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Defining Myocardial Abnormalities Across the Stages of Chronic Kidney Disease: A Cardiac Magnetic Resonance Imaging Study

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Abstract

Objectives: A proof of concept cross-sectional study investigating changes in myocardial abnormalities across stages of CKD. Characterizing non-invasive markers of myocardial fibrosis on cardiac MRI, echo and correlating with biomarkers of fibrosis, myocardial injury, and functional correlates including exercise tolerance.

Background: Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular death. Much of the excess mortality is attributed to uremic cardiomyopathy, defined by increased LV hypertrophy, myocardial dysfunction and fibrosis. The prevalence of these abnormalities across stages of CKD and their impact on cardiovascular performance is unknown.

Methods: 134 non-diabetic, pre-dialysis subjects with CKD stages 2-5 without myocardial ischaemia underwent cardiac MRI (1.5T) including; T1 mapping (biomarker of diffuse fibrosis), T2 mapping (oedema), late gadolinium enhancement and assessment of aortic distensibility. Serum biomarkers including collagen turnover (P1NP, P3NP), troponin T and NTpro-BNP were measured. Cardiovascular performance was quantified by bicycle CPEX testing and echocardiography.

Results: Native myocardial T1 times increased incrementally from stage 2 to 5 (966ms ± 21 vs. 994ms ± 33, $p<0.001$), independent of hypertension and aortic distensibility. Left atrial volume, E/e', NT-pro BNP, P1NP and P3NP increased with CKD stage ($p<0.05$), while effort tolerance (% predicted VO_2 Peak, $\%VO_2VT$) decreased ($P<0.001$). In multivariable linear regression models, eGFR was the strongest predictor of native myocardial T1 time ($p<0.001$). Native myocardial T1 time, left atrial dilatation and high sensitivity troponin T were independent predictors of % predicted VO_2Peak ($p < 0.001$).

Conclusion: Imaging and serum biomarkers of myocardial fibrosis increase with advancing CKD independent of effects of LV afterload and might be a key intermediary in the development of uremic cardiomyopathy. Further studies are needed to determine whether these changes lead to the increased rates of heart failure and death in CKD.

Keywords: Myocardial fibrosis, T1 mapping, Uremic cardiomyopathy

Condensed abstract

Patients with chronic kidney disease (CKD) have increased cardiovascular and heart failure mortality. It is proposed that the increase relates to myocardial abnormalities known commonly as uremic cardiomyopathy which is characterised by LV hypertrophy, myocardial dysfunction and diffuse interstitial fibrosis. In this study, advancing stage of CKD was associated with an increase in markers of myocardial fibrosis on cardiac MRI, serum biomarkers of fibrosis and declining effort tolerance. NTproBNP, procollagen turnover markers and diastolic abnormalities were associated with reduced exercise capacity. These observations are consistent with the paradigm of myocardial fibrosis being an intermediary in the development of uremic cardiomyopathy.

Abbreviations:
CKD; chronic kidney disease,
CMR; cardiac magnetic resonance imaging,
CPESE; cardiopulmonary exercise testing with stress echocardiography, CPET cardiopulmonary exercise test,
GCS; global circumferential strain,
GLS; global longitudinal strain,
LGE; late gadolinium enhancement,
MOLLI; Modified Look Locker Inversion recovery sequence,
P1NP; pro-collagen N-terminal type 1 peptide P1NP,
P3NP; pro-collagen N-terminal type 3 peptide,
VO_2Peak; Peak Oxygen carrying capacity,
%VO_2VT; percent predicted peak oxygen carrying capacity at the ventilatory threshold.

Introduction

Chronic kidney disease (CKD) is a major risk factor for cardiovascular disease (CV) with a graded, inverse relationship between CV risk and glomerular filtration rate (GFR) independent of age, sex and other risk factors (1). The major health care burden of CKD relates to patients with early stage disease in whom CV risk usually outweighs the risk of progression to end stage renal disease (ESRD) (2). Cardiovascular disease associated with CKD is complex. While the prevalence of coronary artery disease (CAD) is increased, most deaths in late stage CKD are due to sudden cardiac death and heart failure and are thought to be a result of heart muscle disease, frequently termed uremic cardiomyopathy (3).

