From Macrocirculation to Microcirculation: Benefits of Preterax

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Maintaining vascular health has become an important target in the management of cardiovascular disease and hypertension-related organ damage. The microvasculature, which is both a target and a determinant of hypertension, contributes to the pathologic changes in the macrocirculation and subsequently to end-organ damage. The major changes in the microcirculation of hypertensive individuals include: (1) an increased wall/lumen ratio of small arteries, (2) a rarefaction of arterioles and capillaries, and (3) an enhanced microvascular permeability. The prevention or regression of hypertension-dependent vascular alterations represents a desirable goal for pharmacologic treatments. Combination treatment with the angiotensin-converting enzyme inhibitor perindopril and the diuretic indapamide (Preterax) has been shown to have positive effects on the microcirculation and macrocirculation and on subsequent cardiovascular disease. In the 1-year pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd (REASON) study, perindopril/indapamide treatment decreased pulse wave velocity and aortic augmentation index, both measures of arterial stiffness and macrovascular health. In addition, data gathered from animal studies show that perindopril/indapamide has a beneficial impact on capillary structure, the endothelium, and angiogenesis. In rat models of renal failure, treatment with perindopril/indapamide prevented glomerular hyalinosis and tubulointerstitial damage, reduced the hypertrophy of superficial glomeruli and the mesangial expansion of deep glomeruli, and positively affected proteinuria and glomerular injury. Together these data suggest that hypertension-related damage to the microvascular and macrovascular system may be manageable through pharmacologic interventions such as combination treatment with perindopril/indapamide. Am J Hypertens 2007;20:15S–18S © 2007 American Journal of Hypertension, Ltd.

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The microcirculation mediates the delivery of nutrients and oxygen to tissues. The disruption of this function, which occurs when microvascular abnormalities develop in response to hypertension, leads to end-organ damage. In the brain, lacunar infarcts lead to slowly progressing dementia; in the heart, microvascular coronary damage causes myocardial ischemia; and in the kidneys, glomeruli damage leads to renal dysfunction.

Although the causes of hypertension are not always well understood, several systems have been implicated. In addition to the kidney, which regulates body fluid volumes,[1] the microcirculation controls vascular resistance and consequently arterial pressure. Thus, not only is the microvasculature the target of hypertension, but it is also one of its main determinants. Furthermore, microvascular damage underlies some of the pathologic changes observed in the macrocirculation of hypertensive individuals.[1]

Maintaining vascular health has become an important target of cardiovascular disease management. Clinical and animal studies suggest that some antihypertensive agents may act directly on the microvascular system to reduce abnormalities.[2–8] This article reviews the pathophysiology of hypertension in relation to the deterioration of the macrocirculation and microcirculation and the role of first-line combination treatment, perindopril/indapamide, in the preservation of vascular health.

Pathophysiology, Role of the Microcirculation and Macrocirculation

The microvasculature, the macrovasculature, and the heart determine the hemodynamics of the circulatory system.[9] As the blood progresses through the arterial tree toward the periphery, the pulsatile pressure and flow that result

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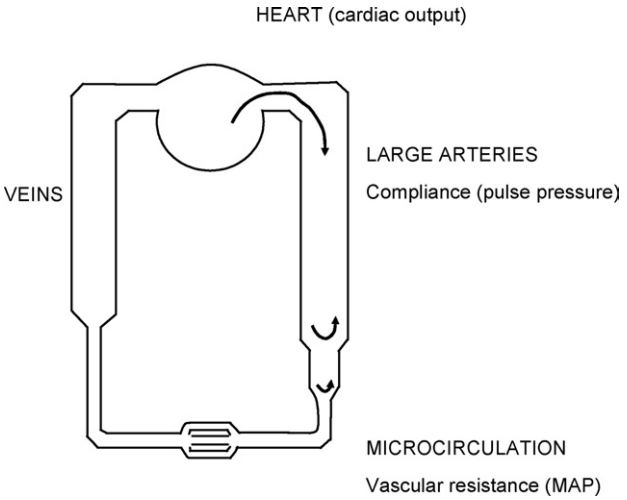

