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STATE-OF-THE-ART

What is new in arterial stiffness clinical research?

Paul GUSBETH-TATOMIR, MD, PhD; Adrian COVIC, MD, PhD, FRCP

Nephrology Clinic, "Dr. C.I. Parhon" Clinical Hospital, Iasi, Romania
"Gr.T. Popa" University of Medicine and Pharmacy, Iasi, Romania

ABSTRACT

Arterial stiffness has been recognized recently as a powerful predictor of cardiovascular (CV) and general mortality both in the general population, in high-risk non-renal patients, and in chronic kidney disease (CKD) patients. Stiffened arteries have significant clinical consequences on cardiac structure, performance, and perfusion. Modern techniques like applanation tonometry are nowadays widely applicable in the clinical setting. The authors discuss recent clinical research published in high-profile journals on the clinical significance of arterial stiffness in various CV high-risk populations.

Key words: arterial stiffness, cardiovascular disease, cardiovascular risk, end-stage renal disease, general population, vascular calcification

INTRODUCTION

Cardiovascular (CV) disease is the leading cause of mortality in the general population and, even more pronounced, in specific populations such as chronic kidney disease, diabetes mellitus or chronic obstructive disease patients. This excessive mortality is traditionally linked to atherosclerosis (due to classical CV risk factors) and its complications, but is increasingly connected to other pathogenic circumstances like the diffuse *arteriosclerosis* (the diffuse stiffening of large arteries, mainly of the aorta). Arterial stiffness is a result of natural aging, but may be influenced by many factors, including genetic predisposition, traditional CV risk factors, inflammation. Arterial stiffness is a major independent determinant of survival in the general population. As renal function deteriorates, the large arteries become stiffer. In renal patients, increased arterial stiffness is due to the excessive clustering of many CV risk factors, including non-traditional ones like vascular calcification, chronic volume overload or increased oxidative stress. Survival of renal patients with severely reduced arterial distensibility is limited (1,2).

In the last decade, simple tools to assess arterial distensibility, to be used in the day-to-day clinical setting, have been developed. Among these, simple, reliable tools like applanation

Address for correspondence:
Adrian Covic, MD, PhD, FRCP, Professor of Nephrology, Nephrology Clinic, "Parhon" Hospital, 50 Carol 1st Blvd., Iasi, Zip Code 700503, Romania
email address: adrianccovic@gmail.com

tonometry (assessing central blood pressure, pulse wave velocity and the augmentation index) and various ultrasound-derived parameters have been developed (for an extensive review, see Covic et al, *Am J Kidney Dis* 2005 (1) and Laurent et al, Eur Heart J 2006 (3)). Prevention of factors related to arterial stiffness and aggressive therapy with medication known to improve vascular compliance may improve morbidity and mortality in populations with high CV risk. This paper discusses the latest achievements in clinical research on arterial stiffness in both renal and non-renal populations. ❑

COMMUNITY-BASED STUDIES

In the last five years, there has been extensive work on arterial stiffness and its clinical determinants in the general population. Mitchell and co-workers (4) investigated the *Framingham Original cohort*, the *Framingham offspring cohort* and the *minority Omni cohorts* in terms of two arterial stiffness parameters: carotid-femoral pulse wave velocity and forward pressure wave amplitude. In subjects with a *low burden of conventional CV disease risk factors*, they found a prevalence of 24-33% abnormal arterial stiffness, mainly (and dramatically) related to increasing age. After adjustment for age, higher mean arterial BP, greater body mass index, impaired glucose metabolism and abnormal lipids were independently correlated with increased arterial stiffness (4). As several major CV events in elderly people have been consistently linked to arterial stiffness, strategies for prevention (and even treatment) of increased arterial stiffness in the elderly are mandatory.

Arterial stiffness has been consistently linked to (micro-)inflammation in the general population, in CV high-risk patients and, particularly, in subjects with chronic kidney disease (2). In another *Framingham Heart Study* investigation in 2409 participants, Schnabel et al (5) investigated the relationship of twelve circulating inflammatory biomarkers and other serum levels of various cytokines to tonometry-derived variables like central pulse pressure, mean arterial pressure, forward pressure wave, reflected pressure wave, carotid-femoral pulse wave velocity, and the augmentation index. Some markers of inflammation like TNF-receptor II, CRP, lipoprotein-associated phospholipase-A2 activity, interleukin-6, and osteoprotegerin were significantly but modestly associated with measures of arterial stiffness and arterial wave reflection. This data suggests that the relationship between inflammation and arterial compliance is more complex than commonly thought and that there is a strong influence of genetic variance related to inflammation.

