Structural Remodeling in Hypertensive Heart Disease and the Role of Hormones

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Abstract In hypertension, the risk of adverse cardiovascular events, including heart failure, is increased in the presence of left ventricular hypertrophy. Morphological studies suggest that it is not the quantity but rather the quality, or structure, of myocardium that confers such risk. Iterations in tissue structure that appear in hypertensive heart disease include a remodeling of intramyocardial coronary arterioles, similar to that found in systemic organs, and a disproportionate accumulation of fibrillar collagen within their adventitia and neighboring interstitial space. Microscopic scars replacing necrotic cardiac myocytes are also evident. These expressions of fibrosis appear in the normotensive, nonhypertrophied right and hypertensive, hypertrophied left ventricles and are linked to the renin-angiotensin-aldosterone system. Cardiac myocyte growth, the major determinant of myocardial mass, is related to ventricular loading. Mechanisms responsible for the reactive and reparative fibrosis with renin-angiotensin-aldosterone system activation are under investigation. In vitro quantitative autoradiography has identified angiotensin II, aldosterone, endothelin, and bradykinin receptors in the myocardium. A nonendothelial tissue angiotensin-converting enzyme, whose binding density is marked in the matrix of heart valves, adventitia, and sites of fibrosis, irrespective of its pathogenic basis, has also been found. This angiotensin-converting enzyme may be responsible for regulating local concentrations of angiotensin II and bradykinin that govern fibroblast collagen turnover. Based on a paradigm of discordant reciprocal regulation in which a relative abundance of stimulators (eg, angiotensin II, aldosterone, and endothelins) of collagen synthesis exceeds inhibitors (eg, bradykinin, prostaglandins, and glucocorticoids), fibrous tissue appears. Chronic elevations in circulating and/or local concentrations of stimulator hormones represent a wound-healing response that has gone awry, with adverse fibrosis the outcome in hypertensive heart disease.

Key Words • angiotensin-II • aldosterone • hypertrophy • angiotensin-converting enzyme • angiotensin II • aldosterone

The appearance of symptomatic heart failure and adverse cardiovascular events, such as myocardial infarction, sudden cardiac death, and stroke, occur with increased frequency in patients with systemic hypertension. For years, the pathophysiological basis for such increased risk has been presumed to be solely related to elevated arterial pressure. More recently, emphasis in conferring risk has been placed on the structural remodeling of the cardiovascular system. For example, in patients with uncomplicated hypertension, risk has been linked to left ventricular hypertrophy (LVH). Viewed not as a separate organ but as an integral component of the cardiovascular system, the heart and its intramyocardial coronary arteries and arterioles participate in a structural remodeling that involves systemic organs as well. The remodeling of systemic arterioles accounts for hypertensive heart disease. The heart in turn responds to enhanced ventricular loading with a hypertrophic growth of cardiac myocytes, and accordingly, left ventricular mass is increased. The diffuse nature of the structural remodeling process, involving the right and left ventricles and systemic organs, suggests a role for circulating substances or substances produced locally within cardiovascular tissue. In this connection, it is noteworthy that risk has also been linked to an activation of the renin-angiotensin-aldosterone system (RAAS). Why is it that both LVH and RAAS activation enhance risk when each are normal adaptive responses? Comparable increments in ventricular mass are a normal adaptation to exercise training, in which ventricular function is not impaired but perhaps even enhanced. Similarly, RAAS activation is a homeostatic adaptation to sodium deprivation and/or intravascular volume contraction.

Microscopic examination of the myocardium in patients with hypertensive heart disease, obtained postmortem or by endomyocardial biopsy, indicates that not only is the quantity of myocardium increased, but its quality, or structure, is abnormal and accounts for abnormal myocardial stiffness and coronary vasodilator reserve. Physiological studies in experimental animals have shown that abnormal myocardial structure, expressed as a disproportionate accumulation of fibrillar collagen, will adversely alter myocardial stiffness and ventricular function and that alterations in structure are linked to effector hormones of the RAAS. This is not the case for an appropriate activation of the RAAS that accompanies inadequate dietary sodium but is related to chronic elevations in circulating angiotensin II (Ang II) and/or aldosterone that are inappropriate for normal or enhanced dietary Na+ intake. Both the hypertensive, hypertrophied left ventricle and normotensive, nonhypertrophied right ventricle are involved inasmuch as each ventricle is a target for these circulating hormones. Cell culture studies, in which hormonal regulation of cell metabolism and mitogenesis have been demonstrated in the absence of hemodynamic factors, further advance the view that the RAAS could regulate tissue structure.
For the heart, a nonclassic target tissue, to respond to Ang II, aldosterone, or other relevant peptides (eg, endothelins and bradykinin), the presence of specific hormone receptors is required. Receptors for Ang II, aldosterone, endothelins, and bradykinin have been identified in the heart.27,31 The heart also has the capacity to generate Ang II,32 bradykinin,33 and endothelin.34 Locally generated hormones therefore could alter tissue structure in an autocrine and/or paracrine manner. In addressing mechanisms responsible for hypertensive heart disease, nonclassic actions of circulating or locally generated effector hormones of the RAAS must be considered. Increased arterial pressure alters the myocardium insofar as it leads to cardiac myocyte hypertrophy.

