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Exploring the elusive link between subclinical fibrosis and clinical events in end-stage renal disease: does cardiac magnetic resonance imaging hold the key?

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Extensive myocardial fibrosis is known to occur in patients undergoing dialysis due to a variety of mechanisms not necessarily restricted to coronary artery disease. Fibrosis may predispose to reentry arrhythmias and long-term myocardial dysfunction, and sudden death and congestive heart failure are the most frequent causes of death in patients undergoing renal replacement therapy. Despite the high accuracy of magnetic resonance for imaging of myocardial fibrosis, its use has been restricted by the risk of inducing nephrogenic systemic sclerosis with the injection of gadolinium. The development of new sequences that allow the detection and quantifying of the severity of extracellular myocardial fibrosis offers a chance to study the pathogenesis of this condition and identify potential interventions to retard or reverse it. Whether these will lead to an improved outcome needs to be prospectively tested.

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The exceedingly high mortality rates of patients with end-stage renal disease (ESRD) on hemodialysis have been a source of consternation for clinicians and researchers alike. Incident hemodialysis patients have a remarkably increased risk of mortality in the first year after initiation of hemodialysis; no appreciable reduction in this risk has been noticeable in contemporary relative to older cohorts.[1] In particular, the mortality risk is nearly 2.7-fold higher within the first 2 weeks among those initiating hemodialysis compared with those who survive the first year; this risk appears to plateau only after the first 90 days.[2] Although it is well recognized that a majority of deaths among patients receiving long-term hemodialysis are attributed to cardiovascular disease, it is less well-known that nonatherosclerotic factors (particularly sudden death, responsible for nearly one fourth of all deaths, and congestive heart failure) account for a majority of deaths, whereas acute myocardial infarction accounts for only a small minority.[3] Hypertension, anemia, metabolic and endocrine abnormalities, as well as electrolyte and hemodynamic fluctuations in the context of underlying pathologic left ventricular hypertrophy and dysfunction, contribute to the high cardiovascular mortality in these patients. These factors underline the importance of distinguishing subclinical disease early in this population to specifically assist the clinician in identifying those at higher risk after initiation of hemodialysis.

Early autopsy studies of chronically uremic patients without significant coronary stenosis revealed a characteristic pattern of fibrosis in >90%, referred to as "noncoronary diffuse intermyocardiocytic fibrosis" but without evidence of amyloid deposition.[4] This pattern of fibrosis was also apparent among uremic nondialysis patients and increased in severity with increasing duration of dialysis. Imaging specialists have attempted to develop noninvasive cardiovascular imaging techniques that may shed light on identifying more vulnerable patient subsets with early subclinical disease who may be susceptible to a higher risk of adverse outcomes. The key to solving this puzzle could lie in the identification of myocardial tissue characteristics of ESRD patients and perhaps, most importantly, the detection of myocardial fibrosis. Precedence in this regard has been established by other conditions associated with pathologic left ventricular hypertrophy, most notably hypertrophic cardiomyopathy and amyloidosis, in which detection of myocardial fibrosis/scarring has been correlated with increased arrhythmia burden and worse outcomes.

Initial work using gadolinium-enhanced cardiac magnetic resonance imaging (cMRI) among patients with ESRD to identify fibrosis was extremely promising. Two groups on opposite sides of the Atlantic described a high prevalence of late gadolinium enhancement (LGE) in

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this population.[5] Intriguingly, there was recognition of not only a pattern of subendocardial LGE ("infarct" pattern) characteristic of coronary artery disease, but also a "noninfarct" pattern of LGE characteristic of a more diffuse process (Figure 1). Importantly, a significant correlation was apparent between left ventricular mass and LGE, lending credence to the fact that the left ventricular hypertrophy of ESRD patients is indeed pathologic. At this point, the research in this field was tantalizingly poised to solve the puzzle by correlating the LGE patterns with clinical outcomes of interest. Unfortunately, any further progress in this direction was thwarted by the recognition of the debilitating clinical entity of nephrogenic systemic sclerosis, described in association with the use of gadolinium among patients with renal impairment. Of interest, certain gadolinium-based contrast agents, particularly "macrocyclic" chelates have been studied by some investigators in patients on dialysis, without any associated incidence of nephrogenic systemic fibrosis.[6] Yet, the use of gadolinium-based contrast in dialysis patients remains the exception rather than the rule in most routine clinical and research practices. In more recent times, MRI investigators started using T1-mapping to assess the myocardial tissue characteristics of patients with a variety of conditions. An increase in T1 relaxation time has been detected in conditions with increased extracellular space/tissue, namely, fibrosis. However, this technique again required the injection of i.v. gadolinium, proscribing its use in dialysis patients. The enthusiasm for correlating subclinical myocardial tissue abnormalities with long-term outcomes has been re-ignited with the introduction of *noncontrast* or native myocardial T1 mapping. In a study of 129 nondiabetic patients with nondialysis chronic kidney disease, native T1 mapping was significantly increased compared with control subjects.[7] Moreover, native T1 time correlated with impaired systolic function, as measured by global longitudinal strain (also assessed using cMRI).

