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The importance of accurate measurement of aortic stiffness in patients with chronic kidney disease and end-stage renal disease

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Abstract

Cardiovascular (CV) disease is the leading cause of death in chronic kidney disease (CKD) and end-stage renal disease (ESRD). A key driver in this pathology is increased aortic stiffness, which is a strong, independent predictor of CV mortality in this population. Aortic stiffening is a potentially modifiable biomarker of CV dysfunction and in risk stratification for patients with CKD and ESRD. Previous work has suggested that therapeutic modification of aortic stiffness may ameliorate CV mortality. Nevertheless, future clinical implementation relies on the ability to accurately and reliably quantify stiffness in renal disease. Pulse wave velocity (PWV) is an indirect measure of stiffness and is the accepted standard for non-invasive assessment of aortic stiffness. It has typically been measured using techniques such as applanation tonometry, which is easy to use but hindered by issues such as the inability to visualize the aorta. Advances in cardiac magnetic resonance imaging now allow direct measurement of stiffness, using aortic distensibility, in addition to PWV. These techniques allow measurement of aortic stiffness locally and are obtainable as part of a comprehensive, multiparametric CV assessment. The evidence cannot yet provide a definitive answer regarding which technique or parameter can be considered superior. This review discusses the advantages and limitations of non-invasive methods that have been used to assess aortic stiffness, the key studies that have assessed aortic stiffness in patients with renal disease and why these tools should be standardized for use in clinical trial work.

Key words: aortic stiffness, cardiovascular disease, chronic renal failure, end-stage renal failure, pulse wave velocity

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Introduction

Patients with chronic kidney disease (CKD) are at significantly elevated cardiovascular (CV) risk [1]. Around 50% of deaths in end-stage renal disease (ESRD) patients are attributed to CV disease (CVD) [2]. These excessive rates of CVD are not solely explained by traditional risk factors [3], and coronary artery revascularization does not improve outcomes in ESRD patients to the same extent as in the general population [4]. The pathophysiological processes that drive CVD in patients with CKD and ESRD are complex and include chronic inflammation, increased arterial stiffness, autonomic instability and the insults of dialysis itself [5, 6]. These factors lead to changes in cardiac structure and function, including left ventricle hypertrophy (LVH), left ventricle (LV) dilatation and myocardial fibrosis, which are typically termed uremic cardiomyopathy [7]. A fundamental factor behind LVH is the development of aortic stiffness, which offsets the finely tuned coupling of the heart and arterial system, or the 'arterial-ventricular interaction' [8]. This arterial-ventricular interaction refers to the ratio between the arterial load exerted on the LV and LV performance (Figure 1). It is physiologically matched, ensuring optimal cardiac efficiency for a given stroke volume; disruption of this ratio impairs CV performance. Typically in this interaction, the ascending aorta provides capacitance. Its stretch and recoil buffer blood pressure (BP), accommodating the stroke volume ejected during systole and maintaining smooth flow to the peripheries during diastole [9]. Disease states that lead to stiffening of the aorta (e.g. CKD) reduce this buffering ability, exposing organs to peaks and troughs in BP [10]. Stiffening also increases afterload; to maintain the coupling ratio, the LV must generate higher pressures to eject blood into a more rigid arterial system, with resultant LVH and dilatation [11].

Factors that influence aortic stiffness

Arterial stiffness increases with age [12–14] and BP [15, 16]. In addition to CKD and haemodialysis (HD) [17, 18], associations with comorbidities such as diabetes [19, 20], CVD [21, 22] and obesity [23, 24] are established. Aortic stiffness may be higher in women [25, 26], although large population studies have shown no effect of gender [27, 28]. It is suggested that the greater aortic stiffness observed in Black and Hispanic populations compared with Whites may contribute to their increased burden of CVD [15, 29].

Aortic stiffening in renal disease

Arterial stiffening in patients with CKD and ESRD occurs at an accelerated rate compared with the normal ageing process and arteriosclerosis (typified by increased collagen, calcification and proliferation of smooth muscle cells in the tunica media), rather than atherosclerosis, is the predominant pathogenic process [8]. This may explain the limited success of interventions targeting hypertension, hyperlipidaemia and diabetes, despite a high burden of these atherosclerotic risk factors in this patient group [30]. The Study of Heart and Renal Protection (SHARP) showed that the benefit of statin therapy for early CKD was not present for dialysis patients [31, 32], implying the risk factors associated with CVD change with CKD progression. As bone mineral metabolism worsens with advancement to ESRD, associated hyperphosphataemia, secondary hyperparathyroidism and inhibited vitamin D synthesis result in vascular calcification that causes hardening of the arteries. Other factors linked to the uremic environment, such as anaemia, endothelial dysfunction, neuro-hormonal activation and inflammation, play important roles [8].