In this review we will address the structural remodeling of the myocardium found in hypertensive heart disease (HHD) and evidence implicating a role for effector hormones of the RAAS in contributing to this remodeling. Finally, we will consider hormone receptor binding in the myocardium—a nonclassic target tissue for nonclassic effects of Ang II and aldosterone.

**Structural Remodeling in Hypertensive Heart Disease**

An increase in ventricular mass, in the absence of other responsible etiologic factors, is an essential first criterion in defining HHD.

**Structural Remodeling**

The myocardium has three compartments—muscular, vascular, and interstitial—each contributing to tissue homogeneity. Iterations in compartment composition and structure lead to tissue heterogeneity, with deleterious consequences on myocardial stiffness and ventricular function. Cardiac myocytes of the left ventricle are enlarged in HHD. This is expressed as an increase in myocyte cross-sectional area due to the in-parallel addition of myofibrillar units.35 Myocyte hyperplasia has been observed in long-standing hypertension.36 Right ventricular myocytes remain normal in size until a pressure overload, caused by pulmonary venous hypertension and left ventricular failure, is present. Myocyte growth in either ventricle is most closely related to ventricular loading.22

Much like systemic arteries and arterioles, coronary resistance vessels are remodeled in HHD.4-7,29 There exists a medial thickening and perivascular fibrosis of intramyocardial coronary arteries and arterioles. Medial thickening is caused by hypertrophy and/or hyperplasia of vascular smooth muscle cells. A structural realignment of these cells with enhanced accumulation of extracellular structural proteins (ie, collagen and elastin) may also contribute.5,38,39 Other features of this vascular remodeling include intimal hyalinization and endothelial hyperplasia.5 Collectively, these changes in coronary resistance vessels serve to reduce their ratio of wall thickness to lumen and adversely influence their capacity for vasodilatation.51

An interstitial fibrosis is another feature of the adverse structural remodeling of the myocardium found in HHD. The pathological accumulation of collagen has several distinct morphological presentations.15-37 It appears around intramyocardial coronary arteries and arterioles, where it represents a perivascular fibrosis. From this perivascular location fibrillar collagen extends into the interstitial space, where it represents an interstitial fibrosis. This is a progressive process involving ever-increasing amounts of the interstitium.40 This reactive fibrosis is found throughout the free wall of the left ventricle and interventricular septum.46 The nonhypertensive, nonhypertrophied right ventricular free wall is involved as well. Individual muscle fibers in both ventricles become encircled by thickened collagen fibers, which impairs their ability to be stretched and to contract. Ultimately, this leads to myocyte atrophy.41 Transvenous endomyocardial biopsy of the interventricular septum has been used to detect this structural remodeling of intramyocardial coronary arterioles and interstitial space in HHD,18,42 in which the increase in collagen volume fraction has been correlated with abnormal diastolic function of the left ventricle.19,20

Quite distinct from this perivascular/interstitial fibrosis are discrete focal collections of fibrillar collagen that often appear within the endomycardium. They represent microscopic scars that replace lost cardiac myocytes and preserve the structural integrity of the myocardium. A similar reactive and reparative fibrosis of the myocardium has been observed in various models of experimental HHD. This includes rats with surgically induced unilateral renal ischemia, in which plasma Ang II and aldosterone are each increased43-47 and both the hypertensive, hypertrophied left ventricle and normotensive, nonhypertrophied right ventricle are affected.45 This implicates a role for these circulating hormones. Captopril prevents this remodeling process in renal ischemia.41 Bilateral renal ischemia, created by supraprenal abdominal aortic banding, is associated with an increase in myocardial collagen synthesis48 that could be prevented by digitoxin.49 This agent would not be expected to reduce arterial pressure; however, it may interfere with the effect of mineralocorticoids. Expression of types I and III collagen mRNAs, the major fibrillar collagens of the myocardium, is increased within days after surgical induction of unilateral renal ischemia50 and is followed by accumulation of fibrillar collagen in perivascular and interstitial locations weeks later.

