Effects of Treatment on Arterial Stiffness and Central Blood Pressure—Points to Consider

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Interventional studies have reported beneficial effects of renin-angiotensin system (RAS) inhibitors, both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), on cardiovascular organ damage and events. These beneficial effects have been observed in hypertensive patients as well as in patients with other cardiovascular conditions such as heart failure and post–myocardial infarction and those at high cardiovascular risk as included in the Heart Outcomes Prevention Evaluation (HOPE), EUROPA, and Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) studies. Based on these results, guidelines are recommending RAS inhibitors for cardiovascular protection beyond and independently from their effects on blood pressure (BP).[1] Therefore, it is of importance to assess the effects of RAS inhibition on intermediate cardiovascular endpoints in populations other than those with hypertension. This has been realized in the study by Raff and colleagues published in this issue of *The Journal of Clinical Hypertension*.[2]

Studies have shown that ambulatory and central BPs are superior to brachial office BP measurements in terms of cardiovascular organ damage prediction and prognosis. Elsewhere, assessment of arterial function and structure using the pulse wave velocity measurement is recommended by international guidelines. The study by Raff and colleagues[2] used these techniques to assess the effects of the ARB olmesartan on BP and arterial stiffness. In addition to the results and discussion reported in their article, some points need to be clarified. In fact, interpretation of the treatment effects on arterial stiffness and central BP must consider the following.

CHOICE OF POPULATION

In order to assess the cardioprotective effect of an antihypertensive medication beyond its antihypertensive effect, it is of interest to include not only hypertensive patients but also normotensive individuals at high cardiovascular risk. The population with the metabolic syndrome (MetS) is a good example. A relationship has been demonstrated between the existence of MetS and increased progression of arterial stiffness of the aorta. Moreover, in a longitudinal study, an acceleration of arterial aging over a period of 7 years, as a function of the number of components of the MetS, has been reported. However, it is not clear whether the role of MetS on arterial health is the same in younger and elderly individuals. In fact, studies have shown that the role of some but not all risk factors decrease in the elderly. The study by Raff and colleagues included patients with middle-aged MetS, which is suitable to assess the arterial effects beyond BP reduction.

USE OF CENTRAL BP

Noninvasive central BP can be obtained with either tonometry-based or pressure transducer–based or cuff-based techniques. The tonometry-based method is the most popular and it uses a "transfer function" to estimate central BP from the radial pulses. This technique, used in the Raff study, has some concerns related to its calibration method and user experience. Overall, it is considered reliable if used properly in experienced hands.

Growing evidence suggests that there are discrepancies in central BP among people with similar brachial BP levels and that central BP may be more relevant than brachial BP in predicting target organ damage and cardiovascular outcomes. Data from clinical trials show that some antihypertensive agents might provide cardiovascular protection beyond their antihypertensive effects.[3] This added protection may be, at least partly, explained by a superior effect on arterial stiffness and central BP. Indeed, randomized trials have shown that central and brachial BP may respond differently to antihypertensive medication and that organ damage and events after treatment are mostly related to central BP than brachial BP. However, it should be noted that central BP has to be considered a "pressure" index measured at the aortic level and not as an "arterial" index even if it is related or determined by arterial characteristics. Moreover, the additive value of central BP beyond brachial BP remains to be confirmed. Thus, although central BP is a useful index for cardiovascular risk assessment and for mechanistic analyses in pathophysiology and pharmacology, more investigation is needed to clarify whether the use of medication to improve central BP will translate into better clinical outcomes.

USE OF PULSE WAVE VELOCITY

Several methods are available to assess arterial function and structure. According to the method, systemic, regional, or local arterial compliance/distensibility can be measured. Arterial stiffness (distensibility) as evaluated using automatic measurement of PWV is considered as the gold standard to assess the *regional stiffness*

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of a segment of artery, eg, carotid to femoral or brachial to radial. This method is well established because of its reproducibility and mainly the important number of studies showing this parameter (method) as an independent marker for cardiovascular morbidity and mortality.[4] In their study, Raff and colleagues used automatic measurements of PWV, which are sensitive enough and therefore suitable to detect the arterial effect of antihypertensive treatment.

CHOICE OF ARTERIAL SITE

Considering that the large (central) arteries differ from the small (peripheral) arteries in terms of histology and pathophysiology, the choice of the arterial segment to be assessed is of great importance. In fact, treatment may affect the large and the small arteries in a different manner. Experts believe that it may be easier to reverse abnormalities of the small arteries (muscular) than the large arteries (elastic). Therefore, results observed at one arterial segment cannot be extrapolated to any other arterial segment. In the study by Raff and colleagues, the carotid-femoral pulse wave velocity (PWV) was correctly chosen to assess aortic stiffness. This is valuable because most of the previous studies establishing PWV as the gold standard have been performed at the aortic level. Moreover, the aortic hemodynamic characteristics are of most importance in terms of arterial compliance (buffering function), coronary perfusion, and cardiac afterload and as a major site of atherosclerosis lesions.

DURATION OF TREATMENT

Treatment may affect the arterial hemodynamics and characteristics in at least three different pathways and mechanisms: (1) distension BP and flow modifications, (2) arterial wall muscular fibers affecting the vasomotion function (constriction and dilation), and (3) arterial wall structure by affecting the elastin/collagen fibers content and organization. Therefore, considering that these modifications (mechanisms) are observed at different times after the treatment initiation, the choice of the treatment duration and time of arterial evaluation is crucial. In fact, experts agree that arterial effects can be classified as acute, short-term, and long-term after treatment initiation. The acute and short-term effects are usually observed following hours and weeks after treatment; they are usually related to the reduction of the distension BP in the artery and the effect on the arterial wall function. The long-term effect is usually related to the arterial wall structure remodeling after several months of treatment. It is well accepted that treatment duration to observe structural modification of the arterial wall may exceed 6 months. The study by Raff and colleagues assessed arterial stiffness after a 6-week treatment period, therefore focusing on the short-term modification of mainly the arterial function.

CHOICE OF THE DOSAGE

All of the available RAS inhibitors have been developed and marketed for their antihypertensive effects. Their recommended dosage has been chosen according to their corresponding dose/effect curves on BP. Studies on arterial function and structure have shown that the dose/effect curves on arterial hemodynamic may differ from those observed for BP reduction with usually higher dosages needed for arterial effect. Moreover, most of the interventional studies showing beneficial cardiovascular protective effects of RAS inhibitors used high dosages of ACE inhibitors or ARBs. In their study, Raff and colleagues used olmesartan 80 mg/d—a dose above the approved maximum daily dose for BP reduction—compared with olmesartan 20 mg and amlodipine 5 mg. This design and dosage are interesting to assess the arterial effect since BP-independent beneficial effects have been observed above the maximum BP dose. Their results show no association between BP changes and PWV changes.

Studies similar to that of Raff and colleagues performed not only in hypertensive patients but also in populations at high cardiovascular risk are important to better understand the pathophysiology and mechanistic hemodynamics in pharmacology and therapeutics. Such studies should facilitate the initiation of further trials based on intermediate parameters such as central BP or arterial stiffness to answer the question of whether the improvement of the central BP/arterial stiffness will result in better patient management and clinical outcomes. Randomized controlled specific studies are still needed.

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