Large and Small Artery Cross-Talk and Recent Morbidity-Mortality Trials in Hypertension
Stéphane Laurent, Marie Briet, Pierre Boutouyrie

The results of recent large clinical trials in hypertension invite re-evaluation of the mechanisms of action of antihypertensive drugs on large and small arteries in the context of their effects on cardiovascular outcomes. By increasing our understanding of the relationship between large and small artery damage, target organ damage, and clinical end points, the trials provide us with new insights into the management of hypertension. This short review aims at analyzing the following: (1) whether β-blockers may exert deleterious effects on cardiovascular CV prevention through the reduction in heart rate (HR) or the lack of arterial remodeling; (2) whether long-term arterial remodeling can explain the “legacy” effect of multifactorial treatment in patients with hypertension and type 2 diabetes mellitus (T2D); and (3) to which level diastolic BP (DBP) can be safely lowered in elderly patients with isolated systolic hypertension (ISH). Because these issues have the concept of large/small artery cross-talk in common, we analyzed it first.

Large and Small Artery Cross-Talk in Hypertension

The damaging effect of local pulse pressure (PP) has been well demonstrated on large arteries and, to a lesser extent, on small arteries. Elevated PP can stimulate hypertrophy, remodeling (increased media:lumen ratio), or rarefaction of small arteries in the microcirculation, leading to increased resistance to mean flow. Recent studies showed a close relationship between microvascular damage in the heart, brain, retina, and kidney and either PP or arterial stiffness. Indeed, significant relationships have been demonstrated between brachial PP and glomerular filtration rate,1,2 microalbuminuria,2 or white matter lesions;2 between arterial stiffness and glomerular filtration rate,4,5 urinary albumin,6 retinal arteriolar narrowing,6,7 white matter lesions,3 or cognitive function;6 and between carotid stiffness and glomerular filtration rate.4,5 Although not all of these relationships are independent of confounding factors,3 there is a large amount of evidence for linking the pulsatility of BP to target organ damage.

A cross-talk between the small and large artery can be exemplified by the following sequence (Figure 1): (1) increased wall:lumen ratio and rarefaction of small arteries9,10 are major factors for an increase in mean BP; (2) the higher mean BP, in turn, increases large artery stiffness through the loading of stiff components of the arterial wall at high BP levels; and (3) the increased large artery stiffness is a major determinant of the increased PP, which, in turn, damages small arteries11 in the heart, brain, retina, and the kidney,12 as seen above, and favors the development of left ventricular hypertrophy, carotid intima-media thickening, and plaque rupture. These various types of target organ damage have been shown to be related to CV events. Thus, the cross-talk between the small and large artery exaggerates arterial damage, following a vicious circle. Antihypertensive treatment, by acting on both small and large arteries, could reverse this vicious circle into a “virtuous” circle: the pharmacological arterial remodeling at both levels should be able to reduce central PP, thus target organ damage and CV events. As we describe below, not all pharmacological classes are equal in this respect.

Deleterious Effects of β-Blockers: Role of HR Reduction and Lack of Arterial Remodeling

In the Losartan Intervention for Endpoint Reduction in Hypertension Study13 and the Anglo-Scandinavian Cardiac Outcomes Trial,14 losartan- and amlodipine-based treatments, respectively, proved to be more effective than atenolol-based treatments for reducing stroke. The recent Perioperative Ischemic Evaluation Study15 showed that, in patients undergoing noncardiac surgery, those receiving metoprolol were at higher risk of stroke than those receiving placebo. Meta-analyses of hypertension treatment trials confirmed the lesser impact of β-blocker–based therapies in preventing stroke, particularly with atenolol, and showed that the risk of myocardial infarction was not significantly different.16 These results have been challenged by recent meta-analyses.17 However, the latter analyzed β-blocker regimens jointly with diuretics and did not provide data on atenolol alone.

