Editorial

Renin–angiotensin–aldosterone system and myocardial fibrosis

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See article by Bishop et al. [26] (pages 57–67) in this issue.

During the past decade, evidence has been provided that the circulating and local renin–angiotensin–aldosterone systems (RAAS) promote the development of myocardial fibrosis in hypertensive heart disease and chronic heart failure [1,2] including in vitro experiments using adult rat cardiac fibroblasts where both angiotensin II (AngII) [3–5] and aldosterone [3] stimulate collagen synthesis in a dose-dependent manner while AngII additionally suppresses the activity of matrix metalloproteinase 1, the key enzyme of interstitial collagen degradation [3], that synergistically leads to progressive collagen accumulation within the myocardial interstitium. This could be proved in in vivo studies in renovascular hypertension [1], with chronic administration of aldosterone [1,6,7], or in the spontaneously hypertensive rat (SHR) model of genetic hypertension [8–12] where a local cardiac AngII generating system is operative [13]. Therefore, the physiological role of RAAS on the development of myocardial fibrosis could be established. In particular, in various models of experimental hypertension with comparable degrees of elevated systolic arterial pressure and left ventricular hypertrophy (LVH), myocardial fibrosis was found only in the presence of stimulated circulating RAAS, i.e., in renovascular hypertension, or when aldosterone was chronically infused via subcutaneously implanted osmotic minipumps to raise plasma aldosterone levels as seen in congestive heart failure. There, interstitial and perivascular fibrosis was found in either ventricle, the pressure-overloaded, hypertrophied left ventricle and the non-overloaded, not hypertrophied right ventricle [1]. In contrast, myocardial fibrosis was absent in either ventricle of hypertensive rats with infrarenal aortic band where RAAS was not activated although LVH was present [1]. Furthermore, low output heart failure models, like rapid pacing in dogs, were associated with activation of RAAS and progressive increase in preload. There, myocardial fibrosis was seen in either ventricle [14]. On the other hand, myocardial fibrosis was not seen in cardiac hypertrophy that accompanies volume overload states due to chronic anemia, an arteriovenous fistula, or atrial septal defect [15,16], i.e., states where RAAS is not upregulated. These findings suggest that the growth of cellular constituents of the various myocardial tissue compartments, namely cardiac myocytes and fibroblasts, which are responsible for myocardial collagen metabolism, may each have different regulatory mechanisms. In contrast to load-dependent growth of cardiac myocytes, mechanical factors would not appear to account for the disproportionate accumulation of collagen that occurs with LVH in some conditions and not others despite comparable elevations in wall stress due to chronic pressure or volume overload of the left ventricle. Moreover, types I and III collagen gene expression and collagen synthesis are temporally dissociated from the onset of myocyte growth [17]. Thus, trophic factors which mediate myocyte and nonmyocyte (i.e., cardiac fibroblast) cell growth of the myocardium can be independent of one another. In arterial hypertension or heart failure, reactive myocardial fibrosis which is not secondary to myocyte necrosis was associated with RAAS activation irrespective of the hemodynamic load. Thus, it appears, that RAAS plays a major physiological role in regulating the myocardial extracellular matrix. Indeed, a large body of evidence has been provided that angiotensin-converting enzyme (ACE) inhibitors, such as enalapril, lisinopril and trandolapril, regress myocardial fibrosis in SHR associated with reduction of ventricular arrhythmias and improvement of myocardial function [9–11,18,19] irrespective of antihypertensive effects [9]. Finally, those experimental findings could be confirmed in patients with hypertensive heart disease due to primary hypertension where the ACE inhibitor lisinopril proved to regress myocardial fibrosis along with improvement of left ventricular diastolic dysfunction [20]. Other antihypertensive drugs, e.g., atenolol [21], minox-
idil [22], \( \alpha \)-methyldopa [23], hydrochlorothiazide [20] or hydralazine [24] have failed to show any significant effect on regression of myocardial fibrosis or even increased myocardial collagen concentration in experimental models of arterial hypertension although blood pressure was well controlled. In contrast, studies with the aldosterone antagonist spironolactone in the rat with either unilateral renal ischemia or hyperaldosteronism have shown that it is possible to even prevent the fibrous tissue response [6,7]. Rats with either renovascular hypertension or primary hyperaldosteronism were pretreated with small or large doses of spironolactone. The smaller dose did not prevent hypertension or LVH, while the larger dose did. With either dose of spironolactone, however, the interstitial and perivascular fibrosis was not seen [25]. What we have learned from those pharmacological intervention trials is that normalization of blood pressure is not necessarily associated with regression or prevention of myocardial fibrosis and reduction of fibrous tissue in the myocardium may occur irrespective of normalization of elevated blood pressure, and that local or circulating RAAS is of primary regulatory importance for the remodeling of the cardiac extracellular matrix.

