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REVIEWS

Arterial Stiffness in Renal Patients: An Update

Adrian Covic, MD, PhD, Paul Gusbeth-Tatomir, MD, and David J.A. Goldsmith, MA, FRCP

• **According to recent data, arterial stiffness is a major independent risk factor for cardiovascular morbidity and mortality in both the general and renal populations. Because of several factors (vascular calcifications among them), large arteries are stiffer in patients with chronic kidney disease compared with the nonrenal population, contributing to the enormous cardiovascular mortality in renal patients. This review briefly analyzes methods for determination of arterial stiffness, focusing on 2 parameters, pulse wave velocity and the augmentation index, particularly useful in assessing arterial compliance in renal patients. Effects of different methods of renal replacement therapy on arterial wall properties also are discussed. Finally, the most promising novel and/or potential therapies regarding reduction of arterial stiffness in renal patients are reviewed. *Am J Kidney Dis* 45: 965-977.**

INDEX WORDS: Arterial stiffness; arterial calcification; augmentation index (AI); chronic kidney disease (CKD); end-stage renal disease (ESRD); pulse wave velocity (PWV).

CARDIOVASCULAR (CV) disease is the most important cause of mortality in patients with chronic kidney disease (CKD). An "epidemic" of CV death, especially in patients with end-stage renal disease (ESRD), has been recognized, accounting for more than 50% of overall mortality in these patients. Compared with the general population, patients with CKD have a 3- to 30-fold risk for succumbing to CV disease; this difference is even more pronounced in young subjects.[1,2] Improvement in dialysis techniques and therapy for CV disease in recent years seems to have brought little change to this dramatic onslaught. Interventions that appear strikingly successful in nonrenal patients (such as lipid-lowering therapy for primary or secondary prevention) may be ineffective in dialysis patients.[3]

Many potential explanations exist for this CV disease epidemic in renal patients. Whether all these are relevant or 1 or more are predominant in certain cohorts (eg, patients with diabetes with CKD) is not yet known. The hypothesis of "accelerated atherosclerosis" in patients with ESRD formulated by Lindner et al[4] seems particularly attractive, but has several weak points (for a comprehensive discussion, see Amann et al[5] and Querfeld[6]). Whether chronic uremia is a major culprit for severe atherosclerosis remains debatable because many patients with CKD already have an impressive accumulation of classic CV risk factors, possibly sufficient to explain the high burden of major CV events.

In the last decade, CV research in the general population has focused increasingly on arterio-

From the Dialysis and Renal Transplantation Center, Parhon University Hospital, Iasi, Romania; and Renal Unit, Guy's Hospital, London, UK.

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Address reprint requests to Adrian Covic, MD, PhD, Dialysis and Renal Transplantation Center, Parhon University Hospital, 50 Carol 1st Blvd, Iasi 6600, Romania. E-mail: acovic@xnet.ro

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sclerosis, the diffuse process of arterial stiffening, as opposed to the focal process of atherosclerosis. Reduced arterial compliance (a synonym of increased arterial stiffness) seems to have a pivotal role in the genesis of high systolic blood pressure (SBP), high pulse pressure (PP), and increased left ventricular workload and hypertrophy and, ultimately, in CV mortality.[7,8] According to recent evidence, the same is true for arterial stiffness in patients with ESRD. In recent years, it became evident that ESRD populations have much stiffer arteries compared with the general population of the same age and blood pressure (BP) level.[9] Underlying mechanisms for increased stiffness in patients with uremia are not well defined, but may include chronic fluid overload, arterial calcifications, microinflammation, sympathetic nervous system overactivity, activation of the renin-angiotensin-aldostorone (RAA) system, increased lipid oxidation, and abnormalities of the nitric oxide system.[10]

Desperately lacking are good epidemiological observational data from CKD and dialysis cohorts. In particular, the important question of the relationship between increased arterial stiffness and renal disease needs a lot more basic population data. It is entirely possible that increased arterial stiffness from whatever cause leads to renal damage by afferent arteriolar barotraumas, just as it is entirely possible that renal disease from whatever cause induces increased arterial stiffness. In this respect, the many cross-sectional series cannot inform us adequately. This situation is reminiscent of the relationship between increased BP and renal disease.

Therefore, influencing the process of reduced arterial compliance by attenuating the age- or treatment-related increase in arterial stiffness with time or, more excitingly, reversing arterial structural changes that led to increased arterial stiffness in renal patients may have an important beneficial impact on morbidity and mortality. This brief review deals with the most recent evidence to date on arteriosclerosis in patients with CKD, focusing on arterial stiffness as a nonconventional CV risk factor in renal patients. Potential and/or novel therapies aimed to reduce arterial stiffness also are discussed briefly.

