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EDITORIAL COMMENT

Arrhythmogenic Potential of Border Zone After Myocardial Infarction

Scar Is More Than Just a Healed Wound…*†

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FIBROSIS IN ISCHEMIC AND NONISCHEMIC MYOCARDIAL DISORDERS

Interstitial fibrosis is a structural substrate for ventricular arrhythmias; the dissociation of a single myocyte or bundles of myocytes promotes re-entrant circuits with arrhythmogenic potential (1). Myocardial fibrosis can be roughly considered as either substitutive (follows the healing processes of myocyte necrosis in acute myocardial infarction [MI]), or reactive (evolves during ventricular remodeling processes in non-MI afflictions). They are also referred to as replacement and interstitial fibrosis, respectively. The components of myocardial fibrosis (collagen fibers, fibroblasts and myofibroblasts, matrix proteins, sparse macrophages, and mast cells) (2) do not carry, by themselves, an arrhythmogenic potential. The origin of arrhythmias is either intrinsic to any defect in myocytes, or triggered by the structural and electrical dissociation of the myocytes induced by the fibrosis. In post-MI fibrotic zones with arrhythmogenic risk are predominantly traced to the border zone (BZ).

The fibrosis replaces the necrotic debris during the healing process after MI. The boundaries between necrotic and morphologically viable myocardium are nonlinear, and the substitutive fibrosis is characterized by irregular edges wherein the islands or bundles of vital myocytes are separated by scar tissue. In the reperfused MI, the repair process gets more complex and must include resorption of the hemorrhagic material because of the loss of capillary integrity (3). The pathologist's view of myocardial fibrosis is limited to 2 dimensions, and serial sections of the same myocardial block show substantial variability of the pathological features, even at a depth of a few tens of microns. This implies that, at the BZ level, there is no geometric uniformity and variably interdigitating fibrosis and viable myocytes may create a perfect arrhythmogenic substrate.

However, the extent and distribution of fibrosis are even more variable in noninfarct-related cardiomyopathic processes, wherein the fibrotic process is less intense but more multifocal (or diffuse) and without obvious myocyte loss (4). The interstitial or reactive fibrosis in myocardial disorders could range from focal to diffuse, mild to extensive, isolated to accompanied by foci of fat tissue, loose to dense, acellular to intensely inflamed, and purely collagenous to accompanied by metaplastic components.

FIBROSIS AND ADIPOSE TISSUE

Replacement fibrosis may include areas of dysplastic or metaplastic but still morphologically viable myocytes (5). Although development of mature fibrotic tissue is the major healing mechanism for replacement of necrotic myocytes, small islands of fat tissue are commonly observed in myocardial scars, both in post-acute-MI substitutive fibrosis and nonischemic cardiomyopathies, but are usually ignored (6). Dysplastic or metaplastic myocytes presenting with features of adipose transformation are conveniently encountered when specifically sought for (**Figure 1**). Their presence is often limited to a few groups of cells, and represents transition from normal viable myocytes to metaplastic viable myocytes undergoing fat transformation. The morphological appearance of the metaplastic

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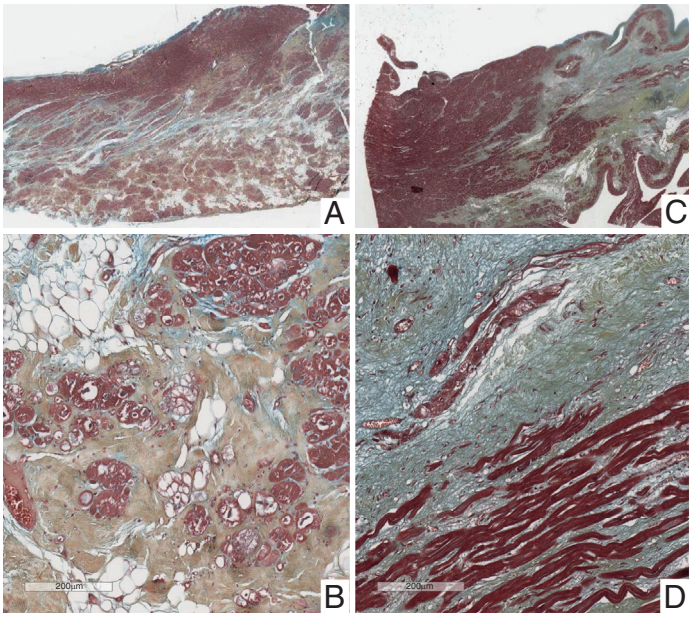
FIGURE 1 Different Pathology Features of Border Zones in the Heart of 2 Patients With Fatal Post-Acute Myocardial Infarction Complications



