EDITORIAL COMMENT

Extracellular Matrix Remodeling in Hypertensive Heart Disease*

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Several decades ago, the severity of heart failure was gauged according to a depression in myocardial contractility, defined as that biochemical property of cardiac muscle that determines the extent of shortening independent of its initial length and the load against which it shortens. Mathematical models were used to derive indices of contractility (1). These theoretical constructs included a contractile element tethered to elastic elements that were situated both in series and in parallel to it. Cardiomyocytes, with their actin and myosin protein microfilaments, constitute the myocardium’s contractile elements, whereas fibrillar collagen is the anatomic correlate of these elastic elements.

Cardiomyocytes are interconnected to form a syncytium of branching cardiac muscle fibers. Once depolarized, these fibers generate a force that is transmitted to the ventricle, proportionally translating into a rise in chamber pressure during systole. When this intracavitary pressure exceeds that in the great vessels, blood is propelled into the pulmonic and systemic circulations. The transmission of this systolic force to the ventricle is facilitated by a collagenous scaffolding that provides for the support and alignment of cardiac muscle fibers. Composed predominantly of type I and III fibrillar collagens, this scaffolding is often simply referred to as the extracellular matrix (2); it also contributes to the size and shape of the ventricle and imparts a certain resistance to tissue deformation during ventricular filling. The tensile strength of type I collagen approximates that of steel. Therefore, it is not surprising that matrix is a major determinant of myocardial stiffness during diastole (3,4).

On the basis of its morphologic features, as seen by scanning electron and light microscopy, this contiguous collagenous network has been anatomically subdivided into epicardial, pericardial, and endomysial: the epicardium is located on endocardial and epicardial surfaces of the myocardium, where it respectively provides substrate for endothelial and mesothelial cells; the endomysium extends into the interstitial space to form a perimysium that surrounds and groups muscle fibers while its strands connect groups of muscle fibers to one another; and the endomysium, which arises from the perimysium to surround individual muscle fibers and whose struts tether muscle fibers together, to their nutrient microvasculature, and to cardiomyocyte actin-myosin microfilaments via their cytoskeletal proteins (5,6). The exteriorized portion of the heart’s collagen matrix forms chordae tendineae and valve leaflets that insert into respective annuli of the mitral and tricuspid valves. An efficient muscular pump is created by contractile elements residing within a fibrillar collagen matrix.

Collagen is a stable protein whose balanced turnover (synthesis and degradation) by cardiac fibroblasts is normally slow (estimated to be 80 to 120 days) (7). This balance can be lost under pathologic conditions related, in part, to the appearance of a more active fibrogenic phenotype termed the myofibroblast because it contains alpha-smooth muscle actin microfilaments and is contractile. Myofibroblast collagen turnover is regulated by factors (autocrine and paracrine) generated within the myocardium and by hormones (endocrine) derived from the circulation. For example, angiotensin II produced locally by activated macrophages and myofibroblasts regulates their expression of transforming growth factor-beta1, a fibrogenic cytokine which, in turn, upregulates the expression of type I and III fibrillar collagen genes (8).

In morphologic terms, the accumulation of collagen can present as a reactive fibrosis (e.g., an adverse accumulation of perimysial collagen) or as a reparative fibrosis (i.e., scar tissue) that replaces cardiomyocytes lost to necrotic cell death to preserve the structural integrity of myocardium (reviewed in Weber [2]). Apoptotic cell death, devoid of an inflammatory cell response, is not accompanied by fibrosis. In biochemical terms, fibrosis is expressed as an increase in myocardial hydroxyproline concentration, an amino acid specific to collagen. Depending upon its location and magnitude, collagen fiber crosslinking, and relative abundance of type I and III collagens, fibrosis can adversely increase myocardial stiffness, leading to diastolic heart failure (DHF), or, as more recently coined, heart failure with preserved ejection fraction (EF) (reviewed in Zile and Brutsaert [9,10]). Diastolic heart failure is commonly seen with the concentric hypertrophy that accompanies arterial hypertension. In the dilated (idiopathic) cardiomyopathic heart, a degradation of fibrillar collagen can dominate. This occurs when the proteolytic activity of latent matrix metalloproteinases (e.g., MMP-1) is activated to overcome endogenous tissue inhibitors (e.g., TIMP-1) (reviewed in Spinaled [11]). A loss of fibrillar collagen leads to muscle fiber slippage, a thinning of myocardium, ventricular chamber dilation and spheroidization, and the appearance of systolic heart failure (SHF) with reduced EF.

Hypertensive heart disease (HHD), ischemic heart disease with previous myocardial infarction(s), and a dilated (idiopathic) cardiomyopathy represent the three major etiologic factors that account for heart failure in this country. The failing heart in HHD may present as predominant DHF or SHF. The clinical syndrome congestive heart failure, with its char-

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acteristic signs and symptoms, can accompany either DHF or SHF. Its origins are rooted in a salt-avoid state mediated by effector hormones of the renin-angiotensin-aldosterone system. Left ventricular hypertrophy (LVH) is a distinguishing feature of HHD; so too is fibrosis, which is found throughout the LV free wall, interventricular septum, and right ventricle. It is not the quantity, but rather the quality (structural remodeling) of myocardium that contributes to compromised function and arrhythmogenicity in HHD. Fibrous tissue is morphologically viewed as a perivascular fibrosis involving the intramural coronary arterial vasculature, an interstitial fibrosis (accumulated perimysium), and microscopic scarring (12). Recent studies suggest the amount of fibrous tissue found in HHD with either DHF or SHF can be comparable, whereas the geometric remodeling of the LV chamber and myocardium are quite different (13). This calls into question the balance between MMPs and TIMPs.

In this issue of the Journal, the investigative team of Javier Díez (13) located at the Centre for Applied Medical Research at the University of Navarra in Pamplona, Spain, address this question. They hypothesized that enhanced MMP-mediated collagen degradation contributes to LV dilation and decline in EF seen with SHF in HHD. Toward this end, they used a multifaceted approach to address the presence and magnitude of MMP-1 and TIMP-1 in tissue obtained by transvenous endomyocardial biopsy and the presence of free MMP-1 and TIMP-1 in blood taken from the heart’s major venous effluent, the coronary sinus, and an antecubital vein. In brief, patients with HHD having a clinical diagnosis of heart failure were found to have cardiac fibrosis, but one whose morphologic presentation differed between SHF and DHF. Perivascular fibrosis and scarring occupied a greater portion of myocardium while interstitial (or perimysial) collagen fibers were reduced in SHF. These morphologic findings were accompanied by increased protein expression of MMP-1 relative to TIMP-1 in tissue and blood, suggesting that an imbalance in the MMP-1/TIMP-1 ratio may underlie LV dilation and reduced EF in SHF. This elegant study raises the question as to address appropriate management strategies.

In closing, iterations in the heart’s extracellular matrix can contribute importantly to a structural remodeling of myocardium that leads to ventricular dysfunction during either diastolic or systolic phases of the cardiac cycle. In HHD, an increase in interstitial collagen is associated with DHF, whereas a degradation of endo- and perimysial components of the collagen scaffolding is accompanied by ventricular dilatation and reduced EF, or SHF. A better understanding of the role played by matrix in the failing, hypertrophied heart in HHD will broaden our perspective of its pathophysiologic expressions. The noninvasive monitoring of collagen turnover using serologic markers related to its synthesis and degradation may offer new insights. Factors regulating collagen turnover (synthesis and degradation) in HHD need to be identified so as to address appropriate management strategies.

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REFERENCES