It is well established that blood pressure (BP) differs markedly between peripheral (brachial) and central arteries (aorta). As the pressure wave travels distally from the heart, mean BP and diastolic BP decrease slightly (1 to 2 mm Hg), but a gradual and significant increase of systolic BP (SBP) and pulse pressure (PP) occurs. This phenomenon is called BP amplification.1 The development of commercially available devices for the assessment of central BP has boosted this field of clinical research.1–3 Numerous studies have shown the close pathophysiological connection between central BP and cardiovascular diseases1–4 and have highlighted the ability of central BP to provide complementary data on cardiovascular risk beyond that provided by brachial BP.2–6

In the present issue of Circulation,7 data from the Conduit Artery Function Evaluation–Lipid-Lowering Arm (CAFE-LLA, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT])8,9 on the effect of statins on central BP is presented. Before commenting on the available data, we briefly summarize the pathophysiology of PP amplification. Finally, we discuss potential strategies based on central hemodynamics that will hopefully improve cardiovascular risk assessment and reduction.

Pathophysiology of BP Amplification and Cardiovascular Diseases

As a consequence of the pulsatile nature of blood flow and of the presence of arterial stiffness/diameter gradient along the arterial tree, pressure wave reflections arise at various sites of the arterial bed.1 The backward-traveling reflected wave sums up with the forward-traveling wave, forming the actual pressure waveform (Figure 1a). Whereas in healthy young subjects the average aortic SBP is 100 to 110 mm Hg, at the same time the brachial SBP is amplified substantially and reaches 120 to 130 mm Hg.10 This difference of 10 to 30 mm Hg expresses the amplification of the SBP (Figure 1a).1,10 Because DBP is practically steady between the aorta and the brachial artery, PP amplification (brachial-aortic PP) is subsequently deduced.

The need for central BP assessment arises primarily from the fact that the BP amplification between the brachial artery and the aorta is highly variable within and between subjects.1,10 In addition to arterial wall properties, which affect the amplification phenomenon per se, aging is the principal factor leading to amplification reduction because it is the main modulator of arterial properties.10 The second factor is heart rate, which should be regarded as a defining factor of the “timing-synchronization” of the forward- and backward-traveling waves.11 For the same reflected wave and similar pulse height of the forward-ejected pressure wave, a prolongation of the cardiac ejection phase, due to lower heart rate, is associated with higher augmentation of the peak SBP by the reflected wave (Figure 1). This is attributed to earlier systolic “timing” of the waves. For example, for a given brachial SBP of 130 mm Hg, aortic SBP may increase from 110 to 120 mm Hg, depending on heart rate level, and thus PP amplification may decrease from 20 to 10 mm Hg (Figure 1a and 1b). Of note, the “timing” (arrival time of the reflected wave [Tr]; Figure 1) depends also on the arterial stiffness (pulse wave velocity) and the distance covered by the reflected wave. In this respect, the third modulator of pressure amplification is the “arterial length,” which should be conceived as the actual distance of the heart from the peripheral arteries. Finally, in healthy normotensive subjects, PP amplification is independently and inversely correlated with mean BP whereas the opposite is observed in treated hypertensive subjects (Figure 2).10–12

From the viewpoint of pathophysiology, for a given brachial PP (eg, 60 mm Hg), a reduction of aortic-brachial PP amplification (eg, from 20 to 10 mm Hg) is expected to be associated with unfavorable hemodynamic effects on central arteries and the heart (Figure 1). In other words, because of the increase in central PP (eg, from 40 to 50 mm Hg) a higher left ventricular afterload and a more intense cyclic stress on the renal and cerebral micro- and macrocirculation is experienced.1,13,14 We have previously shown that in subjects with end-stage renal disease,2 the disappearance of PP amplification after 54 months of follow-up was a strong independent predictor of all-cause and cardiovascular mortality.

