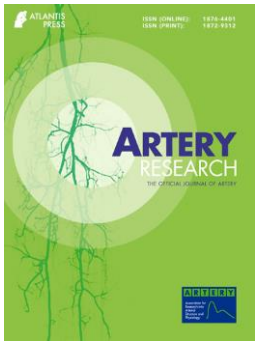

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Effects of drugs on cardiac and vascular function

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Central aortic blood pressure

Among the numerous risk factors associated with cardiovascular diseases arterial hypertension is the main determinant of cardiovascular morbidity and mortality and it plays a major role through its pathophysiological consequences and its high incidence determining cardiac and vascular functional and structural involvement. The impact of hypertension is compounded also because, on the one hand, numerous cardiovascular risk factors, such as dyslipidemia, insulin resistance, diabetes, obesity, lack of physical exercise, and certain genetic mutations are frequently associated with arterial hypertension, so potentiating the cardiovascular damage, while, on the other hand, hypertensive patients frequently display a greater number of cardiovascular risk factors, compared with normotensive subjects.

Both in normotensives and in hypertensives the cardiovascular system may be considered as a hydraulic model consisting of a pump connected to a vascular system with two components, the macrocirculation and the microcirculation. Blood pressure curves of such hydraulic system consist of a steady component (mean arterial pressure) and a pulsatile component (pulse pressure). The heart pump ejects the blood in a cyclic manner into the large arteries. Pressure and flow fluctuate throughout the arterial tree during the cardiac cycle, according to the "cushioning capacity" (compliance) of the large arteries and the timing and intensity of arterial wave reflections.[1,2] Arterial compliance is determined by arterial volume and the elastic properties (distensibility) of the arterial wall. Wave reflection designates the process by which the forward wavefront originating in the heart and propagating toward the microcirculation is reflected as a backward wave returning toward the heart from the peripheral vasculature. In proximal large arteries, arterial volume, which depends on the left ventricular ejection volume, subjects the arterial wall to a passive mechanical stress.

The evaluation of the work-load of the pump both with the propagation of blood pressure through the arterial tree are the keys to evaluating the blood pressure-related cardiovascular damnage. Thus, a correct understanding of blood pressure-related cardiovascular damage requires a holistic approach involving the heart and the arteries. This is a novel concept with relevant therapeutic implications. Arterial stiffness attenuation may reflect the true reduction of arterial wall damage, whereas blood pressure, blood glucose, and lipids can be normalized in a few weeks by using antihypertensive, anti-diabetic, and lipid-lowering drugs, leading to a strong reduction in cardiovascular risk scores, but without yet any improvement of atherosclerotic lesions and arterial stiffness, which requires a long-lasting correction of biochemical abnormalities. A temporal dissociation is thus expected between the improvement of

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cardiovascular risk factors and a decreased arterial stiffness.

Although diastolic blood pressure and mean arterial blood pressure were long held to be the best predictors of hypertension-related cardiovascular risk, we now know that these two parameters only reflect the steady component of blood pressure. Recent epidemiological studies have established the role of systolic blood pressure, and correlation analysis has shown that pulse pressure is positively correlated with the clinical outcome and that it is a particularly good predictor of clinical outcome in middle-aged and elderly subjects. The main determinants of pulse pressure are ventricular ejection, arterial stiffness, and wave reflection (ie, the augmentation index). These parameters can thus be used to predict cardiovascular morbidity and mortality.

The 2007 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guidelines underlined the role of the evaluation at the preclinical phase of target-organ involvement affecting the heart, arteries, brain and kidney.[3]

Until now, the goal of antihypertensive treatment was to reduce mean arterial pressure, in other words, the static blood pressure component. Based on the above considerations, we now need to focus our efforts on reducing the pulse pressure, i.e., the pulsatile component of the afterload. This may be achieved by targeting drug's effects on any of the following: cardiac output, arterial stiffening, and vascular architecture.

In patients with essential hypertension, numerous and different studies have already shown a decrease in arterial stiffness or in left ventricular mass with various pharmacological classes of antihypertensive agents.[4] ACE-inhibitors,[5] Angiotensin II receptors blockers,[6] calcium antagonists[7] and beta-blockers although the percentage of such reductions are different depending on the class of drug considered and such results are obtained for equivalent blood pressure reduction. Indeed certain β-blockers[8] can modify the arterial structure, independently of the effect on Blood Pressure. Resnick et al.[9] demonstrated that ACE-inhibitors, angiotensin II receptors blockers, calcium antagonists have a favorable effect on large and small artery elasticity, while in contrast beta-blockers decreased large and small artery. Classically, reduction in cardiac output is obtained by β-blockade, via a reduction in heart rate. It is still unclear to what extent this affects pulse pressure, in the short and in the long-term. Most antihypertensive treatments decrease arterial stiffness, which is not surprising because blood pressure reduction diminishes the impact of the blood pressure on nonelastic components of the arterial wall such as collagen. It remains unknown whether this beneficial effect is due to an improvement in arterial compliance or to vascular remodeling of the arterial wall via pressure-independent mechanisms such as a reduction in collagen content, an increase in elastin, or changes in smooth muscle cell junctions or in the extracellular matrix.

