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Echocardiographic abnormalities in dialysis patients with normal ejection fraction

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In this edition of Nephrology Dialysis Transplantation, Wang *et al*. describe subtle echocardiographic systolic functional abnormalities in a cohort of 98 maintenance haemodialysis patients and the relationship with left ventricular hypertrophy (LVH). Importantly, these patients had no prior history of coronary artery disease, arrhythmia or New York Heart Association class III or IV heart failure. They also had left ventricular ejection fraction (LVEF) ≥50% and no wall motion abnormalities or severe valvular heart disease on conventional transthoracic echocardiography. These patients would, therefore, be classified as having normal left ventricular systolic function according to the measurements that are familiar to most nephrologists. Their study provides new insights into the cardiovascular abnormalities displayed by haemodialysis patients in the absence of established heart failure or coronary artery disease. In this editorial, we describe the physiological mechanism of these changes and put the findings into the broader context of similar, prognostically significant, findings in the general population.

Though it will vary according to the demographics of the study population, the majority of dialysis patients have preserved LVEF. For example, the mean LVEF in a prevalent dialysis population has been shown to be 52.5 ± 8.3% [1], whilst a further study showed that 87% of patients will have LVEF ≥50% when starting chronic dialysis [2]. Despite this apparent 'normal' test, cardiovascular mortality in these patients is high. The lifetime risk of sudden cardiac death in dialysis patients with normal LVEF is 28% [3], more than double that seen in the general population (11–12%) [4]. The actual LVEF value is of little prognostic significance in preserved systolic function; in the general population, the hazard ratio (HR) for cardiovascular death changes very little above LVEF 45% [5].

One of the most commonly reported cardiac structural abnormalities in patients on dialysis is LVH, present on the echocardiograms of 74% of dialysis patients [6]. LVH is a predictor of cardiovascular outcome in both the dialysis and general populations [7–10], as it can manifest with functional consequences. Importantly, these may not be immediately apparent using conventional imaging, a point exemplified by Wang *et al*. They used newer echocardiographic modalities to reveal subtle left ventricular functional changes, which are more common in LVH [11], and are present despite a normal LVEF. These are promising findings as assessment of the early functional consequences of LVH may help us understand why our patients have significant cardiovascular risk even in the absence of a reduced LVEF.

This and similar studies perhaps also highlight that we as nephrologists need to better understand the use and interpretation of echocardiograms, and the usefulness of more specific measurements, if we are to better identify and manage early cardiovascular risk in our patients. To fully appreciate the methods and the findings revealed by Wang *et al.*, it is helpful to consider certain aspects of left ventricular function and geometry.

During systole, the left ventricle will deform or strain in three ways, according to the three types of muscle fibre insertions: longitudinal, radial and spiral. These three patterns of movement are simplified into a schematic representation in Figure 1. First, there is longitudinal shortening from the base to the apex. This should be distinguished from 'fractional shortening' (FS) on an echocardiogram. The latter is a commonly used measure of systolic function that appears in some of the early landmark studies of echocardiographic abnormalities in dialysis patients [6, 12]. FS is actually a measure of the second deformation pattern, radial strain. This is the inward movement of the ventricular wall at all levels perpendicular to the longitudinal axis. 'Strain' here refers to the proportional change of an object's dimensions relative to its resting state. The term 'strain rate' refers to the rate of deformation during strain. The third component that makes up ventricular contraction is the circumferential rotation or 'torsion' of the myocardium, again relative to the longitudinal axis. This form of strain is analogous to the wringing of a towel.

Though each of these functional changes will produce an independent measure of contractility, they combine to produce multidirectional shear strains which are ultimately represented by ejection fraction. With this in mind, it becomes apparent why 'normal' ejection fraction does not mean normal systolic function because compensatory mechanisms of each type of contractility may have accommodated the abnormalities of others. Hence, detecting

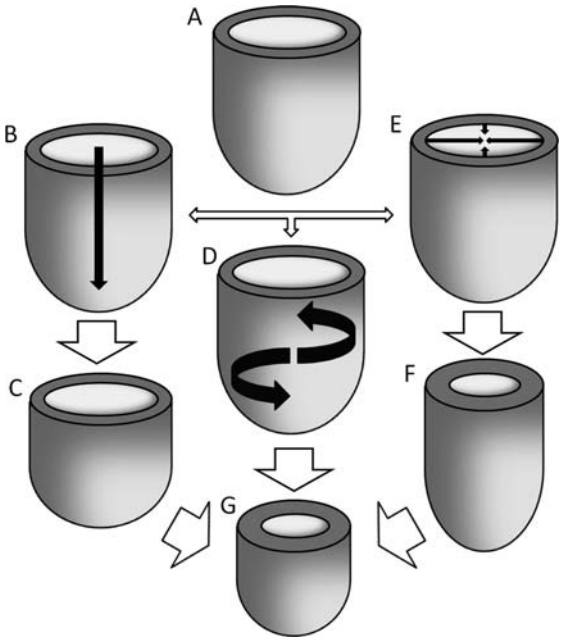

Fig. 1. A schematic representation of the three components of left ventricular contraction. From the end diastolic position of maximum volume (**A**), the ventricle will shorten longitudinally from the base to the apex (**B** to **C**), undergo torsion/twisting around its longitudinal axis (**D**) and radial strain that causes a thickening of the myocardial wall and a narrowing of the perpendicular radius (**E** to **F**). The resultant change in the left ventricular cavity volume (**A** to **G**) represents the ejection fraction.

