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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Jos F. Frencken, M.D., Ph.D.*
Dirk W. Donker, M.D., Ph.D.
Olaf L. Cremer, M.D., Ph.D.
University Medical Center Utrecht
Utrecht, the Netherlands

*Corresponding author: (j.f.frencken@gmail.com).

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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

marker is specific for cardiac injury, though cellular mechanisms beyond myonecrosis may contribute to the protein's release (6).

Sibua and Farkas disagreed with our characterization of hs-cTnI as a potential indicator of inadequate cardiac perfusion and particularly with our rhetorical question of whether hs-cTnI could be applied to guide patient management in the future. A caution against targeting therapy to hs-cTnI decline is valid, noting that a sepsis resuscitation strategy targeting lactate clearance was not superior to one targeting restoration of capillary refill time (7), and there is no evidence warranting a change in clinical practice. We advised against a misinterpretation of elevated hs-cTnI as a marker of cardiac ischemia and highlighted the potential for overuse of cardiac testing as a result. However, we maintain that hs-cTnI may provide information about cardiac organ injury that is not captured by the Sequential Organ Failure Assessment score (SOFA), on which the Sepsis-3 definition (Third International Consensus Definitions for Sepsis and Septic Shock) is predicated (8). If our goal in treating sepsis is to rapidly identify organ dysfunction and sequentially reassess perfusion adequacy, there may be benefit in adopting a broad array of organ injury markers to alert the clinician to potential sepsis-induced organ failures beyond those already codified in the SOFA score.

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Michael P. Bonk, M.D.
Nuala J. Meyer, M.D., M.S.*
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania

ORCID ID: 0000-0003-4597-5584 (N.J.M.).

*Corresponding author: (nuala.meyer@pennmedicine.upenn.edu).

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