Finally, the third Framingham Heart Study-derived discussed data is from Levy and co-workers (6), who examined the relationship of subtle CV risk factors like plasma N-terminal atrial natriuretic factor, B-type natriuretic peptide, adrenomedullin, and homocysteine concentrations in relationship to arterial stiffness in 1962 participants. Although present generally in both genders, the independent relationship of these risk factors to arteriosclerosis was stronger in men, consistent with the higher CV risk with male gender. The gender differences in arterial stiffness were recently examined in non-human primates (7), where aortic stiffness increased more in older male monkeys than in their female counterparts. In both genders, collagen density was maintained, collagen-bound advanced glycation end-products increased, and collagen type 1 decreased. However, elastin density decreased significantly with aging only in males. Furthermore, only old males were characterized by a significant decrease in collagen type 3 (an isoform that promotes elasticity) and an increase in collagen type 8 (an isoform that promotes the miointimal migration of vascular smooth muscle cells). Importantly, in both aging males and females, aortic pulse pressure increased similarly, but aortic stiffness increased selectively in old males, indicating that the tools at the disposal of the clinician (i.e. blood pressure measurement) can be misleading in diagnosing the vessel stiffness associated with aging. This fact became obvious latest with the seminal data of the CAFÉ study (8). In this investigation, despite similar office (brachial) blood pressure control, amlodipine (± perindopril) was definitely better in controlling central BP, as derived from arterial pulse contour analysis, compared to atenolol (± a thiazidic-based diuretic). This highlights a *paradigm shift* on the clinical significance of hypertension: more subtle (although relatively more demanding) methods of BP like applanation tonometry gives a more reliable information on the CV risk related to high BP compared with simple office BP measurements. Furthermore, this data strongly suggests that some antihypertensive agents may be more advantageous com-

pared to others in terms of preventing an unfavorable CV outcome (9). ❑

WHAT IS THE RELATIONSHIP OF ARTERIAL STIFFNESS TO WEIGHT GAIN?

More than 1 billion people worldwide are overweight or obese and therefore, at risk for CV disease. The accumulation of abdominal fat seems to be particularly deleterious. The results of numerous previous studies suggested that obesity is associated with stiffening of the arteries in the cardiothoracic region. A recent clinical study tested the hypothesis that weight gain, even in non-obese healthy persons, increases arterial stiffness. Fourteen volunteers were overfed by an excess of approx. 1000 calories/day for 6-8 weeks, until they had a weight gain of 5 kg. The only correlates of changes of arterial stiffness were the increases in total abdominal fat, total visceral fat and waist circumference. Importantly, the stiffening of arteries determined by abdominal fat gain was independent of the total fat gain, suggesting the paramount influence of abdominal obesity of CV risk (10). ❑

THE CEREBROVASCULAR – ARTERIAL STIFFNESS CONNECTION

Aortic stiffness predicts an excess risk of stroke, supposedly via cerebral small-vessel disease (11). Henskens et al (12) examined the impact of aortic stiffness on cerebrovascular (CBV) disease in 167 hypertensive treatment-naïve patients without a history of CV or CBV disease. Aortic stiffness and pulse pressure were related to each of the cerebral lesions, as assessed by MRI: the volume of white matter hyperintensities, and the presence of lacunar infarcts and microbleeds. Arterial stiffness was associated in multivariate analysis with these findings, with the exception of microbleeds. This data may be particular relevant for such CV high-risk as the CKD population, characterized by many abnormalities of the cerebral vessels as assessed by imaging techniques like MNR or CT.

Is there a link between vitamin D and arterial stiffness?

Andrade and colleagues (13) explored the relationship between vitamin D and arterial stiffness (measured by a composite parameter – the augmentation index) in 131 Canadian outpatients with cardiovascular disease or CKD or both, with a GFR ranging from 25 to 81 ml/min. subjects with a higher serum phosphate or a higher matrix metalloproteinase 9 (a gelatinase involved in collagen and elastin remodeling) levels were found to have a higher Aix. Lower 1,25-OH2D3 levels and lower GFR were independently associated with a higher augmentation index (Aix), a composite parameter of arterial stiffness derived from pulse contour analysis measured by applanation tonometry. Interesting, the associations between arterial stiffness and hidroxylated vitamin D and serum phosphate, respectively, were noted also in the *normal* range (13). This suggests that even high-"normal" serum phosphate and low-"normal" vitamin D serum levels might be hazardous for the vessels in patients with mild-to-moderate CKD. In normal conditions, vitamin D has been shown to inhibit antigen-presenting cell maturation, angiogenesis, and smooth muscle cell proliferation, and also alters the cytokine profile to one that less favors inflammation through interaction with the vitamin D receptor (14).