WHAT IS ARTERIAL STIFFNESS?

Extensive presentation of the pathophysiological characteristics of arterial stiffness is beyond the scope of this review; for an excellent overview of this issue, see London et al.[10]

With age and the influence of several factors (for example, high BP), the walls of large conduit arteries undergo intense remodeling processes leading to alteration in viscoelastic properties. The result is the diffuse process of arteriosclerosis, characterized by stiffer arteries or, in other terms, reduced arterial elasticity or compliance.

Elasticity of the aorta and large arteries is critically important for absorption of energy during systole; just half the blood volume ejected during systole goes directly to peripheral tissues. The other half is stored and pushed forward during diastole by recoil of the distended arteries, which have accumulated energy in systole. In the presence of stiffened arteries, this process is altered, resulting in increased ventricular afterload and left ventricular hypertrophy, reduced coronary perfusion, and altered peripheral tissue blood supply.

As arteries become stiffer, they dilate, and the arterial wall hypertrophies. Obvious clinical consequences are higher SBP, lower diastolic BP, and widened PP. All 3 changes are known as major determinants for high CV morbidity and mortality in the general population. Moreover, as in a vicious circle, high BP per se increases arterial stiffness.[11] Arterial wall calcifications, very frequent in the renal population, also may have a role in the genesis and progression of arterial stiffness.[12]

HOW DO WE MEASURE ARTERIAL STIFFNESS?

In clinical studies, several parameters of arterial stiffness have been investigated (Table 1). Two of these, derived from the application of applanation tonometry, have emerged as particularly valuable: pulse wave velocity (PWV) and the augmentation index (AI). Their merits derive from: (1) a simple method of calculation/measurement, (2) reproducible values, and (3) prospectively validated prognostic significance.[13,14]

PWV is greater in stiffer arteries and, according to recent research (discussed next), is clearly

Table 1. Methods of Assessment and Parameters of Arterial Stiffness

Method	Parameter	Observations
Applanation tonometry using a Millar tonometer and PWV software package	AI	AI: difference between early and late systolic peak of pulse wave contour divided by PP height
	PWV	PWV [m/s] = 1.3L/(T + Tc) where T is time interval between pulse waves at the carotid and femoral sites, Tc is time interval between heart sound S2 and the notch of carotid pulse wave, and L is measured distance in meters between the heart sound microphone and femoral probe
Automated echo-tracking system	DC	DC = 2 (ΔD/D)/ΔP where ΔD is distension from systole to diastole of the vessel wall, D is distension of vessel wall at end-diastole, and ΔP is PP
	Einc (Young modulus)	Elastic modulus/unit area Einc = (ΔP × D)/(ΔD × h) where h is wall thickness
	Stiffness index β	Ratio of the natural logarithm of SBP/DBP to the relative change in diameter = ln(Ps/Pd)/[(Ds – Dd/Dd)]
Whole-body impedance cardiography	PWV	Good agreement with Doppler ultrasound–based PWV (Kööbi et al,[71] 2003)
Automated recording of QKd interval	QKd	QKd (Level et al,[72] 2001)

Abbreviations: DC, distensibility coefficient; Einc, incremental elastic modulus; QKd, time (in milliseconds) between the onset of the electrocardiogram QRS complex (Q) and Korotkoff sound (K) at diastolic pressure (d) heard over the brachial artery; DBP, diastolic BP.

associated with increased mortality in both the renal and nonrenal populations. The AI also is clearly associated with survival (discussed next); AI represents the difference between the first and second systolic peak of the pulse wave contour divided by PP height (Fig 1). AI is a composite parameter because it reflects the reflective properties of the peripheral distal arterial bed and elastic properties of large arteries. Thus, these 2 measures, although correlated, are not interchangeable or synonymous.

Ultrasound measurements using expensive equipment in vascular laboratories (eg, high-resolution echo-tracking systems) have led to the development of several dynamic indices for arterial stiffness, more useful for research studies than for recurrent clinical evaluations. The most prominent of these is the incremental elastic modulus, usually measured in the common carotid artery. Incremental elastic modulus is the slope of the relationship between stress and strain of arterial vessels and is calculated by transcutaneous measurements of common carotid internal diameter, wall thickness, and carotid PP. Common carotid compliance and distensibility (the distensibility coefficient and stiffness parameter β) are determined from changes in carotid artery diameter during systole and simultaneously measured carotid PP.[15]

PWV, AI, AND CKD

Arterial Stiffness and Renal Function

First, it is important to emphasize that in patients with CKD, parameters of arterial stiffness have shown excellent reproducibility. Savage et al[15] showed near-zero intraobserver and interobserver variability for the AI in patients with chronic renal failure. This important issue is confirmed by the study of our group[16]; intraobserver error was 1.6% to 5.2%, with a calculated interobserver error of 3.5%. The same excellent reproducibility is true for PWV, with intraobserver and interobserver variability less than 5% in all important studies.[17] Therefore, PWV and AI assessed by means of applanation tonometry, a simple applicable-at-bedside technique, may be particularly promising in pharmacological studies dealing with the influence of different substances (mainly antihypertensive drugs) on the viscoelastic properties of large arteries.