Pathological fibrous tissue accumulation, however, does not accompany the pressure-overload hypertrophy induced by infrarenal aortic banding.45 It likewise does not appear with either the volume-overload hypertrophy associated with uninephrectomy and a high Na+ diet,46 a compensated arteriovenous fistula,54,55 chronic anemia,52 atrial septal defect,53 or the hypertrophy induced by chronic thyroxine administration.52,54 In each of these latter circumstances the RAAS is not activated.

A perivascular fibrosis of both ventricles and systemic arterioles has been observed in uninephrectomized rats on a high Na+ diet that received either d-aldosterone54,55 or deoxycorticosterone acetate for weeks.56 In these models of chronic mineralocorticoid excess, plasma renin activity and Ang II would each be suppressed. In rats receiving aldosterone, its receptor antagonist spironolactone prevented the perivascular fibrosis of the myocardium. This outcome was observed for both a small dose of spironolactone, which did not prevent hypertension or LVH, and a large dose, which
achieved these end points. To further address the role of arterial pressure, captopril was used to prevent hypertension in rats receiving aldosterone for 8 weeks; given the independent source of aldosterone, captopril did not interfere with the effects of this hormone, and as a result it did not prevent the reactive myocardial fibrosis.

To further address the role of Ang II and aldosterone in promoting myocardial fibrosis, either hormone was administered to rats by implanted minipump in suppressor doses that did not induce an initial elevation in arterial pressure but did increase plasma Ang II and aldosterone levels. Cardiac myocyte injury, as evidenced by abnormal sarcolemmal permeability to myosin antibody or plasma fibronectin, was observed within 24 hours of the exogenous elevation in circulating Ang II. Whether myocyte toxicity was due to a direct or indirect (eg, via catecholamine release) response to Ang II remains to be clarified. In hearts examined at 2, 4, and 6 weeks of hormone treatment, important differences in the temporal appearance of fibrosis were identified. Within 2 weeks of the nonpressor dose of Ang II (see Fig 1), microscopic scars, as well as a perivascular fibrosis of intramural coronary vessels, were present in both ventricles. The fibrous tissue response became more extensive as animals continued to receive Ang II for 4 and 6 weeks. In uninephrectomized rats on a high Na+ diet receiving aldosterone, reactive and reparative fibrosis were also present in both ventricles, but not until 4 weeks. These morphological expressions of fibrosis became more extensive at 6 weeks.
of aldosterone treatment. Thus, although fibrosis was seen in both ventricles with both Ang II and aldosterone models, a combined elevation in circulating Ang II and aldosterone led to a more rapid appearance of the perivascular fibrous tissue response than the elevation in plasma aldosterone alone. Pathogenic mechanisms involved in each case require further investigation.

Spironolactone and amiloride each have K⁺-sparing effects through different mechanisms of action. Each was found to prevent the appearance of microscopic scarring and, by implication, cardiac myocyte necrosis in rats treated with aldosterone for 8 weeks.60,61 Dietary KCl supplementation has a similar protective effect, which has been interpreted to underscore the importance of myocardial K⁺ depletion in leading to the late appearance of myocyte loss in this model of chronic mineralocorticoid excess.62 On the other hand, only spironolactone prevented the perivascular fibrosis,57,64 which is in keeping with another mechanism responsible for this reactive fibrous tissue response.

