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The Effect of Antihypertensive Drugs on Arterial Stiffness and Central Hemodynamics: Not All Fingers are Made the Same

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Abstract: Arterial stiffness and central hemodynamics attract increasing scientific interest within the hypertensive community during the last decade. Accumulating evidence indicates that aortic stiffness is a strong and independent predictor of cardiovascular events and all-cause mortality in hypertensive patients, and its predictive value extends beyond traditional risk factors. The role of central hemodynamics and augmentation index (a marker of reflected waves), remains less established and requires further investigation. Several lines of evidence indicate that antihypertensive therapy results in significant reductions of pulse wave velocity and central hemodynamics. However, beta-blockers seem to be the only exception with significant within-class differences. Conventional beta-blockers, although equally effective in reducing pulse wave velocity, seem to be less beneficial on central hemodynamics and augmentation index than the other antihypertensive drug categories, whereas the newer vasodilating beta-blockers seem to share the benefits of the other antihypertensive drugs. In conclusion, aortic stiffness seems ready for 'prime-time' in the management of essential hypertension, while further research is needed for central hemodynamics and augmentation index.

Keywords: Arterial stiffness, pulse wave velocity, augmentation index, central hemodynamics, aortic blood pressure, antihypertensive drugs, beta-blockers.

INTRODUCTION

Aortic stiffness is considered the most important pathophysiologic mechanism mediating pulse pressure increase and isolated systolic hypertension with ageing. The carotid-femoral pulse wave velocity is a non-invasive method for the measurement of aortic stiffness and is currently considered the 'gold standard' for the evaluation of arterial elasticity. Central hemodynamics have attracted wide scientific interest during the last decade, due to the recognition that peripheral and central blood pressure may differ and that it is the central blood pressure that imposes the load in the heart, brain, and the kidneys.

According to the recent 2013 guidelines of the European Society of Hypertension/European Society of Cardiology for the management of arterial hypertension, the evaluation of carotid-femoral pulse wave velocity should be considered in hypertensive patients to detect large artery stiffening, and this recommendation is based on IIa-B level of evidence [1]. In contrast, the role of central hemodynamics is not yet established, and the guidelines recognize the pathophysiological, pharmacological, and therapeutical interest, but acknowledge the need for further investigation before recommending the evaluation of this parameter in everyday clinical practice [1].

From the clinical point of view, it is important for the practicing physician to know whether aortic stiffness and central hemodynamics possess a strong predictive value for cardiovascular events and all-cause mortality, whether the predictive value extends beyond traditional cardiovascular risk factors, whether the various antihypertensive drugs classes exert different effects on these parameters, and whether within-class differences exist in antihypertensive drug classes. The current review aims to critically evaluate existing literature in this topic and provide clinically meaningful information.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF ARTERIAL STIFFNESS

The pressure waveform is the summation of the forward wave, originating from left ventricular ejection, moving from the aorta to the periphery, and the backward wave, originating from the reflection of the descending wave to the periphery, mainly at the level of resistance arteries.

In younger age and health, the large conduit arteries (like the aorta) preserve their elasticity and the waveform travels with relatively slow velocity towards the periphery. Therefore, the reflected wave meets the forward wave in diastole, resulting in increased diastolic central pressure and thus facilitating coronary perfusion.

Ageing and disease (such as hypertension and other disease conditions) are associated with arterial stiffening, which in turn results in acceleration of the wave movement. Therefore, the reflected wave meets the descending wave during systole, resulting in increased systolic central pressure and rather decreased diastolic central pressure, thus compromising coronary perfusion.

From the above mentioned physiological and pathophysiological mechanisms, it can be concluded that the

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evaluation of the waveforms in two different sites of the arterial tree (usually the carotid and femoral or radial artery) permits for the non-invasive estimation of pulse wave velocity (a measure of arterial stiffness), the augmentation index (a measure of the reflected wave), and central blood pressure. The augmentation index is the ratio of augmentation pressure to pulse pressure, with the augmentation pressure representing the difference between the systolic pressure and the inflection peak.

Several devices have been developed during the last years for the non-invasive estimation of these parameters, with Sphygmocor and Complior being the most widely used. It has to be admitted that invasive methods represent he gold-standard for the accurate and precise measurement of central hemodynamics and arterial stiffness. However, invasive methods cannot be used in everyday clinical practice, and thus the non-invasive evaluation of central hemodynamics and arterial stiffness has prevailed.