Statins, Atherosclerosis, and Pressure Amplification

Statins reduce the incidence of cardiovascular events in subjects with hypertension primarily through their action on...
plasma cholesterol.\textsuperscript{15–18} However, they also have pleiotropic effects on atherosclerotic plaques via improvement of endothelial function and increased nitric oxide bioavailability, as well as antioxidant and antiinflammatory action.\textsuperscript{15,16} Such actions might explain why several studies have shown, yet not consistently, a beneficial effect of statins on central arterial stiffness.\textsuperscript{15} Recently, a large randomized placebo-controlled trial,\textsuperscript{16} as well as a meta-analysis,\textsuperscript{17} indicated that statins have a modest but significant effect on peripheral BP reduction (1 to 3 mm Hg). The emerging question was whether statins might reduce central BP beyond peripheral BP. Conversely, the presence of pleiotropic effects from statins is challenged by the lack of epidemiological evidence on cardiovascular risk lowering beyond cholesterol reduction.\textsuperscript{18}

In the CAFE-LLA study,\textsuperscript{7} the effect of atorvastatin on central BP in treated hypertensive patients was tested in a randomized, double-blind, placebo-controlled trial. After 3.5 years of follow-up, despite a significant and clinically meaningful reduction in cholesterol levels in the atorvastatin arm, no impact was found on any central hemodynamic parameter.

At first approximation, these results may sound surprising because arterial stiffening and atherosclerosis, although different diseases, have overlapping processes due to common cardiovascular risk factors and complications. However, Farrar et al have shown that in animals, hypercholesterolemia induced by cholesterol-rich diet leads to an initial pressure-independent reduction in arterial stiffness,\textsuperscript{19} followed by a progressive increase over time. This process can be reversed by lowering serum cholesterol levels. Raison et al observed similar time-dependent find-
ings in humans and, in their blinded study, did not observe any change in central or brachial BP. All these data imply a time-dependent effect of lipids, and presumably also of statins, on the arterial wall, which may be associated with the stages of plaque pathology (from foam cells to calcification) and which presumably relies on the duration of this interaction.

The interpretation of the present negative results of the CAFE-LLA, may be partly associated with lack of power of the CAFE-LLA to evaluate the hemodynamic outcome. On the other hand, the “too little, too late, too short” hypothesis can be raised. Too little, because a low statin dosage (10 mg per day) was used and because baseline cholesterol levels were only modestly elevated. Most of the available studies on the reduction of aortic stiffness have used higher doses of statins (up to 80 mg of atorvastatin), so that a dose–response curve was firmly established.15 Too late, because the mean age at study entry was 63 years, suggesting that vascular damage may be established to such a degree that it precludes observing any effect of statin therapy on arterial function. Too short, because longer follow-up may be needed to observe significant pressure-independent effects on central hemodynamics. Finally, the authors state inevitably that data demonstrating a beneficial effect of statin therapy on central hemodynamics are likely to be published, but such data are still awaited.

Other Antihypertensive Strategies That Increase BP Amplification

In Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study (REASON), blockade of the renin-angiotensin system with an angiotensin-converting enzyme inhibitor (perindopril) in association with a diuretic (indapamide) was compared in a double-blind randomized manner with a β-blocker (atenolol). After 1 year of treatment, arterial stiffness was reduced, but only the perindopril/indapamide combination reduced large wave reflections, central PP, and cardiac hypertrophy.5,14 Later on, the investigators of the CAFE study6 found similar results when they compared a calcium channel blocker (amlodipine)–based regimen with an atenolol-based regimen. Most importantly, the results of the CAFE Blood Pressure Lowering Arm (CAFE-BPLA) study7 showed that central PP was an independent predictor of mortality and that the reduced incidence of mortality observed in the amlodipine arm might be partially explained by this predominant effect on central BP. Finally, for both the CAFE and REASON trials, we propose the following sequence of events: First, antihypertensive treatment decreases blood pressure, and after ~1 year of treatment arteriolar hypertrophy is reduced.13 Second, a modification of reflection sites and reflection coefficients ensues thereafter, as previously observed.1,5,13 Third, when reflections are modified, a decrease in central SBP and PP occurs, as observed during long-term angiotensin and/or calcium channel blockade but not under β-blockade.5,6

In conclusion, the CAFE-LLA study showed that 10 mg per day of atorvastatin in high-risk middle-aged hypertensive patients has no specific hemodynamic effect on both peripheral and central arteries. The question is: Are there any other strategies to improve central BP beyond peripheral BP (ie, to increase BP amplification) in relation to the current antihypertensive treatment options? The aforementioned data from the REASON and CAFE studies suggest that differences between antihypertensive treatment strategies do exist. Future trials, investigating both peripheral and central hemodynamic parameters, will eventually make it possible to act on aortic BP beyond brachial PP.

Disclosures

None.

References


Key Words: Editorials | pulse pressure | cardiovascular diseases | statins
Statins, Central Blood Pressure, and Blood Pressure Amplification
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Circulation. 2009;119:9-12; originally published online December 22, 2008;
doi: 10.1161/CIRCULATIONAHA.108.824532

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