

EDITORIAL COMMENT

Fuzzy or Sharp Borders of Acute Myocardial Ischemia and Infarction?*



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The sharpness of perfusion territories at the edges of infarcts was a controversial area of research in the 1980s. The advent of cardiac magnetic resonance (CMR) techniques that could determine the extent of myocardial infarction (MI) (1) and the ischemic area at risk (2) has reopened questions about graded ischemia at the edges of the acute myocardial infarction (AMI). In this issue of *JACC*, Jablonowski et al. (3) explore the borders around AMI in a swine model and conclude that gadolinium-based contrast agents overestimate the AMI size on the first day after MI but not on day 7. Increased extra cellular volume fraction (ECV) is proposed as a mechanism to explain why these contrast agents overestimate the extent of infarction. These new data raise important questions about the borders around AMI and how the pathophysiology affects viability assessment with late gadolinium-enhanced CMR imaging in the setting of AMI.

SEE PAGE 1379

In reviewing this new work and previous literature, I find excellent evidence for graded myocardial ischemia around AMI while there are sharp borders between live and dead cardiomyocytes in the same hearts. The concept of sharp borders around the lateral edges of AMI has been studied at many levels, but perhaps most definitively by Axford-Gatley and Wilson (4). In that study, electron microscopy was used to determine perfusion and viability at

a cellular level. Although perfusion was a binary determination, ischemic cellular damage was assessed on a 5-point scale (4 sublethal gradations and 1 lethal grade). This study and others concluded that previous observations of intermediate characteristics at the borders of AMI could simply be explained on the basis of measurements from admixtures of viable and nonviable cells.

Careful re-reading of this classic reference (4) reveals a very different conclusion regarding gradations of ischemia around AMI. Their measurements showed a graded degree of sublethal ischemic injury as a function of time at the cellular level (Figure 1). Ninety minutes and 6 h of ischemia led to sublethal injury scores of 2 and 3. At 24 h, the score finally reached a uniform lethal level. Gradations of ischemia may be critical factors in explaining the sublethal variations observed in the salvaged myocardium on CMR scans.

Similarly, the “wavefront concept” of AMI remains the best model for the relationship between the duration of ischemia and the extent of MI (5). Although this field-defining work has survived the test of time, the supporting data are not without some limitations. For example, in work that described the 3-dimensional distribution of collateral myocardial blood flow during coronary occlusion (6), 3 of 8 experiments did not have sharp borders on injected dyes, but this was explained away in the Results section rather than considered possible evidence of collateral circulation. The study concludes there were virtually no lateral perfusion gradients during coronary occlusion—only transmural gradients. However, their graphical results show lateral perfusion gradients comparable in severity to the transmural gradients.

In humans, there are vessels that connect the left anterior descending coronary artery and right coronary artery beds (Figure 2) (7). Lee et al. (7) reported that “...the infarcts were always smaller than the occluded beds.” MI involved 50% to 88% of the

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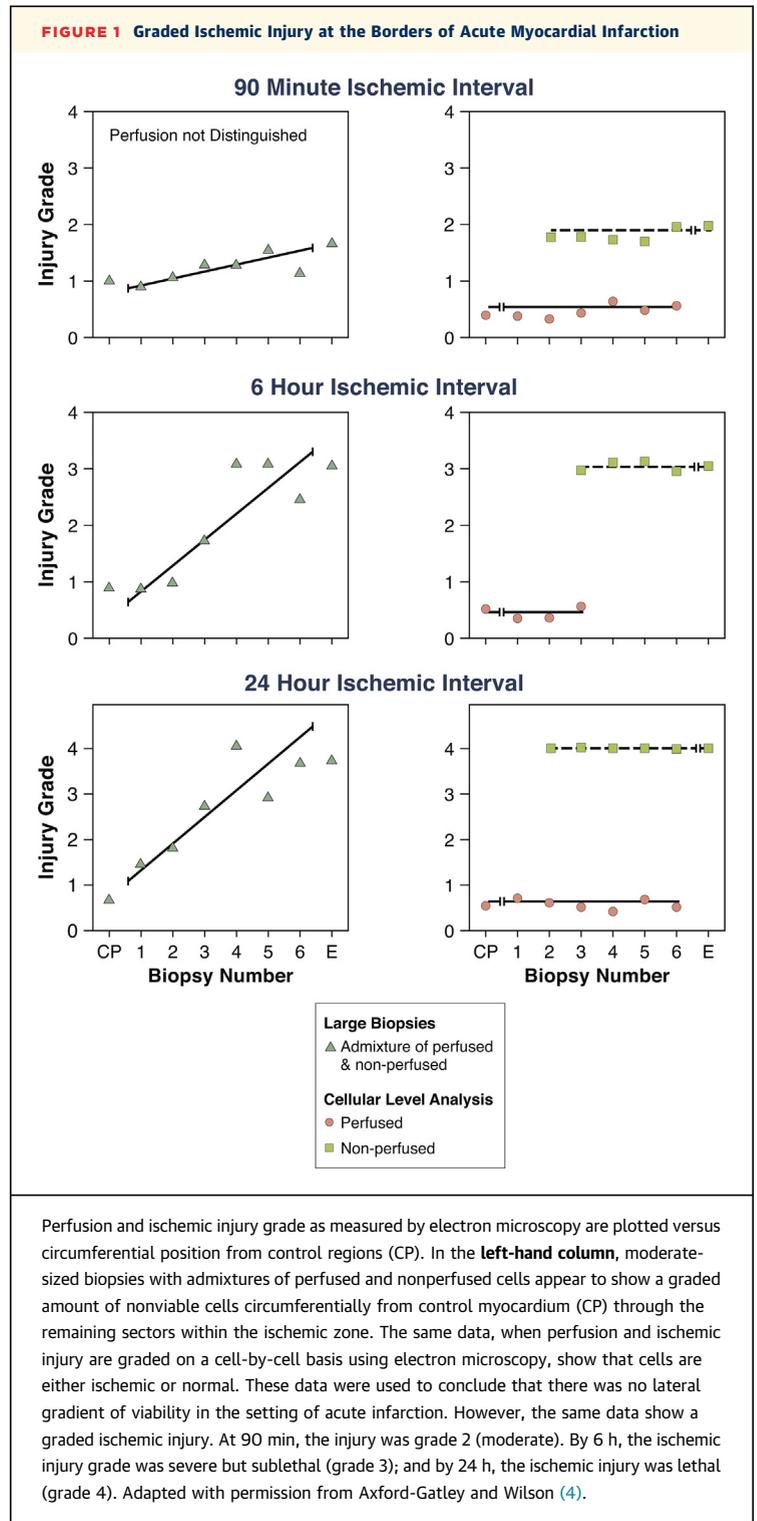
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ischemic bed (mean $69.0 \pm 3.0\%$). They also indicated that "...large collateral connections were frequently observed in the septum between the septal perforating branches of the LAD and RC [right coronary artery]...." Despite verbally recognizing the collateral vessels, sharp borders were drawn to distinguish these coronary territories (Figure 2). "In cases where such collaterals were present, we chose the most narrow point of the connecting vessel as the vascular bed boundary" (7).

