Editorial

Colors of Myocardial Infarction
Can They Predict the Future?

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Late gadolinium enhancement (LGE) cardiovascular magnetic resonance imaging (CMR) is a major achievement in the field of noninvasive cardiac imaging.[1] During the past 2 decades, LGE has not only become the gold standard for characterizing myocardial infarctions (MIs), but it has also been shown to have significant value in predicting clinical outcomes after acute MI. However, a drawback of LGE is that it cannot discriminate between acute and chronic MI, which is a frequent demand in the clinical management of patients with MI. Over a decade ago, noncontrast-enhanced T2-based CMR emerged to fill this gap. Specifically, it was shown that the infarct zone hyperintensity in T2 images, suggestive of edema within the zone, normalizes to that of remote myocardium at 3 months post-MI, presumably because of the resolution of edema in the chronic phase of MI.[2] Thus, a combined evaluation of LGE and T2 CMR has become an accepted strategy for differentiating between acute and chronic MIs.

See Article by Carberry et al

Despite these key advances, there have been evidence in the literature, albeit in small cohorts of patients, that the time for infarct zone T2 hyperintensity to resolve to remote values is highly variable[3,4] and that infarct zone T2 hyperintensity can persist even 1 year after acute MI. These reports, however, did not provide insight into the temporal heterogeneity of edema resolution. The recent study by Bulluck et al[5] has been instrumental in uncovering potential cues for why infarct zone T2 hyperintensity in some acute MIs can persist well after the acute phase of MI. They reported that in patients with acute MI with reperfusion hemorrhage, T2 of infarct territories remains elevated at 6 months relative to the remote myocardium; but in nonhemorrhagic MI territories, T2 values resolved to remote levels at 6 months post-MI. They attributed their observation to the residual iron deposits associated with reperfusion hemorrhage within the infarct zone, which has been shown to drive a persistent, proinflammatory burden within the infarct zone well past the acute phase of MI.[6] Recent preclinical data reinforce their observation and show that the periphery of iron-rich regions within dense scars with T2 hyperintensity are site of active inflammation.[7] Collectively, these studies support the notion that infarct zone T2 hyperintensity is perhaps a nonspecific marker for determining the time course of all MIs and that imaging-based assessment of MI, including staging, should be guided by the wealth of evidence that infarct size is not the only discerning feature of MI that has predictive value.

In this issue of *Circulation: Cardiovascular Imaging*, Carberry et al[8] report on the health outcomes in patients with ST-segment–elevation myocardial infarction followed for a median of 1330 days in whom infarct zone T2 hyperintensity was evident at 6 months post-MI. This is an important study, first, because no prior studies have reported on the adverse clinical outcomes associated with persistent infarct zone T2 hyperintensity; and second, because when taken together with previous studies, it lends additional pathophysiological insights into how persistent (late) microvascular obstructions, identifiable on LGE CMR, might be driving adverse outcomes in post-MI patients. In this single-center study of 283 patients with ST-segment–elevation myocardial infarction (>70% with TIMI [thrombolysis in myocardial infarction] flow grades of 0 or 1 at initial angiography) undergoing CMR on 2 days and 6 months post-reperfusion, ≈2 of 3 patients showed evidence of persistent infarct zone T2 hyperintensity at 6 months relative to the remote myocardium. Notably, patients with persistent infarct zone T2 hyperintensity at 6 months had greater incidence of hypointense infarct core on T2 CMR (suggestive of reperfusion hemorrhage)[9–11] and late microvascular obstruction that were larger than their counterparts (infarcts with resolved T2 hyperintensity at 6 months) on the day-2 CMR. On the 6-month follow-up CMR, patients with persistent infarct zone T2 hyperintensity had reduced left ventricular ejection fraction and worse left ventricular remodeling. In the long-term follow-up for outcomes, persistent infarct zone T2 hyperintensity at 6 months showed a strong trend toward all-cause death or heart failure; and a change in T2 (1- or 10-ms change) was significantly associated with all-cause death and major adverse cardiovascular events (cardiac death, nonfatal MI, and hospitalization for heart failure after the follow-up CMR).

Given that patients exhibiting T2 hyperintensity at 6 months had greater incidence of late microvascular obstruction and a change in T2 was significantly associated with adverse outcomes, study by Carberry et al[8] builds an important link between late microvascular obstructions and adverse outcomes in the chronic phase of MI.[12,13] Recent preclinical studies have shown that late microvascular obstructions can also result in residual iron within MI. Hence, 1 potential mechanistic explanation for this observation may be that the proinflammatory

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burden associated with residual iron from late microvascular obstruction promotes an edematous milieu within the zone of chronic MI.[14] From this vantage point, the findings here may also provide additional insights into the results of the recent CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcomes Study), which showed that adverse cardiovascular events can be significantly reduced in post-MI patients treated with anti-inflammatory agent canakinumab.[15] Notably, canakinumab targets IL-1β (interleukin-1β)—a proinflammatory cytokine that has recently been shown to be directly associated with iron within chronic MI territories. Thus, whether the beneficial effects of canakinumab observed in post-MI patients were partly mediated by suppressing the negative effects of IL-1β within the infarct zone is a possibility when one considers that the incidence of late microvascular obstruction in MI patients is >50%[9,16] and that late microvascular obstructions carry a 4-fold greater risk for major adverse cardiovascular events than infarct size.[13,17] However, causal links or direct connections between the studies with regard to the substrate within MI driving adverse outcomes cannot be drawn because CANTOS trial did not use CMR to assess infarct territories; and study by Carberry et al[8] does not report on T2* CMR, the most sensitive measure for iron, especially when T2 elevations in MI zones are evident.[11]

Although it is likely that edema may be the key contributor to the persistent T2 hyperintensity at 6 months, fat within MI zone, as suggested by the authors, may be another source driving elevated T2 within the chronic infarct zone. It may also be possible that the molecular events responsible for persistent levels of edema within MI drive fat infiltration within the infarcted myocardium,[18] which has also been associated with adverse outcomes.[19] Although additional studies are needed to elucidate the actual substrate(s) driving the persistent T2 hyperintensity in the chronic phase of MIs, what is becoming clear is that scar formation is not the terminal point of MI. It seems that the infarct zone is a dynamic environment with complex molecular events in the months, and years after an MI, ultimately driving outcomes, may actually be determined by the index ischemic event and the interventions that are undertaken to re-establish blood flow.

In summary, study by Carberry et al[8] generates a compelling hypothesis that a tissue-specific imaging marker, persistent hyperintense T2 signals, well after the index event, can serve as a novel predictor of outcome in post-MI patients. Although further investigations are required, noninvasive predictors, such as hyperintense T2 signals, may be immensely valuable in developing patient-specific therapies because they can report on the therapeutic efficacy at the level of the tissue of interest rather than on the basis of nonspecific blood markers. Thus, at the crossroads of drug interventions and noninvasive imaging, both targeting post-MI patients, it is difficult to dismiss the value noninvasive imaging brings for the development of patient-centered heart failure therapies. It is prime time to start reaping the benefits of CMR in drug trials for heart failure.

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