In this context, the studies by Rutherford *et al.*[8] (2016) and Graham-Brown *et al.*[9] (2016) in this issue of the journal serve as promising steps toward elucidating myocardial tissue characteristics of hemodialysis patients. Using native myocardial T1 time, and peak global longitudinal strain (to assess deformation of the myocardium during contraction)

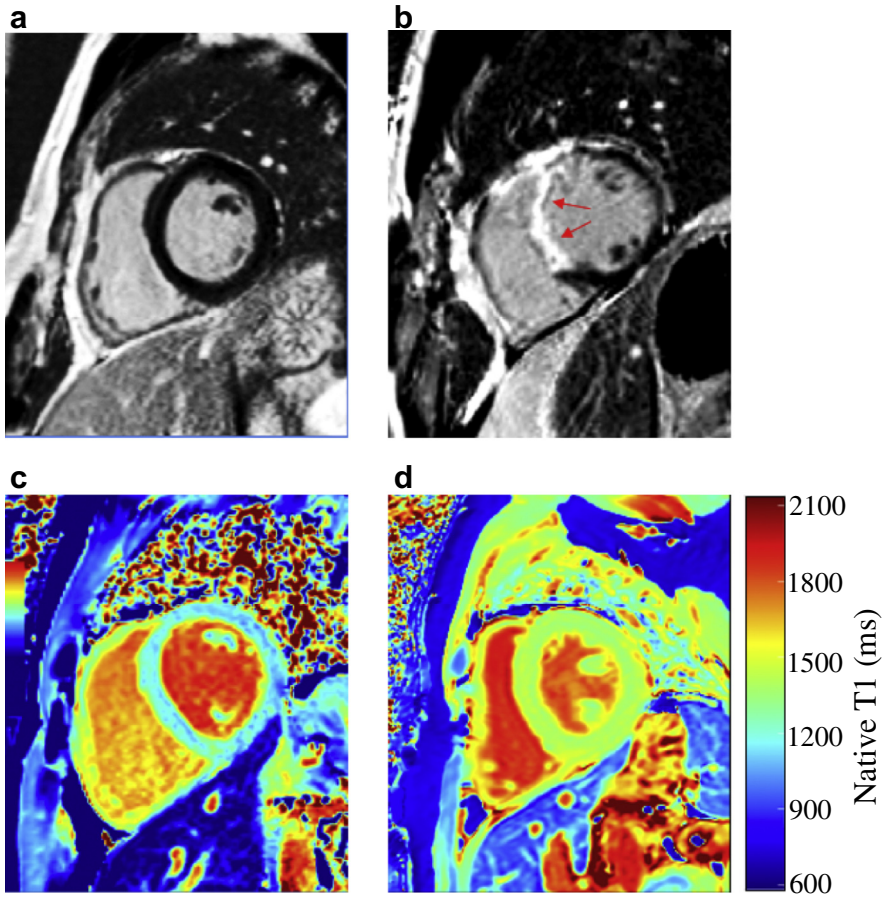

Figure 1 | Late gadolinium enhancement images in a healthy control subject (a) and a nondialysis patient with a transmural septal myocardial infarction (b). The area of scar, appearing bright white, is indicated by the red arrows. Native (noncontrast) myocardial T1 maps in a healthy control subject (**c**) and a long-term dialysis patient (**d**) showing diffusely increased T1 values in the dialysis patient (1350 ± 25 ms) compared with the healthy subject (1235 ± 27 ms). The increased T1 values suggest the presence of diffuse myocardial fibrosis. Data acquired with the modified look-locker inversion recovery T1 mapping sequence at a field strength of 3 T. (Images courtesy of Dr. Richard Thompson, Department of Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada.)

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