CENTRAL HEMODYNAMICS

Central blood pressure is the blood pressure at the proximal segment of the aorta and is currently considered more relevant than the peripheral blood pressure from a physiological point of view, since: a) central systolic blood pressure is the pressure that the heart has to overcome at each systole, in order to maintain blood flow all over the organism, and thus a major contributor to the development of left ventricular hypertrophy in hypertension, b) central diastolic blood pressure is the main determinant of coronary perfusion, and c) central blood pressure is transmitted to the coronaries, the brain, and the kidneys, the organs that mainly suffer from elevated blood pressure.

Peripheral and central blood pressure may differ significantly due to "pressure amplification". Typically, the diastolic blood pressure does not change significantly across the various arterial beds; however, systolic blood pressure is amplified when travelling across the arterial tree, from the aorta to the periphery. Therefore, significant differences between the peripheral and central blood pressure are not unusual and might mislead therapeutic decisions that are typically based on peripheral blood pressure measurement.

PREDICTIVE VALUE OF ARTERIAL STIFFNESS

Accumulating data from many large longitudinal studies with long-term follow-up indicate that increased arterial stiffness, as assessed by pulse wave velocity, represents an independent predictor of cardiovascular morbidity and mortality, as well as of all-cause mortality. The strong predictive value of arterial stiffness has been observed in various populations, in health and disease: in the general population [2-6], in elderly individuals [7-9], in subjects free of any cardiovascular disease not using any cardiovascular medication [10], in patients with impaired glucose tolerance [11], in diabetic patients [12], in patients with essential hypertension [13-16], and in patients with end-stage renal disease [17-20].

It has been recently shown that aortic stiffness is an independent predictor of cardiovascular events and all-cause mortality even in earlier stages of chronic kidney disease and not only in end-stage renal failure [21]. It has been also shown that aortic stiffness is an independent predictor of functionality following an acute ischemic stroke, suggesting that not only the cardiovascular outcomes but also the quality of life is dependent on arterial stiffness [22]. In contrast, augmentation index had no independent predictive value on patients' functional outcome.

A recent meta-analysis reviewed the ability of arterial stiffness to predict cardiovascular events and all-cause mortality [23]. The authors identified 17 longitudinal studies with almost 16,000 patients and a mean follow-up of 7.7 years (2.5-19.6 years). It was found that pulse wave velocity was linearly associated with all studied outcomes, and any increase in pulse wave velocity by 1 m/sec was associated with approximately 15% increments in cardiovascular morbidity, cardiovascular mortality, and all-cause mortality. The pooled relative risk in patients at the highest compared to the lowest tertile of pulse wave velocity was 2.26 (95% CI: 1.89-2.70) for all cardiovascular events, 2.02 (95% CI: 1.68-2.42) for cardiovascular mortality, and 1.90 (95% CI: 1.61-2.24) for total mortality.

Of note, the predictive value of pulse wave velocity was larger in patients with higher baseline cardiovascular risk, such as end-stage renal disease and hypertension (highest versus lowest tertile relative risk for total cardiovascular events: 2.81 in end-stage renal disease versus 2.46 in hypertension versus 1.68 in the general population) [23]. A large French study in hypertensive patients suggests that the predictive value of arterial stiffness was more pronounced in patients at lower cardiovascular risk than in patients at higher cardiovascular risk [24]. Finally, a meta-regression analysis revealed that aortic pulse wave velocity is a stronger determinant of prognosis in younger patients with end-stage renal disease, while the predictive value of aortic pulse wave velocity is independent of age in hypertensive patients and in the general population [23].

A very important issue is whether arterial stiffness possesses the ability to predict cardiovascular events beyond cardiovascular risk factors, establishing its importance in everyday clinical practice by re-stratifying patients' risk. Available data point towards a significant additive value of arterial stiffness in cardiovascular risk prediction, above and beyond traditional risk factors, including the widely used Framingham and SCORE risk scores [25-28]. Evaluation of arterial stiffness leads to re-classification of intermediate risk patients to higher or lower cardiovascular risk in many cases [25, 28, 29]. In a recent large study of patients with moderate and severe chronic kidney disease, it was shown that aortic stiffness improves cardiovascular risk prediction beyond traditional cardiovascular risk factors, with a net reclassification index of 29% [21].

PREDICTIVE VALUE OF AUGMENTATION INDEX AND CENTRAL HEMODYNAMICS

Several longitudinal studies have assessed the impact of central hemodynamics on cardiovascular morbidity and mortality, as well as of all-cause mortality. Relevant studies were performed in various populations, in health and disease: in elderly individuals [30], in subjects free of cardiovascular disease [31], in patients with essential hypertension [32], in patients with end-stage renal disease [33-35], and in patients with coronary artery disease [36-40].

