A prominent pathology textbook used in the United States includes an image illustrating the renal histopathology caused by malignant hypertension. The legend describes striking “onion skin” changes of a renal arteriole. Curiously, a sea of mononuclear inflammatory cells surrounding this arteriole is overlooked both in the legend and in the related text. Moreover, nothing regarding inflammation or immune reactions is discussed. This lack of attention to inflammatory cells is, however, not surprising. Although many experimental studies have implicated inflammation in hypertension, these have largely been performed in experimental animals; there is no proof that inflammation contributes to human hypertension. In fact, some anti-inflammatory or immune-suppressing drugs (eg, nonsteroidal anti-inflammatory drugs and cyclosporine) paradoxically cause hypertension in humans, likely via off-target effects. Often the term “inflammation” is used in the context of cardiovascular disease as a catchall referring to nonspecific phenomena, such as elevation of C-reactive protein or the presence of macrophages in a tissue. Most clinicians and investigators find this vague and difficult to understand. Even more puzzling is that many studies now implicate the adaptive immune response, and in particular, lymphocytes, in hypertension and vascular disease. Traditionally, bacterial, viral, or tumor antigens activate this arm of immune defense. As such, it has been hard to imagine how adaptive immunity could be involved in a disease such as hypertension. In this article, we will attempt to address some of these puzzling questions. We will briefly review components of the innate and adaptive immune response, discuss data from many groups, including our own, that suggest that common forms of hypertension are immune mediated, and provide a working hypothesis of how signals from the central nervous system trigger an immune response that causes hypertension.

General Concepts Regarding Inflammation and Immunity

**Innate Immunity**

The first line of defense against pathogens is the innate immune response. Important components of this system include epithelial cells, which prevent pathogen entry, professional phagocytes (neutrophils, macrophages), the complement system, and pattern recognition receptors. Among the pattern recognition receptors are the Toll-like receptors (TLR) that sense “danger signals” from various pathogens, including double-stranded RNA, bacterial coat proteins, bacterial heat-shock proteins, and other toxins. These are relevant to cardiovascular diseases because they cause dramatic changes in cell signaling that can alter cardiac and vascular function. As an example, oxidized lipoproteins, thought to be important in the genesis of atherosclerosis, share similarities to some bacterial coat proteins and can activate TLR4, which in turn signals a variety of inflammatory responses. Reactive oxygen species (ROS) and reactive nitrogen species, which play critical signal roles in the cardiovascular system, are fundamental components of innate immunity.

**Adaptive Immunity**

In contrast to the innate immune system, the adaptive immune system is highly specific. The traditional concept regarding adaptive immunity is that antigen-presenting cells (APCs) in peripheral tissues take up foreign proteins, such as those of bacteria and viruses, and process them into short peptides that are presented in the context of a major histocompatibility complex (MHC). Activation of CD4+ lymphocytes is predominantly mediated by dendritic cells, which process antigens in phagosomes and present the resultant antigenic peptides within MHC II. Dendritic cells then migrate to secondary lymphoid organs, including the spleen and lymph nodes, where they seek a T cell that has a T cell receptor that recognizes the antigenic peptide. The interaction of the MHC with the T cell receptor occurs at a region termed the “immunologic synapse.” Numerous other ligands and receptors interact at this site, and these promote a coordinated signal that affects both the APC and the T cell. An important additional interaction that occurs at this site, referred to as “costimulation,” involves B7 ligands on the APC (CD80 and CD86) with CD28 on the T cell. Other costimulatory molecules include members of the tumor necrosis factor (TNF) superfamily1 and the inducible costimulator, which helps to sustain T cell activation of B cells.2 In addition to dendritic...
cells, other cells that effectively present antigen include activated macrophages, B cells, and particularly relevant to cardiovascular biology, activated endothelial cells.3,4 As a result of T cell receptor ligation and costimulation, T cells proliferate, produce cytokines, and alter expression of surface receptors that lead to their egress from the secondary lymphoid organs and homing to sites of peripheral inflammation. Helper T cells also bind to B cells and promote antibody formation. In contrast to CD4 cells, CD8 cells are activated by peptides presented within type I MHCs, which are present not only on dendritic cells but also on all nucleated cells. Activated CD8+ cells, referred to as cytotoxic T cells, produce killing molecules such as perforin and granzymes, which cause death of adjacent cells. Like CD4+ cells, CD8+ cells can also produce cytokines that contribute to various pathophysiological processes. Aspects of this classical cellular adaptive immune response are summarized in Figure 1.

