marker for myocardial ischemia only in the appropriate clinical scenario. Outside of a scenario that enriches the pretest probability of ischemic cardiac disease (e.g., angina in a patient at risk), the significance of elevated hs-cTnI is uncertain. Indeed, the authors suggest this by reporting that only 30% of the cohort had troponin levels sent for clinical indications, with only 16 of 29 patients having 12-lead electrocardiography that showed signs of ischemia. Elevated hs-cTnI in the absence of other signs of an acute coronary syndrome is nonspecific and has been documented in many diseases, and even in endurance athletes after strenuous exercise (5). The authors posit "myocardial oxygen supply–demand mismatch," but they offer only indirect evidence for this. They base this postulate on a logistic regression model that associated risk factors for coronary atherosclerosis with elevated troponin levels, but offer no direct evidence of myocardial ischemia as a cause of elevated hs-cTnI. For example, they did not report whether hs-cTnI levels were higher in the 16 patients who had electrocardiographic findings of ischemia than in the 13 patients without such signs. The logical extension of the authors' conclusions would be that endurance athletes with elevated hs-cTnI levels also have myocardial oxygen supply–demand mismatch, which is preposterous. A more likely explanation for the reported observation is that hs-cTnI levels are elevated nonspecifically by a variety of stressors, including serious illness, where elevated hs-cTnI is a marker of disease severity.

Third, the mechanism of hs-cTnI elevation and its causal significance is open to speculation and further exploration. To conclude that hs-cTnI release was caused by myocardial injury due to impaired oxygen delivery is a false syllogism that equates a positive blood test with the presence of a disease (6). This is a form of the base rate fallacy: when a large, undifferentiated population is tested without establishing the true prevalence of the disease, we expect false positives. If a test with less than 100% specificity is used as the sole criterion for diagnosing a disease, the prevalence of the disease will increase in proportion to the prevalence of testing. To suggest that we use hs-cTnI as a screening test for sepsis-induced organ injury and hope for a way to accelerate its clearance is likely to lead to overdiagnosis and therapeutic misadventure.

Frencken and colleagues add interesting observations to the substantial evidence base on troponin elevations in the critically ill. However, mechanistic explanations and clinical applications will require much additional work.

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Reply: Against Another Nonspecific Marker of Perfusion and Troponin in Sepsis

From the Authors:

We thank Siuba and Farkas for their interest in our article and for their thoughtful comments (1). Although respiratory infections can act as triggers for acute myocardial infarction (MI) (2), we agree that elevated troponin levels should not be misinterpreted as a sign of coronary artery disease in critically ill patients with pneumonia who present without clinical signs and symptoms suggesting cardiac ischemia, and we advise caution against performing invasive diagnostic procedures or starting treatment for myocardial injury without signs of MI in the intensive care unit (ICU) setting. Furthermore, we find the use of troponin clearance as a perfusion target during sepsis resuscitation, as suggested by Bonk and Meyer in the editorial that accompanied our publication (3), an interesting concept; yet, we concur that there is currently insufficient evidence to support such an approach. Moreover, mechanisms and kinetics of troponin release and decline during sepsis are complex and still ill defined, which renders troponin as a perfusion marker a challenging target.

The difficulty in providing a satisfying clinical interpretation of troponin release in critically ill patients also seems to underpin most of the critiques expressed by Aberegg and Kaufman (4). First, they suggest that higher cutoff levels for abnormal troponin values should be used in critically ill patients, basing this suggestion on the observation that abnormal values are known to be prevalent in this population and that the pretest probability of having type 1 MI is low. We agree that higher thresholds may increase test specificity for type 1 MI, but this argument seems to be beside the point. We used troponin to assess myocardial injury, not infarction, with the former defined as a troponin level above the 99th percentile upper reference limit in accordance with the universal

definition of MI (5). This distinction is very important. It also renders mute the base rate fallacy argument put forward by Aberegg and Kaufman. Troponin release does not necessarily equal myocyte necrosis. In fact, troponin release during sepsis may result from a transiently increased membrane permeability releasing smaller troponin fragments from cytosolic pools into the systemic circulation without signifying cell death (6, 7). Furthermore, troponin release could be related to myocardial turnover and/or cell apoptosis, as may occur during acute increase in preload or ischemia (8). This uncertainty, in fact, underpins the very premise of our study. Troponin elevations in the ICU setting require more careful consideration than a knee-jerk response of MI versus no MI. We believe that increasing the threshold for what should be considered an abnormal troponin level in ICU patients (and thus for what is considered myocardial injury) would be particularly dangerous, because there is considerable evidence that even minor elevations of troponin are independently associated with increased morbidity and mortality (9, 10). Trivializing these findings by blindly raising the limit of what is considered normal seems unwise (11).

The second point raised by Aberegg and Kaufman claims that our data lend only little support to oxygen supply–demand mismatch as a potential cause of myocardial injury during sepsis. However, the authors seem to have overlooked the fact that this claim was not based simply on a logistic regression analysis yielding associations with preexisting risk factors for atherosclerosis but also on mixed model analyses in which time-dependent factors such as tachycardia and hypotension were independently associated with troponin release. These factors have been labeled as potential causes of type 2 myocardial ischemia in the fourth universal definition of MI (5).

We agree with Aberegg and Kaufman that the causes of troponin release in the absence of an acute coronary syndrome are most likely multifactorial and that the clinical significance of troponin release still requires further study. However, we strongly oppose the sentiment that elevated troponin concentrations during sepsis are nonspecific, merely representing yet another biomarker of general disease severity. This notion echoes a common frustration among clinicians that reflects their uncertainty about what to do with a positive troponin test result in a very sick patient without signs and symptoms of MI. This frustration should not lead to a disregard of the test. Given its clear association with mortality and how common it is, we should be motivated to find out why myocardial injury occurs during severe community-acquired pneumonia and sepsis; just disregarding it would be a poor approach to this clinical problem. Our study was one of the first to systematically investigate troponin release using a longitudinal approach, and this enabled us to identify several—potentially etiologic—factors. Disregarding these episodes and simply labeling them as "troponinemia," "troponinitis," or "troponin leak" would truly be a misadventure.

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Reply: Against Another Nonspecific Marker of Perfusion

From the Authors:

We appreciate the comments from Sibua and Farkas (1) regarding our recent editorial (2). We agree that the mechanisms contributing to elevations of high-sensitivity cardiac troponin I (hs-cTnI) are likely multiple and, as we highlighted, are unlikely to represent ischemic acute coronary events for the vast majority of patients. As an observational study, the MARS (Molecular Diagnosis and Risk Stratification of Sepsis) cohort is not designed to address the mechanism of troponin release; causal inference methodology could be applied if this were the goal and would offer, at best, indirect evidence to support or refute the mechanism. We likewise agree that hs-cTnI may function as a mortality indicator or risk stratification tool rather than specifically indicating cardiac risk, though we note that cardiac events are common in adults, both during and after a sepsis episode (3, 4). Furthermore, because the gene encoding cardiac troponin I protein is exclusively expressed in cardiac muscle (5), this