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EDITORIAL COMMENT

Healing After Myocardial Infarction

A Loosely Defined Process*

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Although all physicians probably have a good intuitive sense of the clinical presentation of acute myocardial infarction (MI), the clinical definitions of acute MI and healing MI are surprisingly imprecise. The redefinition of acute myocardial infarction in 2000 centered squarely on clinical presentation and a typical rise and fall in troponin as a new and better definition of MI (1). Those guidelines advised that the term MI should be preceded by "acute, healing, or healed" as modifiers that relate to the pathological processes underlying each of these phases.

> "An acute or evolving infarction is characterized by the presence of polymorphonuclear leukocytes. If the interval between the onset of infarction and death is brief (e.g., 6 h), minimal or no polymorphonuclear leukocytes may be seen. The presence of mononuclear cells and fibroblasts and the absence of polymorphonuclear leukocytes characterize a healing infarction. A healed infarction is manifested as scar tissue without cellular infiltration. The entire process leading to a healed infarction usually requires five to six weeks or more. Furthermore, reperfusion alters the gross and microscopic appearance of the necrotic zone by producing myocytes with contraction bands and large quantities of extravasated erythrocytes."

Since clinicians cannot see such pathological features except in fatal cases with an autopsy, a less precise definition was introduced using the following time scale as an approximation of the pathological phases: acute (6 h to 7 days); healing (7 to 28 days), healed (29 days or more) (1). The Third Universal Definition of Myocardial Infarction, focused less on the healing phases after MI, simply stated that it takes at least 5 to 6 weeks for an MI to heal (2).

With the exception of not including the first 6 h as part of the definition of an acute MI, I find the 2000 Guidelines definitions of acute and healing phases of MI a useful construct. At the same time, cardiac magnetic resonance (CMR) findings at various times after acute MI have made me reconsider the rather loose definitions of the healing and healed phases.

Along that line, Smulders et al. (10) from Maastricht University Medical Center and from Duke University studied how well various CMR methods can distinguish acute from chronic MI. In brief, a combination of T2-weighted magnetic resonance imaging (MRI), end-diastolic wall thickness, and the presence or absence of microvascular obstruction (MO) accurately categorized the age of the infarct as <1 month, 1 to 6 months, and more than 6 months old. These data are valuable as they help refine our understanding of parameters that are useful for differentiating acute from chronic MI. This work also raises important questions about why T2 abnormalities persist for >1 month after acute MI in so many patients. The implications are broader; the healing process after acute MI takes longer than most clinicians think.

We first became interested in imaging myocardial edema associated with acute MI as a potential method for differentiating acute from chronic MI. We pursued this line of research after we found that a rest CMR scan in the emergency department was quite sensitive to detecting acute coronary syndrome but limited by difficulty differentiating acute from chronic wall motion abnormalities (3). Friedrich et al. (4) had been

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studying T2 as a method to detect myocardial edema in myocarditis and acute MI (5). The concept that tissue characterization with MRI could distinguish acute from chronic MI was exciting and diagnostically relevant. We followed a different tract of trying to understand why the post-MI T2 abnormalities were more extensive than the infarcted myocardium. This led to the realization that T2 in the first 48 h after MI was detecting edema in the ischemic zone or area at risk. However, as the story develops, it is clear that there are important differences between the T2 abnormalities associated with early post-ischemic edema, 1 week post-infarct inflammation, and longer term healing after MI.

Recent work by Fernández-Jiménez et al. (6) brilliantly demonstrates in a swine infarct model that there is a period of ~24 h in which post-ischemic T2 abnormalities are detectable, but this fades faster than in canine models (7). In canine models, the initial post-ischemic T2 abnormalities are still present for at least 48 h. Most interestingly in the swine model, a second phase of T2 abnormality develops to show a T2 abnormality that is as strong as the early abnormalities and likely explained by an inflammatory response. Because inflammatory responses to acute injury do not typically last 6 months, one might reasonably wonder what could explain the abnormal T2 over such a long period of time.

Because there is limited pre-clinical CMR data in the 1- to 6-month time period post-MI, human autopsy data may provide insights into the healing process that parallel what has been observed by imaging. Mallory et al. (8) reported one of the first large pathological series of human autopsies after acute MI (n = 72) in 1939. Several aspects of this classic study caught my attention.

- First, small infarcts healed faster than more extensive infarcts.
- Second, the rate of healing was faster when the remaining circulation was better.
- Third, the majority of human pathological features of healing MI were comparable to the observations in canine experimental MI with a few exceptions (most of which they considered minor).
- The chief difference was that canine infarcts healed more quickly than human infarcts.

In humans, necrosis and polymorphonuclear leukocyte infiltration were common features in the first 7 days. Removal of necrotic cells and replacement by connective tissue dominated the next 5 weeks. The collagen deposition started in the second week and was completed by ~3 months after the acute MI.

In 1978, Fishbein et al. (9) studied the histopathological features seen during the first 90 days after human acute MI in an autopsy series of 192 patients. They confirmed most of the observations of Mallory et al. (8) They specifically described features of edema and the inflammatory response that are relevant to recent imaging studies of acute MI. In particular, they found that intercellular edema was present during the first 1 to 7 days in 96% of human acute MIs (**Table 1**, **Figure 1**). The severity of intercellular edema was most severe on day 1, moderate through most of the rest of the first week post-MI, and generally mild thereafter. Between 36 and 90 days post-MI, edema was not seen in human MIs.