**Interaction Between Innate and Adaptive Immunity**

Although it is convenient to think of innate and adaptive immunity as separate, there is actually enormous interplay between the two. The immunologic synapse, described above, involves an interaction between a phagocytic cell of the innate immune system (the APC) and a highly specific T cell of the adaptive immune system. Nitric oxide and ROS, which are components of innate immunity, can modulate T cell function and survival. Cytokines produced by macrophages, dendritic cells, and other cells in the inflammatory milieu can influence T cell polarization and alter T cell function. Molecules such as nitric oxide, superoxide, cytokines, and ligands for TLRs regulate expression of vascular adhesion molecules and chemokines that promote entry of T cells into target tissues. There is also interdependence between macrophages and T cells. As an example, it has recently been recognized that CD8 cell-derived IFN-γ promotes MMP12 expression and macrophage activation in emphysema induced by cigarette smoke.5 We have found that the TH17 cells modulate entry of other inflammatory cells into the vessel in the setting of hypertension (discussed below).6

The reader is referred to excellent textbooks edited by Abbas and Lichtman and Janeway’s Immunobiology for an in-depth review of the principles mentioned above.7

**Relationship Between Oxidation and Inflammation**

From the early 1990s to the present, a great deal of research has been devoted to understanding how oxidative events contribute to hypertension. Many factors common to the hypertensive milieu, including angiotensin II, aldosterone, cytokines, and altered mechanical forces, such as stretch and shear stress, stimulate enzyme sources such as the NADPH oxidases, uncoupled nitric oxide synthase, and the mitochondria to produce ROS that contribute to hypertension.9 In the central nervous system, ROS promote sympathetic outflow. In the vessel, ROS induce vasoconstriction, whereas in the kidney, they cause sodium and volume retention. Although these events alone could cause hypertension, they also enhance inflammatory responses, which as discussed below, further promote blood pressure elevation. ROS activate proinflammatory transcription factors such as Nrf2, NFκB, and API10,11 These in turn modulate expression of genes, includ-
ing those encoding adhesion molecules and chemokines, which prompt tissue accumulation of inflammatory cells. Endothelial permeability is enhanced by oxidative injury, which increases entry of lipoproteins to the subendothelial space, where they are oxidized and enhance inflammation. Oxidized lipoproteins can interact with TLRs, in particular TLR4, to promote vascular disease. ROS can affect T cell polarization and cytokine secretion. Inflammatory cells, such as macrophages and granulocytes, can release ROS, further amplifying an oxidative environment.

In keeping with this interaction between oxidative injury and inflammation, efforts to reduce ROS decrease inflammation. Antioxidants such as the superoxide dismutase-mimetic Tempol have anti-inflammatory effects in myriad models, including carrageenan-induced pleurisy, septic shock, periodontitis, colitis, and encephalitis. An example relevant to hypertension is the study of Liu et al, in which a peptide inhibitor of the NADPH oxidase was shown to lower blood pressure and to prevent macrophage accumulation in rats during angiotensin II-infusion. Recently, Roson et al showed that the acute infusion of sodium caused an increase in renal levels of chemokine ligand 5 (RANTES), NFκB, and angiotensin II in the proximal tubules of rats, and that Tempol markedly reduced these responses.

There is substantial evidence to show that ROS modulate T cell function. Exogenously generated ROS cause apoptosis and suppress T cell proliferation and production of IL-2. Of note, T cells also produce ROS endogenously via a Nox2-based NADPH oxidase, promoting a TH2 phenotype. Our group found that murine T cells produce angiotensin II endogenously, and that this stimulates the T cell NADPH oxidase, which in turn drives production of TNFα. In this case, selective scavenging of superoxide, but not of hydrogen peroxide, lowers TNFα production.

