normal PET scan who experienced events had systolic dysfunction. Therefore, if we were to define a "normal PET" as also having a normal left and right ventricular function, there would be zero events in this category.

In regard to the low prevalence of extracardiac sarcoidosis, it is important to note that we reported the frequency of extracardiac FDG uptake (which represents active inflammation) as distinguished from other radiological evidence of disease that may represent scar from inactive disease. However, even when accounting for the fact that patients without extracardiac FDG uptake may have had prior extracardiac sarcoidosis, we do believe that the presence of isolated cardiac sarcoidosis is underrecognized. In part, this is because prior clinical criteria, as well as most prior imaging studies, have only included patients with confirmed extracardiac disease. We believe that future criteria should address the fact that cardiac sarcoidosis can be present (and therefore should be diagnosed) even in patients without extracardiac disease. We also agree that a prospective study is needed to define the role of PET in selection of therapy for this challenging group of patients.

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High Sensitivity Cardiac Troponin T

Testing Time Is Also a Learning Time

High-sensitivity cardiac troponin T (hs-cTnT) is excellent for the early diagnosis of myocardial infarction (1). In a recent issue of the *Journal*, Bandstein et al. (2) validated again the outstanding

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value of hs-cTnT to rule out myocardial infarction in chest pain patients in the emergency department. After investigating 14,636 patients who sought medical attention for chest pain, the investigators concluded that patients with chest pain who have an initial hs-cTnT level of <5 ng/l and no signs of ischemia on an electrocardiogram (ECG) can be safely discharged directly from the emergency department. This work is very meaningful for relieving medical burden.

However, the original study did not mention a very common issue—the duration of the onset of chest pain. Although the time of the first detectable low-level elevation of hs-cTnT has become shorter compared with conventional troponin T, it still needs 90 to 180 min after the event (3). This means that within about 1.5 to 3 h after the onset of chest pain, the hs-cTnT level may be undetectable even if the patient is having a myocardial infarction. Correspondingly, in the original study, 15 patients with undetectable hs-cTnT and no signs of ischemia on the ECG had a final diagnosis of myocardial infarction, of which 13 patients had hs-cTnT <5 ng/l within 3 h after the onset of chest pain, and 11 of the 13 patients were found to have hs-cTnT elevation after 3 h (2). Therefore, we presumed that the negative predictive value for myocardial infarction with undetectable hs-cTnT within 3 h after the onset of chest pain was much lower than what the original study reported. Given a lot of patients with chest pain are going to the emergency department within 3 h (4), the low negative predictive value of hs-cTnT might render a number of missed diagnoses. As a consequence, we considered that the conclusion of the original study was too arbitrary, which might inadvertently mislead clinicians into making mistakes.

Besides, a diurnal hs-cTnT rhythm was detected by Klinkenberg et al. (5). The diurnal variation of hs-cTnT was characterized by peak concentrations during the morning hours (by 08:30 h), gradually decreasing values during the daytime (until 20:30 h), and rising concentrations during the nighttime (until 08:30 h the next day) (5), which might also affect the accuracy of hs-cTnT on predicting myocardial infarction.

In conclusion, we think the utilization of hs-cTnT should be combined with the duration of the events and the diurnal hs-cTnT rhythm.

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Undetectable hs-cTnT in the Emergency Department and Risk of Myocardial Infarction

We read with great interest the recent publication by Bandstein et al. (1), and congratulate the authors on their thought-provoking results. If the findings are substantiated, then such an approach could have a major impact on the resources and time required to investigate patients with possible cardiac chest pain. The conclusion is emphatically worded: "All patients with chest pain who have an initial hs-cTnT level of <5 ng/l and no signs of ischemia on ECG [electrocardiogram] have a minimal risk of MI [myocardial infarction] or death within 30 days and can be safely discharged directly from the ED [emergency department]." We therefore ask the authors whether they believe that such an investigative approach is ready for widespread international uptake without further external validation using robust recruitment and follow-up processes? The impressive size of the study was achievable only by making a number of methodological compromises that we shall discuss in the following text.

First, this was an observational trial, and no patients were actually discharged by virtue of their findings. In fact, at least 21% were hospitalized using