This data is in accord with other recent investigations in end-stage renal disease patients, a population prone to vitamin D deficiency. This investigation in renal patients showed independent and strong correlations between low vitamin D levels and markers of a poor CV status: high C-reactive protein, diabetic status and higher CV calcification scores. Interesting, patients who were taking low-dose vitamin D derivates (mainly paricalcitol) showed less calcification (15). Therefore, vitamin D deficiency is suggested, according to recent research, as a potent "non-traditional" CV risk factor both in the renal and in the non-renal population, which deserves full attention by the clinician. However, these findings have to be confirmed in larger randomized controlled trials, examining specifically the role of vitamin D deficiency on survival and possible implications of proper vitamin D therapy.

Specific populations

Chronic kidney disease patients

Pulse wave velocity (PWV) and the (augmentation index) Aix measurements of arterial stiffness and arterial reflective properties based on

applanation tonometry are highly reproducible in CKD patients, with minimal inter- and intraobserver variations (16-18). There is a strong relationship between arterial stiffness and large arterial wall calcification in the general population, but also in CKD and particularly, in end-stage renal disease patients. In fact, vascular calcifications appear as major determinants of arterial stiffening and is directly and independently linked to clinical atherosclerosis. This is true in the non-renal population, and of paramount importance in renal populations, characterized by major abnormalities of the mineral metabolism (19). Therefore, assessment of vessel wall calcification by plain radiography, sonography or electron-beam computer-tomography offers a surrogate marker both of arterial stiffness and atherosclerotic disease.

A simple and inexpensive radiological score of arterial calcification (as an indirect measure of arterial stiffness) is desired in the clinical setting. This score (quantifying the presence of calcifications in the pelvis and on the hand radiograph), first proposed in 2004 (20), correlates well with arterial stiffness, highlighting the paramount contribution of vascular calcification to arteriosclerosis, measured by pulse wave velocity. Moreover, this calcification score, examined cross-sectionally in 101 hemodialysis patients, is independently related to pulse pressure (PP) and to survival. Therefore, clinically simple and inexpensive methods like PP and radiograph-derived calcification score may be used to detect mortality risk in ESRD and may be relevant for guiding therapeutic interventions in dialysis patients (21).

Chronic obstructive pulmonary disease

More patients with COPD die of CV causes than of respiratory causes, particularly from stroke and coronary heart disease. Arterial stiffness is increased in patients with COPD compared with control subjects matched for CV risk factors. Elastin fragmentation and changes in collagen are found in the connective tissue of both emphysematous lungs and stiff arteries. McAllister and colleagues (22) performed a cross-sectional study in 157 patients with COPD, in order to identify if the extent of arterial stiffness is associated with emphysema activity. They found a close independent association between arterial stiffness burden and emphysema severity, independently from classical CV risk factors, degree of inflammation or respiratory parameters like pulse oximetry oxygen saturation or predicted FEV1. The authors speculate that similar pathophysiological processes may be involved in both lung and arterial tissue. The details of these common mechanisms are unknown yet.

HIV infection

According to recent research (23), patients with HIV infection have independently of any other factor more pronounced arterial stiffness than uninfected subjects. This supports the hypothesis that HIV infection is a risk factor for arteriosclerosis. ❑

WOULD THERE BE A HOPE FROM THERAPY?

The seminal data of the CAFÉ study (8) indicated that at equal lowering of brachial (clinical) blood pressure, some antihypertensive agents – amlodipine ± perindopril may act more intense on central BP (as measured by applanation tonometry) than others, like atenolol ± thiazide-based diuretic therapy. Actually, it has been recognized earlier that different antihypertensive drugs actually may have different actions on "central" BP, i.e. on arterial distensibility and this may be more important from a clinical point of view in respect of survival (1,2).

The antihypertensive drugs influencing the renin-angiotensin-aldosterone axis may have protective CV actions beyond their (brachial) BP-lowering effects (24,25). However, some authors questioned whether antihypertensive drugs offer cardio-renal protection beyond BP lowering. Karalliedde et al (26) examined the impact of an angiotensin receptor blocker (ARB, valsartan) on central arterial pressure in type 2 diabetes mellitus patients, compared to a CCB (amlodipine 5-10 mg/d). Despite similar brachial BP, aortic PWV fell significantly (-0.9 m/s) with the ARB, but not with amlodipine. Moreover, the albumin excretion rate was influenced only by valsartan. Therefore, given this and other seminal data, it is likely that further research on antihypertensive therapy would focus on rather central than peripheral blood pressure effect of various drugs. ❑

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