**Neoantigens and Their Potential Role in Cardiovascular Diseases**

The term “neoantigens” was first used in the cancer literature to refer to proteins detected by the presence of antibodies against tumor-associated epitopes. It is often used interchangeably with “autoantigen,” but connotes a special phenomenon in which an endogenous molecule is modified such that it is no longer recognized as self. This could occur in response to the release of a molecule that is generally intracellular, oxidative modification of an endogenous molecule, cleavage of a protein to expose intramolecular sites normally not available for immune attack, or by attachment of a xenobiotic to a molecule in a hapten-like fashion (Figure 1). Such immunoreactive molecules were subsequently found in the serum of humans with cancer, and in inflammatory diseases such as halothane-induced hepatitis, some forms of glomerulonephritis, and osteoarthritis. Molecules suggested to elicit immune responses in atherosclerosis include oxidized low-density lipoprotein, heat shock proteins, platelet glycoproteins, and others, although no specific antigen has been identified with certainty. A recent study has surprisingly shown that the unmodified protein ApoB100 of native low-density lipoprotein can promote an immune response in T cell hybridomas, whereas oxidation of ApoB 100 paradoxically decreases this response.

Special mention should be made of the potential role of heat shock protein (HSP) 70 in hypertension. This molecular chaperone has been intensely studied for more than 40 years and has been implicated in the transport and delivery of antigenic peptides. Various epitopes of HSP70 are immunogenic and induce T cells with anti-inflammatory properties in a neoantigen-like fashion. More than 20 years ago, renal expression of HSP70 was found to be increased in hypertensive animals. HSP70 expression is increased by restraint stress in rats and is elevated in lymphocytes of hypertensive humans. The precise role of HSPs in hypertension remains to be defined but might involve antigen presentation and an ultimate immunologic response.

**Early Studies Supporting a Role of Adaptive Immunity in Hypertension**

Alterations of the immune response have been implicated in the genesis of hypertension for more than 4 decades. For the reader’s convenience, some of these are summarized in Table. In the 1960s, Grollman et al showed that immunosuppression attenuates hypertension in rats with partial renal infarction. The investigators identified antibodies to renal tissue in these animals, and showed that transfer of lymph node cells from rats with renal infarction causes hypertension in normal recipient rats. Several early studies focused on immune perturbations in the spontaneously hypertensive rats (SHR) and suggested that T cell function is paradoxically depressed in this commonly-studied model of genetic hypertension. Of note, Ba et al found that engraftment of normal thymus into SHR restored T cell function and lowered blood pressure. These investigators found that SHR harbored an antibody that was cytotoxic to thymocytes and proposed that this might produce immune suppression. These studies preceded the understanding that some T cells might be suppressive, and thus did not examine T cell subtypes. It is therefore possible that the analyses of T cell function employed in these studies could have missed activation of certain T cell subtypes. Interestingly, the rate of nerve growth into the thymus in young SHR is enhanced compared to Wistar Kyoto rats, suggesting that neural activation of T cells is increased in hypertension. In keeping with a role of immunity in SHR, Bendich et al found that treatment with antithymocyte serum lowers blood pressure in these animals. The immunosuppressant cyclophosphamide also transiently lowers blood pressure in SHR.

Several early studies suggested that T cells are also important in mineralocorticoid-induced hypertension. These showed that although the initial elevation in blood pressure in response to deoxycorticosterone acetate and salt administration is similar between athymic nude mice and normal mice, the athymic, immune-deficient mice do not sustain hypertension. Subsequent experiments showed that transfer of splenocytes from rats with deoxycorticosterone acetate-salt hypertension raises blood pressure in recipient rats.

Despite these compelling early observations, there seemed to be a lack of additional advancement in understanding the role of immunity and inflammation in hypertension in the...
In these studies, we found that chronic angiotensin II infusion increases the percent of cells CD69 and CCR5 positive and CD44high T cells in the circulation. These are markers of activated, effector T cells. Interestingly, angiotensin II also markedly increased vascular levels of RANTES. Thus, like many inflammatory stimuli, hypertension has a dual effect: one is to promote T cell activation, and the second is to increase chemokine and adhesion molecule expression in target tissues to promote tissue entry of activated inflammatory cells. In keeping with this, hypertension also causes a marked infiltration of CCR5+ cells into perivascular fat.55 In preliminary studies, we have also found that hypertension promotes RANTES expression in perivascular fat.

In addition to angiotensin II–induced hypertension, we have also found that T cells are essential for development of deoxycorticosterone acetate-salt and norepinephrine-induced hypertension.55,56 These findings emphasize that many forms of hypertension, beyond that induced by angiotensin II, have an inflammatory component requiring T cells.