An important question is whether β-blockers, particularly atenolol, exert deleterious effects on CV prevention through the reduction in HR or because they fail to remodel large and...
small arteries. Indeed, a number of studies pointed out the lack of arterial remodeling after atenolol. Although atenolol is known to prevent the deleterious effects of catecholamines on the heart, it does not reduce total peripheral resistance and sympathetic drive; it is less effective than blockers of the renin-angiotensin system to reduce small artery damage, ie, vasoconstriction and increased media/lumen ratio; and it is less effective than vasodilators for reducing aortic and carotid stiffness, carotid intima-media thickness, and cerebrovascular resistance in hypertensive patients. Thus, atenolol fails to break the vicious circle of aggravation between small and large arteries. The lack of long-term remodeling of large and small arteries in hypertensives very likely explains the lesser reduction of wave reflection and central aortic BP following nonvasodilating β-blockers than with vasodilating β-blockers (including celiprolol, nebivolol, and carvedilol) and vasodilating agents like calcium channel blockers and renin-angiotensin system blockers (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers).

An alternative hypothesis explaining the possible deleterious effects of β-blockers in general and atenolol in particular is the reduction in HR. A short-term (5-week) crossover study showed that the higher the reductions in HR after atenolol, nebivolol, or placebo, the higher the increase in wave reflection and central aortic PP. In a recent metaregression analysis, Bangalore et al attempted to link the β-blocker–associated reduction in HR with the increased risk of myocardial infarction, CV events, and death in hypertensive patients (however, no relationship between HR reduction and stroke was found). They suggested that the bradycardia-induced dyssynchrony or uncoupling between outgoing and reflected waves could increase central aortic BP. However, the mechanisms of the deleterious effects of β-blockers on the arterial system may be more complicated than the sole bradycardia. Indeed, in a further analysis of the clinical trials included in the above metaregression, we showed that HR at baseline, ie, before any administration of β-blocker, was a better predictor of myocardial infarction than HR at the end of the trial. These findings suggest that the reduction in HR after treatment may not be the main mechanism through which nonvasodilating β-blockers, eg, atenolol, exert deleterious effects on the CV system.

Specific experiments may be designed to determine whether the reduction in HR or the lack of arterial remodeling is prevailing into the deleterious effects of atenolol. For instance, it would be possible to compare the hemodynamic effects of atenolol with a drug that lowers HR to the same extent but is not a β-blocker, eg, ivabradine. Secondly, atenolol could be given to individuals with pacemakers in situ so that they could be paced back up to their basal HR while still having atenolol in their system. However, these experiments, which are more easily performed under acute than chronic conditions, may only partially answer the question, because arterial remodeling is a long-term process, established over months or years.

Long-Term Remodeling of Large and Small Arteries in Patients With Hypertension and T2D, a Possible Mechanism for the “Legacy” Effect

In the randomized Steno-2 Study, after the initial treatment period of 7.8 years, patients were subsequently followed observationally for a mean of 5.5 years, during which BP significantly differed between the intensive multifactorial therapy and the conventional therapy. A postinterventional benefit with regard to both microvascular and macrovascular complications of T2D was reported: at 13.3 years of follow-up, intensive therapy was associated with a lower risk of
death from CV events. Such a legacy effect was also observed during the 10-year follow-up of the intensive glucose control of the United Kingdom Prospective Diabetes Study 80\textsuperscript{28}, in the sulfonylurea-insulin group, the relative reductions in risk persisted at 10 years for any diabetes-related end point and microvascular disease, and risk reductions for myocardial infarction emerged over time, as more events occurred. By contrast, a legacy effect was not observed during the 10-year follow-up of the intensive BP control of the United Kingdom Prospective Diabetes Study 81, during which BP did not differ anymore between groups.\textsuperscript{29} Whether there may be dissociation between long-term impacts of blood pressure versus glucose control remains unclear.

