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EDITORIAL COMMENT

Who Is David and Who Is Goliath?

There Is an Urgent Need to Improve the Reference Standards for Estimation of Myocardial Infarct Size*

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Currently, cardiac troponins (cTn) are well established for diagnosis, risk stratification, and guidance of the therapeutic strategy in patients with suspected acute coronary syndromes (1). Cardiac troponin T and I are ideally suited for the detection of myocardial damage because they are expressed in high intracellular concentrations as cardio-specific isoforms. The vast majority of the troponin complex is immobilized on the thin filament of striated muscle, and only a minor fraction exists as a soluble

See page 523

pool, which eventually represents a precursor pool of sarcomere assembly (2). Following irreversible cell damage, cTn are released by disintegration and degradation of the sarcomere, and can be measured in the blood for days to weeks, despite a short half-life in the circulation of only 90 min. As a consequence, the time-dependent concentration changes of troponin T in the blood of patients with acute myocardial infarction (AMI) reflect distinct washout and release mechanisms that may serve as surrogates of microvascular reperfusion and infarct size. The highly variable blood levels on day 1 clearly correlate with reperfusion therapy and time from onset of symptoms to recanalization of the infarct-related artery. Accordingly, a pronounced washout on day 1 corresponds to successful reperfusion therapy, whereas the absence of an early peak is only observed in nonreperfused myocardial infarction (2). The blood levels of troponin T on day 3 to 4, however, result from degradation of the contractile apparatus and are released at times of resuming blood flow to the infarct zone. This late release is considered a hallmark of irreversible myocardial injury and has been shown to reflect infarct size, both in animals (3) and patients (4,5).

On the other hand, imaging modalities are also well established for infarct imaging and quantification of infarct size including single-photon emission computed tomography (SPECT), positron emission tomography (PET), and late gadolinium-enhanced cardiac magnetic resonance (LGE-CMR) (6).

In this issue of *iJACC*, Miller et al. (7) present their findings on the relationship between serially determined cTnT concentrations and infarct size using gated SPECT myocardial perfusion imaging (MPI) as the reference method. SPECT-MPI was performed a median of 10 days post-AMI. The study cohort comprised 121 patients with first AMI in whom cTnT was obtained serially on presentation, after 12 h, and every 24 h for 4 days or longer. The authors found that the SPECT-defined infarct size closely correlated with cTnT concentrations at 12 to 24 h, on day 2, day 3, and peak cTnT concentrations but not with admission troponin values. In addition, there was a significant inverse correlation between cTnT concentrations on days 1, 2, and 3, and with peak cTnT concentration with left ventricular ejection fractions. Receiver-operating characteristic

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curve analysis determined a peak cTnT cutoff value of 1.5 ng/ml for detection of SPECT-defined infarction that corresponds to 150 × the 99th percentile, the upper limit of normal. Finally, infarct size and peak cTnT were associated with major cardiac events at follow-up, supporting the prognostic relevance of direct and indirect estimates of infarct size. The most interesting finding of this study, however, is that almost one-half (49%) of the patients had no detectable infarct using SPECT-MPI. Thus, this study highlights the increasingly important issue about the appropriateness of current reference standards regarding spatial resolution for accurate estimation of infarct size, in particular when patients with smaller infarcts are analyzed.

SPECT is the most commonly performed cardiac imaging technique in nuclear cardiology. Currently, there are more than 8 million cardiac SPECT procedures but <50,000 cardiac PET procedures performed annually in the United States (8). As compared with PET or SPECT, CMR has the advantage of non-ionizing imaging of myocardial morphology, systolic and diastolic function, and myocardial perfusion and viability with high spatial and temporal resolution. The extent of abnormal gadolinium enhancement linearly correlates with the histological area of myocardial infarction in both acute and chronic myocardial infarction in animal models (9). High spatial resolution enables detection of small, subendocardial infarction, which is difficult to detect with radionuclide imaging. In an animal study using histopathology specimens as the reference, LGE-CMR identified 92% of the segments with a subendocardial infarction, whereas SPECT detected only 28% (10), possibly due to the lower spatial resolution of SPECT of only 10 mm. Thus, infarcts restricted to the subendocardial layers of the myocardium may escape detection by SPECT. Although LGE-CMR may provide higher spatial resolution, it still may not qualify as a reference method for estimation of infarct size in non–ST-segment elevation myocardial infarction (NSTEMI) populations. With the commonly applied method of LGE-CMR imaging, the minimum detectable LGE necrosis is a group of 10 hyperenhanced pixels corresponding to a voxel of 1.9 × 1.4 × 7 mm (11,12). Accordingly, CMR has been reported to visualize infarcts amounting to a mass of 1 to 2 g in clinical studies (12). Thus, in clinical practice, small infarcts may escape detection due to inadequate spatial resolution or partial volume effects at the interface between blood and the endocardial border.

A previous study from our group (4) reported an inferior performance of single-point and serial troponin measurements for detection of small infarcts (<13.6 g), NSTEMI, and nonanterior infarct location. In the present study, Miller et al. (7) provide additional evidence by yet another imaging method that there is currently no appropriate reference method when a small infarct is detected by sensitive troponin assays. In their study, the receiver-operator characteristic curve concentrations of cTnT to detect SPECT-defined infarcts were as high as 1.5 ng/ml, which corresponds to >150 × the 99th percentile, the upper limit of normal. Not surprisingly 49% of all infarcts, particularly NSTEMI, were not detectable by SPECT. More recently, Lim et al. (12) studied 32 patients undergoing multivessel percutaneous coronary intervention to evaluate the relationship between troponin rise and peri-interventional infarctions. The authors failed to detect the majority of cTn-defined post-interventional myocardial infarcts (type IVa) using LGE-CMR imaging. From this finding, the authors draw the conclusion that low cTn thresholds were too sensitive for diagnosis of peri-interventional myocardial infarction, instead of questioning the low spatial resolution of current CMR imaging. Obviously, estimation of the size of smaller infarcts is an issue, not of oversensitivity of the current troponin thresholds, but of undersensitivity of the current imaging modalities as reference standards.

Thus, when smaller infarct sizes have to be assessed, which are detectable by the now widely used troponin assays, better imaging modalities with higher spatial resolution and higher signal-to-noise ratios must be applied. In the near future, this ambitious goal may be achieved by development and broader use of high-field magnetic resonance imaging technology (3-T or higher), improved cardiac radiofrequency coils, novel pulse sequences allowing high resolution T_1 mapping of the heart, and other novel technologies that aim to further increase spatial resolution.

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Key Words: cardiac magnetic resonance ■ cardiac troponin ■ infarct site ■ SPECT.