The results of these various in vivo studies suggest the following: (1) hypertrophy, or the increment in ventricular mass based on cardiac myocyte growth, is regulated by ventricular pressure or volume loading; (2) perivascular fibrous tissue formation is associated with chronic elevations in circulating effector hormones of the RAAS, not arterial hypertension; (3) fibrosis that follows myocyte necrosis is related to toxicity associated with increased plasma Ang II58-59 and to myocardial K⁺ depletion that accompanies chronic mineralocorticoid excess62; and (4) separate regulatory controls determine whether hypertrophy involves a preservation or distortion in tissue structure and accordingly whether LVH will be adaptive or pathological.53

Hormone Receptors in the Myocardium

Autoradiographic Detection

Quantitative in vitro autoradiography has helped identify the presence of Ang II (Fig 2A), endothelin (Fig 2B), aldosterone (Fig 2C), and bradykinin (Fig 2D) receptor binding in the normal rat myocardium.27-30,63 Endothelin receptor binding density was found to be high and widely distributed throughout the myocardium, suggesting that these receptors are probably localized in vascular endothelial cells and/or cardiac myocytes. Ang II (subtype 1 receptor), aldosterone, and bradykinin receptor binding are likewise widely distributed but of lower density. Ang II receptor binding, on the other hand, is marked in sinoatrial and atrioventricular nodes.64 Aldosterone receptors have been localized to cardiac myocytes, endothelial cells of the endocardium, and cardiac fibroblasts.65 The cellular origin of bradykinin receptor presently remains unknown. Endothelin, Ang II, and bradykinin receptors have each been identified in coronary resistance vessels.66 These findings suggest that the heart and its microvessels and specialized conduction tissue are "targets" for receptor-mediated effects of Ang II, aldosterone, endothelins, and bradykinin.

Ang II receptor binding in the myocardium was decreased in animals receiving Ang II for weeks by minipump, and it was increased in those receiving aldosterone; these responses were evident at 2, 4, and 6 weeks of hormone administration. Aldosterone and endothelin receptor binding in the heart, on the other hand, was not influenced by Ang II or aldosterone treatment.

Fibrosis and Tissue Signals

Nonendothelial Tissue

Angiotensin-Converting Enzyme

The concept that circulating Ang II and aldosterone contribute to fibrosis tissue formation emerged from in vivo studies reviewed earlier. The potential for locally generated hormones, such as Ang II, endothelins, bradykinin, and prostaglandins, to regulate fibrous tissue formation also has to be considered. In vitro quantitative autoradiography (see Fig 3), using an iodinated derivative of lisinopril ([125I]-351A), identified a nonendothelial tissue angiotensin-converting enzyme (TACE) that was localized to tissue sites rich in metabolically active fibroblasts and fibrillar collagen. High-density TACE binding, for example, is normally present within the matrix of heart valves (Fig 3A), the adventitia of intramyocardial coronary arteries (Fig 3B), and loose connective tissue of skin.27,65,67,68 "Throughout the remainder of the myocardium ACE binding is present but of low density (Fig 3B). High-density TACE binding is present in fibrous tissue that appears in various disease states, such as the scar that follows myocardial infarction (Fig 3C)29 and the perivascular fibrosis of intramural coronary arteries and microscopic scars that appear in response to Ang II or aldosterone administration (Fig 3D)." Moreover, TACE in these latter models was not subject to feedback regulation by Ang II, as is the case for endothelial ACE.29 Myocardial ACE activity, measured by the conversion of Ang I to Ang II in isolated perfused rat heart, is increased after suprarenal aortic banding.21 This may be related to increased TACE that accompanies the perivascular fibrosis of intramyocardial coronary arteries in both ventricles with RAAS activation.

TACE therefore is an integral feature of fibrous tissue formation, irrespective of its pathophysiological basis, and indeed it represents a marker of fibrosis. TACE may regulate local concentrations of Ang II and bradykinin, depending on its substrate specificity.

Angiotensin II, Aldosterone, and Bradykinin Receptors

Sun and Weber28 used quantitative in vitro autoradiography, together with [125I]-[Sar¹,Ile⁸]Ang II and [1,2,6,7³H]aldosterone, to determine whether Ang II and aldosterone receptors were present in fibrous tissue. Myocardial fibrosis was induced by the chronic administration of either Ang II or aldosterone (uninephrectomy/high Na⁺ diet). Ang II and aldosterone receptors were anatomically coincident with neither the perivascular fibrosis and scarring of the ventricles that appeared in each model nor TACE binding. As a kininase II, ACE uses bradykinin as substrate. Whether bradykinin receptors, identified by [125I]-Tyr³bradykinin and measured by in vitro autoradiography, were present in fibrous tissue and by implication sites of TACE binding in the myocardium was examined28 in rats that received either Ang II or aldosterone. Bradykinin receptors were found in the perivascular fibrosis and myocardial scarring that appeared in each ventricle in these experimental models. Bradykinin receptor binding
Fig 3. Photomicrographs show sites of high-density (white, yellow) nonendothelial angiotensin-converting enzyme binding, or TACE, identified by in vitro autoradiography. A, Matrix of heart valve (arrowheads); B, adventitia of intramyocardial coronary arteries (CA); and C, scar that follows myocardial infarction (MI). Note marked TACE binding in the endocardium of the left ventricle and interventricular septum and at perivascular sites in the right ventricle. D, Perivascular fibrosis of intramural vessels (CA) and microscopic scars (Sr) that appear in the right and left ventricles with chronic angiotensin II administration.