Typical values for AI and PWV in different renal populations are listed in Table 2. These are

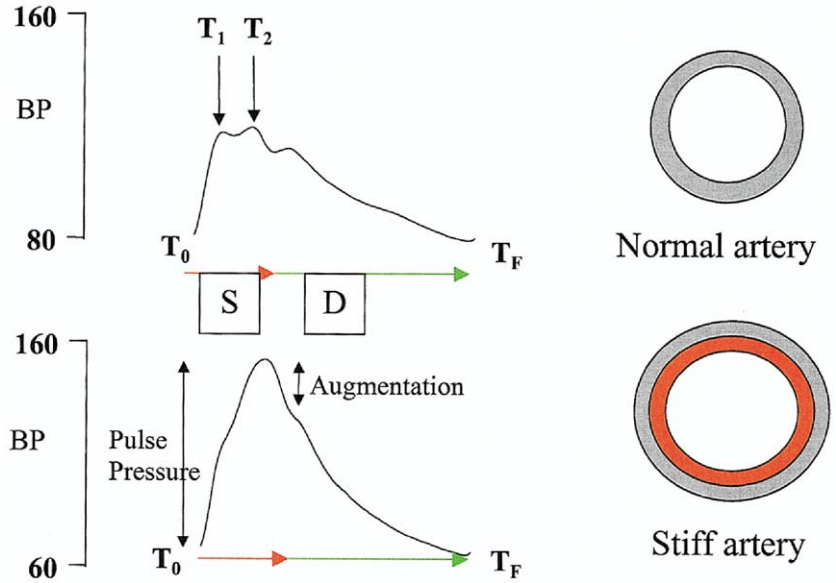

Fig 1. Typical pulse waveforms from (top) normal and (bottom) stiffened conduit arteries derived from percutaneous tonometry tracings. With reference to a normal artery: T_0, time of start of cardiac cycle; T_F, time of finish of cardiac cycle; T_1, time to outgoing pressure peak; T_2, time to peak of reflected wave; S, systole; D, diastole. Peaks at T_1 and T_2 coincide in the stiffened artery, leading to augmentation of arterial pressure. AI is augmentation divided by PP × 100.

significantly greater than values recorded in nonrenal patients. In the general population, aortic and carotid stiffness (evaluated by means of PWV) increase with age by approximately 10% to 15% during 10 years.[18] In renal patients, arteries are always stiffer compared with those in nonrenal subjects (discussed next); in this respect, we can conclude that uremia (and even mild to moderate chronic renal failure) is compatible with a state of premature aging. Factors associated with increased arterial stiffness in the renal population are listed in Table 3.

Mechanisms causing reduced arterial compliance in renal patients are not fully understood; to some extent, increased arterial stiffness is attributable to changes seen in vascular aging (such as mural calcification), high BP, and wall stress and standard CV risk factors, such as plasma glucose and cholesterol levels, smoking, reduced exercise capacity, and overweight.[19,20] However, Mourad et al[20] investigated the possibility that even mild deterioration in renal function may cause increased arterial stiffness. In 1,290 subjects with normal BP or essential hypertension, they found that patients with the lowest tertile of creatinine clearance (CrCl; but still normal serum creatinine level) had a greater PWV, and this association was independent of BP and other classic CV risk factors. The negative association between PWV and CrCl is stronger in subjects younger than 55 years (PWV, 12.64 m/s; mean CrCl, 112 mL/min^{-1}/1.73 m^2 [1.867 mL/s^{-1}/1.73 m^2] versus PWV of 14.57 m/s in subjects $>$ 55 years with a CrCl of 81.4 mL/min^{-1}/1.73 m^2 [1.357 mL/s^{-1}/1.73 m^2). In younger patients, CrCl accounts for 20% of the variance in carotid compliance. Furthermore, a large longitudinal study of patients with essential hypertension[21] showed that serum creatinine level is a major determinant of accelerated progression of aortic stiffness in treated patients with hypertension. These findings are in accordance with data showing that mild renal dysfunction can cause significant endothelial dysfunction.[22]

