CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Unfolding Discoveries in Heart Failure

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Over the past decade, heart failure with preserved ejection fraction (in which the ejection fraction exceeds 50%) has become increasingly prevalent, accounting for 56% of all cases of heart failure.[1] It is not a precursor stage but a highly persistent phenotype, as evidenced by the negligible transition over time to heart failure with reduced ejection fraction.[2] In contrast with the pharmacologic treatment of the latter, the treatment of heart failure with preserved ejection fraction has been disappointing. Because of its rising prevalence and phenotypic persistence and the absence of effective therapies, the condition is sometimes described as that for which the unmet need for treatment is the greatest in modern cardiology.

In heart failure with preserved ejection fraction, high diastolic left ventricular stiffness is of paramount importance because it causes a brisk rise in left ventricular filling pressures during exercise, lung congestion, and therefore effort intolerance. One model of high diastolic left ventricular stiffness in heart failure with preserved ejection fraction holds that coexisting conditions, especially metabolic conditions, induce coronary microvascular inflammation as part of a systemic inflammatory response.[3] This inflammation is presumed to increase diastolic left ventricular stiffness by increasing the deposition of collagen in the myocardial interstitium and reducing the elasticity of titin (the long, distensible, myofilamentary protein that controls the elasticity of cardiomyocytes).[4] Schiattarella et al.[5] recently unveiled a third mechanism through which coronary microvascular inflammation leads to high diastolic left ventricular stiffness in heart failure with preserved ejection fraction — namely, suppression of the unfolded protein response in cardiomyocytes owing to the expression of inducible nitric oxide synthase. The suppression of this response hinders adequate cellular degradation of destabilized proteins and can lead to their interstitial accumulation, such as occurs in transthyretin amyloidosis, a well-established cause of heart failure with preserved ejection fraction (Fig. 1).

How does fibrosis occur, and how does titin become involved? Microvascular inflammation is accompanied by increased expression of adhesion molecules on the luminal surface of cells. These molecules snag circulating monocytes, which then differentiate into macrophages as they infiltrate the microvasculature and secrete transforming growth factor β (TGFβ). TGFβ turns fibroblasts into myofibroblasts that deposit collagen with high tensile strength, such as that found in scar tissue. Microvascular inflammation also uncouples endothelial nitric oxide synthase, leading to lower levels of nitric oxide and higher levels of reactive oxygen species, which are toxic (Fig. 2). In underlying cardiomyocytes, lower levels of nitric oxide ultimately lead to diminished phosphorylation of titin and cardiomyocyte elasticity. Adding insult to injury is a direct effect of reactive oxygen species on titin: the formation of disulfide bonds within the titin molecule, which also reduces its distensibility. (Although both are nitric oxide synthases, the endothelial and inducible forms have different properties and are expressed in different cell types.)

Schiattarella et al. showed that elevated plasma levels of proinflammatory cytokines boost expression of inducible nitric oxide synthase in cardiomyocytes. Elevated levels of this synthase result in reduced activity of two proteins that control the unfolded protein response: an isoform of the X-box binding protein 1 (XBP1) and inositol-requiring enzyme 1α (IRE1α). The latter splices XBP1 messenger RNA to yield XBP1s. It remains to be demonstrated whether suppression of the unfolded protein response in the cardiomyocyte results in myocardial accumulation of destabilized proteins.

