Beyond Blood Pressure
Subtle Effects of Drug Classes

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I
n this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Schillaci et al\(^1\) raise an interesting possibility—that a drug class (protease inhibitors) can have subtle arterial ill effects, which are not apparent from conventional blood pressure recordings. The authors provide evidence of aortic stiffening (measured as carotid–femoral pulse wave velocity [PWV]), increase in wave reflection from peripheral vessels (measured as aortic augmentation index [AIx]), and impairment of left ventricular subendocardial supply/demand ratio (measured as Buckberg index). Studies to date on arterial stiffening and its implications have concentrated on how age, gender, body height, exercise, lifestyle, and disease affects these properties, and how arterial properties, when deranged by disease, can be improved by drug therapy.\(^2\) Such adverse arterial hemodynamic changes with drugs have not been sought before. Before approval of a new drug, government regulatory bodies have required only measurements of cuff brachial systolic and diastolic pressures and assurance that these were not significantly altered. The question arises from the study of Schillaci—is this enough? Is it possible that drug classes may have adverse long-term effects that are not exposed by conventional cuff measurements? The question is relevant to the present concerns on long-term ill effects of COX 2 inhibitors (coxibs), with rofecoxib withdrawn from the market and the subject of legal action in US courts.\(^3\)

The potential importance of the findings of Schillaci et al on protease inhibitors is unquestioned. These drugs have revolutionised the treatment of AIDS and find routine use in persons who are seropositive to the HIV virus. There were no HIV-positive persons in this study who were not treated with protease inhibitors. Studies of the drugs quoted by Schillaci are in recent issues in the world’s highest impact journals. I will not pursue such important implications to HIV and AIDS, but will refer to interpretation of the indices used by the authors, and the wider implications to the pharmaceutical industry, drug regulators, and clinical trialists.

I see the present study on protease inhibitors as a pilot. HIV-positive persons taking protease inhibitors were compared with age-matched hospital staff who served as controls. There is need for long-term prospective trials to confirm. Problems in this study include the control group. Are hospital staff apt to be more careful of their general health than those who become HIV-positive? Is it possible for operators to be blind to an individual’s status when one group comprised hospital patients and another group hospital coworkers? Were the findings a result of the HIV infection or a consequence of the drug used to treat the infection? If the latter, was the effect a direct one or was it induced by the metabolic syndrome? The differences in PWV, AIx, and Buckberg index described by Schillaci et al were statistically significant, but were relatively small and within the range seen in a population of normal 41-year-old men and women.

Normal populations show a wide range of values for the three measures described by Schillaci et al.\(^2\) Some variations are explainable on the basis of age, gender, height, and lifestyle, but some are not. On account of this biological variability, it has been difficult to establish differences even between diabetics and normal subjects. To the uninitiated, arterial stiffness and its measurement can be very confusing. There are however some relatively simple principles, explanations, and implications.

“Aortic” PWV is the best accepted measure of large artery stiffness, and is measured from the foot of the pressure wave at central (usually carotid) and distal lower body site (usually femoral artery). Distance between sites is divided by the time delay to calculate PWV. PWV is a measure of aortic stiffness—the higher the value, the stiffer the artery. Typical values for aortic PWV are 500 cm/sec in an adolescent and 1200 cm/sec in an 80-year-old. Experienced operators can usually measure wave foot accurately, but different groups have used different measures of distance. Some measure the distance between central and femoral sites; some subtract a multiple of distance from aortic arch to carotid artery. There is no established convention, but this is emerging.\(^4\) There are different ways to measure pressure augmentation.\(^2\) Schillaci used the SphygmoCor system to generate the aortic pressure waveform from the radial wave. I favor this, but others favor direct recordings from the radial artery or from the carotid artery. There are consistent relationships between sites. My preference relates to difficulties in getting reproducible carotid measurements and from difficulties in determining the inflection point on the radial pressure wave, especially in young subjects, or when heart rate is high or vascular tone low. The principal difficulty is in identifying the early systolic inflection on the central pressure wave which marks the peak of flow, because measures of augmentation depend on the subsequent rise from this point to the secondary peak or shoulder.\(^2\) Measures of aortic AIx are not as accurate as of derived aortic systolic or pulse pressure.\(^2\)

Subendocardial viability ratio is an index introduced by Buckberg\(^6\) to express myocardial supply/demand and propensity to ischemia. It becomes important when ventricular hypertrophy,
causing prolonged ejection duration, is combined with tachycardia causing shortening of diastolic period. Differences seen by Schillaci’s are unimportant at rest, but would be important if maintained under conditions of stress.

The method used by Schillaci for determination of aortic AIx also generates the aortic pressure waveform from the radial waveform and corrects the distortion of the pressure wave as it is transmitted down the upper limb. One can calculate central systolic peak pressure from this, using the brachial cuff method to calibrate the radial waveform. With this, one can examine the effects of variable wave reflection on aortic systolic pressure (Figure). This is a major clinical application of the method, and the one which could be most useful in further clinical trials of protease inhibitors. One would expect that any increase in aortic pulse wave velocity and AIx would be associated with a greater increase in central aortic than brachial systolic pressure.

Differences between central and brachial systolic pressure have been shown between control therapy and arterial dilating agents such as nitrates, calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). These drugs reduce wave reflection and thereby decrease aortic AIx. As with nitrates, this causes greater reduction in central systolic than brachial systolic pressure (Figure). For the dose of ramipril used in the HOPE study (10 mg) compared with 100 mg of atenolol, the difference was 5 mm Hg. HOPE and LIFE studies found 1 to 3 mm Hg difference in brachial systolic pressure for ramipril and losartan and initially described the substantial (10% to 40%) reduction in cardiovascular events as “beyond blood pressure lowering.” LIFE investigators now concede that central blood pressure should be assessed in future antihypertensive drug trials. Staessen et al have emphasized the general relationship between systolic pressure fall and cardiovascular events. They have shown that such relationship is most evident if one considers difference in central systolic pressure. This issue—the relationship between cardiovascular events and site of blood pressure lowering with different drugs—will be further clarified in the ASCOT study and its CAFE tonometry study.

What then is the possibility that central aortic pressure is raised by other drug classes? Might the findings for protease inhibitors apply to other drug classes such as COX 2 inhibitors for which premarketing trials showed no significant rise in brachial arterial pressure? We do not know, because no studies of arterial stiffness or wave reflection were undertaken pre or post-marketing. A meta-analysis of post marketing studies however has shown a 3.9 mm Hg higher central systolic pressure for coxibs compared with placebo therapy. This is higher than in HOPE and LIFE. In the most recent studies of gastroenterostinal events, blood pressure data are not available, but cardiovascular events were doubled with rofecoxib.

The cause of cardiovascular problems with the coxibs is not known. But elevation in brachial pressure is a clue, though attention to this was not sufficient to prevent a variety of coxibs getting to market then escaping scrutiny when in widespread clinical use.

In studies of modern drug classes, including protease inhibitors, COX 2 inhibitors, even ACEIs, CCBs, ARBs, and nitrates, too much has been expected of the nineteenth century cuff sphygmomanometer. New methods of clinical assessment are desirable and are available. Their use is likely to improve clinical practice by explaining beneficial effects of old drugs and potential problems of the new.

References


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