Arterial Stiffness and Vascular Calcifications

Guérin et al,[23] using a semiquantitative calcification score based on ultrasound B-mode measurements of calcification sites, showed that the presence of vascular calcifications in large arteries was associated with increased arterial stiffness in dialysis patients. Furthermore, in prospective studies, the same group showed that both increased arterial stiffness and large-artery calci-

Table 2. Values of Arterial Stiffness Parameters in Renal Compared With Nonrenal Patients

Reference	Parameter of Arterial Stiffness	Renal	Nonrenal
Blacher et al[73]	Carotid incremental elastic modulus	0.48 kPa in younger patients, 0.90 kPa in elderly patients	0.41 kPa in younger patients; 0.71 kPa in elderly patients
Benetos et al[21]	PWV, progression of PWV (ΔPWV) = increase in PWV between measurements at distance	ΔPWV, 147 mm/s/y in treated patients with hypertension	ΔPWV 66, mm/s/y in treated patients with hypertension
Konings et al[42]	Distensibility coefficient	12.6 kPa in predialysis patients with chronic renal failure, 11.6 kPa in HD patients, 14.7 kPa in PD patients	16.7 kPa in patients with essential hypertension
Tycho Vuurmans et al[39]	AI and PWV	Pre-HD PWV, 9.9 m/s; post-HD PWV, 9.3 m/s; pre-HD AI, 35%; post-HD AI, 28%	PWV, 7.5 m/s, and AI, 25%, in healthy volunteers
Shinohara et al[74]	Aortic PWV	9.7 m/s in predialysis patients with chronic renal failure, 8.9 m/s in the HD group	7.4 m/s in healthy subjects
Covic et al[37]	AI and PWV	Pre-HD AI, 27.9%; post-HD AI, 18.2%; pre-HD PWV, 7.19 m/s; post-HD PWV, 7.89 m/s	AI, 16.5%, and PWV, 6.34 m/s, in patients with essential hypertension

Abbreviation: QKd, time (in milliseconds) between the onset of the electrocardiogram QRS complex (Q) and Korotkoff sound (K) at diastolic pressure (d) heard over the brachial artery.

fications were major predictors of general and CV mortality in renal patients.[12,24] However, the method used a composite semiquantitative scoring system involving plain x-ray films and vascular ultrasound, significantly inferior to computed tomography (CT)–based calcification quantification methods.[25] Therefore, our group[26] extended the search on the arterial calcification-stiffness relationship by using a more precise method for detecting vascular calcifications: electron-beam CT (EBCT). We found that PWV strongly correlates with total calcification scores assessed by means of EBCT, even after correction for age, dialysis therapy duration, prescribed dose of calcium-containing phosphate binders, and microinflammatory status (assessed by means of time-averaged C-reactive protein levels). Calcification scores were significantly different when compared according to PWV tertiles; therefore, as PWV increased, calcification scores also increased proportionally ($P = 0.0001$).[26] EBCT measures calcification in coronary arteries, whereas PWV measures arterial stiffness principally in the aorta; therefore, for definitive proof, upstudies combining multislice CT of the aorta with simultaneous aortic PWV measurement should be performed. Nevertheless, data from Guerin et al[23] and our findings[26] are potentially relevant because arterial calcifications may be one of the few preventable factors associated with arteriosclerosis in patients with ESRD.

Use of a non–calcium-containing phosphate binder, such as sevelamer hydrochloride, significantly reduces the extent of progression of coronary calcifications determined by means of EBCT and also has a favorable effect on lipid profile.[27] Whether sevelamer has a beneficial long-term effect on arterial stiffening has yet to be determined (but trials are underway). Another interesting issue regarding arterial calcifications in patients with uremia is the role of bone morphogenetic proteins, overexpressed in the arterial wall of rodent models; inhibition of these bone proteins in the arterial wall may have a beneficial impact on arterial distensibility.[28,29] According to recent data, use of calcium-sensing receptor antagonists (calcimimetics) is associated with the effective reduction of parathormone and phosphate serum levels without increasing serum calcium levels.[30] Therapy with calcimimetics has the theoretical potential to ame-

