Impact of T Lymphocytes on Cardiac Remodeling in Hypertension
More Questions Than Answers

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In their intriguing article appearing in this issue of Hypertension, Yu et al.¹ provide evidence for a role of T lymphocytes in modulating cardiac matrix remodeling resulting from hypertension. The investigators compared the impact of comparable N⁶-nitro-L-arginine methyl ester (L-NAME)–induced hypertension on cardiac function and matrix composition among 3 strains of mice with widely different T-lymphocyte profiles. They found increased ventricular stiffness, accompanied by enhanced collagen deposition and cross-linking in the strain of mice that were Th2 dominant (BALB/c). In contrast, in mice that were Th- (and B-) lymphocyte deficient (C57BL/6 SCID), hypertension resulted in a diminution of collagen content and cross-linking that was generally associated with heart dilation. No changes in ventricular stiffness or collagen were observed in mice that were Th1 dominant (C57BL/6 WT). Because these different responses of the heart to hypertension were observed under pre-existing dissimilar and extreme immune backgrounds, an obvious question is what impact, if any, T lymphocytes have on hypertension-associated cardiac remodeling in more common scenarios. Will it turn out that the well-established neurohormonal input into cardiac remodeling is actually an immunoneurohormonal system or only that the neurohormonal component of remodeling is susceptible to modulation by extreme immune conditions? Other than this broad question, several specific questions come to mind from the work of Yu et al.

First, how relevant is the use of L-NAME to induce hypertension and cardiac remodeling? Chronic pressure overload of the heart in animal models typically induces changes in the heart that include both increased extracellular matrix deposition and so-called compensatory left ventricular hypertrophy because of enlargement of individual cardiac myocytes.² In contrast, whereas inhibition of NO synthesis with L-NAME causes prominent hypertension, left ventricular hypertrophy does not occur (as in the study of Yu et al.) or is minimal. The reason for this has never been adequately explained but may have to do with reduced venous return. An inhibitory effect of L-NAME on amino acid membrane transporters and protein synthesis likely plays a role too.³ Nonetheless, chronic treatment of rats with L-NAME was found to induce a concentric geometric pattern of cardiac remodeling, characterized by a reduction in left ventricular chamber size relative to wall thickness.⁴ Echocardiography has shown that this pattern is in fact slightly more common than concentric hypertrophy among individuals with arterial hypertension.⁵ Conventional thinking is that the concentric geometric pattern is an early stage, preceding concentric cardiac hypertrophy, in the ongoing remodeling of the heart in response to hypertension that ultimately leads to heart dilation and failure.

A related question is what impact L-NAME had on T-lymphocyte function and subpopulation profile or, more broadly, the immune systems of the different strains of mice? Cytokines are a major means by which cells of the immune system communicate with one another, and NO synthesis is induced by many cytokines, especially interferon (IFN)-γ. Evidence shows that regulated NO signaling is important in the behavior and actions of T cells, in determining the Th1/Th2 balance, and in the interaction between the innate and adaptive immune systems.⁶ In this context, analysis of the cytokine profile and Th1/Th2 ratio (in the BALB/c and C57BL/6 WT mice) over the course of L-NAME treatment, not just before, would be informative. Might that consideration explain the apparent contradiction between the findings of the present study and a previous one by this laboratory? In that study,⁷ evidence was reported that selective induction of Th1 lymphocytes in C57BL/J mice caused increased ventricular stiffness through decreased matrix metalloproteinase (MMP) activity and increased collagen synthesis and cross-linking. In contrast, enhanced MMP activity and decreased collagen synthesis and cross-linking, leading to ventricular dilation and decreased stiffness, was observed with Th2 enhancement.

How might T lymphocytes respond to increased wall stress in the heart? A likely answer is provided by the sequela of L-NAME–induced hypertension, which involves much more than increased vascular tone because of NOS inhibition.⁸ Chronic L-NAME administration has been shown to result in enhanced activity of both the renin–angiotensin and sympathetic nervous systems, as well as enhanced production of prostaglandins and superoxide anions. In addition, L-NAME was shown to upregulate expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in the aorta and to induce inflammatory cell infiltration in the heart.⁹ Thus, the overall consequence of L-NAME administration is a condition of cardiovascular inflammation. The proinflam-
matory actions of L-NAME may be because of increased levels of angiotensin II, which, in unrelated studies, has been shown to have a number of proinflammatory actions, such as inducing the generation of reactive oxygen species and the expression of cytokines, chemokines, and adhesion molecules. Angiotensin II also has direct effects on T cells. In this respect, L-NAME treatment reproduces what is generally seen in hypertension, because a wealth of data implicates angiotensin II–driven inflammation as contributing to the remodeling of the heart and arteries in essential hypertension.

What contribution, then, did other immune cells, in particular neutrophils, macrophages, eosinophils, and mast cells, make to the differences that were observed in cardiac remodeling in the study of Yu et al, and of course what impact did L-NAME have on them? Histological analysis of the remodeled hearts would have not only answered that question but perhaps also explained the progression to heart dilation that was seen with L-NAME treatment in SCID mice. Interestingly, pure diastolic heart failure as defined by a reduced chamber capacitance in the absence of systolic dysfunction has been reported to occur in infiltrative cardiac diseases. Were the L-NAME–treated BALB/c mice in the study of Yu et al on the way to developing diastolic heart failure? Longer treatment with L-NAME should be carried out to answer that question, as well as whether the “nonresponsiveness” of the C57BL/6 WT hearts to hypertension foreshadows a (quicker) progression to heart failure.

Paradoxically, L-NAME administration also induces expression of inducible NO synthase (iNOS), which may be functional and coupled to NO production. Although once considered strictly harmful, iNOS is now recognized as an important mediator of cardioprotection. The balance between the harmful and deleterious effects of NO may be determined by the amount produced and its site of production. Recent evidence suggests that the same may be true of IFN-γ as well. Although IFN-γ has multiple proinflammatory effects, this cytokine appears to have multiple anti-inflammatory actions on cardiac immune responses. As described by Taqueti et al, IFN-γ from Th1 cells may act to upregulate iNOS and NO production by neutrophils, which in turn would inhibit the actions of, or induce apoptosis of effector T cells. IFN-γ may also upregulate expression of receptor molecules on endothelial cells that inhibit T-cell activation. In addition, IFN-γ has direct inhibitory effects on T cells. Could then the lack of cardiac remodeling in the L-NAME–treated C57BL/6 WT mice in the study of Yu et al be attributed to less inflammation in their hearts because of the synergistic effect of L-NAME and IFN-γ from Th1 cells on iNOS expression, as well as NO-independent protective actions of IFN-γ?

The work by Yu et al demonstrates that T lymphocytes are an important determinant of the outcome of cardiac remodeling in response to hypertension. Whereas the inflammatory underpinnings of the cardiac remodeling process in hypertension are already established, their study to my knowledge is the first to demonstrate that the adaptive immune system can play such an active role. Their work raises many questions about how the heart deals with chronic inflammation and the role of cross-regulation of the innate and adaptive immune systems. Answering these questions will hopefully lead to new, more effective therapeutic strategies to prevent or treat heart failure.

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