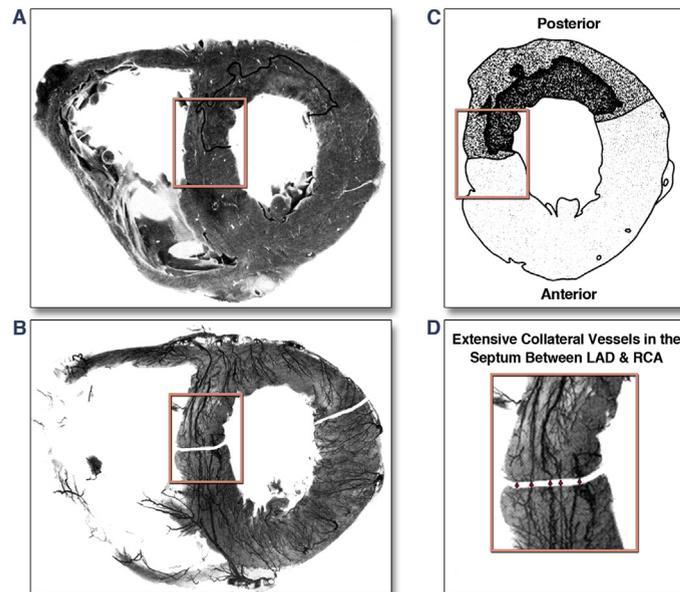
The purpose of critically reviewing these classic studies is not to denigrate important previous work, but to help readers think critically about how newer data relates to previous findings and to encourage current scientists to keep an open mind to new data that seems to conflict with dogma. Raw data from classic studies seems to conflict with the most stringent interpretation of the wavefront concept of infarction. There are gradations in the severity of perfusion defect in both the transmural direction and the lateral aspects of the ischemic zone.

How do these pathophysiological issues about the borders around AMI relate to the current study by Jablonowski et al. (3)? At in vivo CMR resolutions (~500,000 cardiomyocytes/voxel), admixtures of viable and nonviable cells occur at the edges of all infarcts and lead to partial volume error. The result is an intermediate measurement between normal and abnormal, a problem comparable to what fueled the controversy in the 1980s. Jablonowski et al. (3) acknowledge that some of their intermediate abnormalities in the ECV might be explainable by partial volume errors. However, the same partial volume errors should also have existed on day 7, a time when overestimation of the infarct size was not observed.

There are pathophysiological explanations for the elevated ECV beyond the edges of the infarct. These lateral and transmural gradations in perfusion cause sublethal ischemic changes in myocardium adjacent to the AMI. These intermediate injuries probably cause myocardial edema. Gadolinium accumulates to a lesser, but detectable, degree in edematous myocardium compared with MI. In the pig model, the late gadolinium enhancement images overestimated the infarct size due to this increased ECV at the edges of the infarct. CMR can detect elevated ECV in recently ischemic but viable myocardium (8), and lateral perfusion gradients are associated with a less severe transmural extent of MI (9). Thus, post-ischemic edema in salvaged myocardium likely contributes to the overestimate of the infarct size on day 1 after MI in swine.



In patients, we should avoid over-interpretation of AMI size by CMR. AMI size could dissuade physicians from pursuing interventions. If CMR overestimates AMI size in humans, then it is critical to define when the infarct size is truly accurate.

FIGURE 2 Evidence for Macroscopic Coronary Collaterals in Humans

(A) The anatomy was displayed with the left anterior descending at the bottom (inverted compared with current conventions). The **black line** delineates the infarcted myocardium. The **pink boxes**, **red arrows**, and zoomed view (D) were added for this editorial. Despite *ex vivo* x-ray evidence of collateral vessels (**red arrows**) connecting the left anterior descending coronary artery (LAD) and the right coronary artery (RCA) in human hearts (**B and D**), sharp borders between these different perfusion territories were drawn and used to assess the width of the lateral border zone between the infarct and the edge of the ischemic zone (C). Adapted with permission from Lee et al. (7).

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