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## **How to treat arterial stiffness beyond blood pressure lowering?**

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In recent years aortic stiffness has been recognized as an important predictor of cardiovascular events (1), adding predictive value to classical cardiovascular risk scores like the Framingham risk score (2). In the Framingham Heart Study aortic stiffness expressed as aortic pulse wave velocity (PWV) predicted major cardiovascular events while other hemodynamic measures like carotid-radial (muscular artery) pulse wave velocity, central pulse pressure, pulse pressure amplification and augmentation index did not (3). Aortic stiffness has been proposed as target organ damage by the 2007 ESH/ESC hypertension guidelines (4) and advocated for use in daily practice. An aortic stiffness expressed as carotid-femoral pulse wave velocity above 12 m/s has been considered of prognostic value. One should realize that this cutoff point only applies to aortic pulse wave velocities using the direct carotid to femoral distance. Many different estimates of the traveled distance of the pulse wave have been used. Each of them results in different absolute values and the cutoff value should be adapted accordingly. A formula has been established to calculate direct distance (carotid to femoral) from subtracted distance (suprasternal notch to femoral artery minus suprasternal notch to carotid artery) making use of height and vice versa (5). Recently reference values for aortic pulse wave velocity have been published using

80% of the direct distance (6). Based on MRI and invasive studies (7,8), this distance is probably closer to the real traveled distance.

Whereas evidence for predictive value of aortic stiffness is well established (9) and methods to measure it are becoming more accurate, less evidence is present on how to treat arterial stiffness.

In single dose or short term studies, ACE-inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), selective beta<sub>1</sub>-blockers, beta-blockers (BB) with vasodilating properties and some diuretics could improve arterial stiffness (10, 11). It, however, was not clear whether this effect was limited to the decrease in blood pressure, or whether also an effect beyond the effect of blood pressure reduction was present. After a 6-month treatment period for a similar reduction in blood pressure, the ACE-inhibitor perindopril showed a more pronounced improvement of carotid artery stiffness than the diuretic

amiloride/hydrochlorothiazide (12), showing that the de-stiffening potency differs between antihypertensive drugs and suggesting that some may have an effect beyond the effect due to blood pressure decrease. It, therefore, is of interest to investigate which classes of antihypertensive drugs may have a de-stiffening potency beyond blood pressure reduction.

In this issue of the Journal Ong et al (13) present the results of a meta-analysis of individual data from 15 randomized controlled trials (RCT) including 294 hypertensive subjects treated with a variety of blood pressure lowering drugs. This meta-analysis showed that in short-term studies (defined by the authors as a duration <4 weeks) only ACE-inhibitors reduced PWV beyond the blood pressure effect, while in long-term studies (4 weeks or more) all studied drug classes were effective. Vasodilation may at least in part account for the effect beyond blood pressure reduction of vasoactive drugs like ACEI, ARB, CCB and BB with vasodilating properties. The mechanisms by which diuretics and selective beta<sub>1</sub> blockers would reduce stiffness beyond blood

pressure values are unknown. For BB it is not clear whether the reduction in heart rate may play a role (14). Of interest, Ong et al (13) observed a comparable effect for selective beta<sub>1</sub> blockers and diuretics on PWV compared to the vasoactive drug classes in their meta-analysis. The latter may suggest that apart from the antihypertensive property of the antihypertensive drug, the sustained unloading of the arteries by blood pressure reduction itself may contribute to structural de-stiffening of arteries within a few months. Since ACE-inhibitors were found to improve arterial stiffness also in short term studies, this class of drugs may accelerate this de-stiffening process.

The strengths of the meta-analysis by Ong et al. (13) are the Gold Standard outcome variable, a meta-analysis on individual data from homogeneous study populations, the use of uniform standard operating procedures, and the centralized data analysis in a well qualified center.

Important limitations of this study are the relatively small number of inclusions and the lack of inclusion of studies conducted outside their laboratory. In addition, authors' cut-off of 4 weeks for so called long-term studies is arbitrary and in fact since no study exceeded 6 months of follow-up long-term results in the usual meaning of the term are not available. These limitations make this study to be confirmed by studies with a larger number of patients and longer duration of treatment.

