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EDITORIAL COMMENT

Extracellular Volume in Dilated Cardiomyopathy

Interstitial Fibrosis and More?*

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EXTRACELLULAR VOLUME IS EXPANDABLE

In the myocardium, the extracellular volume (ECV) corresponds with the extracellular matrix normally occupied by a tiny network of collagen fibers, sparse cells (mainly fibroblasts), and intramural vessels including capillaries (with a 1:1 myocyte ratio) and arteriolar, venular, and lymphatic vessels (comprised by smooth muscle cells, endothelial cells, and pericytes). Sparse mast cells and macrophages are usually localized around vessels (1). Any condition that modifies the composition of the extramyocyte spaces should modify the relative amount of volume. The quantitative assessment of ECV by cardiac magnetic resonance (CMR) is mainly intended to be a measure of "extramyocyte" volume. The ECV is obtained from changes in the T1 longitudinal relaxation rate before and after administration of the contrast medium (2). The extramyocyte volume expands due to the presence of inflammatory cells and edema in myocarditis (3,4) (**Figure 1A**), whereas the extracellular volume expands due, for example, to interstitial deposition of fibrillar proteins in cardiac amyloidosis (5) (**Figure 1B**). In nonamyloid and noninflammatory myocardial diseases, that is, the cardiomyopathies, among others, the ECV expands due to interstitial fibrosis that characterizes the left ventricular (LV) remodeling processes (6) (**Figures 1C to 1D**). The possibility of imaging the ECV in vivo provides important information about LV remodeling (7–9). The detection of myocardial fibrosis is gaining clinical relevance for its proarrhythmogenic role, particularly in cardiomyopathies.

INTERSTITIAL FIBROSIS IS COMMON IN NONISCHEMIC DILATED CARDIOMYOPATHY

Interstitial (or reactive) fibrosis without manifest loss of myocytes is a common finding in nonischemic dilated cardiomyopathy (DCM) (10). The pattern of distribution of interstitial fibrosis varies from case to case. Specifically, it can surround individual myocytes or bundles of myocytes; it may have a focal, perivascular, or diffuse distribution; or it can predominantly be localized in the subendocardial, subepicardial, or mid myocardial layers of the ventricular myocardium. The topography of the nonreplacement, interstitial myocardial fibrosis does not produce similar or identical patterns (as commonly observed in ischemic myopathy) and each heart with DCM might demonstrate a unique distribution pattern. Furthermore, interstitial fibrosis can be dense or loose. In the former, the collagen fibers are compact, whereas loose collagen fibers seem to be dissociated from each other in a noncompact fashion. Granulation tissue, with angioneogenesis and loose cellular fibrosis, usually follows necrotizing myocardial insults, such as acute myocarditis. Beyond causes and pathogenetic mechanisms that can explain the interstitial fibrosis, the effect is the structural, and therefore electrical, isolation of single myocytes or groups/bundles of myocytes. The "structural" separation of myocytes may constitute the substrate for electrical activity, as it promotes reentry circuits, thereby exerting an arrhythmogenic effect (11).

IN VIVO CORRELATION OF PATHOLOGY AND IMAGING: LIMITATIONS AND CONTRIBUTIONS

The pathological in vivo study of interstitial fibrosis in DCM may be limited to the subendocardial layers in