Fig 4. Photomicrographs show bradykinin receptor and tissue angiotensin-converting enzyme (TACE) binding in serial sections taken from rat myocardium as detected by autoradiography. After 6 weeks of angiotensin II administration, TACE (A) and bradykinin receptor (B) binding density are high (yellow), corresponding to sites of perivascular fibrosis involving coronary arterioles (CA) and microscopic scars (Sr). Bradykinin receptor and TACE binding are seen to be anatomically coincident in these serial sections of the same heart.

Fig 5. Photomicrographs show tissue angiotensin-converting enzyme (TACE) is inhibited by the ACE inhibitor lisinopril. A, High-density TACE binding is seen within the perivascular fibrosis (CA) and scars (Sr) that accompany 2 weeks of angiotensin II administration. B, In angiotensin II-treated animals that also received lisinopril, TACE binding within sites of the reactive and reparative fibrosis is markedly reduced.
and TACE binding were anatomically coincident (see Fig 4). TACE may therefore regulate local concentrations of bradykinin in the rat myocardium.

**TACE Inhibition**

Whether TACE is a chymase was addressed by its response to an ACE inhibitor. Chymase activity would not be suppressed by this intervention. Quinapril inhibits TACE in the scar tissue that follows coronary ligation. As seen in Fig 5, TACE present in the perivascular fibrosis and endomyocardial scars that accompanied 2 weeks of Ang II administration was likewise inhibited by lisinopril. Moreover, at 2 weeks fibrous tissue formation was retarded at these sites in lisinopril-treated animals. By inhibiting TACE, thereby preventing the degradation of bradykinin, fibrous tissue did not develop normally, or it did not occur at all. This suggests that TACE may contribute to fibrous tissue formation by regulating local bradykinin levels that act as an inhibitor of fibrosis. Responsible mechanisms remain to be ascertained.

**Cardiac Fibroblast Collagen Turnover**

Types I and III fibrillar collagens are the major collagens found in the myocardium of rats, nonhuman primates, and humans. Type I collagen predominates in both the normal and diseased heart. Cardiac fibroblasts contain the mRNAs for types I and III collagen, and therefore these cells or fibroblast-like cells are probably responsible for the fibrous tissue responses found in the myocardium.

**Angiotensin II**

With the use of [3H]proline incorporation, collagen synthesis of confluent adult rat cardiac fibroblasts was found to be increased by Ang II in a concentration-dependent manner, and this response is mediated by the type I receptor subtype. Type I collagen synthesis and its transcription in these cells were found to be increased by Ang II. Ang II also reduced collagenase activity in fibroblast culture medium, and this response involves the type 2 receptor subtype. Each of these nonclassic responses in these nonclassic target cells suggests that locally generated Ang II could have autocrine and/or paracrine effects that would promote fibrous tissue formation. These findings raise the intriguing prospect that such a tissue hormonal system constitutes a local wound-healing response that could be activated even in the absence of injury and that would lead to perivascular and interstitial fibrous tissue formation.

**Aldosterone**

Aldosterone likewise was found to increase fibroblast collagen synthesis in a concentration-dependent manner; however, it did not alter collagenase activity. The aldosterone receptor antagonist spironolactone could prevent the rise in collagen synthesis. Dexamethasone, a glucocorticoid, did not alter and even reduced collagen synthesis. Type I collagen synthesis and its mRNA expression were increased in cardiac fibroblasts incubated with aldosterone. Thus, this mesenchymal cell is mineralocorticoid responsive. Immunohistochemical studies of intact tissue have demonstrated that cardiac fibroblasts possess aldosterone receptors.

