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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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...
disease, 23 or diabetes mellitus. 24,25 In the Verona diabetes study, PP was a predictor of cardiovascular and cerebrovascular mortality. An 86% increase in risk of cerebrovascular death was recorded for a 10 mm Hg increase in PP. 25 Aortic stiffness and PWV in patients with end-stage renal disease and with or without diabetes mellitus is an independent predictor of cardiovascular mortality. 13,26,27

Perindopril/Indapamide Acts on the Microcirculation and Macrocirculation

Although the prevention or regression of these hypertension-dependent vascular alterations represents an attractive goal for pharmacologic treatments, normalization of vasculature has been incomplete in the studies using diuretics, β-blockers, calcium antagonists, and α1-receptor blockers. Angiotensin-converting enzyme (ACE) inhibitors, however, seem to be more promising.

The impact of combination treatment with the ACE inhibitor (perindopril)/diuretic (indapamide) on the macrocirculation and microcirculation and subsequent cardiovascular disease is being evaluated. In the 1-year, double-blind, randomized, pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd (REASON) study of 471 patients with essential hypertension, perindopril/indapamide treatment decreased brachial and central systolic BP and PP. Pulse wave velocity and aortic augmentation index, which reflect arterial stiffness and contribute to systolic BP and PP, were also decreased. 28,29

In the Conduit Artery Function Evaluation (CAFÉ) study, derived central aortic systolic BP was significantly decreased with amlodipine/perindopril treatment compared with atenolol/thiazide treatment. These substantial differences in central aortic pressures and hemodynamics were hypothesized to be due either to a reduction in pressure wave reflections during systole due to a shifting of the pressure wave reflection sites distally as a consequence of small artery remodeling, or to differences in the timing of systolic ejection as a consequence of a slower heart rate. 30

Lastly, in a 6-month pilot study, perindopril/indapamide improved coronary vasodilator reserve in hypertensive patients with or without left ventricular hypertrophy. These data suggest that perindopril/indapamide may improve coronary microcirculation by affecting the structure of small vessels and endothelial function and by reversing microvascular rarefaction. 2

These data are consistent with those gathered from animal studies in which perindopril/indapamide had a beneficial impact on capillary structure, the endothelium, and angiogenesis. 3–8 In rats with renovascular hypertension, treatment for 4 weeks with perindopril/indapamide reversed microvascular rarefaction and normalized arteriolar and capillary densities. 5 Perindopril/indapamide also increased capillary and myocyte densities, as well as external and internal diameters, in spontaneously hypertensive rats at risk of stroke. Angiographic scores and blood flow perfusion were also increased. 4 At a more molecular level, perindopril/indapamide treatment increased vascular endothelial growth factor and endothelial nitric oxide synthase levels in a model of ischemia-induced angiogenesis 3 and normalized endothelium-dependent relaxations and aortic constitutive nitric oxide synthase (cNOS) activity, an enzyme that synthesizes the vasodilator nitric oxide, in hypertensive Dahl sensitive rats. 8 In all of these models, microvascular benefits were accompanied by improvements in BP and cardiac hypertrophy.

In rat models of renal failure, treatment with perindopril/indapamide protected renal structure and function. 6,7 Perindopril/indapamide therapy prevented focal and segmental glomerular hyalinosis and tubulointerstitial damage and reduced the hypertrophy of superficial glomeruli and the mesangial expansion of deep glomeruli. 6 These effects were accompanied by beneficial effects on proteinuria and glomerular filtration and injury. 6,7

Conclusions

Because abnormalities in the microvasculature may contribute significantly to risk and may explain individual differences in cardiovascular disease prognosis, the reversal of vascular damage is likely to be the most effective approach to reduce end-organ damage and preserve cardiovascular health. Hypertension-related damage to the microvascular and macrovascular system may be manageable through pharmacologic interventions such as combination treatment with perindopril/indapamide.

References


