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Predisease biological markers: early diagnosis and prevention of arterial hypertension

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Abstract

This review examines 2 potentially important morbid changes that may precede the onset of hypertension—capillary rarefaction (CR) and large artery rigidity (LAR). The mechanisms responsible for CR, currently measured in the skin microcirculation, as well those responsible for LAR, have yet to be fully delineated. Nor has the duration been determined of the latent period between the occurrence of these lesions and the onset of blood pressure elevation. It has been known for 2 decades that, because of the kidney's relatively rigid capsule, alterations in the abundant postglomerular microcirculation network (which can accommodate circa 80% of total renal blood flow) can lead to endothelial plasma leakage. Even a small amount of plasma leakage can increase interstitial pressure and lead to capillary collapse and CR. Simultaneously, or at a later time, these alterations could have an impact on the reflection wave profile in the thoracic aorta and, via abnormal endothelial proliferation and other vascular effects, give rise to LAR. Nonpharmacologic and/or pharmacologic interventions have been shown to exert positive effects on CR and/or LAR. Recent studies have demonstrated the beneficial actions of a bradykinin B2-receptor antagonist (HOE140) in the spontaneously hypertensive rat, the classic rat model for *essential* hypertension. The fact that CR and LAR both precede blood pressure elevation could serve as a basis for designing strategies to prevent hypertension from occurring. Because modern tools capable of measuring CR and LAR noninvasively have been developed, it should soon be feasible to identify these 2 prehypertension markers in individual patients.

1. Capillary rarefaction

Until recently, capillary rarefaction (CR), an unusual vascular phenomenon, has attracted little attention as a predictor of later disease. Nevertheless, within the last few years, its presence within such organs as the visceral peritoneal membrane, the cremaster muscle, and the skin has been validated in animal models of hypertension (HT) and, more recently, in human subjects [1]. Capillary rarefaction has been found to be present before and after the development of HT [2]. Candidate mechanisms responsible for this phenomenon include (*a*) unsatisfactory embryological development, (*b*) lack of angiogenesis, and (*c*) collapse of existing capillaries (potentially reversible) due to increased interstitial pressure.

Studies of CR in human subjects have remained limited, in part because of the technical difficulties involved in imaging capillaries and the fact that CR's relationship to the pathophysiology of arterial HT has yet to be worked out in detail. However, several reports suggest that CR may contribute significantly to HT's causation. For example, when the responses of the skin's microcirculation to such challenges as externally applied heat and venous occlusion-induced ischemia are measured, human subjects with a familial history of HT are found to exhibit a significant reduction in the number of open capillaries [2]. A recent study where a vascular endothelium growth factor antagonist, bevacizumab, was given to patients with cancer disclosed a relationship between the reduction in skin capillaries and elevation of blood pressure [3].

Endogenous factors that could be responsible for the defective angiogenesis implicated in the causation of CR include interleukin-13 and nitric oxide. Innovative imaging technology has allowed investigators to assess the individual and combined roles of these vascular modulators of

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capillary recruitment. Their effects were found to be additive, increasing by several-fold the number of functional vessels in the skin microcirculation of normal rats [4].

We favor the concept that the type of CR that predicts and contributes to later HT is characterized by a potentially reversible collapse of key capillary systems in the renal microcirculation. The renal microcirculation is the body's most developed capillary network, accommodating more than 20% of the cardiac output and exhibiting the highest oxygen consumption per gram of tissue. Indeed, various pathophysiologic changes in the kidney have been implicated in the causation of a number of vascular diseases. Moreover, the renal capsule is well known to have a limiting effect on the kidney's expansion capacity [5].

In 1968, removal of the renal capsule in the sodium-fed, spontaneously hypertensive rat was found to result in an increase in urinary sodium excretion and blood pressure reduction. These improvements in function were associated with normalization of interstitial hydrostatic pressure within the kidney [6]. Many years later, our group [7] reported that enhanced capillary permeability in the renal microcirculation network increases albumin leakage into the renal interstitium, with a resulting increase in interstitial pressure. This sequence of events can result in CR involving the renal microcirculation.

Based on the growing evidence that points to the importance of CR as a predisease phenomenon in arterial HT, we propose that elevation of renal interstitial pressure through albumin leakage from the privileged peritubular microcirculation networks into the heterogeneous cortical and medullary fluid compartments can lead to significant capillary collapse within those networks. In a study performed in groups of normotensive and hypertensive rats 4 to 12 weeks of age, the key role played by the bradykinin B2 receptor as a determinant of the leakage was demonstrated, inasmuch as its specific blockade with HOE140 completely normalized the albumin leakage.

