Relationship Between Aortic Stiffening and Microvascular Disease in Brain and Kidney

Cause and Logic of Therapy

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Abstract—A close relationship has been established between microvascular damage in brain and kidney and indices of age and hypertension (pulse pressure, aortic pulse wave velocity, and augmentation index). The mechanism of such association has not been established, nor has rationale for prevention and treatment of microvascular damage. A logical pathophysiological explanation can be offered on the basis of differential input impedance in the brain and kidney compared with other systemic vascular beds. Torrential flow and low resistance to flow in these organs exposes small arterial vessels to the high-pressure fluctuations that exist in the carotid, vertebral, and renal arteries. Such fluctuations, measurable as central pulse pressure, increase 3- to 4-fold with age. Exposure of small vessels to highly pulsatile pressure and flow explains microvascular damage and resulting renal insufficiency and intellectual deterioration, according to the mechanism established by Byrom 50 years ago. The logical approach to prevention and treatment requires reduction of central pulse pressure. Because the aorta and large arteries are not directly affected by drugs, this entails reduction of wave reflection by dilation of conduit arteries elsewhere in the body. This can be accomplished by regular exercise and by drugs such as nitrates, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. The explanation given here accounts for greater and earlier vascular damage in diabetes mellitus (relative microvascular fragility) and is similar to that given for vascular changes of pulmonary hypertension caused by ventricular septal defects and other congenital vascular shunts. (Hypertension. 2005;46:200-204.)

Key Words: arterial pressure ■ microcirculation ■ pulse ■ cerebrovascular disorders ■ renal disease

The purpose of this article is explore the relationship between degenerative chronic disease in the large arteries and more acute, potentially reversible disease in the smallest arterial and capillary vessels of the brain and kidney. Our approach from the great city of Paris is to stand back, as from an impressionist painting, and seek a perspective that might merge multiple details into a compelling image.

Epidemiological Studies and Clinical Trials

Recent studies have established a strong association between indices of arterial stiffening (peripheral pulse pressure, central pulse pressure, aortic pulse wave velocity, central augmentation index, pressure wave amplification), and cardiovascular events. Most of these studies have been conducted in patients with end-stage renal disease on hemodialysis (whose event rate is extraordinarily high), but similar findings have been noted in larger studies of hypertensive and elderly patients. Although the principal cardiovascular events have been myocardial infarction, lethal cardiac arrhythmia, and cardiac failure, and attributable to atherosclerotic disease and/or increased left ventricular load, many are caused by progressive microvascular disease leading to strokes and dementia, and to renal failure. Such microvascular disease is accentuated in patients with diabetes mellitus. The cause for this association (large-artery stiffness and microvascular disease) has not been established.

Over the past 2 decades, since the landmark Systolic Hypertension in the Elderly Program (SHEP) study, there have been a host of studies directed at treatment of elevated systolic pressure in elderly persons with stiffened arteries. Although these have confirmed, uniformly, that reduction in systolic pressure reduces cardiovascular events, debate continues as to which agents are most effective for reducing different events. Findings are complicated by a number of issues, including the fact that most patients with hypertension require a cocktail of drugs for adequate control. Another issue is the fact that most studies have used the cuff sphygmomanometer alone rather than specific indices of arterial stiffness such as central pressure, aortic augmentation index, or aortic pulse wave velocity. When such specific indices have been measured, there has been a more clear-cut difference seen for the effects of different drugs, notably for angiotensin-
converting-enzyme inhibitors (ACEIs),14 angiotensin receptor blockers (ARBs),15 and calcium channel blocker (CCBs)16 over conventional diuretics and β-blockers. A major point of the present debate, set out in recent meta-analyses, is whether the new agents, ACEIs, ARBs, CCBs, or nitrates are superior to the conventional older drugs.17,18 A view, supported by the recent Anglo-Scandinavian Cardiac Outcome Trial (ASCOT),19 is that they are superior, with respect to microvascular disease in kidney and brain, and that for the kidney, ACEIs and ARBs may have an edge, whereas for the brain, dihydropyridine CCBs may have the edge.17,18 Data interpretation is complicated by a number of factors, including the point that for vascular dementia, long-term antihypertensive treatment may be beneficial at an early stage, but that aggressive antihypertensive treatment may be detrimental at a later stage if not carefully titrated.20

The challenge of this article is to set out basic principles that can explain some of the conflicting data and may provide a framework for explaining past therapeutic trials and for planning new studies.