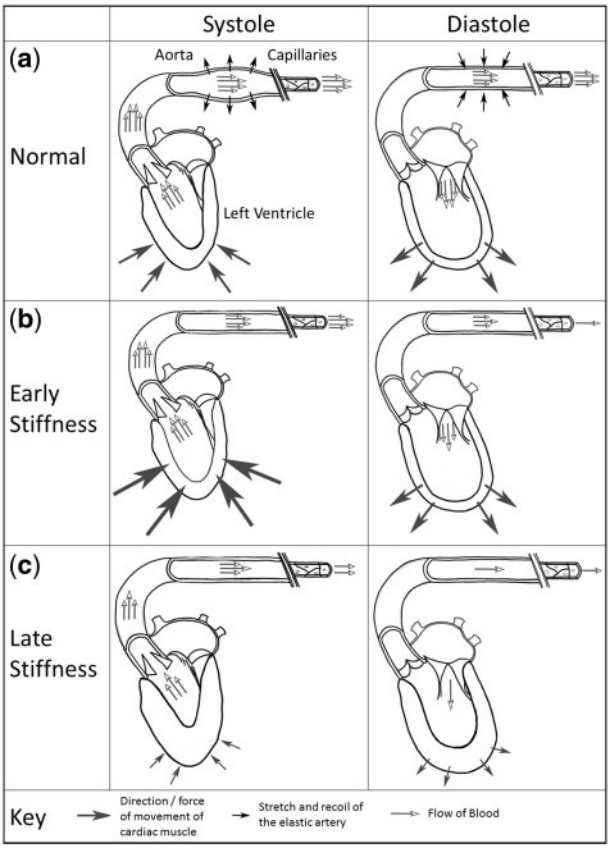

Fig. 1. The arterial–ventricular interaction and the effect of aortic stiffening. (**a**) In systole, stretch of the aortic walls stores a proportion of the stroke volume while blood flows to the capillaries; this reduces the systolic pressure necessary for cardiac output to the peripheries. Aortic recoil maintains diastolic pressure (despite ventricular relaxation); this displaces stored blood, enabling continued blood flow. The LV workload is attenuated and capillary perfusion is sustained. (**b**) Stiffening of the aorta diminishes this storage capacity. The LV must work harder in systole to attempt to eject the entire stroke volume to the peripheries. Poor aortic recoil in diastole reduces flow to the capillaries. Systolic pressure is increased and diastolic pressure decreases. (**c**) Increased afterload on the LV and poor perfusion of the coronary arteries leads to concentric hypertrophy and fibrosis, impacting LV contraction and relaxation.

Arterial stiffening is one of the earliest signs of CV dysfunction in CKD, detectable before ejection fraction or diastolic filling are overtly impaired [11, 33, 34]. Earlier and enhanced quantification of aortic stiffness in patients may improve disease risk stratification and is an attractive imaging biomarker for use in clinical trials. The gold standard for measuring aortic stiffness involves invasive catheterization of the aorta; this is expensive, carries some risk and is not clinically practical. This review will discuss non-invasive methods of assessing aortic stiffness in patients with CKD and ESRD.

Assessment of aortic stiffness

The capacitance of large arteries is described by the parameters 'compliance' and 'distensibility', which are the absolute (ΔV) and relative ($\Delta V/V$) volume change for a given pressure change (ΔP). Aortic distensibility (AD), as a measure of compliance relative to blood volume in the vessel, is better allied to stiffness of the wall itself and decreases in vessels injured by arteriosclerosis and atherosclerosis. AD is calculated as:

$$\text{AD} = \frac{(\text{maximum aortic area} - \text{minimum aortic area})}{(\text{minimum aortic area} \times \Delta P)} \quad (1)$$

where AD is aortic distensibility and ΔP is the change in pressure.

As the axial length of arteries does not change significantly in expansion or recoil, cross-sectional area is a good estimation of volume in clinical research [35].

Ejection of the stroke volume into the aorta propagates an easily detectable pressure waveform. Pulse wave velocity (PWV) is the velocity at which this wave is transmitted through the arterial system. It is calculated as the distance travelled divided by the transit time, expressed in m/s. A rigid vessel will show less deformation in response to pressure and consequently PWV increases. This relationship is expressed by the Bramwell–Hill equation:

$$\text{PWV} = \sqrt{\frac{\Delta P \times A}{\rho \times \Delta A}} \quad (2)$$

where A, ρ and ΔA refer to area, density of blood and change in area, respectively.

Simply, aortic PWV (aPWV) is inversely proportional to AD [36]. As the waveform progresses to the peripheries, branching vessels cause wave 'reflection' back to the central arteries, amplifying systolic pressure, although the relevance of this phenomenon is contentious [37].

Parameters for measuring aortic stiffness

Carotid–femoral PWV (cfPWV), assessed by calculating pulse wave transit from the carotid to femoral artery, is a widely accepted non-invasive estimate of central aPWV [38]. Many studies have used cfPWV as an indirect measure of aortic stiffness, utilizing a number of different modalities [39, 40]; Doppler, mechanotransducer and applanation tonometry techniques are commonly used. AD has recently emerged as a direct measure of aortic stiffness. While distensibility has been measured with ultrasound [41, 42], developments in cardiac magnetic resonance (CMR) imaging promise more precise measurement of AD. While the early evidence for directly measuring stiffness using CMR is promising, AD is a relatively new parameter and thus requires further validation.

Brachial–ankle PWV (baPWV) has been used as a simple measure of peripheral artery PWV. Indeed, baPWV was an objective indicator of CV risk in a recent meta-analysis [43]. Nevertheless, Pannier *et al.* [44] found that PWV calculated centrally, at the aorta, had greater prognostic power than peripheral measurements. Capacitance, and its loss, is most significant at the aorta and plays a larger role in the pathogenesis of CVD. Peripheral measurements are a gauge of smaller, muscular arteries; it is unknown whether changes in peripheral values directly represent the central arterial–ventricular interaction or simply correlate with general vascular improvement. Alternative parameters, such as the augmentation index, do not represent aortic stiffness or predict mortality [45, 46]. Table 1 lists the advantages and disadvantages of common techniques used to measure aortic stiffness in ESRD populations. Importantly, CMR-derived parameters (AD and aPWV) measure stiffness locally, at the aortic arch, whereas other modalities use cfPWV to make a regional assessment of the aorta.