A recent meta-analysis calculated the predictive value of central blood pressure and derived central hemodynamic indices for cardiovascular events and all-cause mortality [41]. In this meta-analysis, 11 longitudinal studies were identified with more than 5,500 patients and a mean follow-up of 45 months (3-94 months). The adjusted pooled relative risk of total cardiovascular events was 1.088 (95% CI: 1.040-1.139) for a 10mmHg increase of central systolic blood pressure, 1.137 (95% CI: 1.063-1.215) for a 10mmHg increase of central pulse pressure, and 1.318 (95% CI: 1.093-1.588) for a 10% increase of augmentation index. In addition, a strong association between augmentation index and all-cause mortality was found: for a 10% increase of augmentation index the adjusted pooled relative risk for total mortality was 1.384 (95% CI: 1.192-1.606). However, when central pulse pressure was compared with peripheral pulse pressure, the pooled relative risk for cardiovascular events was marginally but not significantly higher.

Of note, wave pressure was found to be higher in the atenolol arm compared to the amlodipine arm of the CAFÉ study, and predicted cardiovascular events independent of all other cardiovascular risk factors, while central blood pressure and augmentation index failed to predict cardiovascular events [42].

PREDICTIVE VALUE OF STIFFNESS AND CENTRAL HEMODYNAMICS REDUCTION

Although a vast amount of evidence exists regarding the predictive value of arterial stiffness, there is a relative paucity of data regarding the predictive value of stiffness reduction. A study specifically addressing this issue revealed that patients with significant stiffness reduction had lower mortality rates than patients in whom stiffness reduction was not achieved [43]. It has to be noted however, that this study was conducted in patients with end-stage renal failure and extrapolation of its findings in hypertensive patients needs confirmation by further studies.

Regarding the impact of central blood pressure reduction on cardiovascular outcomes, some indirect data point towards beneficial effects of central blood pressure reduction. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the combination of newer antihypertensive drugs (ACE-inhibitors + calcium antagonists) was found superior to the combination of older drugs (beta-blockers + diuretics) in cardiovascular outcomes, despite a rather similar office (peripheral) blood pressure reduction [44]. The Conduit Artery Function Evaluation (CAFE) study, a sub-study of the ASCOT study, showed that the combination of newer drugs resulted in significantly higher central blood pressure reduction than the combination of older drugs; the difference in central systolic blood pressure was 4.3 mmHg and the difference in central pulse pressure was 3.0 mmHg [45]. However, whether this difference was the reason for the better outcomes with newer drugs or other mechanisms were also implicated remains to be clarified.

EFFECTS OF ANTIHYPERTENSIVE DRUGS ON ARTERIAL STIFFNESS

Based on a vast amount of evidence, there is no doubt that antihypertensive treatment is associated with significant reductions in arterial stiffness. The comparison of active antihypertensive therapy with placebo shows that pulse wave velocity is significantly reduced with active treatment, whereas it remains unchanged with placebo [46-55]. The anticipated reduction in pulse wave velocity is about 1.0-1.5 m/sec during long-term (>3 months) therapy, while a smaller reduction of 0.5-0.7 m/sec is observed acutely after administration of antihypertensive drugs [53-55]. It has to be admitted however, that available data comes from studies which suffer from small study samples, significant differences in study populations, and most importantly from a relatively short follow-up period (usually up to 6 months).

Antihypertensive therapy is a life-long requirement and the practicing physician needs to know whether the beneficial effects of antihypertensive drugs on arterial stiffness are sustained over the years and attenuate the age-induced increase in pulse wave velocity. However, it is highly unlikely that such information will ever become available, since it is unethical to use a placebo arm for long time periods in hypertensive patients, given the established benefits of antihypertensive therapy. There are only two patient populations, in whom there is no strong evidence regarding the benefits of antihypertensive therapy: very elderly patients (>80 years) with stage I hypertension, and young patients with mild hypertension and low cardiovascular risk. It would be interesting to design long-term clinical studies evaluating the effects of antihypertensive therapy on arterial stiffness and cardiovascular outcomes in these patient populations.

DIFFERENCES BETWEEN ANTIHYPERTENSIVE DRUG CLASSES

Pulse Wave Velocity

Despite a widespread belief that newer antihypertensive agents (angiotensin receptor blockers, ACE-inhibitors, and calcium antagonists) are superior to other agents (diuretics, beta-blockers) in arterial stiffness reduction, available data from small, randomized clinical studies suggest that there are no significant differences between drug categories regarding their effects on arterial stiffness [56-67]. Once again, available studies suffer from the small number of participants and the relatively short follow-up time (less than a year).