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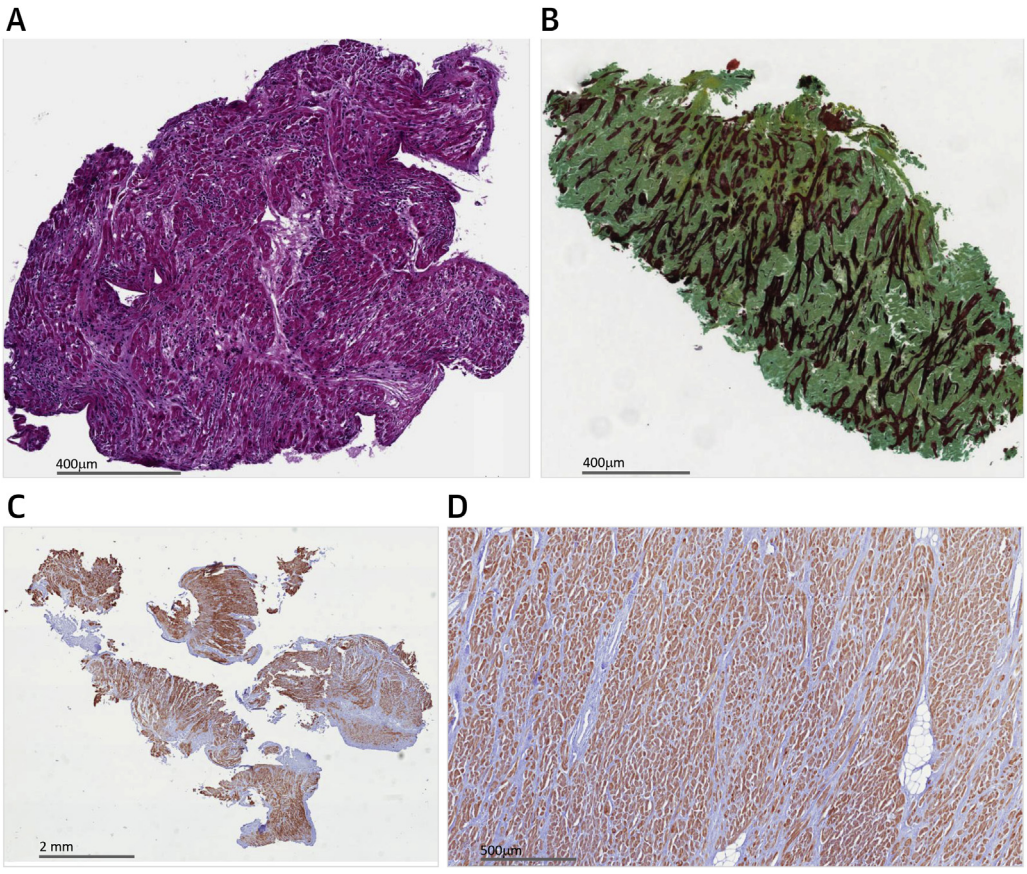
FIGURE 1 **The Extramyocyte Volume**



Extramyocyte volume (EMV) expansion by **(A)** myocarditis, **(B)** cardiac amyloid deposition, **(C and D)** interstitial reactive fibrosis in endomyocardial biopsies (EMB) versus mid-left ventricular (LV) wall in hearts excised at transplantation. **(A)** EMB (hematoxylin eosin stain). Acute myocarditis. The interstitial space is infiltrated by lymphocytes. **(B)** EMB: Wild-type transthyretin cardiac amyloidosis. The EMV is largely occupied by amyloid deposits (depicted in **green** in Movat pentachrome stain). **(C)** Dilated cardiomyopathy: EMB. Antitroponin I immunostain **(brown)**; interstitial fibrosis **(light blue)**. **(D)** Sample from the LV (same case as in **C**) from the heart excised at transplantation. Low magnification view of the mid-ventricle. The fibrosis in the EMB (in **C**) looks quantitatively similar to that of the mid-portion of the LV, in which small spots of adipose tissue are also present.