The pathophysiological mechanisms responsible for a legacy effect of intensive BP and/or glucose control may involve large and small artery remodeling and associated changes in arterial function. Data concerning the long-term effects of glucose-lowering drugs on large and small artery structure and function are lacking. Concerning antihypertensive agents, a number of mechanisms have been proposed, including the reduction of inflammation, oxidative stress, and advanced glycation end products. We suggest that antihypertensive agents may play a role through the large/small artery cross-talk, as seen above. Indeed, they demonstrated an effect on both large and small arteries in hypertensives with T2D. These effects may be potentiated through the following sequence: by acting on large artery mechanical properties and reducing stiffness and central PP, these drugs can induce a long-lasting pharmacological remodeling of small arteries, reducing the media:lumen ratio and increasing vasodilatory capacities. The structural and functional changes in total peripheral resistance can, in turn, lower mean BP, thus reducing arterial stiffness, and reduce wave reflection, thus reducing central PP.

Long-lasting pharmacological remodeling of arterial structure takes time. For instance, a significant reduction in the media:lumen ratio was observed after 1 year ofvalsartan in hypertensives with T2D,\textsuperscript{30} whereas a reduction in endothelial dysfunction was observed after only 3 months of candesartan. A dose-dependent (8-mg versus 4-mg) increase in carotid distensibility was observed after 6 months of perindopril treatment in hypertensives with T2D.\textsuperscript{31} We suggest that long-lasting structural changes of large and small arteries after renin-angiotensin system blockers may be mutually reinforcing, thus becoming large enough to provide a legacy effect. Whether this applies to antidiabetic drugs and other antihypertensive agents remains to be studied.

The Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation (ADVANCE) Study\textsuperscript{32} showed that a 5.6/2.2-mm Hg reduction in BP with perindopril/indapamide, compared with placebo after a median of 5 years of follow-up, was effective at reducing the incidence of combined major macrovascular and microvascular events, primarily through a reduction in coronary events, with no significant effect on cerebrovascular events, and a reduction in nephropathy, with no significant effect on retinopathy. A longer treatment period could have led to significant changes in cerebrovascular events and retinopathy through long-term remodeling of small and large arteries. The results of the Steno-2 Study and the United Kingdom Prospective Diabetes Study 80 and the late separation seen in the Kaplan-Meier curves of the ADVANCE Study suggest\textsuperscript{33} that long-term risk reduction in major macrovascular events and death from any cause in the ADVANCE Study would have become significant if subjects had been followed for a sufficiently long period.

To What Level May DBP Be Safely Lowered in Elderly Patients With ISH?

Although ISH can be considered as a predominantly “large artery disease,” the large/small artery cross-talk suggests that a pharmacological remodeling of small arteries (and associated increased vasodilatory capacities) may occur in response to the long-term lowering of central PP, thus contributing to the beneficial effects of antihypertensive agents despite a fall in DBP below the supposedly deleterious threshold of the J-shaped curve.

Indeed, the recent Hypertension in the Very Elderly Trial (HYVET)\textsuperscript{34} showed a 30% (−1% to 51%; \textit{P}=0.06) reduction in the rate of fatal or nonfatal strokes (primary end point) after BP lowering in response to the perindopril/indapamide combination in patients >80 years of age compared with those taking a placebo. Mean BP values were lowered from 173/91 mm Hg to 143/78 mm Hg (systolic BP/DBP) in the active group, with fewer serious adverse events than in the placebo group. These results should be reassuring for many physicians who are reluctant to reinforce antihypertensive treatment in elderly hypertensives because they fear that lowering BP in these elderly patients, often presenting with ISH, would be associated with more adverse events and coronary complications.

There is indeed a misconception, based on the J-shaped curve\textsuperscript{35} for DBP, that lowering SBP would lead to an excessive reduction in DBP, reaching a similar extent as the systolic fall, jeopardizing coronary blood flow (which occurs during diastole) in patients at high risk of myocardial infarction. The resulting effect is then opposite to what is expected, because less intensive antihypertensive treatment leads to a higher SBP and a higher number of CV events.