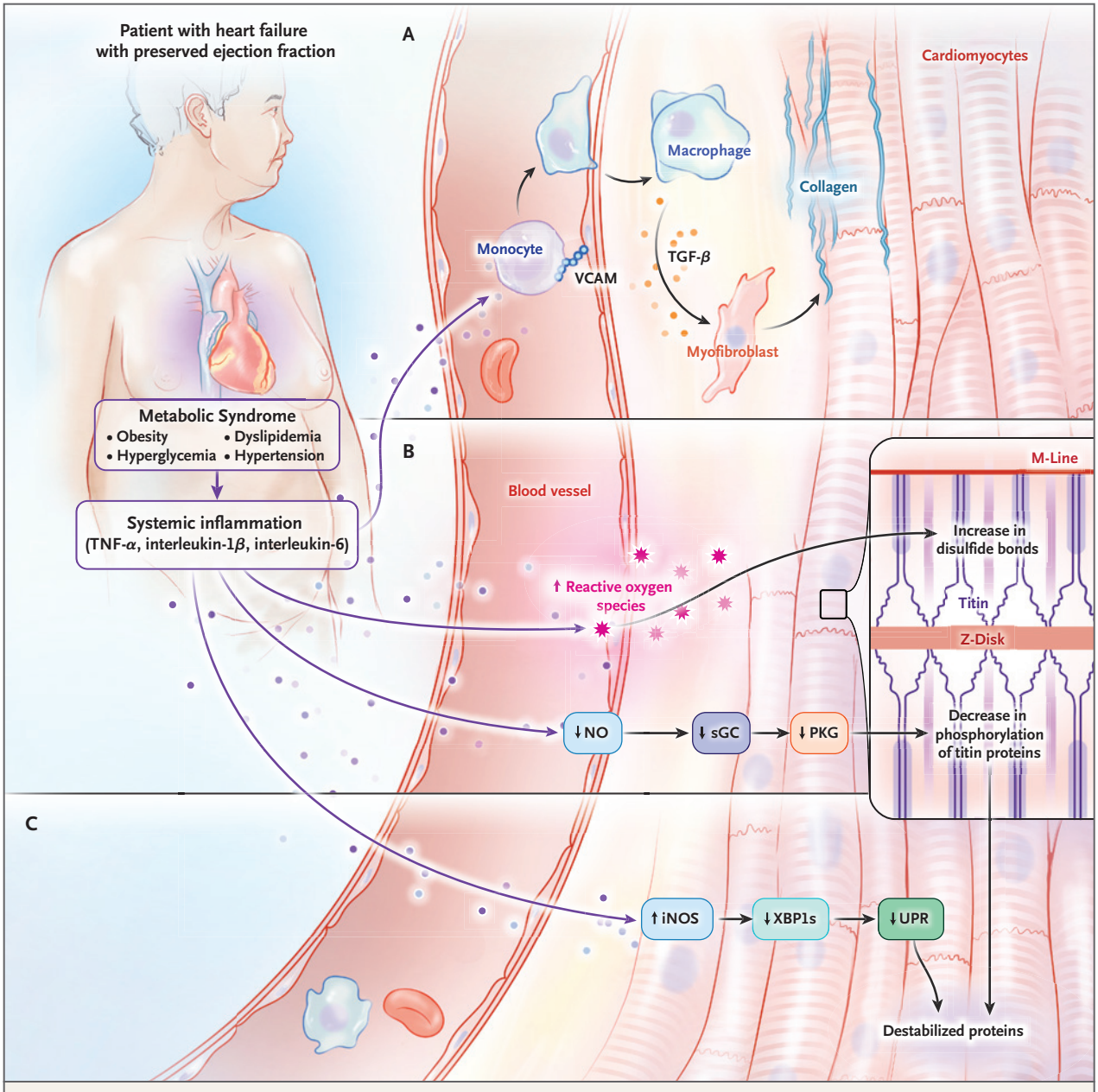

Figure 1. Modeling Routes from Systemic Inflammation to Diastolic Left Ventricular Stiffness.

The deposition of collagen, a key event in fibrosis, is one route by which systemic inflammation leads to diastolic left ventricular stiffness (Panel A). Systemic inflammation triggers expression of vascular-cell adhesion molecules (VCAMs). These molecules snag monocytes that become macrophages that secrete transforming growth factor β (TGF-β), which stimulates myofibroblasts to deposit collagen (Panel A). The rigidification of titin is another route through which systemic inflammation leads to diastolic left ventricular stiffness (Panel B). A study of heart failure with preserved ejection fraction in rats and analysis of myocardial biopsies of specimens obtained from persons with this condition support the view that systemic inflammation, characterized by the presence of tumor necrosis factor α (TNF-α), interleukin-1β, and interleukin-6, is associated with lower endothelial production of nitric oxide (NO) and lower soluble guanylate cyclase (sGC) and protein kinase G (PKG) activity in cardiomyocytes,[6] thereby reducing titin phosphorylation. Systemic inflammation also causes production of reactive oxygen species, which leads to the formation of disulfide bonds within titin. Both hypophosphorylation and the formation of these bonds rigidify titin. Schiattarella et al.[5] recently described a third route to systemic inflammation: a deficient unfolded protein response (UPR). Systemic inflammation boosts expression of inducible NO synthase (iNOS), which in turn lowers levels of X-box binding protein 1 spliced (XBP1s) and suppresses the expression of proteins that execute the unfolded protein response, potentially leading to an accumulation of destabilized proteins that is similar to the accumulation of transthyretin in amyloidosis.

Evidence supporting such accumulation is provided by the elevation of plasma troponin in patients with heart failure with preserved ejection fraction, which is more likely to result from the accumulation of destabilized myofilamentary proteins than from cardiomyocyte cell death (the latter of which has not been observed in myocardial biopsy specimens obtained from patients with heart failure with preserved ejection fraction).