More recently, Crowley et al have examined the hypertensive response in mice that have severe combine immunodeficiency.57 These animals have a genetic abnormality leading to abnormal somatic recombination, such that they do not develop T or B cells, in a manner similar to RAG-1−/− mice. Crowley et al confirmed that T cells are essential for full development of angiotensin II–induced hypertension, and showed that these animals have reduced left ventricular hypertrophy, reduced cardiac fibrosis, and reduced albuminuria following angiotensin II administration. Other histological parameters of renal injury are reduced or absent in severe combine immunodeficiency mice. Importantly, the investigators showed that the pressure diuresis and natriuresis caused by hypertension is greater in severe combine immunodeficiency mice than in wild-type mice. This is associated with a marked increase in expression of the endothelial isoform of ANG II also markedly increased vascular levels of RANTES.
nitric oxide synthase and nitric oxide production in kidneys of severe combine immunodeficiency mice.

Role of Cytokines in Hypertension
Based on our own studies and those such as Crowley’s, a working hypothesis has emerged in which hypertensive stimuli promote accumulation of activated T cells in perivascular fat and in the kidney. In these sites, these cells release cytokines that affect adjacent vascular cells and tubular epithelium in the kidney. In keeping with this concept, several recent studies have supported the concept that cytokines produced by T cells and other inflammatory cells contribute to hypertension. The TNF-α antagonist etanercept reduces the hypertension caused by fructose feeding,58 prevents vascular dysfunction, and blunts the hypertension caused by angiotensin II,55 as well as lowers blood pressure in an autoimmune model of chronic inflammation.59 In some cases, TNF-α antagonism prevents end-organ damage without lowering blood pressure. As examples, etanercept prevents renal injury in salt-dependent hypertension without lowering blood pressure,60 and reduces albuminuria and renal inflammation in a transgenic hypertensive rats.61 Interleukin-6 has also been implicated in angiotensin II–induced62–64 but not salt-sensitive hypertension.65 More recently, we found that the novel, proinflammatory cytokine IL-17 contributes to hypertension. This cytokine is produced by TH17 cells, a subset of CD4+ T cells, which are distinct from TH1 and TH2 cells. IL-17 has been implicated in a variety of diseases including rheumatoid arthritis, inflammatory bowel disease, psoriasis, and airway inflammation.66 IL-17 is also made by CD8+ cells,67 neutrophils,68 and natural killer T cells.69 We found that the increase in blood pressure in mice lacking IL-17 (IL-17−/− mice) is similar to that observed in wild-type mice, but that IL-17−/− mice do not sustain hypertension. Moreover, the increase in superoxide production and reduction of endothelium-dependent vasodilatation observed in wild-type mice does not occur in IL-17−/− mice. IL-17 promotes chemotaxis of other inflammatory cells, in part by stimulating release of chemokines.70,71 In keeping with this, we found that the vascular accumulation of leukocytes (including T cells) caused by angiotensin II is markedly reduced in IL-17−/− mice. Thus, IL-17 might contribute to the vascular pathophysiology of hypertension not only by its direct effects, but also by recruiting other inflammatory cells to the perivascular tissue.

Role of T Regulatory Cells and IL10 in Hypertension
In addition to TH1 cells, another subset of CD4+ cells that differ from the TH1 and TH2 subsets are T regulatory cells (Tregs). These cells, characterized by expression of the forkhead transcription factor FoxP3 and surface expression of CD25, play a critical role in maintaining self-tolerance.72 Genetic deletion of these cells by ablation of FoxP3 leads to a severe, fatal lymphoproliferative disorder.73 Recent studies have suggested that Tregs have a protective effect in hypertension. Kvaken et al found that adoptive transfer of these cells did not affect the hypertensive response to angiotensin II, but it had marked effects on the cardiac damage caused by angiotensin II. Treg adoptive transfer reduced the cardiac inflammation, hypertrophy, and fibrosis caused by chronic angiotensin II–induced hypertension.74 The authors also showed that Treg adoptive transfer reduced the percent of circulating activated T cells and improved electric stability during angiotensin II infusion.