Recently, imaging studies using echocardiography and cardiac magnetic resonance imaging (CMR) have re-defined uremic cardiomyopathy in CKD as a distinct phenotype consisting of prognostically significant changes including left ventricular (LV) hypertrophy, left atrial dilatation, diastolic dysfunction and reduced myocardial deformation – a surrogate of myocardial fibrosis (4-6). The application of CMR native T1 mapping techniques, a biomarker of interstitial fibrosis, demonstrated increased T1 times in ESRD with associations between elevated T1 times and serum markers of fibrosis, myocardial strain and levels of serum troponin (7,8). Increased native myocardial T1 times are also increased in patients with early stage CKD compared to hypertensive and healthy controls (9). However, the pathophysiological and functional significance of increased interstitial fibrosis in CKD is not yet clear. The aim of this cross-sectional proof of concept study was to investigate myocardial changes in CKD stages 2 to 5. Associations were sought between native myocardial T1 values and indices of exercise tolerance, ventricular deformation, serum concentrations of biomarkers of fibrosis and bone mineral metabolism which have all been implicated in the development of uremic cardiomyopathy.

Methods

Pre-dialysis patients with CKD stages 2 to 5 (eGFR ≤90 to ≥15 ml/min/1.73m^2) were recruited from renal clinics in Birmingham, UK between August 2015 and May 2018. Pre-screening of clinics was performed ensuring inclusion / exclusion criteria. Patient information sheets were posted in advance and patients were approached and formally screened at their clinic appointment. Recruitment was stratified by CKD stage (4-variable Modification of Diet in Renal Disease formula). Exclusion criteria were; diabetes mellitus, known coronary artery disease (angina, myocardial infarction, prior percutaneous or surgical revascularisation, evidence of myocardial ischaemia on non-invasive testing), heart failure, moderate or severe valvular heart disease, stroke or peripheral vascular disease. Myocardial ischaemia was excluded in all cases using either exercise stress echocardiography with LV opacification (Sonovue®, Bracco, It) or 99m Technetium-tetrofosmin single-photon emission computed tomography with computed tomography attenuation (CT SPECT, Symbia T16, Siemens, Erlangen, Germany). The study was approved by the National Research Ethics Service - East Midlands (15/EM/0280). Patient participation was voluntary and all subjects gave written informed consent.

Demographic, medical co-morbidities, blood and proteinuria data were collected. Subjects underwent assessment as follows.

Cardiac magnetic resonance imaging: All studies were performed at 1.5T (Siemens Avanto, Erlangen, Germany). Standard protocols for LV function and mass were performed using steady state free precession imaging (10). Myocardial characterisation was assessed using T1 mapping, T2 mapping, and inversion recovery imaging after gadolinium (if eGFR≥30ml/min/1.73m^2). An ECG-gated Modified Look-Locker Inversion recovery (MOLLI) sequence with a 3(3)3(3)5 heart beats sampling protocol (Siemens WIP 448) was

performed pre-contrast (to assess native myocardial T1) and post contrast (for extracellular volume [ECV]) at basal and mid short axis levels in diastole. Typical acquisition parameters were: pixel bandwidth 977 Hz/pixel; echo time = 1.1 ms; flip angle = 35°; matrix = 144x256 slice thickness 6mm. T2 mapping (T_2-prepared single-shot SSFP technique) was performed at identical basal and mid short axis levels as T1 maps. Typical T2 acquisition parameters: 3 single shot images were acquired at different T2-preparation times (0ms, 24ms, and 55ms, respectively), ECG triggered, TE = 1.12ms, flip angle = 70°, voxel size 2.2×1.8×6.0mm, slice thickness 6mm. Motion correction and fitting were performed to estimate coefficients of the decay function, which were then used to estimate T2 times. Standard inversion recovery imaging was performed 7-10 minutes after gadolinium-based contrast agent (Gadovist® 0.15mmol/Kg) for assessment of late gadolinium enhancement (LGE).