Since there no ethical considerations to compare antihypertensive drugs in the long-term, relevant studies evaluating the effects of different classes on arterial stiffness need to be conducted, which have to be large, multicenter, randomized, and long-term (>3-4 years). It has to be noted that the pharmaceutical industry is not likely to support the conduction of such studies. Therefore, either authorities like the NIH and the European Commission, or scientific societies like the European and the American Society of Hypertension, or even independent groups of experts have to design, organize, and conduct such studies. Apart from the obvious financial difficulties in funding such a study, one more factor has to be taken also in account: only one third of patients (approximately) will achieve blood pressure control and remain in monotherapy providing clear findings, while the majority will require combination therapy and decrease the clarity of study findings.

Augmentation Index

The augmentation index is a marker of the wave reflection and subsequently of the additional load on the left ventricle. Most antihypertensive drugs reduce the augmentation index and there are no significant differences between drug classes [46, 48, 59, 64, 68-70], with the remarkable exception of beta-blockers. Beta-blockers not only fail to reduce augmentation index but actually result in increased augmentation index values [64, 65, 69]. This effect of beta-blockers might be attributed to their effect on heart rate. It is known that experimentally-induced tachycardia, via right atrial pacing, is associated with reductions in augmentation index; for every 10 beats increases in heart rate, a 5% reduction in augmentation index is observed [71]. It is therefore anticipated that beta-blockers result in augmentation index increments through bradycardia. In the CAFÉ study, a strong, inverse relationship between heart rate and augmentation index was observed, suggesting increased wave reflection at lower heart rate [72]. Heart rate was found to be a major determinant of central systolic and pulse pressure, and adjustment for heart rate greatly attenuated the difference in central blood pressure between the atenolol and amlodipine arm of the CAFÉ study.

However, bradycardia by itself cannot explain the whole effect of beta-blockers, and several other explanations might be proposed: a) the failure of beta-blockers to reduce the wall/lumen ratio of resistant arteries, which are the main source of wave reflection, and b) the delay in forward's wave peak due to the prolongation of ventricular ejection time caused by beta-blockers; therefore, the reflected wave confronts higher values of the forward wave and subsequent increments in the augmentation index occur.

A recent meta-analysis reported that ACE-inhibitors were superior to other classes of antihypertensive drugs in reducing the augmentation index [73]. However, this finding was ought to the superiority of ACE-inhibitors over beta-blockers, while no significant differences were observed with other classes of antihypertensive drugs apart from beta-blockers, when the comparisons were performed separately.

Studies comparing beta-blockers to angiotensin receptor blockers highlight the superiority of angiotensin receptor blockers over beta-blockers on central hemodynamics and wave reflection. In a study of 21 patients with untreated hypertension, atenolol was compared to eprosartan for 6 weeks. It was found that atenolol had less impact on central systolic blood pressure than eprosartan and resulted in increased augmentation index [74]. In a larger and long-term randomized study of 156 hypertensive patients, irbesartan was compared to atenolol for 18 months. Atenolol therapy was associated with an increase in augmentation index and a decrease of pulse pressure amplification, whereas irbesartan therapy exhibited beneficial effects on wave reflection [75].

The inferiority of beta-blockers compared to other antihypertensive drug classes on augmentation index and central hemodynamics seems to be maintained with combination therapy as well. A recent large, multicenter, prospective, randomized study (the EXPLOR study) of 393 hypertensive patients compared the combination of amlodipine with either atenolol or valsartan for 24 weeks [76]. Both combinations reduced peripheral blood pressure and pulse wave velocity to the same extent. However, the central systolic blood pressure, the augmentation index, and the heart-rate adjusted augmentation index were significantly more reduced with the valsartan combination than with the atenolol combination.

WITHIN-CLASS DIFFERENCES

There is no clear evidence that within-class differences among the various antihypertensive drug classes exist regarding their effects on pulse wave velocity and augmentation index. The only exception is once again beta-blockers. It has been shown that not all beta blockers result in augmentation index increments.

In a retrospective study of 242 hypertensive patients it was found that for similar office blood pressure and aortic stiffness, treatment with atenolol was associated with higher central systolic pressure and wave reflection compared to treatment with either vasodilating beta-blockers (nebivolol, carvedilol) or angiotensin receptor blockers [77].

In a study of 43 obese, African-American hypertensives it was found that nebivolol therapy for 8 weeks resulted in significant improvements of arterial compliance, as assessed by aortic augmentation index and time to wave reflection [78].