endomyocardial biopsies (EMB), cover the entire ventricular myocardial walls in hearts removed during cardiac transplantation, and involve the apices of the LV in patients who receive ventricular assist device systems (12) and hearts excised at transplantation after ventricular assist device implantation (13). Each of these conditions has limitations for pathological correlation with in vivo imaging studies. In EMB, the pathological information is limited to a few millimeters of subendocardial cardiac tissue and can be influenced by procedure-related tissue distortion. Specifically, contraction bands induced by the sampling can dislocate intracellular organelles and modify the structural relationships between myocytes and extracellular matrix. If the EMB is performed in the right ventricle, pathological data do not necessarily provide information regarding the LV. The hearts removed for transplantation show the end-stage phenotype of the DCM and, as interstitial fibrosis is dynamic, correlation may be limited by the interval between the last imaging and harvesting of hearts at transplantation. The LV apex samples removed during ventricular assist device implantation provide information on only a portion of the left ventricle (12). Overall, the comparative pathology-imaging studies might not provide sameness of data, but can provide evidence of correlation between fibrosis observed at pathology and fibrosis diagnosed with imaging.

IMAGING–PATHOLOGY CORRELATION STUDIES

In this issue of *iJACC*, Nakamori et al. (14) describe their experience in 36 patients diagnosed with DCM, who underwent both pre- and post-contrast T1 mapping as well as late gadolinium enhanced CMR at 3-T and EMB in a close temporal sequence. Collagen volume fraction and extracellular space were quantified in EMB samples. In 40% of patients diagnosed with DCM demonstrating late gadolinium enhancement, the collagen volume fraction was higher than that observed in patients without late gadolinium enhancement. Both the native T1 value and ECV correlated with biopsy-proven collagen volume fraction ($p < 0.05$). ECV also demonstrated a strong correlation with the extracellular space in EMB ($r = 0.86$)

SEE PAGE 48

versus native T1, which showed a moderate correlation ($r = 0.55$). The comparable ability of native T1 and ECV to detect and measure a collagen volume fraction that correlates with histology indicate that interstitial fibrosis may be assessed by native T1 mapping without administration of gadolinium in patients with DCM (14). The presence of both inflammation and fibrosis may limit the estimation of diffuse myocardial fibrosis (15). Other studies are needed to characterize the pattern of interstitial fibrosis in DCM and to assess whether different distributions and evolving patterns correlate with arrhythmogenic risk, evolution of disease, or worsening of LV function and remodeling (16).

THE EMERGING ROLE OF INTERSTITIAL FIBROSIS IN PROGNOSTIC STRATIFICATION OF DCM

As long as myocardial fibrosis has been confined to a descriptive finding in pathological studies without a real impact in the clinic, its precise characterization has not come to clinical attention. Today, we know that myocardial fibrosis in DCM has a pro-arrhythmic role and its detection in vivo contributes not only in prognostic stratification, but also in therapeutic decisions as well as indications and timing for ICD implantation for primary prevention (17). The contribution of imaging-pathology correlation studies thereby becomes more relevant as the in vivo diagnosis of interstitial fibrosis becomes a potentially worthy component of decision making or monitoring the beneficial effects of medical treatments. For detection and quantification of myocardial fibrosis, CMR is the noninvasive gold standard. In DCM, the lingering question is detectability of tiny, diffuse interstitial fibrosis. In addition, interstitial fibrosis may not coincide with extramyocyte volume, which can differ from fibrosis when edema or inflammation are present. The concept of extramyocyte volume in DCM is emerging from imaging more than from pathology, and consequently the question of whether ECV coincides with interstitial fibrosis is pertinent. Therefore, pathology-imaging correlation studies can still contribute to define the level of detectability of interstitial fibrosis by CMR.

FUTURE RESEARCH

Mapping and monitoring interstitial fibrosis in patients with DCM caused by different etiologies could represent the evolution of translating CMR in clinical practice. The early detection of fibrosis could contribute to risk stratification in disorders such as cardiolaminopathies (18). The concept of "mapping" also implies potential monitoring applications. Therefore, a new dynamic scenario of the natural history of DCM could emerge that predicts both arrhythmogenic risk and worsening of the morpho-functional phenotype. The current study confirms that more pathology-imaging correlation studies are needed to characterize, classify, and consolidate disease-specific patterns of interstitial fibrosis.

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