Offline analysis: Analysis of LV function, volume and mass was performed with delineation of papillary muscles and trabeculations using thresholding (CVi 42®, version 5.3.4, Circle Vascular Imaging, Canada) as previously described (10). Tissue tracking for 2-D myocardial global longitudinal (GLS) and global circumferential (GCS) strain was performed using standard views and indexed for LV end-diastolic volume as previously described (11). T1 and T2 times were measured from the parametric maps with endocardial and epicardial borders delineated and a 20% offset used to avoid blood pool contamination. Anterior and inferior septal borders were defined with semi-automated segmentation of the LV in accordance with the American Heart Association 17-segment model. Septal T1 time (average of antero- and infero-septal segments) was reported, avoiding measurement in any region with LGE. Extracellular volume (ECV) and indexed ECV (ECV fraction × LV end-diastolic myocardial volume normalized to the body surface area) was calculated using validated formulae as previously described (10). Intra and inter-observer variability for T1 were assessed using data

from 30 anonymised subjects, randomly assessed from the cohort and analysed by observers' blind to all clinical data. A T1 Mapping and ECV standardisation phantom was scanned fortnightly during the study period to ensure stability of measurements (12).

Aortic distensibility: A breath held retrospective ECG-gated axial SSFP cine of the ascending aorta at the level of the pulmonary artery was acquired. Typical acquisition parameters were TE = 1.2ms, TR = 56.8ms, flip angle = 61°, voxel size = 1.8×1.4×6 mm^3, number of cine images = 1. Aortic lumen was detected and segmented automatically using a dedicated analysis tool developed in Matlab (Mathworks). The maximal and minimal cross-sectional lumen area (mm^2) were measured as the average from 3 systolic (A_{max}) and 3 diastolic (A_{min}) images in the ascending aorta to calculate the change in aortic lumen area $(A_{max} - A_{min})/A_{min}$. Aortic distensibility was obtained dividing the aortic area change by the pulse pressure measured as the average of 3 non-invasive blood pressure readings taken at the time of cine acquisition.

Cardiopulmonary exercise testing with stress echocardiography (CPESE): A maximal bicycle ergometer cardiopulmonary exercise stress echocardiogram (CPESE, GE Case ES V6.61) was performed using an individualised Ramp protocol based on gender, age, and weight (13). Ventilatory gases were analysed breath-by-breath and averaged over 10-second intervals. Subjects exercised until exhaustion. A respiratory exchange ratio ≥ 1.1 and %predicted heart rate ≥ 85% were used as markers of adequate effort tolerance. Ventilatory threshold (VT) was defined as the point of intersection between the line of departure of VO_2 from the line of identity drawn through a plot of VCO_2 versus VO_2 (the v-slope method) (14). Parameters of exercise tolerance included; %predicted VO_2Peak and %predicted peak oxygen capacity at the ventilatory threshold (% predicted VO_2VT).

Systolic function (ejection fraction, myocardial strain), diastolic function (LA volume index, ratio transmitral E-wave/lateral myocardial TDI e' wave; E/e') and evidence of myocardial ischaemia were assessed by rest and stress echocardiography (EPIQ, Phillips). Myocardial strain values were indexed for LV volume to adjust for volume load. In subjects with myocardial ischaemia excluded by CT-SPECT as a part of their kidney transplant workup, only cardiopulmonary exercise test (CPET) was performed.

Blood biomarkers: Plasma and serum were tested for pro-collagen N-terminal type 1 peptide (P1NP) and pro-collagen N-terminal type 3 peptide (P3NP) using the Elecsys total P1NP kit and the Orion UniQ P3NP RIA kit respectively. Plasma was also tested for human-FGF-23 (C-term; Immunotopics, Inc) and human alpha Klotho (IBL International) using ELISA assays. NT pro-BNP and troponin-T were measured using standard diagnostic assays (Roche diagnostics).

Sample Size Justification and Statistical Analysis

Previous in-house T1 data in subjects with CKD demonstrated a standard deviation of 30-35ms, which is consistent with published data (9,15). A sample size of 33 subjects per stage of CKD (n=132 total) was needed to provide 80% power to detect a minimal detectable difference between groups of 30ms with an alpha value of <5%. With this sample size, treating eGFR as a continuous variable would yield 80% power to detect a correlation coefficient with T1 of 0.24.