This form of heart failure has been modeled in rats and in large animals such as older dogs with hypertension and pigs with multiple conditions. Schiattarella et al., however, used a mouse model with two "hits." The first hit was a high-fat diet (leading to metabolic compromise) and the second was long-term administration of N^{ω}-nitro-L-arginine methyl ester, which through its potent inhibition of endothelial nitric oxide synthase causes arterial hypertension. This new mouse model durably manifests many of the specific features of clinical heart failure with preserved ejection fraction, such as weight gain with glucose intolerance and a left ventricular ejection fraction (LVEF) exceeding 50% for up to 50 weeks. The importance of metabolic compromise in the development of heart failure with preserved ejection fraction was illustrated by comparing mice in this new model with mice that have transverse aortic constriction, in which "opposite" findings developed, including an elevated level of XBP1s expression in cardiomyocytes and a substantial decline in LVEF, which was evident after only 3 weeks. Both of these observations support the hypothesis that heart failure with preserved ejection fraction is driven by systemic inflammation resulting from coexisting metabolic conditions and not by mechanical overload. The advantage of modeling the disease in mice is that it is relatively easy to test proof of concept through genetic manipulation. Accordingly, Schiattarella et al. genetically suppressed inducible nitric oxide synthase and overexpressed XBP1s in affected mice. Each intervention ameliorated the phenotype with heart failure with preserved ejection fraction: the treated mice had lower left ventricular filling pressures and lower lung weight and could run a greater distance than control mice. Moreover, suppression of inducible nitric oxide synthase confirmed that its suppression decreased the activity of inositol-requiring enzyme 1α through S-nitrosylation, impairing its ability to splice XBP1 messenger RNA to generate XBP1s.

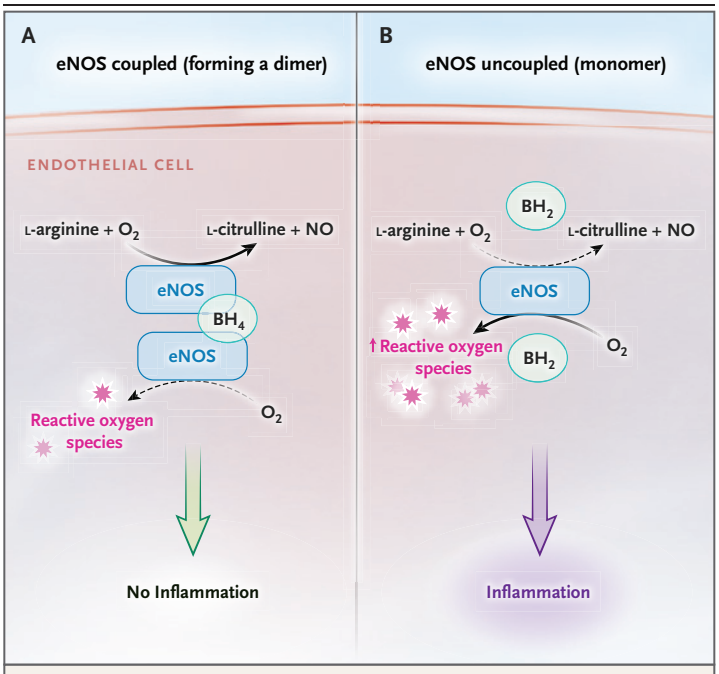

Figure 2. Effect of Inflammation on Nitric Oxide Synthase.

In physiologic conditions, molecules of nitric oxide synthase (eNOS) are coupled through the cofactor tetrahydrobiopterin (BH_4), forming dimers, and the pathway yielding nitric oxide (NO) is favored (Panel A). During inflammation, the dihydrobiopterin BH_4 is not recycled from BH_2, and eNOS dimers uncouple to form monomers (Panel B). Monomeric eNOS favors an alternative pathway that yields reactive oxygen species, instead of converting L-arginine and oxygen to L-citrulline and NO. Underlying cardiomyocytes lose their elasticity because lower levels of NO result in a reduction in the activity of kinase G and thus a reduction in the phosphorylation of titin. The resulting elevation in levels of reactive oxygen species then causes the formation of rigidifying disulfide bonds within titin.

These new insights into the pathophysiological mechanisms of high diastolic left ventricular stiffness support a reset of therapeutic targets in patients with heart failure with preserved ejection fraction. A stratified approach, with alignment of therapy to prevailing mechanisms, should be explored. When myocardial fibrosis is present, antifibrotic therapy could be effective. In the absence of myocardial fibrosis, antiinflammatory therapy or inhibition of inducible nitric oxide synthase may be appropriate. Finally, if the interstitial accumulation of destabilized proteins is confirmed, protein stabilization or inhibition of protein synthesis would represent experimental strategies for treatment.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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