well as myocardial oxygen supply–demand mismatch). Troponin elevations generally do not reflect acute coronary occlusion or stenosis. Rather, troponin elevation in this context functions largely as a marker of mortality (3).

These articles are important for promoting awareness of the frequency of troponin elevation in critically ill patients. All too often, such elevations are misinterpreted as evidence of coronary artery disease, leading to inappropriate use of anticoagulation and cardiac catheterization. This potential cascade of downstream testing and procedures that may result from the widespread application of hs-Tn suggests that we should exercise restraint in obtaining this test.

One conceivably rational use of troponin in the context of a severely ill patient with pneumonia could be as a disease severity marker to facilitate risk stratification. For example, patients with a troponin above a certain level are at increased risk for death, and therefore might potentially benefit from more intensive care. However, we already have validated risk-stratification tools to determine which patients require more intensive care, such as the American Thoracic Society criteria. Furthermore, Frencken found that hs-Tn was less specific as a mortality indicator compared with standard troponin assays. Thus, it is doubtful that hs-Tn could add independent and useful information beyond available risk-stratification tools.

Bonk and Meyer opined that troponin might be used as a perfusion target for resuscitation, perhaps based on the finding by Frencken and colleagues that a downward trajectory of hs-Tn was associated with lower mortality compared with persistent elevation (1). We caution against this approach for many reasons. The mechanism of elevated troponin in these patients is complex, multifactorial, and not necessarily closely related to perfusion. Furthermore, troponin can be elevated by a diverse range of pathologies (e.g., pulmonary embolism, chronic kidney disease, and heart failure) (4). With an extensive list of possible mechanisms and etiologies that may often coexist, it is unclear how this single laboratory test could specifically assess perfusion. If troponin were related to myocardial oxygen supply–demand mismatch, how would we change our approach from the default (i.e., treating the underlying cause)? And importantly, how many patients might suffer from the iatrogenic effects of additional interventions?

Wide application of hs-Tn to assess perfusion in the critically ill would be, at best, another blunt instrument among many unhelpful tools in guiding patient management. Consider the current state of assessing and treating serum lactate, widely practiced because of Surviving Sepsis Guidelines. Evidence supporting this practice is lacking, with a recent study suggesting that lactate was no more effective at gauging perfusion than capillary refill time (5). Given the current state of evidence, we advocate for targeted use of troponin testing for the evaluation and management of suspected myocardial ischemia based on history, physical exam, point-of-care echocardiography, and electrocardiogram findings only.

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Troponin in Sepsis

To the Editor:

Frencken and colleagues measured high-sensitivity cardiac troponin I (hs-cTnI) levels in patients with community-acquired pneumonia and sepsis, and reported elevations above the upper limit of normal in 85% of their cohort (1). Their interpretation of this result was that myocardial injury due to oxygen supply–demand mismatch was responsible for the elevated hs-cTnI.

The authors' findings are interesting, and the associations between elevated hs-cTnI and abnormalities in laboratory tests related to inflammation and coagulation deserve exploration. Nevertheless, we are troubled by certain aspects of the report.

First, the upper limit of normal for elevated hs-cTnI is based on levels in a reference population of healthy volunteers without apparent disease. To apply that cutoff to patients with severe acute disease may not be appropriate (2). Indeed, recent data suggest that the cutoff for abnormal hs-cTnI in acutely ill hospitalized patients may be over four times higher (3). The results of the current study serve mainly to confirm prior studies showing that elevated troponin is a common finding in patients with sepsis (4).

Second, the claim that elevated hs-cTnI represents myocardial ischemia appears to be largely unsupported. Hs-cTnI is a specific

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