Recently, Viel et al studied rats harboring the Dahl salt-sensitive (SS) genome except for chromosome 2 of the Brown Norway strain (SSBN2) rats.75 Chromosome 2 contains genes associated with both hypertension and inflammation and has quantitative trait loci for hypertension. The authors found that SSBN2 rats have reduced hypertension, fewer inflammatory cells in the aorta, and less vascular hyper trophy than do Dahl SS rats. They also showed that the aorta of these animals has more aortic Treg cells as evidenced by an increase in mRNA for FoxP3b compared with Dahl SS animals. IL-10 represents an important anti-inflammatory cytokine that both induces and is produced by Treg cells. Tregs of SSBN2 rats were found to produce more IL-10 than did Tregs from Dahl SS rats. The authors concluded that Tregs play an important role in mitigating both blood pressure elevation and end-organ damage in the SSBN2 animals. In keeping with an important protective role of IL-10, Didion et al found that incubation with angiotensin II causes marked endothelial dysfunction of carotid arteries from IL-10−/− mice, but does so without altering endothelium-dependent vasodilatation of arteries from normal mice.76 These investigators further showed that angiotensin II increases vascular superoxide production in IL-10−/− mice, but not in wild-type animals.

Central Nervous System and Inflammation: Concept of Inflammatory “Priming” in Hypertension
Several studies have linked the central nervous system to inflammation. Lymph nodes and the spleen are richly innervated with sympathetic nerves that terminate in T cell rich areas.77,78 The principal neurotransmitter released at the sympathetic nerve terminal is norepinephrine, which can both inhibit and stimulate T cell activation and proliferation.79 The pre-existing state of the T cell seems to determine the ultimate effect of β-adrenergic activity. Norepinephrine stimulates naïve CD4+ lymphocytes cultured under TH17-promoting conditions to produce 3- to 4-fold more IFNγ than in nonstimulated cells.80 Importantly, Ganta et al have shown that intracerebroventricular administration of angiotensin II increases splenic sympathetic nerve activity, which in turn increases mRNA expression of IL-1, IL-2, IL-6, IL-16, and TGF-β1 in splenocytes. Splenic sympathectomy abrogates these responses, clearly linking the central effects of angiotensin II to peripheral immune activation.81 Fannon and Phillips showed that prolonged infusions of either substance P or angiotensin II into the brains of Sprague-Dawley rats increased the percentage of circulating T cells, while also decreasing circulating B cells.82

Recently, we performed additional studies to understand the link between central nervous system stimulation, inflammation, and hypertension. In initial studies, we sought to enhance the central effects of angiotensin II by deleting...
Hypertensive stimuli
Eg. Ang II, High Salt, ROS, etc.

CNS
Sympathetic Activity
Blood Vessels
Kidneys

Oxidation, altered mechanical forces protein fragment-ation, etc.

nAg

Dendritic Cell
Neoantigen formation
and antigen presentation
T Cell
T cell proliferation, migration
and infiltration

Pre-Hypertension
Overt hypertension and inflammation

Figure 2. Proposed role of T cells and inflammation in hypertension. Hypertensive stimuli such as angiotensin II and salt cause a modest elevation in pressure (prehypertension), in large part because of central stimuli and via direct effects on the kidney and vasculature. We hypothesize that this leads to neoantigen formation, promoting T cell activation as shown in Figure 1. Activated T cells enter the kidney and vasculature. T cell–derived signals such as IL-17 promote entry of other inflammatory cells such as macrophages. These inflammatory cells release cytokines that cause vasoconstriction and promote sodium and water absorption, ultimately causing severe hypertension.

The CVO, and in particular the subfornical organ, contain an NADPH oxidase that produce ROS, which in turn promote sympathetic outflow. Administration of an adenovirus encoding Cre recombinase, we were able to delete SOD3 specifically from the CVO in these mice. This increased sympathetic outflow, as estimated by analysis of blood pressure variability, caused a modest elevation of blood pressure at baseline, and markedly enhanced the hypertensive response to a low dose of angiotensin II (140 ng/kg per min) that alone had minimal to no effect on blood pressure. More importantly, whereas this dose of angiotensin II did not affect activation of T cells or vascular infiltration alone, following deletion of SOD3 in the CVO, there was a marked increase in circulating T cells bearing CD69 and CD44high, and a striking increase in vascular infiltration of inflammatory cells. There was also a striking elevation of the percent of circulating double-negative (CD3−, CD4−, CD8−) T cells. The precise role of these double-negative T cells remains unclear, but in other settings they promote inflammation, and we find that they represent up to one third of vascular infiltrating T cells in hypertension. Thus, these experiments clearly show that

central stimuli promote the systemic inflammatory response to angiotensin II.