Other strategies to reduce PWV beyond blood pressure lowering

Apart from inhibitors of the renin-angiotensin-aldosterone system (RAAS), nitrates and nitric oxide (NO) donors (see below), advanced glycation end products (AGE) breakers and statins may be of interest (15). Besides their vasoactive effect, RAAS inhibitors may have de-stiffening

effects by preventing and reducing collagen accumulation. The AGE-breaker alagebrium can decrease stiffness by breaking cross-links and showed promising results in man (16).

Mixed results have been published for statins on PWV in a meta-analysis (17).

Life style changes may also decrease arterial stiffness. In some selected studies the effect size of life style changes was comparable to the reported effect size in the meta-analysis of Ong et al (13). However the effect size of these studies should be cautiously interpreted as some of these studies might not have been ideally designed or analyzed. Among the attempts to reduce PWV by life style change one should mention physical activity, smoking cessation and salt reduction. Recently a highly significant decrease of carotid-femoral PWV has been reported by interval training in treated hypertension (18). A final conclusion might be unwarranted as many positive older studies had a doubtful (statistical) design and analysis and some did not show positive results. Jatoi et al (19) demonstrated that smoking cessation reduced PWV while it took a decade of nonsmoking before returning to baseline PWV. On the contrary a recent meta-analysis (20) was unable to confirm these findings due to conflicting and low quality data. Also for salt reduction the effects on PWV are far from univocal ranging from no effect at all to a significant reduction in blacks (21), while regular habitual cocoa consumption was associated with low arterial stiffness (22). Weight reduction and a balanced diet are other non-pharmacological measures worthwhile further studying in the near future.

## Implications

Antihypertensive drugs are currently the only well-established treatment options for arterial stiffness available. The meta-analysis by Ong et al (13) suggests that sustained unloading of the

vessel wall by blood pressure reduction may structurally improve arterial stiffness. Current antihypertensive drugs decrease systolic and diastolic blood pressure. A further decrease of the already low diastolic blood pressure by classical antihypertensive drugs may be harmful in a subset of patients with isolated systolic hypertension and coronary artery disease (23). This rapidly growing group of patients needs antihypertensive drugs that decrease pulse pressure, thereby decreasing systolic blood pressure without further decreasing diastolic pressure. Those drugs act mainly on large artery stiffness without a substantial effect on resistance arteries.

Among the available vasoactive drugs nitrates are the most selective to large arteries. But some NO donors may be still more selective to large arteries than to resistance vessels than nitrates, and should be further investigated (24).

Although arterial stiffness can be improved even beyond the effect due to blood pressure lowering, data on improved survival due to a decrease in arterial stiffness are still scarce (25). The expected beneficial effect of this decrease in arterial stiffness on hard endpoints should be further established. Therefore, the meta-analysis by Ong et al (13) is not likely to induce changes in therapeutic strategy published in the 2009 reappraisal of the European hypertension guidelines (26).

## Conclusions

In the absence of commercially available specific de-stiffening drugs, improvement of arterial stiffness in hypertensive patients will still be discussed in terms of efficacy and efficiency of drugs classes and strategies with a propensity for hypertension-related risk factors.

Antihypertensive drugs are a first and logical choice not only for improvement of arterial stiffness but essentially because they improve outcome. As suggested by the meta-analysis by

Ong et al (13) in this issue of the Journal there seems to be a mid-term effect on arterial stiffness beyond the effect on blood pressure of all classes of these drugs, suggesting that a sustained unloading of the arterial wall itself by a decrease in blood pressure may lead to a further decrease in arterial stiffness. More and larger studies are needed to confirm these results and to further investigate the potency of different antihypertensive drugs in reducing arterial stiffness beyond the effect of blood pressure. An increasing therapeutic problem may exist in patients with isolated systolic hypertension and coronary artery disease, as evidence is growing that a further lowering of the already low diastolic blood pressure may be harmful. New antihypertensive drugs that decrease systolic blood pressure without decreasing diastolic blood pressure appear to be urgently needed for this rapidly growing subgroup of elderly patients. The arterial de-stiffening potency of other drugs like AGE breakers and statins or lifestyle changes (salt reduction, smoking cessation, regular exercise, habitual cocoa consumption, a balanced diet with weight reduction) remains to be further established in the near future.

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