Regional modalities for assessing aortic stiffness: Doppler, mechanotransducer and applanation tonometry

Commercial devices that measure aortic stiffness regionally are distinguished by the signal they detect (pressure, distension or flow), whether they identify waveforms at sites simultaneously and the use of electrocardiography (ECG) gating. The cfPWV is often measured using applanation tonometry, with the SpyghmoCor apparatus (AtCor Medical, Sydney, NSW, Australia) commonly used. The tonometer compresses the artery to record a waveform (Figure 2A); consecutive readings are taken at the carotid and femoral arteries using ECG gating to measure the time difference between arrival of the waveform upstroke at these points (Figure 2B) [38]. Doppler ultrasound is employed similarly using ultrasound transducers to take sequential or simultaneous readings at carotid and femoral sites. The Complior system (Colson, Les Lilas, France) uses mechanotransducers to detect waveforms. It is ECG independent, simultaneously recording the waveform at the two arterial points [48].

As a regional measure, cfPWV includes parts of the femoral and iliac arteries, which have different elastic properties than the aorta. Furthermore, stiffening is not a homogeneous process; this is not accounted for in cfPWV measurement, which provides an average of compliance of the whole aorta [48]. Consequently, small patches of disease may be underrepresented in the final calculation. Notably, it is not possible to obtain specific information about the ascending aorta, a prognostically important site [49].

CMR imaging to assess aortic stiffness

CV magnetic resonance imaging (MRI) proffers a comprehensive way to assess cardiac and arterial function in one investigation. It is the gold standard for quantification of LV dimensions and function [50]. CMR permits local measurement of aortic stiffness, allowing the effects of stiffening on different regions of the aorta to be discerned and inclusion of the ascending aorta in measurements [51]. Scanners apply varying magnetic fields and radiofrequency pulses to affect the magnetization properties of protons. Tissues are distinguished by the signals they emit in response and variations in pulses generate different images to highlight tissue characteristics [52]. Studies in ESRD have mostly used 1.5T platforms, but 3T platforms offer increased temporal and spatial resolution. Imaging at higher field strengths increases tissue distinction with less background noise, producing crisper images, but at the risk of amplifying artefacts [53]. Whether 3T platform imaging improves diagnostic accuracy has not been determined.

Figure 3 describes typical methods for calculating PWV and AD using images obtained by CMR [54]. Variations on these methods exist, dependent on the software utilized. For example, methods of calculating transit time can utilize velocity or flow curves; velocity is a measure of distance travelled over time, whereas flow rate refers to volume travelled over time. These vectors are generally proportional, and in fact, using either curve has been demonstrated not to influence aPWV values [55]. Different methods, however, can influence the reproducibility of results [55, 56]. These variations should be standardized before CMR-derived parameters can be considered viable biomarkers. Additionally, compared with regional methods, the time required for CMR image analysis is

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Table 1. Imaging modalities used for the assessment of aortic stiffness and the relative advantages and disadvantages of each

	Modality (device)	Parameter	Advantages	Disadvantages
Regional stiffness	Doppler	cfPWV[a]	• Inexpensive, portable • Can assess other cardiac and arterial features, e.g. LV hypertrophy, strain • Does not require a specific device • Faster than applanation tonometry • Identification of anatomical landmarks aids repeatability of measurement position • Can detect occlusive/atherosclerotic lesions that may affect PWV	• Operator-dependent skill • Sites of measurement limited by acoustic window • Lacks versatility for anatomical variations • Method of distance measurement overestimates distance • Calculation of cfPWV includes iliac and femoral arteries and excludes ascending aorta In addition: • Transit time is determined through visual assessment using digital calipers, limited by temporal resolution
	Mechanotransducer (Complior)	cfPWV	• Similar to Doppler In addition: • Automated device • Simultaneous measurements	• Similar to Doppler In addition: • Variations in transit time algorithms used • Underestimates PWV compared with applanation tonometry • Cannot provide local wall assessment, where aortic condition may vary
	Applanation tonometry (SpyghmoCor)	cfPWV	• Inexpensive, portable	• Similar to Doppler In addition: • Two consecutive recordings needed, heart rate variability may cause confounding • Local wall assessment not possible
Local stiffness	CMR	aPWV and AD	• Local and regional assessment of aorta possible • Relatively operator independent • Full visualization of the entire vessel • Imaging planes can be precisely placed with good repeatability • Greater spatial and temporal resolution (especially 3Tesla CMR) to study the temporal shift over smaller distances • Measurement not affected by anatomical variations, peripheral vascular disease or problems with using probes to detect waveforms • Other aspects of cardiac and arterial function can be assessed, e.g. strain and deformation	• Focal measurement may be prone to sampling error • Image analysis can be time-consuming and user dependent • Expensive • Longer examination time than other methods • Not possible with patients with metal implants, or with claustrophobia • PP is usually determined non-invasively and peripherally as it is more feasible than invasive measurement

[a]It is possible to undertake a local measurement of arterial distensibility using Doppler techniques but there is little evidence using it in ESRD populations and that is beyond the scope of this review.

significant, although future software developments promise to improve this.

Issues surrounding measurement techniques

Calculation of distance for PWV

Techniques that do not visualize the aorta may not accurately measure aortic length. Direct carotid–femoral measurement is known to overestimate distance, so adjusted calculations have been developed [38]. Unfortunately, the choice of calculation alone introduces up to 30% variation in cfPWV values [57] and studies that have employed different calculations of aortic length are not directly comparable, even if the same device was used. Additionally, the aorta becomes increasingly tortuous with age and variations in waist circumference may confound external measurements [38, 51]. In contrast, CMR enables visualization of the aorta (regardless of vessel angle or acoustic window) and direct measurement of length and accounts for anatomical variations [51]. A single sagittal oblique view of the aortic arch is used for the calculation of distance when measured with CMR. This is a limitation of the technique, as it does not facilitate visualization of aortic tortuosity in other planes. Nevertheless, this assumption aids simplicity in measurement and is unlikely to make a significant difference.