All data were analysed using SPSS version 24 (SPSS Inc., Chicago, Il, USA). Normality was assessed using the Shapiro-Wilk test. Parametric variables are shown as mean ± standard deviation, with median (interquartile range) used for non-parametric data. The Jonckheere-Terpstra test was performed to assess for trend in continuous variables across CKD

stages. Categorical variables were compared across stages using the chi-square test. Pearson's or Spearman's correlation coefficients were used for continuous parametric and non-parametric variables respectively. Linear regression modelling was performed to assess for the effect of potential confounders. Initially, univariate linear regression models were produced for each factor and the residuals were interrogated to assess the goodness of fit. Logarithmic-transformation was applied to factors with a poor fit and goodness of fit reassessed, before producing multivariate linear regression models. A variance inflation factor >5 was taken to represent collinearity. For the regression model with native myocardial T1 as the dependent variable, only factors thought to be clinically relevant to the question being asked were entered into a multivariate model alongside aortic distensibility. For the model with exercise capacity as the dependent variable, factors of clinical interest and factors that were significant on univariate analysis (p values <0.05) were considered for inclusion into the multivariate model. A backward stepwise approach was then used to remove those factors that were not independently associated with exercise capacity. A p value of <0.05 was considered statistically significant.

Results

Patient Characteristics

In total, 139 subjects were recruited. Two subjects were excluded following positive stress tests for ischaemia. Patient characteristics are detailed in Table 1. The leading causes of renal disease were primary glomerulonephritis and polycystic kidney disease. Blood pressure was well controlled across the cohort with 127/137 (93%) on anti-hypertensive medication. Blood pressure with higher in more severe kidney disease. There were also differences in

haemoglobin, phosphate, parathyroid hormone and proteinuria with worsening CKD stage (Table 1).

Left Ventricular Structure and Function on CMR

CMR data was available for 134 subjects following exclusion of 3 patients for claustrophobia (Table 2). LV hypertrophy (defined by age and gender-matched normal range) was evident in 14 subjects (10%). Indexed LV volume and mass did not differ significantly across CKD stages though mass was higher in CKD stage 5 (Central Illustration). Indexed left atrial volume increased with stage of CKD ($p = 0.006$). Neither indexed CMR myocardial strain nor aortic distensibility differed between CKD stages.

Myocardial Tissue Characterisation

*Native T1 times and ECV***:** There was a significant trend for native myocardial T1 times to increase with advancing CKD stage (native T1 $p< 0.001$) (Central Illustration, Figure 1) and a correlation with LV mass (native T1 $r=0.231$, $p=0.008$). Gadolinium was administered to 67 of 74 eligible subjects (eGFR $\geq$30 ml/min/1.73m^2). Post-contrast myocardial T1 times decreased with worsening CKD (post contrast T1 $p=0.023$). Extracellular volume and extracellular volume index did not differ between CKD stages 2 and 3. No data was available for CKD stage 4 and 5 (Table 2).

Native T2 times: Myocardial T2 times increased with progressive CKD severity (test for trend $p=0.033$). On univariable analysis, myocardial T2 time was correlated with native myocardial T1 time ($r=0.541$, $p<0.001$).

Late gadolinium enhancement: LGE was present in 29/67 (43%) subjects with the patterns; right ventricular insertion point (RVIP) 21/67 (31%) and mid-wall / sub-epicardial 8/67 (12%).

No patient had sub-endocardial LGE indicative of infarction. There was no difference in the patterns of LGE seen between the CKD stages 2 and 3 groups.

Blood Biomarkers of Myocardial Fibrosis and Dysfunction

There was a significant trend for serum biomarkers of heart failure (NT-pro BNP: $p< 0.001$), myocardial injury (high-sensitivity troponin-T: $p< 0.001$) and myocardial fibrosis (P1NP: $p<0.001$; P3NP: $p<0.001$) to increase with advancing CKD stage (Table 1 and Central Illustration). Aldosterone (test for trend: $p=0.03$) and FGF-23 (test for trend: $p<0.001$) also increased with worsening CKD, with no difference in alpha-Klotho levels. There was no association between native myocardial T1 time and biomarkers of fibrosis. Native myocardial T1 time was correlated with NT-pro BNP ($r=0.404$, $p< 0.001$) and FGF23 ($r=0.202$, $p=0.002$) but not with high sensitivity troponin T. There was no association between LGE and NT-pro BNP or high sensitivity troponin T.

