Editorial

Monitoring Vascular Sclerosis in Hypertension
A New Window of Opportunity

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The pressure with which circulating blood is contained in the arterial circulation is related to a number of factors. Prominent among these is the structure of resistance vessels, or arterioles, and conduit vessels, or arteries. For a normal intravascular volume and cardiac output, pathological distortions in arteriolar structure are accompanied by intravascular pressures greater than the expected norm. Such abnormalities include endothelial cell hyperplasia; intimal hyalinization; vascular smooth muscle cell hypertrophy and/or hyperplasia; and increased vessel wall collagen, including its adventitia, here referred to as perivascular fibrosis. Subsequent to such arteriolar remodeling and rise in arterial pressure are iterations in conduit vessel structure. This includes medial thickening and increased concentrations of collagen and elastin in arteries and the aorta. Arteriolosclerosis and arteriosclerosis, a thickening and hardening of arterioles and arteries, respectively, of systemic organs, such as kidney, heart, brain, and eyes, account for and sustain arterial hypertension. Such arteriolar and arterial remodeling is associated with increased risk of adverse cardiovascular events, including myocardial infarction, heart failure, and stroke. Effective monitoring of arteriolosclerosis and arteriosclerosis would have important clinical applications. An example addresses vascular remodeling in response to pharmacological intervention that offers potential as either a cardioprotective or cardioreparative strategy.

How Can Vascular Remodeling Be Monitored?

Microscopic examination of biopsied tissue provides an opportunity to address the presence and extent of arteriolar remodeling in hypertensive patients. It has been effectively used by a number of investigators. The invasive nature of this approach, however, detracts from its broad-based application to the many millions of individuals with hypertension.

Funduscopic examination offers a “window to the vasculature,” albeit primarily the external features of the retinal circulation. It is an essential feature in the examination of hypertensive patients. In an important and widely recognized study published in 1939, Keith et al reported on vascular remodeling observed in the optic fundi of their patients with hypertension of various levels of severity. Findings used to classify the severity of vascular remodeling included arteriolar diameter and fibrosis (or sclerosis); arteriolar sclerosis in association with compression of neighboring retinal veins; and the presence or absence of complications, such as hemorrhages, exudates, and optic disk edema. Retinopathy was related to the severity and duration of hypertension. The extent of optic fundus remodeling offered prognostic information and served to predict patient survival in this and other studies, as recently reviewed. The severity of these changes correlated with the incidence of cardiac and renal complications in essential hypertension and predicted the presence and extent of angiographically demonstrable coronary artery disease. The utility of direct ophthalmoscopy in the assessment of mild or moderate hypertension has been questioned.

Are There Alternative Strategies to Monitoring Vascular Sclerosis?

Arteriolosclerosis includes the adverse accumulation of types I and III fibrillar collagens in the adventitia. This perivascular fibrosis involves intramyocardial coronary arterioles found in the normotensive, nonhypertrophied right ventricle and the hypertensive, hypertrophied left ventricle. From the perivascular space of these intramural vessels, collagen fibers extend into the contiguous interstitium, creating an interstitial fibrosis. Such vascular sclerosis can be found in systemic organs as well. The association between cardiac fibrosis and chronic elevations in circulating angiotensin II and/or aldosterone has been reviewed previously.

The adverse accumulation of fibrillar collagen in the heart has a number of functional consequences. It accounts for a rise in ventricular diastolic stiffness; a continued accumulation further impairs diastolic function and compromises systolic function. The presence of symptomatic heart failure is related to the increment in left ventricular collagen concentration. Microscopic examination of endomyocardial biopsy tissue obtained from patients with hypertension identifies coronary arteriolosclerosis and is associated with impaired response of vasodilator reserve to pharmacological provocation. Fibrosis enhances the arrhythmogenic potential of atria and ventricles. Echocardiographic characterization of tissue composition is under development and offers promise in the detection of ventricular fibrosis.

Fibrosis is a histological term that characterizes the morphological features of tissue remodeling by fibrillar collagen. Fibrosis has long been assumed to imply a static condition of diseased tissue. To the contrary, however, fibrous tissue often connotes a dynamic state of tissue repair—an ongoing process of progressive collagen deposition based on a persistence.
of fibroblast-like cells and their continued turnover of collagen. A dynamic state of fibrogenesis exists when collagen degradation fails to keep pace with increased collagen synthesis. A monitoring of collagen turnover would address formation and degradation of extracellular matrix in disease states when organ fibrosis is present.