Measurement of BP for AD

Calculation of AD by CMR techniques requires external input of aortic pulse pressure (PP), usually substituted with values from

non-invasive peripheral BP measurement; this is a potential limitation. Due to PP amplification, peripheral values are not representative of aortic PP and it is central pressure that is directly allied to cardiac workload [58]. Moreover, variability in amplification is marked with increasing aortic stiffness, which limits validity when comparing stiffness between groups if peripheral BP has been incorporated [59, 60]. It is difficult to isolate AD from PP as a causal factor behind clinical outcomes, since widened PP, due to arterial stiffening, has also been associated with mortality in ESRD [61]. Non-invasive oscillometric devices underestimate invasive brachial pressures by ~10 mmHg [60]. Nevertheless, these devices are used in CMR studies to analyse the AD of CKD patients [34, 62].

Validation of methods

Neither regional nor CMR methods of measuring stiffness have been validated against invasive values in patients with renal disease.

Doppler, mechanotransducer and applanation tonometry measurements of aortic stiffness

Validation studies in cardiac patients have shown that Doppler correlates well with PWV derived from invasive catheterization ($r = 0.93$, mean difference $= 0.13 \pm 0.79$ m/s) and with greater precision than results derived from Complior ($r = 0.74$) [63, 64]. Agreement between SpyghmoCor and invasive PWV varies by the method of distance measurement, with mean differences ranging from 3.3 ($r = 0.77$) to 0.2 m/s ($r = 0.73$) [65]. These validation studies are limited by using correlation coefficients, as strong correlations do not necessarily signify good agreement [66].

CMR measures of aortic stiffness

The aPWV derived from 1.5T CMR has been validated against invasive catheterization in patients with coronary heart disease, with good agreement between mean values [6.5 versus 6.1 m/s for MRI and invasive PWV coefficient of variation (CoV) 16%] [67]. AD is yet to be validated against invasive values.

Reproducibility of methods

Measurement of PWV and AD is operator dependent. An acceptable level of agreement within individual practices, between operators and between studies is needed for recognition as a reliable biomarker. Good reproducibility is especially important in patients with CKD and ESRD, where variations in BP, volume status and comorbidities may confound values.

Doppler, mechanotransducer and applanation tonometry measurements of aortic stiffness

The studies that have assessed the reproducibility of regional measures of aortic stiffness are of variable quality. Studies using Doppler in ESRD patients have reported intra-observer CoVs between 5.3 and 5.8% [68, 69]. Similarly, good interobserver variability has been reported for cfPWV, with an intraclass correlation coefficient (ICC) of 0.97 in a population of diabetic, hypertensive and CKD patients [70]. Mechanotransducer techniques have good intraobserver and inter-observer variability when used by experienced operators, with ICCs of 0.93 and 0.89 [71]. When applanation tonometry was applied to ESRD and healthy subjects, the ESRD cohort had an inter-observer variability of 0.87 and inter-study reproducibility of 0.83 [72]. Greater variation in mean operator differences existed for the controls than ESRD patients. Analysis of Bland–Altman plots revealed that one operator consistently overestimated cfPWV in the measurements of controls. The improved agreement between operators for ESRD results could be because this group was tested second. This reflects the experience needed by SpyghmoCor operators to obtain reproducible results.

CMR measures of aortic stiffness

No studies have assessed the interstudy repeatability of aPWV or AD in CKD patients. In patients with coronary heart disease, interstudy repeatability of aPWV measured by 1.5T CMR was good (ICC = 0.9) where examinations were repeated on the same day [67]. Similarly, interstudy repeatability at 3T using healthy volunteers was excellent (ICC = 0.96) [56]. However, when repeated examinations had a larger time difference (mean 13 days), interstudy repeatability decreased (ICC = 0.77) [73]. Inter- and intraobserver variability of aPWV measured at 1.5 and 3T has been excellent, with reported

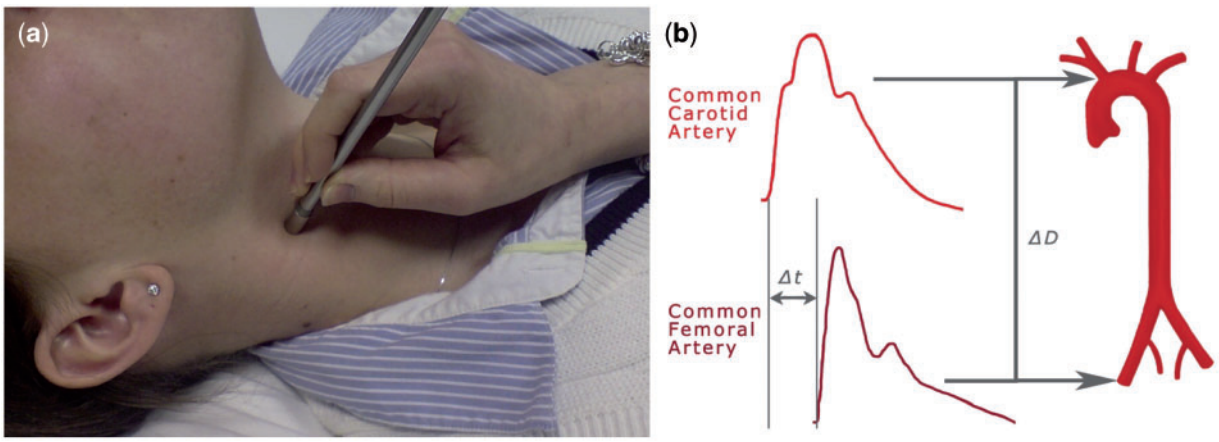

Fig. 2. Applanation tonometry to calculate cfPWV. (**a**) Applanation tonometry at the carotid artery using a micromanometer. Reproduced from Wilkinson *et al.* [47]. (**b**) Calculation of cfPWV using the upstroke of the waveforms to define transit time. Δt, time difference in the arrival of the foot of the waveform; Δ*D*, distance.