Table 3. Determinants of Increased Arterial Stiffnesss in Renal Patients

Reference	Study Population	Parameter	Determinant
Blacher et al[73]	208 patients with hypertension with and without ESRD	Elastic incremental modulus	Age, mean arterial pressure, presence of ESRD
Covic et al[16]	51 stable HD patients	AI	Height, weight, radial SBP, radial diastolic BP, central SBP, left ventricular mass (versus predialysis AI)
Aoun et al[75]	122 patients with diabetes, 122 patients without diabetes	PWV, AI	Diabetes mellitus, reduced glomerular filtration rate (irrespective of presence of diabetes)
Level et al[72]	24 HD patients, half with normotension	Automated recording of the QKd interval	Renal failure, serum calcium level, duration of HD
Tycho Vuurmans et al[39]	18 HD patients	PWV, AI	Volume overload, angiotensin II
Benetos et al[21]	187 hypertensive treated subjects, 296 normotensive controls	PWV	Uncontrolled hypertension: accelerated arteriosclerosis *v* patients with normotension and hypertension with drug-controlled BP; high heart rate and high serum creatinine determinants of accelerated progression in treated patients with hypertension
Seyrek et al[14]	32 HD patients	Elastic incremental modulus	Age, SBP, PP, serum calcium, alkaline phosphatase, C-reactive protein
Beerenhout et al[76]	117 patients with chronic renal failure from several causes	Distensibility coefficient	Age, mean arterial pressure, serum calcium, type of renal disease (vascular or diabetic *v* others) in younger patients
Booth et al[77]	31 patients with systemic vasculitis	PWV, AI	Age, mean arterial pressure, C-reactive protein

Abbreviation: QKd, time (in milliseconds) between the onset of the electrocardiogram QRS complex (Q) and Korotkoff sound (K) at diastolic pressure (d) heard over the brachial artery.

liorate arterial calcifications significantly and, consequently, arterial stiffness associated with these. Urgent clinical trials are needed on these novel therapies that may retard arterial calcifications.

Impact of Arterial Stiffness on Survival in the Renal Population

Parameters of arterial stiffness have been associated significantly with CV morbidity and mortality in patients with essential hypertension (Table 4).

Aortic stiffness is an independent predictor of primary coronary events in these patients.[31,32] Furthermore, increased PWV (>13 m/s) is a potent and independent predictor of CV death in hypertensive patients, even without clinically evident atherosclerosis. The same is true for the AI, a strong predictor of premature coronary artery disease in the nonrenal population.[33]

In the study of Blacher et al,[33] the odds ratio for being in a high CV mortality risk group (ie, >5% for 10 years) for patients in the upper quartile of PWV was 7.1 (95% confidence interval, 4.5 to 11.3). These findings were confirmed by others[7] and are true even for normotensive elderly individuals without renal impairment[34] (Table 4).

Table 4. CV Morbidity and Mortality Risk Caused by Arterial Stiffness in the Nonrenal Population

Author	Study Population	Results	Observations
Blacher et al,[78] 1999	710 hypertensive patients	OR for being in the high CV mortality group (>5% at 10 y) for patients in the upper quartile of PWV, 7.1; 95% CI, 4.5 to 11.3	PWV > 13 m/s, taken alone, strong predictor of CV mortality
Laurent et al,[7] 2001	1,980 hypertensive patients	OR for all-cause and CV mortality for 5 m/s PWV, 2.14; 95% CI, 1.71 to 2.67 and 2.35; 95% CI, 1.76 to 3.14	Association independent of previous CV disease, age, and diabetes
Meaume et al,[34] 2001	141 elderly people (mean age, 87.1 y)	OR, 1.19; 95% CI, 1.03 to 1.37 for CV mortality	Antihypertensive drug therapy and BP values, no additive role
Boutouryie et al,[31] 2002	1,045 hypertensive patients	RR, 1.42; 95% CI, 1.10 to 1.82 for coronary events and 1.41; 95% CI,1.17 to 1.70 for any CV event associated with a 3.5-m/s (1 SD) increase in PWV	PWV independent predictor after adjustment for Framingham score or classic risk factors
Cruickshank et al,[79] 2002	397 patients with diabetes *v* controls	HR, 1.08; 95% CI, 1.03 to 1.14 for each 1-m/s increase in PWV in patients with diabetes	Similar results in patients with impaired glucose tolerance
Laurent et al,[80] 2003	1,715 patients with hypertension	RR for a fatal stroke, 1.72; 95% CI, 1.48 to 1.96 for each SD increase in PWV (4 m/s)	RR, 1.39; 95% CI, 1.08 to 1.72 after full adjustment for classic CV risk factors, including age, cholesterol level, diabetes, smoking, BP, and PP
Weber et al,[32] 2004	465 consecutive patients with suspected CAD undergoing coronarography	OR for the presence of CAD for patients with highest versus lowest AI, 6.91; 95% CI, 1.08 to 1.72; after adjustment for age, height, hypertension, HDL cholesterol, and the use of β-blockers, ACE inhibitors, statins, and nitrates, the association with CAD remained significant	Effect driven by patients < 60 y

Abbreviations: OR, odds ratio; CI, confidence interval; RR, relative risk; HR, hazard ratio; HDL, high-density lipoprotein; CAD, coronary artery disease.