How Can Vascular Collagen Turnover Be Monitored?
Fibrillar types I and III collagens are triple helices. In the case of type I collagen, there are 2 α₁ and 1 α₂-polypeptide chains; 3 α₁-chains make up type III collagen. These collagens are synthesized and secreted as larger procollagen or precursor molecules that contain additional peptide sequences, called propeptides, located at the amino-terminal and carboxy-terminal ends of these polypeptide chains. These propeptides are cleaved from collagen molecules before their assembly into a triple helix. Free propeptides of type I and type III collagens that appear in the circulation reflect collagen deposition. This is based on certain stoichiometric considerations reviewed elsewhere. Collagen degradation is provided by an extracellular pool of matrix metalloproteinases (MMPs), including MMP-1 (or collagenase), that normally exist in latent form bound by tissue inhibitors of metalloproteinases (TIMPs). Serological markers of collagen synthesis and degradation have been used to monitor wound healing and fibrous tissue accumulation in injured lung and liver, myeloproliferative disorders associated with myelofibrosis, and type I collagen formation and degradation in metabolic bone disease. The use of such noninvasive biochemical markers to detect organ fibrosis has been reviewed.

In recent years and as recently reviewed, this approach has been extended to address tissue repair in the injured heart, such as after myocardial infarction. Díez and coworkers in Pamplona, Spain, have used this biochemical approach to address cardiac fibrosis in hypertensive animals and patients. Their studies have provided a number of provocative and important advances.

In rats with genetic hypertension, Díez et al used the carboxy-terminal propeptide of procollagen type I (PIP) as a marker of type I collagen synthesis and pyridinoline cross-linked telopeptide domain of collagen type I (CITP) as a marker of type I collagen degradation. Microscopy and immunohistochemistry confirmed the expected cardiac fibrosis that consisted of type I collagen and that others have shown is morphologically expressed as a perivascular fibrosis of intramyocardial coronary arterioles and arteries with contiguous interstitial fibrosis. Compared with age- and sex-matched normotensive genetic controls, serum PIP was significantly increased in 36-week-old hypertensive rats, whereas CITP was no different between groups. A direct correlation between ventricular collagen volume fraction and PIP was found. PIP and collagen volume fraction were equivalent to 36-week-old controls when a 20-week course of an antihypertensive dose of quinapril was introduced at age 16 weeks. CITP tended to be higher in hypertensive rats treated with quinapril but was not statistically different from controls. It was proposed that serum PIP could be used as a marker of type I collagen-related cardiac fibrosis in this hypertensive rat model.

These investigators also demonstrated that serum PIIIP and PIP were higher in patients with never-before-treated essential hypertension than in normotensive control subjects. Direct correlations in the hypertensive group were found between serum PIIIP and plasma renin activity and between serum PIP and LV mass and graded severity of ventricular arrhythmias recorded during ambulatory ECG monitoring. Inverse correlations were evident between these markers and maximal early and late transmural flow velocities, Doppler echocardiographic markers of left ventricular diastolic dysfunction. After 6 months of lisinopril treatment, which normalized arterial pressure, diastolic filling improved, together with a regression in LV mass and reduced number of ventricular extrasystoles. It was therefore suggested that these markers serve to demonstrate increased collagen synthesis in the cardiovascular system, an adverse association between such collagen turnover and the mechanical and electrical dysfunction of the heart, which could be ameliorated by lisinopril.

In the present issue of Circulation, Laviades et al apply serological markers of collagen turnover in never-before-treated patients with essential hypertension. They address whether type I collagen degradation is reduced in this hypertensive population. Serum CITP was monitored as a marker of type I collagen degradation together with serum concentrations of total MMP-1 and TIMP-1 and the MMP-1/TIMP-1 complex. Measurements were repeated after 12 months of lisinopril treatment and compared with untreated normotensive control subjects. At the time of study enrollment, baseline free MMP-1 was decreased, free TIMP-1 increased, and CITP no different from control levels.

Hypertensive patients with LVH were found to have even lower baseline values of free MMP-1 and higher values of TIMP-1 than their counterparts without LVH. After treatment with lisinopril, free MMP-1 and CITP each increased, whereas free TIMP-1 was reduced. The importance of bradykinin and associated substances (nitric oxide and prostaglandins) in promoting degradation of established fibrosis by an ACE inhibitor remains to be investigated.

Taken collectively, these studies by Díez and coworkers suggest that extracellular matrix collagen synthesis in the cardiovascular system is enhanced and its degradation reduced in patients with essential hypertension. These biochemical features favor a progressive arteriosclerosis and arteriolsclerosis of the heart and other organs that would lead to organ fibrosis and ultimately organ failure.

Additional work is needed before the usefulness of this provocative approach is fully realized. This notwithstanding, Díez and coworkers have provided a stimulus: a new window of opportunity with which to noninvasively monitor vascular sclerosis in hypertension.

References

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