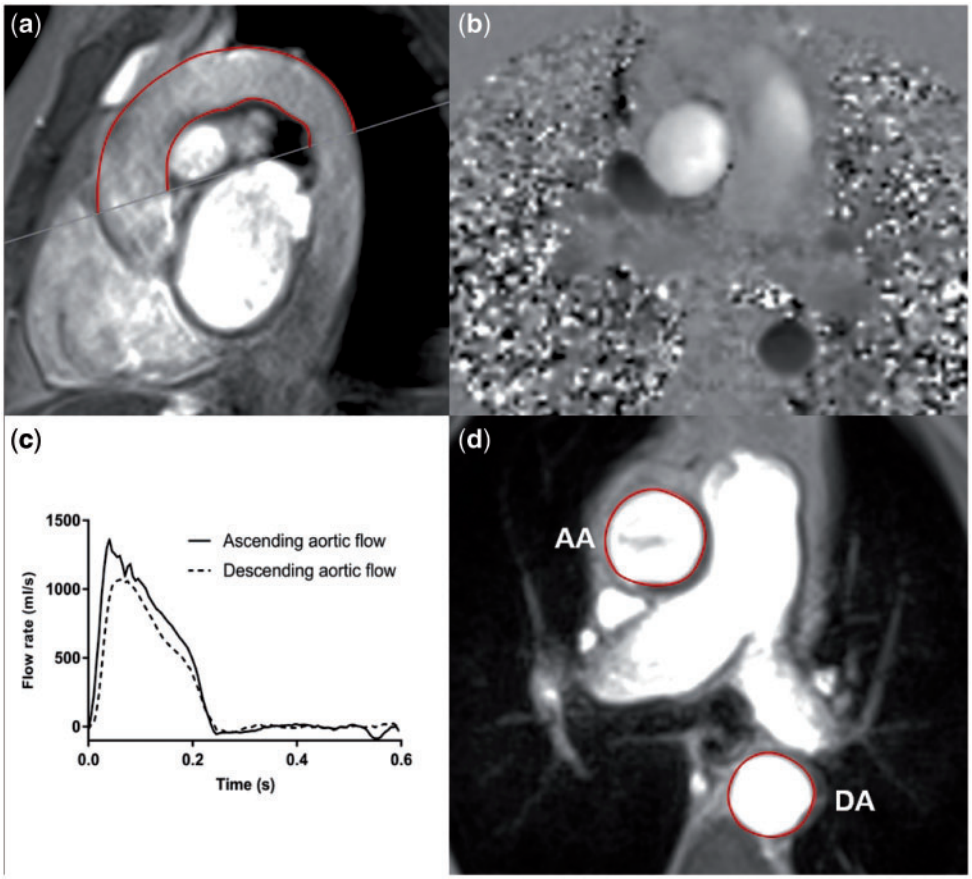

Fig. 3. Assessment of aPWV and AD using two-dimensional phase contrast CMR. **(a)** For aPWV calculation, distance is measured using an oblique sagittal cine transecting the ascending and descending aorta. (**b**) Phase contrast sequences are contoured to derive (**c**) ascending and descending aortic flow curves, from which the temporal shift between the curves can be determined. This gives transit time (the time difference between waveform arrival at the ascending and descending aorta). AD is calculated from axial cine images, taken at the bifurcation of the pulmonary trunk, by contouring the change in (**d**) the aortic area and a PP measured simultaneously. AA, ascending aorta; DA, descending aorta.

ICCs of 0.99 and 0.94, respectively [56, 73]. Regarding AD, a study involving CKD patients reported interobserver and intra-observer ICCs of 0.89 and 0.99, respectively [49]. The possibility to perform repeatable CMR analyses without extensive experience was supported by low interobserver variability (0.02 ± 0.38 m/s) despite a lack of operator experience [74].

Aortic stiffness in patients with CKD and ESRD

Doppler, mechanotransducer and applanation tonometry studies

Multiple studies using regional techniques have found increased cfPWV in CKD and ESRD patients compared with controls [68, 75–77], although the point where arterial stiffening becomes apparent is unclear. In a study of patients with CKD Stages 1–3, cfPWV was only significantly different from controls in patients with CKD Stage 3 [78]. Conversely, other study cohorts exhibit elevated cfPWV from early CKD [77, 79], although not all have shown an increasing trend of PWV with progression of disease [76]. There is also debate about whether higher cfPWV predicts incident CKD in the general population [80, 81].

Briet *et al.* [82] demonstrated that aortic stiffening in renal disease exceeds the effects of BP alone, as cfPWV in a CKD cohort was 7 and 19% higher than in hypertensive and normotensive subjects, respectively. The direct influence of HD on aortic stiffness, beyond the effects of advanced CKD and uremia, is not conclusive. One study suggested that aortic stiffness is greater in pre-dialysis patients than those on HD [83]. The assertion by investigators, however, that increased stiffness is related to uremia rather than HD itself may be misleading; PWV was measured in the HD group 2 h after dialysis. The reduction in cfPWV could reflect a transient improvement in volume and uremic status. Additionally, volume-overloaded pre-dialysis patients could have an increased cfPWV due to elevated stroke volume, though there are no good trial data to support this theory. The study's cross-sectional design also introduces survivor bias, where patients with the highest PWV (and highest risk) may have died, leaving an HD cohort that is systematically healthier. This is an issue limiting most cross-sectional studies in these patients, as there is an escalation in mortality within the first 6 months of starting HD [84]. Other studies have noted increased cfPWV in HD compared with moderate CKD or over time [17, 18], although it is difficult to discriminate the effects of ageing and uremia from HD itself.