The specificity of corticoid receptors to aldosterone is conferred by 11β-hydroxysteroid dehydrogenase (11β-HSD), a membrane-bound enzyme that inactivates glucocorticoids to their inactive 11-keto metabolites. Slight et al demonstrated 11β-HSD activity, expressed by the conversion of corticosterone to 11-dehydrocorticosterone, in rat cardiac fibroblasts and rat adrenal cells but not vascular endothelial cells. Licorice root derivatives (eg, glycyrrhizic acid and carbenoxolone) inhibited 11β-HSD activity.

**Endothelins**

Guarda et al have found that endothelin-1 (ET-1) and ET-3 each increase cardiac fibroblast collagen synthesis and the synthesis of its types I and III phenotype in a concentration-dependent manner. Both ET_A and ET_B receptors were involved in this response. The expression of types I and III collagen mRNAs was increased by ET-1 and ET-3. Collagenase activity was reduced by ET-1 but not ET-3, which could be blocked by an antagonist to the subtype A receptor. Endothelin receptors in cardiac fibroblasts have recently been characterized by Katwa et al and found to be predominantly subtype B.

**Endothelial Cell–Derived Signals**

Vascular endothelial cells elaborate substances that influence vascular tone. These same substances can act as promoters (eg, Ang II and endothelins) or inhibitors (eg, bradykinin, prostaglandins, and nitric oxide) that influence the growth and metabolic behavior of neighboring nonendothelial cells. Fibroblasts, in a similar manner, reduce endothelial cell production of endothelin. Such cell-cell signaling is now recognized to represent an important modulator of vascular structure. The perivascular fibrosis of intramyocardial coronary and systemic arteries seen with RAAS activation may involve one or more endothelial cell–derived signals.

To address the influence of endothelial cells on fibroblast collagen turnover, Guarda et al used coculture methodology. Vascular endothelial cells were plated in microporous wells positioned above but physically separated from cultured cardiac fibroblasts. Endothelial cell–conditioned medium gained access to fibroblasts through microporous openings in their wells. Hormones, such as Ang II and aldosterone, could be added to endothelial cell wells to address whether they produced an activation of endothelial cell–derived signals. Alternatively, receptor antagonists, such as DuP 753 (losartan), PD 123177, or spironolactone, could be added to fibroblast wells to assess their potential inhibition of endothelial cell–derived responses in collagen turnover. Collagen synthesis was assessed by [3H]proline incorporation, while collagen degradation was monitored by assessing collagenase activity usingzymography. Endothelial cell–conditioned medium was found to increase fibroblast collagen synthesis and collagenase activity of fibroblast culture medium. The nature of this signal or signals is unknown. However, it does not appear to be Ang II or aldosterone because their respective receptor antagonists did not prevent this response. Moreover, Ang II and aldosterone did not augment these responses in collagen turnover when they were added to endothelial cells.
Wound-Healing Paradigm

A link between the RAAS and wound-healing response may provide insights into why a chronic activation of the RAAS contributes to the progressive remodeling of the myocardium in HHD. The healing response eventuates in fibrous tissue formation. Locally generated hormones, acting alone or together with cytokines, serve as chemical mediators of fibrosis. Circulating hormones of the pituitary-cardiovascular-renal-adrenal axis, including RAAS, are involved when injury is extensive (including blood loss). In this setting homeostasis is restored through blood coagulation, platelet aggregation, vasoconstriction, tachycardia, and sodium and water retention. Each of these effects is an established hormonal property of Ang II, endothelin, aldosterone, and norepinephrine (see Fig 6). Studies of cultured adult rat cardiac fibroblasts indicate that Ang II, endothelin, and aldosterone serve to enhance collagen formation and reduce collagenolytic activity and therefore promote wound healing. By virtue of their biologic economy of action, Ang II, endothelin, and aldosterone can be viewed as stimulators that subserve both homeostasis and healing. This yin of reciprocal regulation is also derived from tissue sources, where inhibiting counterbalance these hormones may be generated from vascular endothelial cells and fibroblasts. Inhibitors to these stimulator hormones (not shown) include nitric oxide, atrial natriuretic peptide, bradykinin, glucocorticoids, and prostaglandins.

Reciprocal regulation in the wound-healing paradigm exists between organs and tissues at the cellular and molecular levels. A distortion of this coordinate balance between yin and yang normally occurs as a compensatory response to injury. A discordant balance in reciprocal regulation, which occurs in the absence of injury and on a chronic basis, as we would propose is the case in HHD, represents a wound-healing response gone awry and accounts for a progressive structural remodeling of the myocardium.

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