There are ≥3 arguments for convincing physicians that they should not fear lowering DBP when there is a need to lower SBP. First, coronary perfusion is impaired by exaggerated aortic stiffness and central SBP rather than the reduction in DBP. Animal experiments showed that reducing aortic compliance in anesthetized dogs by aortic banding\textsuperscript{36} not only increased aortic SBP and PP but also limited the rise in endocardial flow in response to isoproterenol stimulation by comparison with control dogs. Thus, in elderly patients with ISH, the chronically decreased aortic distensibility can contribute to a further decrease in coronary flow reserve, inducing subendocardial ischemia even in the absence of coronary artery stenosis. Reducing aortic stiffness and SBP with vasodilators would reduce subendocardial ischemia, exceeding the possible impairment of coronary perfusion by an excessive DBP lowering. A complementary mode of action is represented by the reduction in large artery stiffness and central PP, inducing a long-lasting pharmacological remodeling of small arteries, reducing the media:lumen ratio and
increasing vasodilatory capacities, as seen above, thus increasing the possibilities of reversing target organ damage, particularly the myocardial arteries, and reducing the risk of CV events.

The second one is illustrated by the Windkessel (or compliance) function of the aorta. ISH can be considered a model of predominant aortic stiffening, contributing to early reflected waves that arrive in early systole, superimpose on the forward wave, and boost the systolic BP further, whereas mean and DBP are marginally modified. Indeed, animal experiments showed that the replacement of the normal aorta by a stiff Dacron graft in dogs, increased to a large extent SBP and PP, minimally lowered DBP and did not change mean BP, as predicted by the mechanical properties of the arterial system. This observation implies that lowering BP with vasodilators should theoretically lower DBP to a much lesser extent than SBP. This is indeed the case in the Systolic Hypertension in the Elderly Program,38 Systolic Hypertension in Europe Study,39 Losartan Intervention for Endpoint Reduction in Hypertension Study-ISH,40 and HYVET34 in which active treatment led to a 3-fold less reduction in DBP than in SBP (Figure 2). The fall in DBP after active treatment was consistently composed between −7 and −13 mm Hg, whereas the fall in SBP was 3-fold higher (between −23 and −30 mm Hg). The meaning of the J-shaped curve, which shows that patients with the lowest DBP values, either at baseline or during the clinical trial, have a higher risk of myocardial infarction, is still a matter of controversy. A likely possibility is that these patients correspond with those with a high SBP, thus even higher PP and a higher risk of myocardial infarction. Because SBP is a major determinant of coronary events, the resulting effect of a 3-fold higher reduction in SBP than DBP would be largely beneficial, with the reduction of risk attributed to SBP lowering largely exceeding the possible increased risk attributed to DBP lowering.

Third, despite a fall in DBP below the supposedly deleterious thresholds of J-shaped curves, randomized, double-blind clinical trials showed a clear CV benefit. For instance, the Systolic Hypertension in the Elderly Program,38 Systolic Hypertension in Europe Study,39 and Losartan Intervention for Endpoint Reduction in Hypertension Study-ISH,40 including elderly patients with ISH, have shown the effectiveness of reducing SBP for preventing CV events.实现了 mean DBP values, which were between 68 and 79 mm Hg at the end of the study, were much lower in patients belonging to the lowest 95th percentile (mean value minus 2 SD), between 50 and 63 mm Hg. Similarly, in the HYVET34 which included only 32% of patients having ISH but 100% >85 years of age, the benefit of active treatment compared with placebo was significant, with a 30% reduction in all stroke and no coronary events. These beneficial effects occurred despite a significant reduction in DBP (−13±9 mm Hg) versus baseline, reaching a 31-mm Hg reduction in the 95th percentile.

In conclusion, antihypertensive agents may prevent CV events, at least in part, through the large/small artery cross-talk. By acting on large artery mechanical properties and reducing stiffness and central PP, these drugs can induce a long-lasting pharmacological remodeling of small arteries, reducing the media:lumen ratio and increasing vasodilatory capacities. The structural and functional changes in total peripheral resistance can, in turn, lower mean BP, thus reducing arterial stiffness, wave reflection, and central PP, all changes that, in turn, reduce target organ damage and CV events.

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