CMR studies

Studies have shown that AD is significantly decreased in CKD and dialysis patients compared with controls [49, 85–87]. PWV is increased in dialysis populations [86, 87] and one study revealed

Table 2. Studies showing an association between LVM and aortic stiffness in patients with ESRD

Author	Population	Age, mean ± SD (years); male sex (%)	Inclusion criteria	Study design	Modality (parameter)	Outcome
London *et al.* [68]	92 HD patients 90 controls	49.9 ± 15.9; 52 50.8 ± 15.8	• Not given	• Cross-sectional	• Doppler (cfPWV) Echo (LVM)	• LVM was increased in HD patients (246 ± 56 versus 198.4 ± 52 g, P = 0.0001) and correlated with aPWV ($r = 0.576$, $P < 0.0001$)
London *et al.* [96]	138 HD patients	Responders: 48.2 ± 14.4; 60 Non-responders: 53.2 ± 17; 53	• HD ≥ 3 months, pre-dialysis BP > 160/90, good quality echocardiography, follow-up ≥ 9 months	• Observational, 4.8-year mean follow-up	• Doppler (cfPWV) Echo (LVM)	• 'Responders' were those whose cfPWV decreased in response to treatment. Decreased cfPWV correlated with reduced LVMI ($r = 0.566$, $P < 0.001$). Changes in cfPWV and LVM were independently correlated with serum CRP ($P < 0.001$)
Nitta *et al.* [11]	49 HD patients	60.4 ± 1.6, 55	• HD ≥ 6 months	• Cross-sectional	• Mechano-transducer (brachial and tibial PWV) Echo (LVMI)	• LVMI correlated with PWV ($r = 0.439$, P = 0.001)
Kim *et al.* [97]	391 incident HD patients	54.7 ± 13.2; 59	• HD patients: Age ≥18 years, enrolled within 6 months of HD initiation	• Cross-sectional	• Applanation tonometry (cfPWV) Echo (LVMI)	• Univariate regression (a) and multivariate regression (b) showed no significant relationship between PWV and LVMI: (a) $\beta = -0.42$ (−1.78, 0.94), P = 0.55; (b) $\beta = 0.19$ (−1.41, 1.79), P = 0.82.
Edwards *et al.* [34]	117 patients with Stage 2–3 CKD 40 controls	CKD 2: 55.9 ± 11.6; 50 CKD Stage 3: 53.8 ± 11.8; 68 50.3 ± 9.2; 50	• 18–80 years, Stage 2 or 3 CKD. No overt CVD, DM or PVD	• Cross-sectional	• 1.5T CMR (AD and LVM)	• LVM was inversely correlated with AD ($r = -0.284$, $P < 0.001$)

HD, haemodialysis; LVM, left ventricular mass; LVMI, left ventricular mass index; CRP, C-reactive protein; parametric data presented as mean ± SD.

no significant difference in AD or aPWV between HD patients and patients with severe coronary artery disease [86]. An elegant study by Moody *et al.* [88] revealed that healthy donors developed increased aortic stiffness 1 year after donating a kidney, following the expected drop in glomerular filtration rate. This suggests that aortic stiffness is an early development and is related to CKD itself, as these patients were devoid of other CV risk factors. A randomized controlled trial on the effects of cooled dialysate suggests that aortic stiffness in ESRD might be modifiable [89]. AD significantly increased in control patients undergoing standard HD at 37 °C compared with patients who dialysed at 0.5 °C below body temperature. This was paralleled by a reduction in LV mass (LVM) and preservation of cardiac function in the intervention cohort, demonstrating the capacity of CMR to globally quantify the response of myocardium and vasculature to treatment [89].

Aortic stiffness and LVM in CKD and ESRD

LVH affects up to 75% of ESRD patients [90] and is an established marker for CV morbidity and mortality in the CKD population [91–93]. A reduction in LVM (with an associated reduction in aPWV) has been associated with improved survival in HD patients [94]. However, a recent systematic review and meta-analysis suggested there is no definitive relationship between intervention-related LVM reduction and improved mortality [95]. While LVM remains an important outcome measure, this highlights the value of assessing additional imaging biomarkers to strengthen existing risk stratification or endpoint measures. Table 2 summarizes the studies discussed.

The association between aortic stiffness and LVH in CKD and ESRD is not only described in clinical studies, but is also emphasized by biological plausibility. Chronic volume overload in CKD leads to eccentric cardiac hypertrophy, while pressure overload due to arterial stiffness and hypertension accounts for concentric hypertrophy. Concentric remodelling describes thickening of the LV wall and is defined by an elevated LVM:volume ratio. In patients with ESRD, it independently predicts CV risk beyond the ability of LVH [98]. The loss of the aorta's buffering action on BP subjects the myocardium to higher systolic pressures, haemodynamic instability and increased LV workload. Subsequent compensatory hypertrophic responses result in increased oxygen demand, impaired relaxation and contraction and interstitial fibrosis [99]. Widening of PP due to aortic stiffening also impairs diastolic coronary filling, exacerbating ischaemia in a progressively fibrotic and hypertrophied myocardium [8]. This may also aggravate HD-associated cardiac ischaemia, suggested by the inverse relationship between AD and troponin-T [87].