In patients with ESRD, work from the group of Gerard London in France showed that for any increase in PWV index (measured PWV – theoretical PWV determined by means of ultrasonography) by 1 m/s, there was a 14% increase in adjusted CV and overall mortality.[35] In a cohort of 180 dialysis patients followed up for 52 months, Safar et al[36] investigated carotid PP by means of applanation tonometry and aortic PWV by means of Doppler ultrasonography. Brachial BP, including PP, had no predictive value compared with carotid PP. Conversely, aortic PWV was a strong predictor of all-cause and CV mortality.[36]

The effect of increased arterial stiffness on CV mortality is particularly strong; Shoji et al[13] compared patients with ESRD with and without diabetes. As expected, Kaplan-Meier analysis showed greater all-cause and CV mortality rates in renal patients with diabetes and also in pa-

tients with and without diabetes with a greater PWV. When aortic PWV was included as a covariate in the analysis, the impact of diabetes on survival was no longer significant, whereas PWV was a significant predictor of CV and overall death.[13]

WHAT IS THE IMPACT OF HEMODIALYSIS ON ARTERIAL STIFFNESS?

The acute effect of hemodialysis (HD) on arterial stiffness is very variable. Our group[16] described 4 patterns of arterial behavior in response to the dialysis session: (1) AI was negative before HD and became even more negative after HD; (2) AI was positive before and became negative after HD (a significant proportion of patients); (3) AI was positive before HD and decreased afterward, but remained positive (most patients); and (4) AI was positive before HD and increased afterward. The overall reduction in pulse wave reflections measured by means of AI was 88%. Nonresponders (ie, those with no or nonsignificant decreases in AI from the HD session) may be at increased CV risk compared with responders.[16]

That the HD session can acutely improve arterial wave reflections has been confirmed in another study from our group[37] showing the same large variability in AI. We also found that, either pre-HD and post-HD, endothelial-independent vascular reactivity (tested by means of nitroglycerin administration) was significantly greater than endothelial-dependent vasodilatation elicited by means of a β_2-agonist. A smaller response to nitroglycerin was associated with a greater left ventricular mass, a well-defined CV risk factor in a dialysis population. Using another technique, Joannides et al[38] showed a similar pattern of endothelium-independent vasodilatation in HD patients. A challenging finding from our more recent study was divergent behavior of the 2 arterial stiffness parameters in response to an HD session; unlike AI, PWV was increased by the dialysis session.[37] The several different methods used to evaluate arterial stiffness are not superimposable or interchangeable. Some, like AI, represent a composite vascular function, including the effect of greater PWV caused by a stiffer aorta and the effect of the reflective properties of peripheral arterial sites. Thus, complex interventions might elicit the divergent behavior of PWV and AI, as, for example, after an HD session (as discussed) or as described by Tycho Vuurmans et al[39] after angiotensin-converting enzyme (ACE) inhibition. Currently, we have just begun to understand how these complex interventions (changes across an HD session or ACE inhibition and BP lowering) alter various aspects of vascular tone, stiffness, and/or reflective properties of the periphery. Additional studies are needed to assess the impact of various levels of kidney dysfunction. However, based on data from renal and nonrenal cohorts and the simplicity and reproducibility of measuring PWV and AI, we advocate using both these parameters.

ARTERIAL STIFFNESS: HD VERSUS PERITONEAL DIALYSIS

Recent years have brought a plethora of discussions on whether peritoneal dialysis (PD) or HD would have a more favorable impact on the CV profile of patients with ESRD. There are several conflicting results, almost certainly biased to some degree by selection for one or the other of renal replacement therapies. However, overall, PD patients seem to have a worse CV profile compared with HD patients. This finding is not explainable by only selection bias, but also by a greater CV burden in PD patients caused by less successful blood volume control, worse lipid profile, and greater oxidative stress caused by PD solutions.[40]

In a study examining factors associated with increased PWV in PD patients, Stómpor et al[41] found in multiple regression analysis that age and SBP were related to augmented arterial stiffness. Not surprisingly, plasma basic fibroblast growth factor levels also were associated independently with reduced arterial compliance. Data on similar arterial stiffness in PD and HD patients are rather modest; Konings et al[42] found that the distensibility coefficient of the common carotid artery in PD patients is significantly less than in the nonrenal population. Furthermore, carotid distensibility in PD patients in this study was better than in HD patients and even in predialysis patients with chronic renal failure. However, Covic et al[43] analyzed arterial function in patients dialyzed using different modalities of renal replacement and found that overall, PD patients

had a greater PWV and AI compared with HD patients. Furthermore, in this study, endothelial-dependent and endothelial-independent vascular function was more blunted in PD patients compared with patients with ESRD treated with HD.