In a randomized study of 40 untreated hypertensives, nebivolol was compared to atenolol for 4 weeks [79]. Both agents reduced pulse wave velocity to a similar extent. However, only nebivolol reduced augmentation index and increased pulse pressure amplification, suggesting a beneficial role in small muscular arteries, possibly due to increased nitric oxide bioavailability.

Another randomized, placebo-controlled, crossover study of 16 naïve patients with isolated systolic hypertension compared the effects of nebivolol and atenolol for 5 weeks [80]. It was found that both agents reduced peripheral blood pressure and aortic stiffness to the same extent. However, nebivolol was superior to atenolol in reducing aortic pulse pressure and increasing the augmentation index.

Similar differences with atenolol have been reported with other beta-blockers as well. Dilevalol (an isomer of lebetalol) was compared to atenolol for 12 weeks in a double-blind, crossover, placebo-controlled study of 12 patients with essential hypertension [81]. Both drugs were equally effective in reducing peripheral blood pressure and pulse wave velocity. However, the augmentation index was significantly lower with dilevalol than with atenolol.

In a prospective, randomized, open label study of 41 hypertensive patients, carvedilol was compared to atenolol for 4 weeks [82]. Both drugs reduced peripheral and central systolic and diastolic blood pressure to a similar extent. However, the augmentation index was increased with atenolol and slightly decreased with carvedilol.

From the above mentioned studies, it can be assumed that conventional beta-blockers (such as atenolol) do not exert beneficial effects on augmentation index, while vasodilating beta-blockers (such as nebivolol, carvedilol, and labetalol) share the beneficial effects of the other antihypertensive drug categories on augmentation index. This assumption is further

reinforced by a recent study comparing two conventional beta-blockers, such as atenolol and bisoprolol. In a large, prospective, randomized, open label study of 209 hypertensive patients, atenolol was compared to bisoprolol (a second-generation beta-blocker with high beta-1 selectivity) for 12 weeks [83]. There were no significant differences between the two drugs in their effects on central and peripheral blood pressure, pulse wave velocity and augmentation index.

FUTURE DIRECTIONS

Accumulating data strongly point towards the ability of antihypertensive therapy to reduce arterial stiffness even in the very elderly individuals or after decades of elevated blood pressure. However, a critical view of available bibliography raises several questions that need to be answered with future research. Such questions include:

- Pulse wave velocity reduction appears in all patients or 'responders' and 'non-responders' exist?
- Are there any predictors of 'stiffness response'?
- Do age, blood pressure severity and duration, and baseline blood pressure and pulse wave velocity values affect 'stiffness response'?
- Which is the effect of comorbidities and concomitant medication?
- Which is the definition and the clinical meaning of 'stiffness response'?
- Is there any association of 'stiffness response' and reversal of other target organ damage?
- Is blood pressure reduction a pre-requisite for pulse wave reduction?
- Pulse wave reduction is ought to solely blood pressure fall or effects beyond blood pressure reduction exist?
- Are there any differences between antihypertensive drugs on 'stiffness response'?
- Are there within-class differences among different agents in the same class?
- Does aggressive antihypertensive therapy exert better effects than standard therapy?
- Are standard doses of antihypertensive drugs adequate for maximum 'stiffness reduction'? What is the effect of low doses or supra-high doses?
- Which are the effects of different combinations of antihypertensive therapy on 'stiffness reduction'?
- Which is the effect of treatment discontinuation? Are there any 'legacy' effects?
- Are the beneficial effects equally distributed in all vascular beds or differences exist?

Providing answers for some of the above mentioned questions might significantly improve the management of hypertension and cardiovascular disease. Arterial stiffness and central hemodynamics represent a hot topic and research in this area is very intense. Technological advances might also be very helpful for improving our knowledge in this exciting topic, which has major significance from the physiologic, pathophysiologic, pharmacologic and therapeutic point of view.

CONCLUSIONS

The interest about arterial stiffness and central hemodynamics in the pathophysiology and management of essential hypertension is steadily increasing over the years. A vast amount of evidence indicates that aortic stiffness is a strong and independent predictor of cardiovascular events and total mortality in hypertensives and other patient populations, and its predictive value extends beyond traditional risk factors. Therefore, aortic stiffness seems ready for 'prime-time' in the management of arterial hypertension. The role of central hemodynamics and augmentation index (a marker of reflected waves) requires further investigation before reaching everyday clinical practice. There is no doubt that antihypertensive therapy reduces significantly arterial stiffness and central hemodynamics. However, conventional beta-blockers seem to be less beneficial on these parameters than the other antihypertensive drug categories, whereas the newer vasodilating beta-blockers seem to share the benefits of the other antihypertensive drugs.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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