abnormalities of each contractility pattern will be more sensitive in identifying early cardiovascular risk than relying on a change in LVEF alone. Indeed, if these are precursors to worsening cardiac function, this early stage of abnormal contractility may be the best time to intervene.

The echocardiographic method used to assess these strain patterns is speckle tracking [13]. The speckles' are the precise patterns of acoustic reflection in each section of myocardium on an echocardiogram. Each area of myocardium will have its own unique speckle pattern, and these can be followed ('tracked') as they move in each plane during systole and diastole. Such assessment requires specific software outside of that used in routine clinical practice for echocardiography. The methodology is not user-dependent, other than in the acquisition of adequate images. This removes some operator bias. The accuracy of speckle tracking has been validated against more invasive 'gold-standard' methods of detailed cardiac assessment such as magnetic resonance imaging. This means that it can be considered as a viable bedside tool [14].

Much of what we know of the clinical importance of strain comes from the assessment of patients with heart failure and preserved systolic function [15]. This term usually indicates that LVEF is $\geq 50\%$, though the cut-off and definition vary [16]. Reduction in longitudinal contraction is most commonly the first-strain abnormality seen in heart disease [17]. In a study of 101 hypertensive heart failure patients, longitudinal strain was significantly abnormal even in patients with normal ejection fraction, whereas radial strain was abnormal only in those with NYHA III-IV, where the mean ejection fraction was most often <50% [18]. As previously implied, in some cases longitudinal strain may be reduced with an associated compensatory increase in radial strain to preserve LVEF. In a study of 53 diabetic patients with preserved LVEF and no LVH, longitudinal strain was $21 \pm 4\%$ lower than in non-diabetic controls, but this was offset by a $23 \pm 4\%$ increase in radial strain [17]. However, we know that as cardiovascular disease worsens, radial and circumferential contractility are also liable to decline, eventually leading to significantly reduced LVEF.

Alterations in longitudinal and circumferential strain have been compared with conventional LVEF abnormalities in predicting the outcome following acute heart failure admissions. Here, the global circumferential strain (GCS) pattern was the next most powerful predictor of future cardiac events after age (HR for cardiac events in patients with abnormal versus normal GCS = 1.15, P = 0.007) [19]. The prognostic capabilities of speckle tracking are likely to extend further and with encouraging results in other disease areas this enhanced form of echocardiography may soon become the norm in clinical practice. Hence, strain has been evaluated as a prognostic marker following myocardial infarction [20], in chronic ischaemic cardiomyopathy [21], in patients with aortic stenosis [22] and in predicting response to cardiac resynchronization therapy in chronic heart failure [23]. With this in mind, and given the high cardiovascular risk in chronic kidney disease (CKD) even with normal conventional echocardiographic measures, the work of Wang *et al*. highlights the need for the nephrology community to embrace and explore this technique.

Small studies have evaluated speckle tracking in patients with CKD. Yan *et al.* utilized speckle tracking in dialysis and non-dialysis CKD patients, and controls ($n = 36$, 17, 18 respectively, each with mean LVEF >60%) showing reductions in longitudinal, radial and circumferential strain in both the CKD categories compared with control, but unlike Wang *et al*. they did not speculate as to which clinical factors associated with CKD were responsible [24]. A second study involved pre- and post-dialysis echocardiography in 29 patients and found that peak systolic longitudinal strain (PSLS) decreased following dialysis (PSLS pre-dialysis = $-18.4 \pm 2.9\%$ versus $-16.9 \pm 3.2\%$, post-dialysis, P < 0.001) [25]. This finding is in line with previous studies of dialysis-induced cardiac dysfunction that observed regional wall motion abnormalities [26], but, notably, those subgroups of patients most at risk were not studied.

The adverse impact of LVH in CKD cannot be overstressed. Helpfully, Wang *et al.* compared longitudinal strain patterns in dialysis patients with the normal ejection fraction, categorized according to both the presence or absence, and morphology of LVH, whilst adjusting for other clinical co-variates. So why should we see a difference between these types of LVH? Hypertrophy is the response to excess pre-load or afterload. LVH associated with afterload is seen with hypertension and increased arterial stiffness and will occur in the presence of normal left ventricular cavity dimensions. This is concentric LVH. Hypertrophy associated with excess pre-load occurs in the setting of volume overload and consequent dilatation of the left ventricular cavity. Because of the 'outward' growth of the ventricle, this is

eccentric LVH. In physical terms, these changes relate to the law of Laplace in which the pressure exerted on a vessel wall by the fluid within is proportionate to its diameter. Larger vessels therefore require a thicker wall. A simple analogy would be that trans-continental water pipes are made from thick concrete, whereas drinking straws are not!