The foregoing findings lead one to ask several questions: (*a*) How might the roles of CR and LAR be linked together as precursors of the structural and physiologic alterations of resistance arteries that result in a rise in blood pressure? (*b*) In what order do these 2 conditions set the stage for the onset of arterial HT? (*c*) How might therapeutic interventions that target CR and LAR before HT becomes manifest prevent the disease from occurring?

2. Large artery rigidity

The impact on the luminal surface of large conduit arteries of blood flow alterations that arise from changes in absolute hydrostatic pressure, pulse pressure, and shear stress has been extensively examined over the past decade [8]. The endothelial surface and intima of large vessels, with their macromolecular constituents—proteoglycans and fibronectin, respectively—are capable of triggering an increase in circulating blood cells and/or stimulating the adjacent matrix of the intima, including elastic fibers sensitive to changes in parallel flow [9-12]. In addition to the response of the aortic intima to increased pulse pressure, 2 other important structures are affected, namely, the vascular smooth muscle cell (VSMC) subpopulations (longitudinal and circular) and the interstitial matrix, which contains collagen, elastic material, and proteoglycans. Subpopulations of smooth muscle cells have been shown to react in different (sometimes opposite) ways to vasoactive hormones [13-15]. The interaction of negatively charged macromolecules (proteoglycans) with sodium and water also potentially influences large artery stiffness [16] via alterations in luminal and *vasa vasorum* endothelial permeability [17]. Of special interest, elastin fibers play a critical role in vascular calcification, a prominent feature in the remodeling of large conduit vessels—the process that is, at first, microscopic and undetected by traditional x-rays. Arterial blood pressure and blood flow patterns also can have exacerbating effects on the morbid process, which, interestingly, involves the in situ enzyme carbonic anhydrase or its release from traumatized red blood cells [18,19].

The last, but most neglected, segment of large conduit arteries, from the thoracic aorta to the coronary arteries, is the adventitia with its specialized microcirculation network, the *vasa vasorum*. The potential importance of such networks—responsible for nourishing circa 70% of the conduit vessels—is receiving increasing investigative attention [20]. Two important questions arise from a consideration of the potential roles of the outer lining of conduit arteries in the pathogenesis of HT: First, is the adventitia involved in the development of large artery rigidity (LAR)? Second, does LAR have a morbid impact on the adventitia?

The second question addresses the likelihood that, in conduit arteries, hydrostatic changes in velocity or pressure will cause plasma to leak from the lumen into the vascular wall [21]. This phenomenon, although likely, has yet to be clearly documented.

The first question has recently become more salient after the recent demonstration that, within the adventitia, there are stem cells capable of differentiating into endothelium, smooth muscle, macrophages, and fibroblasts that can produce interstitial macromolecules [22,23]. The mechanisms involved in the structural and functional reorganization of conduit arteries secondary to increased intraluminal pressure and blood flow have some resemblance to the morbid vascular processes induced by calcifying vascular cells [24].

3. Clinical interventions

At the present time, predisease diagnosis of arterial HT can be undertaken by 2 different noninvasive techniques designed to identify the presence of CR and/or LAR. In

the clinical examination of hypertensive or potentially hypertensive subjects, skin CR can be evaluated by nail capillaroscopy, a simple microscopic measure of open and functional skin capillaries, expressed per square millimeter under-nail surface. Large artery rigidity, inferred from pulse wave velocity (PWV) expressed in meters per second, is usually measured between the carotid and femoral arteries by ultrasonography. The reproducibility of the latter approach has been carefully validated in large populations that included both normotensive and hypertensive patients [25].

Other approaches intended to identify LAR (some more invasive than others) have been developed and validated [26]. The approaches presently available to measure CR are not as well established and have not been validated in large human studies. The problem that arises when one wishes to evaluate the role of CR in the pathogenesis of arterial HT results from the fact that the most accessible microcirculation network—the skin—is probably not representative of the capillary networks elsewhere that may contribute to a greater extent to the causation of arterial HT. This is because, in addition to nourishing cells, skin capillaries play a key role in the regulation of body temperature. Moreover, the skin (and presumably its capillaries) appears to be especially vulnerable to the effects of exposure to the ravages of the environment, as well as to the effects of a variety of endogenous and exogenous influences, including anxiety and other emotions affecting the autonomic nervous system, level of recent physical activity, and changes in ambient temperature and humidity [27].

Methods developed to examine LAR have received more attention in recent years; yet, they remain underused in clinical practice. Among the currently available methods, measurements of peripheral (carotid/femoral and carotid/radial) as well as central PWVs have found increasing use in large clinical trials [28-30] and in studies of individuals with borderline HT [25].