**Function of the Normal Arterial Tree: Unique Features of Brain and Kidney**

The normal arterial tree is beautifully designed for its function of conduit and cushion.21 It receives blood in spurts from the heart and passes this on in a near-steady stream through peripheral arterioles and capillaries. Its conduit function is so good that mean pressure decreases by <1 mm Hg between the ascending aorta and a peripheral artery such as the radial.22,23 Its cushioning function is so good that normally <10% of additional work is lost in pulsatile phenomenon within the circulation than if the heart’s output were continuous (ie, nonpulsatile).24 Arterial design is such that pulsatile energy is in the main restricted to the major arteries and is absorbed in these as a consequence of blood and arterial wall viscosity. The renal, central, and coronary beds, however, are different to all others. They receive (relatively) torrential flow at rest to filter blood, sustain sensitive brain cells, and maintain cardiac action, respectively. The heart pulsates because it fills and empties, but the brain and kidneys pulsate as well because of the high pulsatile flow into and within these organs. The lungs are the only other organs that pulsate to a similar degree, and venous efflux into the left atrium carries pulsations that are transmitted right through the pulmonary capillaries.25,26

In the systemic circulation, the brain and kidney are unique in that their cells are passively perfused throughout systole and diastole by pulsatile flow, whereas their smallest arteries are exposed to high pulsatile pressure on account of vasodilatation upstream. The coronary system is different in that arteries within the left ventricular wall are squeezed shut during systole and are not exposed to high systolic pressure. Flow into the coronaries supplying the left ventricle during systole is entirely caused by passive distension of the epicardial arteries.27 Coronary circulation will not be considered further on this account.

The unique features of the kidney and brain are that they are continually and passively perfused at high-volume flow throughout systole and diastole. Their vascular resistance is very low, so that in comparison to other vascular beds resistance is closer to input and characteristic impedance (Figure 1). Impedance and flow patterns in other vascular beds during vasodilatation are similar to those normally seen in kidney and brain (Figure 2).21 Wave reflection from kidney and brain is very low and pulsations of pressure and flow extend well into these organs, just as they do into the lungs.25,26 These 2 organs throb with each beat of the heart, and their venous efflux, like that of the lungs, retains pulsations transmitted through the capillary network. The brain and kidney are accustomed to such flow conditions and work well throughout normal life. They are, however, susceptible to influences upstream that may increase fluctuations of pressure and flow, whereas small vessels in other organs are protected by relatively intense vasoconstriction upstream.

Early studies in this area dealt with mean flow and pressure and vascular resistance.28,29 More recent studies have shown the additional effects of pulsatile phenomena.30–32

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**Figure 1.** Left, Vascular impedance in the femoral artery of a dog under control condition. Impedance modulus at zero frequency was ~20-times the value of characteristic impedance and there were strong fluctuations in modulus and phase up to 20 Hz. (From O’Rourke & Taylor. Vascular impedance of the femoral bed. Circ Res. 1966;18:126–139.) Right, Vascular impedance in the renal artery of a dog under control conditions. Impedance modulus at zero frequency was less than twice the value of characteristic impedance and fluctuations of modulus and phase were very small.34 Impedance modulus is the ratio of pressure to flow as a function of frequency. Modulus at zero frequency is equivalent to peripheral resistance. Characteristic impedance is impedance modulus in the absence of wave reflection.
Function of the Human Arterial Tree With Aging

With aging, the aorta progressively stiffens. This is apparent as a 2-fold increase in aortic pulse wave velocity between age 20 and 80 years, denoting a 4-fold increase in elastic modulus. Such changes are accompanied by degeneration of the orderly elastic lamellar architecture of the aorta and can be attributed to the fatiguing effects of cyclic strain on these fibers. Effects of these changes are amplified by the early return of wave reflection from the peripheral arterioles. Input impedance at the ascending aorta at and about heart frequency is quadrupled (Figure 3). It is doubled by the aortic characteristic impedance itself and doubled again by the early return of wave reflection. In consequence, pulse pressure in the aorta and central arteries for the same flow ejection is quadrupled. Brachial pulse pressure is known to increase with age, but such increase belies the real increase in central pulse pressure (Figure 4).