FIG. 1. The microvasculature, the macrovasculature, and the heart. The pressure wave in the arterial tree consists of two components. Mean arterial pressure (MAP) is determined by cardiac output and vascular resistance in the microcirculation. Pulse pressure is the result of an interaction between cardiac output, arterial compliance, and wave reflections from branching points in both the macrocirculation and the microcirculation. Adapted with permission.[9]

from the intermittent ventricular ejection of the blood are smoothed out, thereby allowing a steady oxygen flow to the tissues. The blood pressure (BP) curve, therefore, has two components, the constant mean arterial pressure (MAP), a measure of cardiac output and vascular resistance, and the pulse pressure (PP), a measure of the pressure fluctuations, the elasticity of large arteries, and the timing, velocity (pulse wave velocity [PWV]), and intensity of the arterial wave reflections (Fig. 1). Pulse pressure varies across the arterial tree. It increases peripherally with the decline in artery diameter and the increase in arterial stiffness.[1,9]

Vascular resistance and MAP are the main hemodynamic components that are determined by the microvasculature. Increases in MAP noted during hypertension are largely due to increases in vascular resistance. Studies performed in hypertensive animals and humans have determined that in response to the chronic increase in vascular resistance, cells of the arterial vessels adapt structurally and functionally. Not only is the extracellular material rearranged, but smooth muscle cells, which get activated, migrate and proliferate. Together, these two events alter the thickness of the arterial wall. The overall result is a reduction in the caliber and number of small arteries and arterioles.[1,9]

Pulse pressure, large artery stiffness, and pressure wave reflections are measures of the macrocirculation, all of which are increased with hypertension and microvascular damage. Greater large artery stiffness leads to a decrease in the ability of the arteries to accommodate the volume of blood ejected from the left ventricle. This occurrence combined with the rarefaction of arterioles and capillaries leads to increased PWV and thus to a faster return of wave reflections. As a consequence, central systolic BP and PP are increased, thereby leading to greater left ventricular afterload, myocardial hypertrophy, and myocardial oxygen consumption. The accompanying decrease in central diastolic BP leads to a decrease in coronary perfusion, and consequently to myocardial ischemia.[1,9]

End-Organ Damage, the Microcirculation and Macrocirculation

The health of the microcirculation and macrocirculation determines in large part the degree of end-organ damage. The kidney, for example, is particularly sensitive to alterations in the microcirculation and macrocirculation. Pulsatile pressure in the glomerulus is relatively high, thereby allowing glomerular filtration to take place. The kidney is thus particularly exposed to the potentially damaging effect of an increased PP and reliant on the myogenic tone of afferent arterioles and on a tubuloglomerular feedback mechanism to regulate renal blood flow. In hypertensive patients where PP and arterial stiffness are increased, aortic PWV is increased, glomerular filtration is decreased, and renal function degradation is frequent.[10] Similarly, in patients with type 2 diabetes, systemic arterial hypertension, increased carotid artery stiffness, and carotid intima–media thickness lead to arteriolar dilation, greater glomeruli permeability, and excess protein filtration.[11] The resulting tubular damage, inflammation, and scarring ultimately result in end-stage renal disease. The combination of these pathophysiologic events further increases hypertension and therefore end-organ and cardiovascular damage.

Secondary cardiomyopathies, which are frequent in both hypertensive and diabetic patients, may also be attributable to microvascular dysfunction. Abnormal coronary flow reserve, for example, has been identified in some hypertensive patients with angiographically normal coronary arteries and no left ventricular hypertrophy. These data are believed to suggest the presence of a remodeling of intramural arterioles and a decreased density of the coronary microvasculature.[12]

Consistent with this pathophysiologic understanding of hypertension and end-organ damage, PP, aortic stiffness, and pressure wave reflections have been shown to be independent predictors of cardiovascular risk.[13–21] In the Framingham Heart Study, PP was determined to be superior to systolic BP as a predictor of coronary heart disease in subjects more than 60 years.[19] In another study, with every 10 mm Hg increase in 24-h PP, the adjusted risk of cardiac events increased by 35%.[20] Interestingly, at least one study has shown that increases in PP are better correlated with cardiovascular events than with cerebrovascular events.[21]

This relationship between brachial PP and cardiovascular risk is maintained in high risk groups such as individuals with left ventricular dysfunction,[22] end-stage renal