Multiple mechanistic studies and clinical trials have provided insights into unique cardiovascular effects independent of blood pressure reduction. ACE-inhibitors and angiotensin receptors blockers (ARBs) protect the vasculature against structural remodeling and inhibit atherosclerosis.[10] At least one dihydropyridine calcium antagonist appears also to inhibit vascular remodeling.[11] These pharmacological effects may be mediated by restoration of endothelial function. Beta-blockers do not appear to favorably affect vascular remodeling, except that the new generation and vasodilating beta-blockers seem to have a more favorable effect on the vasculature.[12] Alpha blockers appear to protect neither the vasculature nor the heart, even though they lower blood pressure.[13] Diuretics have not been subject to as much careful study, perhaps because they are so inexpensive, but it is likely that they exert a favorable effect on vascular remodeling in hypertensive individuals.

The effects of a given drug on arterial stiffness are complex and vary with time. The effects of a vasodilator drug on the arterial wall may be direct, occurring by relaxation of the smooth muscle predominantly in the arterial media or improving endothelial function. The effects may be indirect, occurring as a consequence of both a decrease in wave reflection, in response to the dilation and an increase in small artery elasticity in response to dilation of resistance arterioles. Other indirect effects are structural and are due to the changes in vessel lumen or wall structure under long-term treatment.

Pharmacologic trials for vascular health protection should focus not only on large arteries, but also on small arteries.[14] It is known that in normotensive subjects reduced small artery elasticity is a significant predictor for the development of hypertension and the question remains to be answered if medical therapy increasing small artery elasticity should be associated with delaying the process of development of hypertension.

There is also evidence that lipid-lowering therapy, especially statin therapy improve arterial elasticity.[7] It is a logical finding because lowering cholesterol will improve endothelial function, reduce vascular inflammation and consequently will reduce arterial stiffness. Clinical studies have also demonstrated that some anti-diabetic therapy will also improve arterial elasticity. Further studies are necessary if these improvements in arterial elasticity will also be linked in improvement in cardiovascular outcome.

Recent epidemiological studies of hypertension-related risk have therefore redirected their attention from the steady component of blood pressure to the pulsatile component and sought to evaluate the relationship linking pulse pressure to cardiovascular clinical events.[15] In this context, three aspects have to be considered whose relationships are still unclear: endothelial dysfunction, development of atherosclerosis, and fatigue of structural vessel components.

The consequences of hypertension on the endothelium are not limited to changes in endothelial vasomotor function. It is well known that the endothelium possesses potent anti-inflammatory properties. One of the difficulties in evaluating the efficacy of treatments acting on endothelial dysfunction is in distinguishing between the direct effects of these drugs on endothelial dysfunction and the indirect protection afforded by the decrease in blood pressure.

The pulsatile component of the blood pressure exposes arteries in vivo to pulsed perfusion and experimental data indicate that different signal transduction pathways are activated by phasic and/or static stress interactions. Constant flow and pulsed perfusion generate different responses in endothelial nitric oxide synthesis, protein phosphorylation, and oxidative stress signaling. Arterial compliance mediates endothelial nitric oxide synthesis and mechanosignaling. These data may explain the increased cardiovascular risk resulting from arterial stiffening.

We need to select among the large range of antihypertensive treatments available today, those that ensure, in addition to effective blood pressure reduction, the highest degree of target-organ protection and cardiovascular event prevention. To address these issue, a substudy of the pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd (REASON) study it has been conducted to determine whether treatment with the low-dose combination of perindopril/indapamide was associated with significant changes in left ventricular mass, in comparison with atenolol, and whether these changes correlated with brachial or central blood pressure.[16,17] The results of this study showed that the first line perindopril/indapamide combination resulted in a more significant reduction in left ventricular hypertrophy than the standard comparator atenolol despite similar reduction in mean blood pressure. This effect on left ventricular mass was associated with beneficial effects on large artery function and central wave reflection, with a subsequent reduction in central systolic blood pressure and in pulse pressure. The mechanisms of blood pressure reduction of the beta-blocker atenolol differ substantially from those of the perindopril/indapamide combination, as the former acts essentially by reducing mean blood pressure, whereas the latter induces changes in arterial stiffness of conduit arteries and in wave reflections. [18,19]

Recently, a substudy of ASCOT, CAFÉ, examined the effect of either an amlodipine-perindopril or an atenolol-diuretic based Blood Pressure lowering regimen on derived central aortic BP and hemodynamics in a large cohort of patients ($n = 2199$). Despite similar effects on brachial BP, the amlodipine-perindopril based regimen substantially reduced central BP and central pulse pressure, compared with the atenolol-based regimen. In the CAFE study, central PP was a significant determinant of a composite outcome of total cardiovascular events/procedures and development of renal impairment. Thus central aortic pulse pressure emerges as an important determinant of clinical outcomes in hypertensive patients. [20]

In conclusion hypertension-related cardiovascular risk and target-organ damage result from an increase in mean arterial pressure and in pulse pressure. Deleterious changes to the heart, the large arteries, and the microcirculation result in an increase in the static and pulsatile components of the blood pressure, which alter the propagation of the pressure wave through the arterial tree. Until now, treatments have targeted only the static component of the pressure wave; on the contrary, recent findings suggest that the goal of a cardiovascular effective treatment should be adressed both to the static and the pulsatile components of the cardiovascular system so as to ensure a better and complete target-organ protection and therefore obtain a higher cardiovascular risk reduction.

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