In the general population, the prognostic implications of LVH depend on the geometry. The HR for death and non-fatal cardiovascular events is higher in concentric versus eccentric LVH when compared with a reference group with normal left ventricular geometry [concentric HR = 5.4, 95% confidence interval (CI) 3.4–8.5, eccentric HR = 3.1, 95% CI 1.9–4.8] [27]. The reason for this may be that concentric remodelling occurs to a degree greater than that which is physiologically needed to overcome the increase in afterload [28], and this may be due to activation of the renin–angiotensin–aldosterone system and fibrotic remodelling. The resultant scarring can affect myocardial blood flow and conductivity which may form the substrate for arrhythmia generation and adverse cardiovascular events (e.g. sudden cardiac death). Whilst it is firmly established that LVH is associated with adverse cardiovascular outcomes in CKD patients, the differential impact of eccentric and concentric LVH may be different from that seen in the general population. In a sub-study of CREATE (cardiovascular risk reduction by early anaemia treatment with epoetin beta), the risk of cardiovascular events was similar in patients with eccentric and concentric LVH (HR = 1.37, P = 0.27) [29].

Cardiovascular risk is also thought to be related to diastolic dysfunction, and Wang *et al*. explored this in some detail. They showed that left atria were enlarged in patients with LVH compared with controls. A rule of thumb for the non-cardiologist is that if the left atrium is not enlarged, there is unlikely to be significant diastolic dysfunction. Although left atrial dilatation is associated with poor outcome, it is not specific to diastolic dysfunction as it is also associated with valvular disease, arrhythmia and volume overload. Wang *et al*. also assessed other conventional echocardiographic measures such as LVMI and FS. However, the former was indexed against height rather than the body surface area, and FS measured using mid-wall FS. These are not necessarily the methods used in a standard clinical echocardiographic protocol but they have been shown to be better prognostic indicators when applied in dialysis patients [30]. This emphasizes an important point—that the parameters measured by echocardiography of the dialysis patient should be part of a protocol specifically designed with them in mind (as opposed to one applicable for the general population). This also leads to the discussion of the optimal timing of an echocardiogram in relation to a haemodialysis session. Wang *et al*. undertook imaging 2 h after dialysis, whereas others have performed scans on a non-dialysis day to avoid any influence of dialysis-induced ischaemia and associated functional abnormalities [26]. Generally, studies are performed when patients are deemed to be at optimal dry weight. The difficulty here is that we do not know how well the timing of the study, together with the findings, translate into real-life practice. It is unknown whether there are particular parameters which would be significantly associated with the outcome in chronically overloaded patients as opposed to other patients. A further point is that as dialysis-associated cardiac functional changes are of prognostic significance, perhaps echocardiography should be undertaken during dialysis as a matter of routine assessment.

In summary, it is safe to say that echocardiography continues to form an integral part of cardiovascular risk assessment for dialysis patients. However, we are becoming aware that conventional imaging protocols have limited capability to identify the full cardiovascular risk of our patients. There is much more to an echocardiograph than mere 'ejection fraction'. Novel techniques such as speckle tracking have great promise and will help us understand the complex pathophysiological relations between the heart and the kidney, but these need to be evaluated in large-scale prospective studies consistently linking these parameters with the clinical outcome. Furthermore, a better understanding of echocardiography and its interpretation amongst the nephrology community would seem to be an invaluable advance in helping us predict and manage the high cardiovascular risk of our patients.

Conflict of interest statement. The results presented in this paper have not been published previously in whole or part, in any form.

(See related article by Wang *et al.* Multidirectional myocardial systolic function in hemodialysis patients with preserved left ventricular ejection fraction and different left ventricular geometry. *Nephrol Dial Transplant* 2012; 27: 4422–4429.)

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FGF-23 in children with CKD: a new player in the development of CKD–mineral and bone disorder

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Abstract

Disturbances in mineral and bone metabolism in children with chronic kidney disease (CKD) lead to specific abnormalities of skeletal homeostasis called CKD–mineral and bone disorder (CKD-MBD). These disturbances should be diagnosed and managed appropriately to prevent bone deformities and disturbed growth. Changes in the vitamin D and parathyroid hormone (PTH), and the subsequent alterations in calcium (Ca) and phosphate (P) homeostasis are considered responsible for the development of CKD-MBD. Recently, a phosphaturic hormone, the fibroblast growth factor-23 (FGF-23), has been reported as a key regulator of P and vitamin D metabolism. A number of recent studies in paediatric populations have documented that the FGF-23 levels are increased early in CKD, before any abnormalities in serum Ca, P or PTH are apparent. The elevated FGF-23 levels result in a negative P balance to maintain P homeostasis, inducing phosphaturia, independently of PTH, and