For additional study of the role of the central nervous system in peripheral vascular inflammation, we created lesions of the anteroventral 3rd ventricular (AV3V) region in mice. Lesions in this region prevent almost all forms of experimental hypertension, and we found that they markedly blunted the hypertensive response to high-dose angiotensin II (490 ng/kg per min). AV3V lesions also prevented activation of circulating T cells and the infiltration of leukocytes caused by angiotensin II. This finding was quite revealing, because it showed that the direct actions of angiotensin II on T cells and peripheral tissues are not responsible for the inflammation caused by this octapeptide, but that its central actions are required. In contrast to angiotensin II, AV3V lesions did not prevent the hypertension, circulating T cell activation, or the leukocytic vascular infiltration caused by chronic norepinephrine infusion. These findings could have been explained in 2 ways. First, it is possible that the systemic inflammation caused by angiotensin II is caused by increased sympathetic outflow, or perhaps by other central signals, which were blocked by the AV3V ablation. In this case, norepinephrine administration “by-passed” the effect of the central lesion by directly acting on peripheral adrenergic receptors in a fashion suggested by Ganta et al. Another possibility is that angiotensin II–induced T cell activation and vascular inflammation is a direct effect of blood pressure elevation, which was prevented by AV3V-lesioning. To differentiate between these 2, we administered hydralazine to prevent the hypertensive response to angiotensin II or to norepinephrine. In both cases, hydralazine completely prevented T cell activation and vascular accumulation of inflammatory cells. This was not because of a direct effect of hydralazine on T cell activation,
as hydralazine did not alter the immunologic response in another model of ovalbumin immunization.

Based on these studies in which we both increased and decreased the central effects of angiotensin II, we have proposed a new paradigm to explain how hypertensive stimuli promote inflammation and elevations in blood pressure in a 2-step, feed-forward fashion. This working hypothesis is summarized briefly in Figure 2. We suggest that stimuli such as angiotensin II, sodium, and others cause a modest elevation in blood pressure to values of ~135 to 140 mm Hg. These initial elevations in pressure are largely because of central actions, but also require direct effects of angiotensin II on peripheral sites. This first phase of modest pressure elevation, often referred to as prehypertension, brings about an inflammatory response, likely by generating neoantigens that activate T cells. This inflammatory response leads to entry of effector-like T cells into the perivascular fat and the kidney. Macrophage infiltration is also promoted, in part because of signals from T cells. Cytokines and other inflammatory mediators released by these cells work in concert with the direct effects of angiotensin II, catecholamines, and salt to cause vascular and renal dysfunction, promote vasoconstriction, vascular remodeling; this causes a shift in the pressure-natriuresis curve and sodium retention, promoting a second phase of severe, sustained hypertension. The inflammatory response in hypertension is very dependent on oxidative events, and is modulated by up- and down-regulation of critical ROS-generating enzymes such as the NADPH oxidase and by administration of antioxidant such as tempol, superoxide dismutase or etsobolin. One possibility is that oxidative modification of proteins, lipids, or DNA causes neoantigen formation, which initiates the second wave of hypertension illustrated in Figure 2.

Conclusion

This review summarizes a growing body of research supporting a role of inflammation and immunity in hypertension and cardiovascular disease. As reflected in Figure 2, we propose that inflammation and immune activation represent responses to modest elevations of blood pressure that are generally considered benign. We emphasize that the paradigm shown in Figure 2 represents a working hypothesis, and is likely simplistic. Our data and those of others, however, currently support this proposal. They also support the importance of the clinical condition commonly referred to as “prehypertension,” which although controversial, likely represents a condition in which inflammation initiates a more severe hypertensive state. This emphasizes the benefit of lowering blood pressure by virtually any therapeutic approach and by preventing even the most modest elevations in resting blood pressure. More importantly, it is conceivable that immunotherapy might be useful to treat severe forms of either resistant or malignant hypertension. It is even conceivable that vaccination might be used to prevent hypertension in the future.

Acknowledgments

We appreciate editorial comments of Dr. William Lewis, Department of Pathology, Emory University, Atlanta, GA.

Sources of Funding

This work was supported by grants NIH R01HL039006, P01HL058000, and P01HL095070. P.J.M. and M.M. were supported by NIH F32 post-doctoral fellowship grants. S.T., H.L., and A.V. were supported by post-doctoral fellowships from the American Heart Association. T.J.G. was supported by the European Molecular Biology Organization Young Investigator Program and the Polish Ministry of Science and Technology.

Disclosures

None.

References