Such increase in arterial pulse pressure has little effect on the systemic circulation to most bodily tissues because their flow is determined by mean pressure, and because cells are protected by the vasoconstricted arteries and arterioles upstream. The brain and kidney cells receive no such protection because arterial vessels remain dilated. The 4-fold increase in arterial pressure is applied to all the distributing arteries in these organs while mean flow is maintained. Brain and kidney arteries of all sizes are thus subjected to higher pulsatile circumferential stress and higher longitudinal shear stress. Their ability to withstand increased stresses depends on their resilience, and this is markedly decreased in a number of diseases, particularly diabetes mellitus. Aging changes of large arteries thus promote a “set-up” for small arterial disease and the types of changes elegantly elucidated by Byrom and others 50 years ago.

Effects of Arterial Stiffening on the Kidney and Brain Microvasculature

Byrom’s work was initially conducted on rats but was applied to the small-vessel disease seen in human hypertension. He showed that damage to small arteries could be induced by increased pulsatile stress and could lead to tearing of their endothelial and smooth muscle cells with disruption of the vessel. He thus explained development of small arterial dilations and aneurysms, and the features of lipohyalinosis and of fibrinoid necrosis as seen in the brains and kidneys of
hypertensive disease. Byrom further showed that these changes were largely reversible when disrupting forces were reduced.38

Logical Therapy of Microvascular Disease in Brain and Kidney of Older Humans

To date, renal microvascular disease has usually been seen in terms of local disturbance of the renin-angiotensin system, with need for specific local treatment with ACEI or ARB drugs. Cerebral microvascular disease is usually regarded as different and a target for general blood pressure reduction and/or for use of cholesterol-lowering therapy. These considerations suggest that microvascular disease at the 2 sites may be of similar cause and may warrant similar treatment.

The most logical therapy of such microvascular disease is to reduce arterial stiffening and thus reduce abnormally high pulsatile stresses in cerebral and renal microvessels. Although ACEI treatment has been shown to reduce aortic pulse wave velocity and delay progression of renal-related complications,39 most studies have shown little direct benefit of drugs on the degenerate aorta.40,41 In contrast, drugs such as ACEIs, ARBs, CCBs, and nitrates can markedly reduce wave reflection, and thereby substantially reduce central augmentation and central pulse pressure.14–16,40,41 This would be expected to have a marked benefit on microvascular function; and this has been observed.42 Exercise training34 can likewise reduce wave reflection and central pressure augmentation through improvement in endothelial function. Exercise training has well-known benefits in maintenance of health and prevention of cardiovascular events.

Ironically, drugs that dilate arteries of systemic vascular beds create the same possibility of vascular damage within the beds as occurs with aging in the kidneys and brain. Nitrates, for instance, can be observed to cause digital throbbing as a consequence of arterial dilation. However, the effects of these drugs are generalized and induce less dilation than normally present in the brain and kidneys. Further, the cells of the organs are less specialized and less subject to damage.

There is another situation in which the mechanisms described can account for microvascular damage. Similar lesions are seen in the lungs with development of pulmonary hypertension in the presence of ventricular septal defect, patent ductus arteriosus, and other congenital arteriovenous shunts. These lesions are different to those seen in passive pulmonary hypertension accompanying mitral stenosis or left ventricular failure43 and are also induced by high pressure and flow pulsations into a dilated vascular bed.

In summarizing his work 36 years ago, Byrom cautioned that any hypothesis requires ongoing scrutiny and examination. Such caution are equally applicable to what we present here. We can only hope that our presentation endures as well as that of this great but under-recognized scientist.44

Perspectives

The arguments presented here provide a possible explanation for the association between aortic stiffening and disease of small blood vessels in the vasodilated vascular beds of the brain and kidney. We note that recent studies indicate that the protective effects of ACEI and ARB drugs are shared by long-acting dihydropyridine CCBs. We suggest that such benefits are not caused by direct effects on the vessels in the brain and kidney, but rather by effects on other arterial vessels throughout the body. We suggest that the beneficial effects are caused by reduction in wave reflection and aortic pulse pressure. We believe that such possibilities should be tested in future studies.

References

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