(A) Low-magnification view of left ventricle wall surrounding the infarct area: fibrosis and adipose tissue. **(B)** Higher magnification of 1 of the multiple and similar areas observed in **A**, showing the mixed fibrous and adipose tissue, and the dystrophic myocytes. **(C)** Low-magnification view of the border zone of a transmural acute myocardial infarction **(right side)**. The border zone is characterized by prominent dense substitutive fibrosis with scarce and focal adipose tissue. **(D)** Bundles of myocytes with dystrophic changes in the context of the substitutive dense fibrosis. **(A to D)** Movat pentachrome, original magnification: **A** and **C** = x2.8 μm; **B** and **D** = x200 μm (shown in bar scales).

inclusions may look similar to that seen in arrhythmogenic cardiomyopathy. Therefore, the question is whether the fat foci or the metaplastic myocytes can exert a proarrhythmic effect that could add to the arrythmogenicity produced by the intermixed myocyte and fibrotic tissue of the BZ. Can cardiac magnetic resonance (CMR) recognize these small foci in the context of border scars or is fat characterization by CMR largely dependent on the extent of myocardial fat replacement (6)?

THE IN VIVO STUDY OF MYOCARDIAL FIBROSIS

CMR offers valuable information pertaining to localization, quantitation, and distribution of replacement myocardial fibrosis. The integration of in vivo imaging and electromapping studies has allowed better definition of the arrhythmogenic areas for guiding ablation procedures. The fibrosis-related arrhythmogenic risk in the BZ depends on the interruption of the myocyte continuity, which promotes re-entrant circuits; this concept has been referred as "conducting channels" (7). These conducting channels appear as BZ corridors on contrast-enhanced CMR (8) and can be identified with 3-dimensional reconstruction (9). Their origin is easy to understand when considering the possible multifocal distribution of coagulative necrosis in the infarct border areas (**Figure 2**).

However, the nonreplacement reactive fibrosis occurs without overt loss of myocytes. It forms slowly, flanking remodeling myocytes in various forms of myocardial disorders (10). The morphological spectrum is wide and the distribution throughout the left ventricle wall is variable. The conducting channels are less likely to be encountered on noninvasive imaging as compared with replacement fibrosis. However, nonhomogeneous fibrosis typically occurs in nonischemic cardiomyopathies and inflammatory heart diseases. In end-stage cardiomyopathies, the extent and distribution of fibrosis may appear similar to substitutive fibrosis; the difference, however, is the slowly evolving fibrosis and the absence of overt preceding clinical events.

CONDUCTING CHANNELS AND TARGET ABLATION OF VENTRICULAR TACHYARRHYTHMIAS

The importance of conducting channels might be closely related to the selective target ablation of the areas associated with formation of background circuits (9,11). The elimination of conducting channels is critical to prevent inducibility of ventricular arrhythmias (12), hence the importance of characterization and mapping for ablation. Therefore, the concept of BZ channels, in patients receiving resynchronization therapy, expands the possibility of testing for fibrosis, arrhythmogenic outcomes, and prospective evolution of remodeling of the conducting channels. It is conceivable that resynchronization therapy would result in reverse remodeling and might not need concurrent application of a defibrillator should there be no BZ corridors in ischemic cardiomyopathy (13).

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In this issue of *iJACC,* Acosta et al. (14) report the results of Scar Characterization to Predict Life-threatening Arrhythmic Events and Sudden Cardiac Death in Cardiac Resynchronization