Thus, myocardial edema cannot explain the more prolonged increases in myocardial T2, as observed by Smulders et al. (10) in this issue of *iJACC*, as the authors correctly discuss. The time course is more complicated

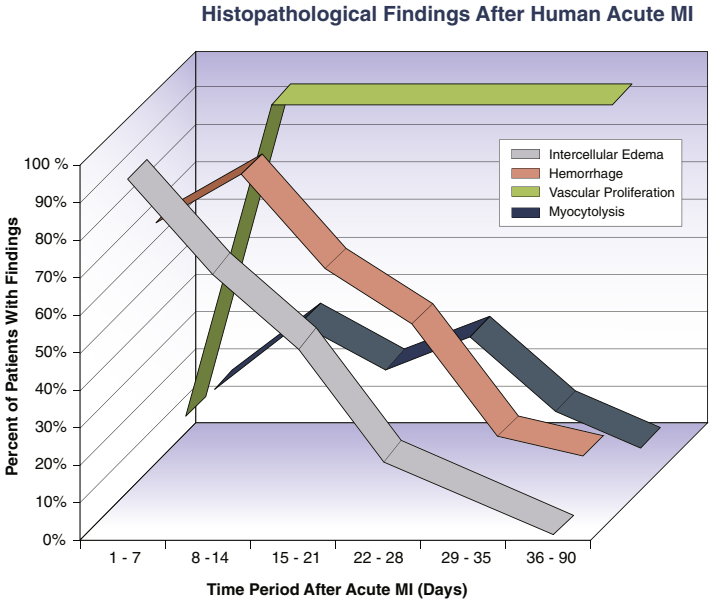
TABLE 1 Time Course of Pathologic Findings After Human Acute Myocardial Infarction

Days	n	Necrosis	Waviness and Thinning	Myocytolysis	Intercellular Edema	Hemorrhage	Vascular Proliferation
1–7	121	96	94	16	96	77	17
8–14	30	97	73	33	70	90	100
15–21	14	71	57	21	50	64	100
22–28	10	50	30	30	20	50	100
29–35	10	20	0	10	10	20	100
36–90	7	0	0	0	0	14	100
Combining Days 1–28 for Correlation With Smulders et al. (10)							
1–28	175	160 (91)	147 (84)	35 (20)	146 (83)	134 (77)	74 (42)

Values are % or n (%). The top of the table summarizes the human pathological findings throughout the first 90 days after acute myocardial infarction, equivalent to the way the data were first presented in 1978 by Fishbein et al. (9). The additional analysis condensed the "acute" phase as a combination of the first 28 days after the infarct was added to represent the data as closely to those of Smulders et al. (10), who defined acute MI as the first 30 days after MI.

Pts = patients.

FIGURE 1 Time Course of Components of the Healing Process After Acute MI



Intercellular edema resolves by ~35 days post-MI. Vascular proliferation and continued remodeling of the collagen scar in the time period 36 to 90 days post-MI likely play a role in the more prolonged abnormalities seen in myocardial T2. Adapted with permission from Fishbein et al. (9). MI = myocardial infarction.

and more prolonged than many imagers have assumed with back of the hand arguments. Edema is a prominent factor in the first 24 to 48 h after acute MI. Myocardial T2 in the healing phases after acute MI is more than simply edema (**Table 1**). However, T2-weighted imaging after acute MI is intriguingly sensitive to at least 3 of the known pathological processes that take place in the first 7 days (edema, hemorrhage, and the inflammatory response). T2 is also sensitive to post-MI healing processes observed during the next 7 to 90 days (resolving edema, hemorrhage, inflammation, and prolonged hypervascularity). Edema, inflammation, and increased vascularity all affect T2 by increases in water content. Hemorrhage and the transition to a dense collagen scar can decrease T2. Thus, there is likely a combination of competing factors in the later time period that affect the T2 properties of the healing acute MI.

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Smulders et al. (10) suggest that lack of blinding or selection of patients at extremes of time post-infarct in previous studies may have explained why the sensitivity of T2-weighted imaging was higher in those papers than in the current study. An equally plausible explanation relates to the present study-specific definition of "acute MI" as <30 days post-infarct. As described in the human autopsy studies, there are many processes changing over the first 30 days. The Fishbein et al. (9) study indicates that edema should be present in ~83% of subjects at 30 days if one combines all of their data between day 0 and day 28. Thus, the sensitivity of T2 in the present study (88%) is about what one might expect for the 0 to 30-day time frame post-MI. The larger issue with T2 seems to be specificity (66% in the current study), a problem that might be helped by quantitative methods (either T2 maps or T1 maps) (11). Combinations of microvascular obstruction, increased wall thickness, or T2 seem to perform better than any single characteristic.

Ultimately, one can learn from pathological imaging correlations. We can improve our understanding of both the diagnostic features seen on imaging as well as the underlying pathophysiology if we keep an open mind. Although the ability to intervene in acute MI has focused so much attention on the first few hours of presentation and treatment, the healing process is more complicated and more prolonged than many physicians might guess.

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