Cardiopulmonary Stress Echocardiography (CPESE)

CPESE data were available for 127/137 subjects (Table 3). Six subjects could not cycle; 2 declined the test, and 2 could not tolerate the face mask. Effort tolerance was inversely associated with worsening CKD severity as measured by several CPESE biomarkers including %predicted VO_2Peak, %predicted VO_2 at the ventilatory threshold (%predicted VO_2VT) and VE/VCO_2. Indexed myocardial GLS on resting echocardiography also reduced with worsening CKD stage ($p<0.001$), while indexed left atrial volume and resting E/e' increased (LA vol $p=0.040$; Resting E/e' $p=0.009$). (Figure 1)

Regression Models for Prediction of Native T1

Multivariable regression modelling was performed to assess whether the association between native myocardial T1 time and eGFR was independent of LV afterload as measured by systolic pressure and aortic distensibility. In a multivariable regression model with septal T1 time as the dependent variable and covariates of systolic blood pressure, age, eGFR, aortic distensibility and gender, no measure of afterload was independently associated with native T1 time. Decreasing eGFR (p=0.004) and female gender (p=0.039) were the only significant independent predictors (Supplementary data).

Functional Correlates of Myocardial Fibrosis

CPESE and T1: On univariable analysis, no CPESE variables correlated with native myocardial T1 time, but both %predicted VO_2Peak and %predicted VO_2VT were positively associated with myocardial GLSi on echocardiography (%predicted VO_2Peak: r=0.206, p=0.039; %VO_2VT: r=0.325, p=0.001) and CMR (%predicted VO_2Peak: r=0.063, p=0.491; %VO_2VT: r=0.274, p=0.002). GLSi and native myocardial T1 time were inversely correlated (r=-0.227, p=0.021). Resting and exercise E/e' were also associated with native myocardial T1 time (rest: r=0.201 p=0.028; exercise: r=0.235 p=0.025).

CPESE and serum biomarkers of fibrosis: Exercise capacity (%predicted VO_2Peak and %VO_2VT) were associated with P3NP, (r=-0.352, p<0.001; r=-0.233, p=0.010 respectively). P3NP was also associated with echo GLSi (r=-0.212, p=0.031) and E/e' (rest: r= 0.304, p=0.001).

Predictors of Exercise Tolerance

Given the potential for multiple associations between confounding markers of exercise tolerance and factors such as LV mass, myocardial strain, fibrosis, haemoglobin, eGFR and age, multivariable backward linear regression modelling was performed with %predicted

VO_2Peak as the dependent. Female gender (p=0.003), haemoglobin (p=0.012), and left atrial volume (p=0.002) were positive predictors of %predicted VO_2peak, while BMI (p=0.011), high-sensitivity Troponin T (p<0.001) and native myocardial T1 time (p=0.008) were negative predictors. This model was positive with a p value of <0.001 and it explained 56% of the variability seen.

Reproducibility

No systemic bias was detected by Bland-Altman analysis between intra- and inter-operator agreement for native myocardial T1 times. The mean intra- and interobserver differences [mean ± SD (95% limits of agreement)] were −1±6ms (−12 to 10) and −1±7ms (−13 to 11) respectively.

Discussion

In this cross-sectional study of subjects with pre-dialysis non-diabetic CKD in whom myocardial ischaemia was excluded, native myocardial T1 time, a histologically validated marker of interstitial myocardial fibrosis, had a graded inverse relationship with kidney function. The association was independent of the effects of LV afterload including hypertension, aortic distensibility and LV hypertrophy. Serum biomarkers of fibrosis also increased, and echo based global longitudinal strain decreased with stage of CKD. Both native myocardial T1 on CMR and serum pro-collagen biomarkers of fibrosis were associated with surrogate markers of elevated left ventricular end-diastolic pressure, increasing diastolic stiffness (NT-pro BNP and mitral E/e') and progressive functional limitation on cardiopulmonary exercise testing, thereby supporting the hypothesis that myocardial fibrosis contributes to impaired cardiac performance in CKD.