DOES RENAL TRANSPLANTATION LEAD TO IMPROVEMENT IN ARTERIAL STIFFNESS?

Renal transplantation is the preferred method of renal replacement therapy in most patients with ESRD because renal transplantation restores to a great degree renal function and patient quality of life and, last but not least, considerably improves survival, including CV morbidity and mortality, compared with dialysis patients, but not with the general population.[1,44]

Data on the effect of renal transplantation on arterial stiffness are relatively scarce. In the largest cross-sectional study to date,[45] conducted in 250 stable renal graft recipients, Ferro et al[45] identified several factors associated with arterial stiffness, reflected by an increased AI: mean arterial pressure, persistence of arteriovenous fistula, total time on renal replacement therapy, immunosuppression with cyclosporine, age, and height. Our group[46] showed that AI and PWV in living-related renal transplant recipients were significantly lower than in HD patients, but similar to those in controls with essential hypertension. Furthermore, both endothelial-dependent and endothelial-independent endothelial function (assessed by means of arterial stiffness parameters under challenge with salbutamol and nitroglycerin) were improved with renal transplantation compared with HD patients.[46]

Our data are supported by a recent well-conducted study of 36 patients that claimed a significant improvement in several arterial stiffness parameters 1 year after transplantation, along with other CV risk factors, including brachial BP, lipid levels, and homocysteine levels. Arterial stiffness, measured by means of PWV, was reduced by 7% to 22%.[47] One possible explanation for this effect on arterial distensibility is the large use of calcium channel blockers, in accordance with findings of London et al.[48] In the study by Zoungas et al,[47] the decrease in AI seemed to be more pronounced with tacrolimus-based immunosuppression compared with cyclosporine A, suggesting a more favorable impact of the former on the CV profile of the former calcineurin inhibitor. However, in a recent study by our group, by using applanation tonometry and duplex ultrasonography, we showed that Neoral cyclosporine A (Novartis Pharma, Bern, Switzerland) acutely improved large arterial compliance function and did not induce an acute increase in intrarenal resistance in stable renal transplant recipients with normal renal function. We speculate there may be dissociation between the acute and chronic effects of cyclosporine A on arterial function in renal allografts.[49]

CAN WE IMPROVE ARTERIAL STIFFNESS?

A recent study suggested that an exercise program for dialysis patients could lead to improvement in arterial wave reflections (a contributing factor to increased arterial stiffness and best represented by using AI).[50]

Interventional studies regarding the effect of drugs on arterial compliance are rare and rather modest in their scope in both renal and nonrenal populations. Acute effects of different drugs on arterial compliance in healthy volunteers have been studied by Kahonen et al.[51] Both 25 mg of captopril and 40 mg of propranolol significantly reduced PWV compared with placebo, whereas verapamil had no acute effect on arterial stiffness. Nitroglycerin had a highly significant effect on AI, but just a minor effect on PWV, suggesting that the former parameter may be more useful in pharmacological studies.[52]

In vitro investigations in recent years have suggested that aldosterone may interact directly with the large artery wall (for review, see Van Bortel et al[53]). In this regard, aldosterone inhibition may be particularly attractive; Benetos et al[54] showed that spironolactone prevents accumulation of aortic and myocardial collagen, independent of BP changes, in spontaneous hypertensive rats. However, a study in which spironolactone was administered for short term in humans showed that the drug did not change brachial artery compliance significantly.[55] Investigations on the long-term effect of spironolactone on arterial stiffness are underway.

Counting the multiple effects of the renin-angiotensin-aldosterone (RAA) axis on the endothelium, RAA inhibition seems particularly attractive in reducing arterial stiffness. Compared with a thiazide diuretic, losartan significantly improved the AI.[56] In patients with essential hyper-

tension, both ACE inhibition and blockade of angiotensin receptor 1 reduced arterial stiffness. This effect was even more pronounced by the "dual" blockade of the RAA system.[57] A significant reduction in arterial stiffness also is obtained by low-dose perindopril combined with indapamide compared with a β-blocker.[58] The angiotensin receptor blocker valsartan had a favorable effect on arterial stiffness parameters (along with a reduction in left ventricular mass) in a small study of PD patients.[59]

One study of patients with essential hypertension claimed a positive effect of long-duration antihypertensive therapy on arterial remodeling, paralleled by improvement of viscoelastic properties of the large arteries.[60] Antihypertensive therapy improves arterial stiffness mainly by reducing BP, as a major determinant of diminished arterial compliance.