Measurement of PWV has been used to assess the effectiveness in the prevention of target organ damage of different classes of antihypertensive drugs, including the angiotensin-converting enzyme inhibitors and angiotensin AT1 receptor blockers, as well as combinations of these drugs with traditional diuretics [29]. Interestingly, the less expensive drugs and drug combinations were found to be as therapeutically effective as their more expensive counterparts [30]. The importance of the beneficial pharmacologic effects of extrarenal diuretics on large blood vessel walls, as well as on resistance arteries, also deserves emphasis. The action of extrarenal diuretics on interstitial fluid compartments via modulation of

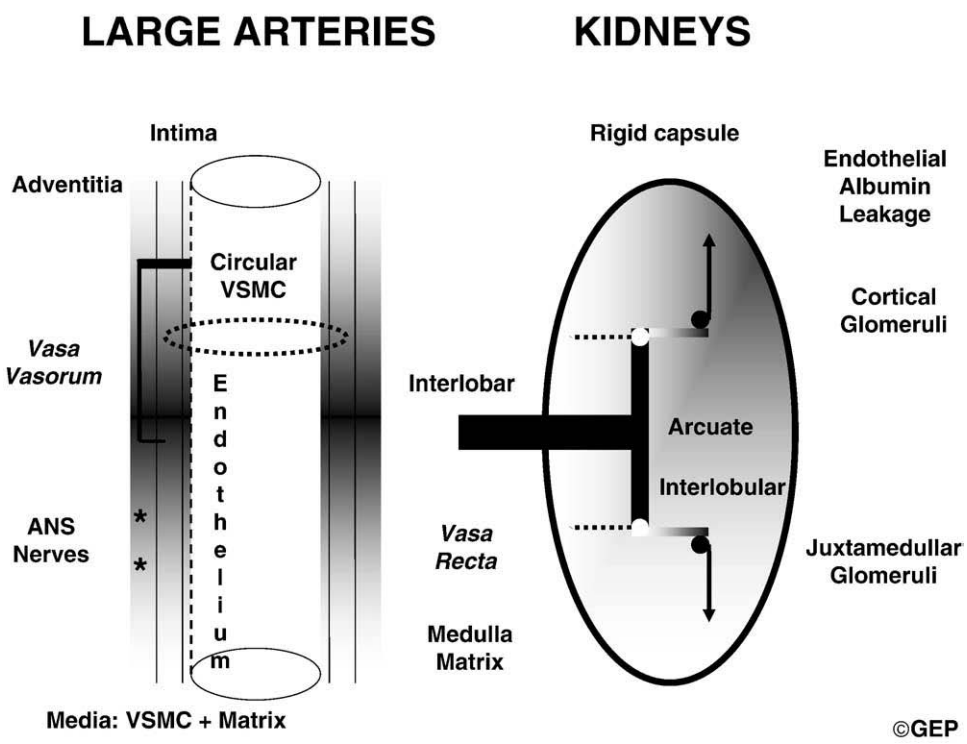

Fig. 1. This figure represents the 2 predisease events detectable before the resistance arterial alterations, responsible for the development of HT, occur. In the right portion of the figure, kidney CR is shown as a consequence of endothelial albumin leakage in the interstitial matrix, where hydrostatic pressure elevation is related to its rigid capsule. The rich renal capillary vessels collapse and lead to CR in this organ, which receives more than 20% of cardiac output. In addition, and as a consequence, the central role of the kidney in the maintenance of sodium balance is altered. In the left portion of the figure, LAR, mainly responsible for aortic elevation of vascular central pulse pressure, is the result of structural and/or functional alterations in the luminal endothelium, media VSMCs, and matrix, as well as in the *vasa vasorum* of the adventitia. In addition, selective contraction of the aortic circular VSMC subpopulation contributes to LAR.

glycosaminoglycans sulfation may help counteract the abnormality in sodium homeostasis displayed by hypertensive patients with the metabolic syndrome [16]. Finally, use of bradykinin B2-receptor antagonists such as HOE140, or drugs with a similar pharmacologic action, should be considered as a promising approach to the prevention of *essential* HT (EHT) in individuals at risk of developing this disorder [7].

4. Conclusion

Based on more than half a century of research, new and promising approaches designed to prevent EHT are under active investigation. The success of such approaches depends on the ability of the physician to detect key predisease morbid events at an early stage. Capillary rarefaction, an abnormality affecting a segment of the vascular system distal to the resistance arteries responsible for elevation of blood pressure, and LAR, a component of the oxygenated segment of blood vessels proximal to resistance arteries, have both been implicated in the development of EHT. The relationship between these 2 potential physiopathologic events is still under investigation (Fig. 1). Which one of those morbid events comes first, or do they arise simultaneously? The most likely places in the body where CR and LAR could occur concomitantly would seem to be the thoracic aorta with its encircling *vasa vasorum* and the renal microcirculation networks (especially those that service the juxtamedullary nephrons).

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