LVM increases with worsening AD in patients with CKD [34] and reductions in AD have been correlated with concentric LV

Table 3. Studies demonstrating the association between aortic stiffness and CV mortality assessed by Doppler, mechanotransducer, applanation tonometry and CMR

Author	Population	Age, mean ± SD (years); male sex (%)	Inclusion criteria	Study design	Modality (parameter)	Outcome
Blacher *et al.* [100]	241 ESRD patients	51.5 ± 16.3; 61	• On HD ≥ 3 months, no pre-existing clinical CVD	• Observational, 6-year mean follow-up	• Doppler ultrasound (cfPWV)	• Patients with the highest cfPWV had increased risk of CV mortality: HR = 5.9 (2.3–15.5). Increased cfPWV (per 1 m/s) gave an RR = 1.39 (1.19–1.62) for all-cause mortality Aortic stiffness was correlated with LVH ($r = 0.23$, P = 0.0007)
Guerin *et al.* [101]	150 ESRD patients	52 ± 16; 60	• On HD ≥ 3 months, no clinical CVD preceding	• Prospective cohort, 4.3-year mean follow-up	• Doppler ultrasound (cfPWV)	• Adjusted RR for CV mortality in non-responders was 2.35 (95% CI 1.23–4.51, P < 0.01) compared with responders. For a 1 m/s decrease in PWV in response to BP, RR = 0.79 (95% CI 0.69–0.93) for CV mortality
Shoji *et al.* [102]	265 ESRD patients (50 had type 2 DM)	55.4 ± 10.5; 41	• On HD ≥ 3 months	• Observational, 5-year mean follow-up	• Mechanotransducer (cfPWV)	• Increased cfPWV (per 1m/s) strongly predicted CV mortality: HR = 1.16 (95% CI 1.0–1.36, P < 0.05), independent of diabetic status
Zoungas *et al.* [45]	315 Stages 4–5 CKD patients[a]	55 ± 13; 67	• Age >18 years, defined CKD, dialysis therapy to start ≤6 months or already established	• Observational, 5.3-year mean follow-up	• Applanation tonometry (cfPWV)	• Increased cfPWV (per 1 m/s) gave a HR = 1.14 (95% CI 1.07–1.26, P < 0.001) for adverse CV outcome • PWV >9.9 m/s gave HR = 3.38 (1.70–6.73, P = 0.001) versus PWV ≤9.9 m/s for CV events.
Mark *et al.* [62]	144 CKD patients (110 on dialysis)[b]	51.5 ± 11.2; 62	• CKD: eGFR <15 mL/min/1.73 m^2	• Prospective observational, 2-year median follow-up	• 1.5T CMR (AD)	• AD was associated with CV mortality: HR = 0.135 (95% CI 0.019–0.948, P = 0.044), although diabetes had a stronger association (HR = 4.2)
Verbeke *et al.* [103]	1084 dialysis patients	68.1; 59	• Age ≥18 years, on HD/PD ≥3 months	• Observational, 2-year follow-up	• Applanation tonometry (cfPWV)	• A PWV >12 m/s gave an HR = 1.94 (95% CI 1.38–2.73). Increased cfPWV (per 1 m/s) gave an HR = 1.15 (95% CI 1.09–1.23, P < 0.001) for CV mortality
Karras *et al.* [104]	439 CKD patients	59.8 ± 14.5; 74	• Stages 3–5 CKD, not yet on dialysis	• Prospective observational, 4.7-year mean follow-up	• Mechanotransducer (cfPWV)	• Increased cfPWV (per 1 SD) gave an RR = 1.35 (95% CI 1.05–1.75, P = 0.021) for fatal and non-fatal CV events
Baumann *et al.* [105]	135 CKD patients	59.2 ± 15.1; 46	• Stages 2–4 CKD	• Prospective observational, 3.7-year mean follow-up	• Oscillometric method (PWV)	• PWV >10 m/s gave an OR = 5.1 (95% CI 1.1–22.9, P < 0.05)
Sulemane *et al.* [106]	106 CKD patients	55.9 ± 2.8; 51	• No overt CVD, normal LV ejection fraction, not on HD	• Prospective observational, 4-year median follow-up	• Applanation tonometry (cfPWV)	• Increased cfPWV (per 1 m/s) gave an HR = 1.31 (95% CI 1.05–1.41, P = 0.021)

HD, haemodialysis; DM, diabetes mellitus; HR, hazard ratio; OR, odds ratio; RR, risk ratio; 95% confidence intervals presented in brackets.

[a]207 had cfPWV assessment.

[b]122 patients had AD analysed.

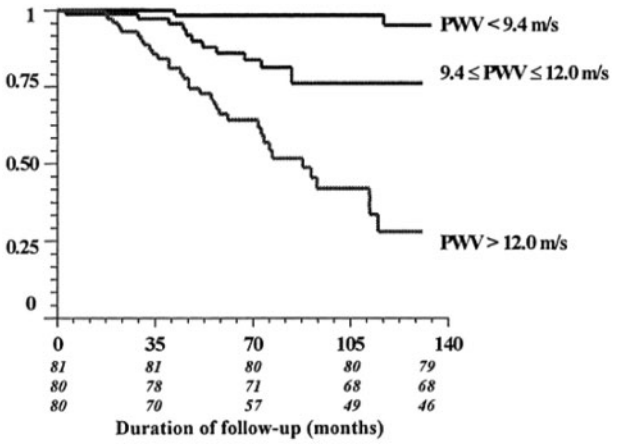

Fig. 4. Kaplan–Meier survival curve for CV deaths in an ESRD study population separated into tertiles based on cfPWV. Reproduced from Blacher *et al.* [100].

remodelling [87]. Edwards *et al.* [34] also demonstrated that while there was an increase in the absolute values of aortic stiffness and LV elastance in early CKD, the arterial–ventricular coupling ratio was preserved. This suggests that aortic stiffness drives an increase in LV contractility and this initial response maintains the coupling ratio. However, this compensation is short-lived and impaired diastolic relaxation and LVH followed. While some studies show a positive relationship between aPWV and LVM [68], others have found no relationship [97], although this latter study was of younger, incident HD patients rather than the prevalent populations comprising other studies [11, 68, 87, 100]. Furthermore, an interventional study in HD patients by London *et al.* [96] indicated that reductions in LVM in response to treatment for hypertension and anaemia correlated with reductions in cfPWV ($r = 0.566$, $P < 0.001$).