Currently used antihypertensive drugs that potentially may alter arterial stiffness carry the risk for inappropriately decreasing diastolic BP, thus jeopardizing coronary reserve.[61] Furthermore, high BP alone definitely does not determine arterial stiffness, which is also influenced by BP-independent structural modifications of large artery walls. Therapeutic studies focusing on structural improvement in vessel walls are just beginning. Promising targets in this respect are the matrical proteins. During degenerative processes of the arterial wall, these proteins are establishing nonenzymatic links to glucose (and other similar molecules), generating advanced glycation end products (AGEs). These AGEs are cumulating slowly at the level of low-turnover proteins, such as collagen and elastin, increasing arterial (and myocardial) stiffness. Reducing AGE generation may improve arterial compliance, as studies in primates have shown.[62,63] These theoretical considerations may be particularly attractive in patients with ESRD, a state characterized by high rates of AGE formation.[64]

To date, a favorable effect of AGE inhibition has been shown in humans with essential hypertension. The thiazolinic compound ALT-711 administered for 56 days improved total arterial compliance by 15% compared with placebo, reducing PWV by 8%.[65] The therapeutic potential of the AGE inhibitor pimagedine (aminoguanidine) has been investigated extensively in animal models and phase 3 clinical trials with promising results.[66]

Supporting the importance of lipid fraction abnormalities in the etiopathogenesis of increased arterial stiffness in patients with CKD are findings from Shoji et al,[67] in which an independent association between aortic PWV and plasma lipoprotein level was reported. Therapy with statins, because of their pleiotropic effects, also may improve arterial stiffness. A recent placebo-controlled investigation[68] of 22 normocholesterolemic HD patients with diabetes showed promising results at 6 months of statin therapy; PWV decreased from 19.91 to 17.09 m/s with fluvastatin therapy (along with significant reductions in oxidized low-density lipoprotein cholesterol and serum C-reactive protein levels), whereas in the placebo group, arterial stiffness increased significantly. These findings have to be confirmed in larger studies. Another placebo-controlled study of renal transplant recipients showed an improvement with 300% of endothelial-dependent vasodilatation after 12 months of statin therapy; this effect was sustained at 36 months.[69]

However, the disappointing results from the 4D study (Deutsche Diabetes Dialyse Studie), in which impressive reductions in low-density lipoprotein and total cholesterol levels were achieved by using 20 mg of atorvastatin in a large cohort of patients with type 2 diabetes on dialysis therapy, must temper to some degree the optimism that alteration in lipid fractions, endothelial function, or arterial stiffening (not examined in 4-D) can confer survival benefit.[3]

Endothelin 1 in vitro leads to an increase in PWV and AI (as it does to mean arterial pressure and peripheral resistance); the endothelin blocker VML-88 reduces these parameters and may be another promising agent for reducing arterial stiffness.[70]

In an analysis of potential interventions to attenuate or prevent arterial stiffening in patients with CKD, we should carefully distinguish between functional and structural effects of drug therapy on arterial stiffness. Endothelin blockers, angiotensin II blockers, calcium channel blockers, and statins (as well as the HD session per se) might have important functional effects on arterial wall properties, whereas therapy for arterial calcifications, AGE cross-link breakers, and inhi-

bition of the renin-angiotensin axis could beneficially impact on structural abnormalities associated with reduced arterial compliance. This distinction may be useful from a pathophysiological point of view, but one also should expect that any initial functional improvements after drug therapy may be followed by structural improvement of the arterial wall.

CONCLUSION

The virtually ubiquitous and diffuse process of large-artery stiffening is a prominent feature of CV disease in patients with CKD. Reduced arterial elasticity is shown even in patients with mild renal impairment and worsens with additional decrease in kidney function, reaching a climax in those on dialysis therapy. PD patients may be at a particularly high risk. Vascular calcifications clearly are a major determinant of arterial stiffness in renal patients. Renal transplantation restores large-artery elasticity to some degree. Increased arterial stiffness in renal patients has become of major interest in recent years because it represents an important determinant of CV morbidity and mortality. Several factors have been proposed to increase arterial stiffness, but research regarding viable therapeutic interventions is in its infancy, in part because only recently have reproducible and reliable methods for measurement become available. Effective reduction of BP and ACE inhibitors, particularly for their vasoprotective effects, may be helpful, along with other therapies, such as AGE inhibition. We urgently need studies to examine these therapies and interventions. If we also could identify reliable surrogate end points to record, this could significantly shorten the time scale of these investigations. Renal transplantation seems to be an effective method in reducing altered vascular distensibility, as it is in reversing (to some degree) left ventricular hypertrophy. Reducing arterial stiffness may be one of the more challenging, but important, tasks for nephrologists in the future years in the difficult and, to date, frustrating attempt to reduce the still very high CV mortality in renal patients.

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