These data add to previous observational reports demonstrating increased native T1 times in ESRD (7,8) and increased T1 times and ECV in early stage CKD (9). The prevalence of myocardial late gadolinium enhancement was low (8/67) in keeping with previous reports (16) and highlights the limitation of LGE imaging for detecting subtle diffuse interstitial changes although we acknowledge the lack of histological validation of T1 and fibrosis in CKD. Our finding that myocardial T2 time also increased with worsening CKD and was correlated with myocardial native T1 time, suggests a possible contribution of myocardial oedema as previous reported in ESRD before and after dialysis (17). Further research is required to define the relative contributions of water and fibrosis to the elevated T1 times in CKD. The lack of correlation between native T1 and serum biomarkers of fibrosis suggests no single biomarker appears sufficient to characterize the myocardium comprehensively due to a heterogeneous response. This finding is similar to recent data in aortic stenosis (18) and we speculate that imaging and serum biomarkers might offer independent "signals" of myocardial fibrosis thus requiring an integrative approach.

Functional limitation was demonstrated on cardiopulmonary exercise testing with a progressive deterioration with advancing stage of CKD. This finding is consistent with data from a large cross-sectional study demonstrating a graded reduction in VO_2Peak and peak cardiac power with worsening kidney function (19). Exercise tolerance was inversely correlated with serum biomarkers of fibrosis and echo derived global longitudinal strain – a validated surrogate biomarker of myocardial fibrosis and a prognostic marker of outcome in CKD (20). Although causation cannot be demonstrated from our data, the results support a hypothesis that diffuse interstitial myocardial fibrosis (and possibly myocardial oedema) may be drivers of myocardial dysfunction and exercise intolerance as CKD advances.

Both native myocardial T1 times and circulating levels of P3NP have been independently correlated with histologically proven myocardial fibrosis including in

hypertensive cardiomyopathy, aortic stenosis and idiopathic dilated cardiomyopathy (21). While histological correlation of fibrosis with native T1 time is lacking in CKD there is other evidence of fibrotic disease. Galectin-3, a serum biomarker of fibrosis, increases as eGFR falls, and has been associated with progressive abnormalities of GLS and all-cause mortality in CKD (8, 22). Our study has demonstrated an inverse relationship between eGFR and serum biomarkers of collagen turnover as well as FGF-23, a hormone linked to development of LVH and heart failure (23).

Limitations

This was a cross-sectional study so neither longitudinal progression nor a causal relationship between imaging/serum biomarkers and declining kidney function can be assumed. A longitudinal follow-up study would be necessary to better understand the influence of declining kidney function on the progression of variables under study and clinical outcomes but would be prolonged, difficult and expensive to undertake. The study population was highly selected, enrolling subjects without a history of diabetes mellitus or CAD and hence applicability to the wider CKD population is limited. The high proportion of subjects with vasculitis (17%) means that we are unable to exclude an independent influence of myocardial inflammation and scarring due to these disorders. Only a small proportion of our patients received gadolinium contrast for these research CMR studies due to guideline recommendations for use with eGFR >30ml/min/1.73m^2. This limited ECV measurement and detection of irreversible reparative fibrosis detected by LGE. Our study was also limited by size. The increase in native myocardial T1 times were smaller than predicted from power calculations and below our pre-specified minimal detectable difference as were changes in echo markers of diastolic function across stages of CKD. There was no significant difference in

ECV between CKD stage 2 and 3. However this difference may have been underestimated as the sample size was small due to the limited eligibility for gadolinium.

Conclusion

In subjects across the spectrum of non-dialysis CKD without diabetes or ischaemic heart disease, myocardial fibrosis assessed by native myocardial T1 time showed a graded inverse association with kidney function independent of the effects of LV afterload. The observed deterioration in diastolic function and effort tolerance, coupled with a rise in validated biomarkers of fibrosis, heart failure and myocardial injury, are consistent with a role for myocardial fibrosis as an early and key intermediary in the development of uremic cardiomyopathy. Non-invasive and non-contrast based myocardial characterization with CMR T1 mapping is robust and might allow better risk stratification of myocardial disease and potentially targeted anti-fibrotic therapy.