Aortic stiffness and CV mortality in CKD and ESRD

Increased PWV is a robust, independent predictor of CV mortality in patients with CKD and ESRD [45, 100, 101–106]. There are data regarding AD, but its predictive power has been assessed in CKD patients [62]. A meta-analysis of 27 studies in healthy and disease populations found a 1-SD increase in cfPWV conferred close to a 50% increased risk of CV death. Furthermore, cfPWV was a better predictor of outcome in higher-risk individuals (such as those with ESRD) than in the general population [107, 108]. Table 3 describes studies that have evaluated the relationship between arterial stiffness and mortality.

Doppler, mechanotransducer and applanation tonometry studies

A seminal paper by Blacher *et al.* [100] demonstrated the ability of Doppler-calculated cfPWV to predict CV mortality, despite adjustment for common prognostic variables (Figure 4). The oft-quoted 39% increased risk of all-cause mortality for each 1-m/s increase in PWV [100] has been emulated in studies involving populations across the spectrum of CKD; they demonstrate that a 1-m/s or 1-SD increase in cfPWV is independently associated with increased risk of CV mortality [45, 102–106] (Table 3). The concept that accurate measurement of aortic stiffness may serve as an early biomarker of CV risk was underscored in a CKD cohort with no clinical or echocardiographic evidence of CVD [106]; a 1-m/s elevation in cfPWV still gave a 30% increased risk of major CV event over the 49-month follow-up. Akin to previous findings, cfPWV was a stronger indicator of risk in more advanced CKD stages, although the low event rate in the early CKD group influences this result.

There is evidence that improving aortic stiffness improves mortality in patients with ESRD. HD patients whose cfPWV failed to improve following modification of BP had an increased relative risk ratio for all-cause mortality of 2.59 [95% confidence interval (CI) 1.51–4.43] and for CV mortality of 2.35 (95% CI 1.23–4.41) compared with HD patients whose cfPWV improved with BP modification [101]. While an interesting observation, there was no apparent correction for differences in baseline cfPWV, and the study cannot prove a direct and causal relationship between cfPWV modification and improved survival.

CMR studies

A CMR study in CKD and HD patients showed decreased AD predisposed to CV mortality [62]. In Cox regression analysis, diabetes, systolic BP and AD were independent predictors of survival. Results were similar between pre-dialysis and dialysis groups, and in keeping with accepted thinking about ageing and arterial elasticity, AD decreased with age. Despite this, neither age nor HD vintage was associated with CV outcome, implying that it is vascular ageing rather than temporal ageing that affects outcomes. There are no CMR studies that have reported aPWV and mortality in patients with renal disease.

Conclusions

CV risk assessment using conventional risk factor models is imprecise in CKD and ESRD. Applying the Framingham score in CKD patients underestimates CV events, predicting only 13.9% (in men) and 4.8% (in women) of events over 10 years [109]. Identifying and quantifying new biomarkers that translate into clinical practice may improve the prediction of CV risk in these patients. Measurement of aortic stiffness is one such biomarker. It encompasses the known and unknown elements of arteriopathy that contribute to increased CV burden. Practical understanding of its significance has been helped by establishing normal cfPWV and CMR-derived values in the general population [28, 110]. The amenability of aortic stiffness to interventions and its translation into outcomes needs further exploration.

An accurate, reliable measure of aortic stiffness is vital for its application to the real world. Choice of technique can lead to up to 40% variance in patient CV risk stratification [111]. An ideal method would (i) measure aortic stiffness directly and non-invasively, (ii) be validated in clinical studies across patient groups, (iii) provide useful information about an individual patient's current health and future risk, (iv) assess secondary effects on the heart, and (v) be acceptable to clinicians and patients. Recent advances mean that CMR has the potential to follow these stipulations, but further studies in renal disease are needed to investigate the significance of CMR-derived values. The ease of measuring local aortic stiffness within routine imaging and the ability to concurrently track a variety of other cardiac parameters adds to the advantages of CMR. While imaging is relatively operator independent, analysis software and techniques require standardizing. Improvement of machine-learning capabilities could improve reproducibility and streamline the process.

The relationship between aortic stiffness and CV health in CKD and ESRD has been substantiated through application of regional cfPWV methods and, most recently, through local measurement of aPWV and AD by CMR. Although improvements are

necessary, local assessment could represent a step towards more precise evaluation of the arterial–ventricular relationship. Whether CMR techniques can be established to the same standards as regional methods is to be seen. A logical step may be to directly compare regional and CMR-derived measurements in a CKD population to quantify agreement.

Authors' contributions

S.F.A.: manuscript draft, figure preparation, final preparation.
M.P.M.G.B.: manuscript revision, final preparation.
F.M.T.L.: figure creation and preparation.
J.O.B.: manuscript revision.
G.P.M.: revision and final approval of manuscript.

Conflict of interest statement

None declared.

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