In the paper by Bishop et al. in this issue of Cardiovascular Research [26], the transgenic (mREN2)27 rat (TGR) model was used to separate the role of cardiac tissue RAAS and blood pressure on myocardial structure. Driven by the hypothesis that high blood pressure per se represents an important stimulus for the development of myocardial fibrosis, Bishop et al. found that 20-week treatment of TGR rats with high doses of the ACE inhibitor ramipril prevented the occurrence of myocardial fibrosis along with normalization of blood pressure while low doses of ramipril neither affected blood pressure nor fibrosis although plasma and cardiac ACE activities were significantly reduced that nicely supported their hypothesis. However, they found as well that 12-week treatment with the calcium channel blocker amlodipine did not normalize blood pressure, i.e., it remained significantly elevated above control, while myocardial fibrosis could be prevented that did not support their hypothesis like a broad list of literature reviewed above.

The transgenic rat line bearing the murine Ren-2 renin gene cloned from the DBA/2J mouse strain is thought to provide a monogenic model of hypertension in which the genetic basis, i.e., the additional murine renin gene, is known [27]. Heterozygous animals as used in the study by Bishop et al. are characterized by severe hypertension, unchanged or even suppressed plasma concentrations of angiotensinogen, active renin, AngI, and AngII compared with transgene-negative littermates. On the tissue level, renin is suppressed in the kidneys and murine renin is expressed at very high levels in the adrenal glands [27] while cardiac AngI and AngII concentrations are reduced [28]. In Bishop’s study, no significant difference of cardiac ACE activity was found in TGR compared with Sprague–Dawley controls. Therefore, this model does not appear to be appropriate to sort out the influence of local cardiac RAAS on myocardial structure because cardiac RAAS appears to be not stimulated compared with normotensive Sprague–Dawley control rats and any further suppression of cardiac RAAS may not have any relevance. Although this transgenic rat line represents a monogenic model of hypertension the actual mechanisms responsible for elevating blood pressure remains unclear. The cause of high blood pressure is clearly not an overexpression of renin in the kidneys and the suppression of plasma and kidney renin is certainly a secondary event to elevated blood pressure.

It appears that tissue RAAS of the adrenal glands is of primary importance in this model. Such a perception is supported by findings that production and secretion of adrenocortical 18-hydroxylated steroids, i.e., 18-hydroxy-11-deoxycorticosterone, 18-hydroxycorticosterone, and aldosterone are elevated [29] associated with hypertrophy of zona glomerulosa cells and enhanced urinary aldosterone excretion [27]. Since mineralocorticoids like aldosterone are known to promote myocardial fibrosis [1,6,7,25] the fibrotic myocardium of TGR rats could find a reasonable explanation irrespective of the absence of stimulated cardiac RAAS. As soon as AngII type 1 receptors of zona glomerulosa cells are blocked or adrenal ACE is inhibited in TGR rats the fibrotic tissue response of other organs like the heart could be abolished where AngII is a major stimulator for adrenal aldosterone synthesis and trophic responses to mineralocorticoids depend on the distribution of corticoid type I receptors which are present in the heart. The fulminant hypertension of TGR rats might be caused by overexpression of both adrenal and local vascular RAAS [30].

In conclusion, the TGR model appears to be primarily a model of overexpressed adrenal RAAS with endocrine effects on myocardial structure and does not serve the purpose of focusing on local cardiac RAAS which is not stimulated in this model. Best suited for assessing the detrimental influence of RAAS on myocardial collagen matrix remodeling is still the 2-kidney-1-clip model of renovascular hypertension in the rat which is associated with a marked release of renin, the key enzyme of RAAS. Within days of inducing renovascular hypertension by unilateral renal ischemia, type I and III collagen gene expression is increased [17] and progressive myocardial fibrosis is known to occur [8–11,31]. This type of fibrosis is termed reactive fibrosis (versus reparative fibrosis or scarring), because it is not secondary due to myocyte necrosis [31]. At 8 weeks of renovascular hypertension in the rat, diffuse perivascular and interstitial fibrosis leads to an increase in collagen volume fraction of the hypertrophied left ventricle by threefold [1], at 12 weeks by fourfold [31], and at 32 weeks by sixfold above control [32]. At the early stage of renovascular hypertension, myocardial diastolic stiffness and contractility are each
increased while at the late remodeling stage of hypertensive heart disease the functional consequence is a downward shift of the systolic stress–strain relationship together with a marked elevation in diastolic stiffness [32]. Thus, finally combined diastolic–systolic dysfunction of the left ventricle occurs as result of progressive myocardial fibrosis and that is of utmost relevance for the development of heart failure. There are certainly various potential pathomechanisms leading to myocardial fibrosis, e.g., ischemia, radiation, hormonal cascades, growth factor- and cytokine-mediated pathways. In arterial hypertension and heart failure, local and circulating RAAS appear to be of primary importance.

References