Perspectives:

Competency in Medical Knowledge 1: Heart failure and sudden death rates are the primary cause of death in advanced renal disease and risk increases as glomerular filtration declines.

Competency in Medical Knowledge 2: Myocardial fibrosis has been detected on cardiac biopsies in patients with end-stage renal disease and is postulated to contribute to uremic cardiomyopathy. This finding has been supported by the surrogate marker of high native T1 myocardial times on cardiac MRI T1 mapping techniques and abnormalities of deformation on echo. The functional impact of this finding is no known.

Competency in Patient Care 1: Diffuse interstitial myocardial fibrosis assessed by CMR and blood biomarkers increases with stage of CKD and is associated with deleterious changes in the heart and exercise tolerance.

Translational Outlook 1: Myocardial fibrosis might be a target for pharmacological treatments in CKD.

Translational Outlook 2: Treatments to reduce myocardial disease in CKD might reduce the disproportionate cardiovascular event rate.

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Figure Legends

Central Illustration – A conceptual overview of myocardial abnormalities across the spectrum of CKD.

Native myocardial T1 times increased with worsening stage of CKD and were accompanied by a rise in serum biomarkers of fibrosis and heart failure. LV mass only increased in severe CKD.

Figure 1 – Trend in Myocardial Native T1 Times, LV mass, Exercise and Echo-based Global Longitudinal Strain across the Stages of CKD.

The p values are derived from the Jonckheere Terpstra test for trend. The maximum height of the whisker is 1.5 times the interquartile range.

Tables

Table 1 – Patient Characteristics

Data are presented as mean ± SD or median (interquartile range). The Jonckheere Terpstra test was used to assess for trend in continuous variables across the CKD stages. The chi squared test was used to assess the difference in categorical variables across the CKD stages. A P value <0.05 (bold) was considered to be statistically significant.

Abbreviations: ACEi; angiotensin converting enzyme inhibitor; ACR; albumin to creatinine ratio; ARB; angiotensin receptor blocker, BMI; Body Mass Index, BPM beats per minute, CCB; calcium channel antagonist/blocker, eGFR; estimated glomerular filtration rate, FGF-23; fibroblast growth factor 23, HS Troponin T; high sensitivity troponin T, GN glomerulonephritis, NT-pro BNP; N-terminal pro b-type natriuretic peptide, P1NP pro-collagen N-terminal type 1 peptide, P3NP; pro-collagen N-terminal type 1 peptide, PTH; parathyroid hormone.

Table 2 – Left Ventricular Structure and Function on Cardiac MRI

Data are presented as mean ± SD or median (interquartile range). The Jonckheere Terpstra test was used to assess for trend in continuous variables across the CKD stages. The chi squared test was used to assess to difference in categorical variables across the CKD stages. A P value <0.05 was considered to be statistically significant. *Based on the N=67 who were administered gadolinium. Patterns; RVIP 21/67, mid wall 8/67, subendocardial 0/67. Indexed ECV is calculated as using the following equation: iECV ml/m^2 = (ECV% x indexed LV mass) / (1.05 x 100). †Independent samples T-test was used to calculate this P Value as there were only 2 variables of interest.

Abbreviations: ECV; extracellular volume, GCSi; indexed global circumferential strain, GLSi; indexed global longitudinal strain, LA left atrial; LV left ventricular, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF; left ventricular ejection fraction.

Table 3 – Data from Cardiopulmonary Exercise Testing with Stress Echocardiography

Data are presented as mean ± SD. The Jonckheere Terpstra test was used to assess for trend in continuous variables across the CKD stages. A P value <0.05 was considered to be statistically significant.

Abbreviations: bpm; beats per minute, e'; early diastolic tissue velocity measured at the level of the mitral valve annulus, E/e'; ratio of transmitral early blood flow velocity to early diastolic tissue velocity, GLSi; Echo global longitudinal strain on echo, HR; heart rate, LA Vol; left atrial volume, METS; metabolic equivalents, RER; respiratory exchange ratio, VE/VCO2; ratio of minute ventilation to carbon dioxide produced, VO2; Peak peak oxygen uptake, VO_2VT; peak oxygen uptake at the ventilatory threshold.