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# Diffuse interstitial fibrosis and myocardial dysfunction in early chronic kidney disease

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DOI: 10.1016/j.amjcard.2015.02.015

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Document Version Peer reviewed version

#### Citation for published version (Harvard):

Edwards, NC, Moody, WE, Yuan, M, Hayer, MK, Ferro, CJ, Townend, JN & Steeds, RP 2015, 'Diffuse interstitial fibrosis and myocardial dysfunction in early chronic kidney disease', *The American Journal of Cardiology*, vol. 115, no. 9, pp. 1311-7. https://doi.org/10.1016/j.amjcard.2015.02.015

Link to publication on Research at Birmingham portal

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PII: S0002-9149(15)00708-0

DOI: 10.1016/j.amjcard.2015.02.015

Reference: AJC 20983

To appear in: The American Journal of Cardiology

Received Date: 18 December 2014

Revised Date: 2 February 2015

Accepted Date: 3 February 2015

Please cite this article as: Edwards NC, Moody WE, Yuan M, Hayer MK, Ferro CJ, Townend JN, Steeds RP, Diffuse Interstitial Fibrosis and Myocardial Dysfunction in Early Chronic Kidney Disease, *The American Journal of Cardiology* (2015), doi: 10.1016/j.amjcard.2015.02.015.

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Diffuse Interstitial Fibrosis and Myocardial Dysfunction in Early Chronic Kidney Disease

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Running title: Myocardial fibrosis in Chronic Kidney Disease

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Funding sources: None

Early stage chronic kidney disease (CKD) is an under recognised, highly prevalent cardiovascular (CV) risk factor. Despite a clustering of conventional atherosclerotic risk factors, it is hypothesised that non-atherosclerotic processes, including left ventricular (LV) hypertrophy and fibrosis, account for a significant excess of cardiovascular risk. This cross-sectional observational study of 129 age-(mean age 57  $\pm$  10 years) and gender-matched subjects examined: non-diabetic CKD stage 2-4 (mean GFR 50  $\pm$  22 ml/min/1.73m<sup>2</sup>) with no history of CV disease, hypertensive subjects with normal renal function, and healthy controls. Cardiac MRI (CMR) was performed for assessment of LV volumes and systolic function (myocardial deformation). Diffuse myocardial fibrosis was assessed using T1mapping for native myocardial T1 times before contrast and myocardial extracellular volume (ECV) after gadolinium administration in combination with standard late gadolinium enhancement techniques (LGE) for detection of coarse fibrosis. Patients with CKD had increased native T1 times  $(986 \pm 37 \text{ms})$  and ECV  $(0.28 \pm 0.04)$  compared to controls  $(955 \pm 30 \text{ms}, 0.25 \pm 0.03)$  and hypertensive subjects (956  $\pm$  31ms, 0.25  $\pm$  0.02, p<0.05). Both T1 times and ECV were correlated with impaired systolic function as assessed by global longitudinal systolic strain (r = -0.22, p<0.05 and r = -0.43, p<0.01 respectively). There were no differences in LV volumes, ejection fraction or LV mass. T1 times and ECV did not correlate with conventional CV risk factors. In conclusion diffuse myocardial fibrosis is increased in early CKD and is associated with abnormal global longitudinal strain, an early feature of uremic cardiomyopathy and a key indicator of adverse cardiovascular prognosis.

**Key words:** chronic kidney disease; cardiovascular magnetic resonance imaging; myocardial fibrosis.

#### Introduction

Large cross-sectional studies have demonstrated that cardiovascular (CV) risk begins to increase in early stage chronic kidney disease (CKD) when estimated glomerular filtration rate (eGFR) levels are ~75 ml/min/1.73m<sup>2</sup> and that risk increases progressively as eGFR falls.<sup>1</sup> There is increasing evidence that adverse changes in cardiac structure and function are present early in the course of CKD; the prevalence of left ventricular (LV) hypertrophy on 2D echocardiography rises with a graded inverse relationship to eGFR<sup>2</sup> and sub-clinical systolic and diastolic dysfunction is detectable using tissue Doppler echocardiography.<sup>3</sup> It is not known however, whether diffuse interstitial fibrosis occurs in early stage CKD and if present, whether it is associated with adverse changes in LV function. We hypothesized that diffuse interstitial fibrosis measured using cardiac magnetic resonance imaging (CMR) is present in early stage CKD and is associated with myocardial dysfunction.

#### Methods

Patients were prospectively recruited from renal clinics at the Queen Elizabeth Hospital Birmingham, England between 2012 and 2014. Inclusion criteria were: CKD stage 2 (eGFR 60-89 ml/min/1.73m<sup>2</sup> with other evidence of kidney disease: proteinuria / haematuria / structural abnormality / genetic), stage 3 (eGFR 30-59 ml/min/1.73m<sup>2</sup>) and stage 4 (15-29 ml/min/1.73m<sup>2</sup>) with no history or symptoms of CV disease or diabetes. Estimated GFR was measured by the 4-Variable Modification of Diet in Renal Disease formula. Subjects were compared to i) age and gender matched healthy controls recruited as part of an on-going clinical study<sup>4</sup> and ii) age and gender matched, treated hypertensive patients referred to a dedicated hypertension clinic. The study was approved by the National Research Ethics Service – South Birmingham (12/WM/0250) and all subjects gave informed consent.

Subjects underwent CMR (1.5T Avanto, Siemens Healthcare, Erlangen, Germany). Left and right ventricular volumes, mitral annular plane systolic excursion (MAPSE), ejection fraction (EF) and LV mass index (LVMI) were acquired in line with standard CMR protocols. Left atrial volumes (LA) were calculated using the biplane area-length method. The four-chamber and short axis steady-

state free precession (SSFP) cine images (ECG-gated, True-FISP; temporal resolution 40-50ms, TR 3.2ms, TE 1.6ms, -FA60°, slice thickness 7mm) at the mid LV (papillary muscle) were used for myocardial deformation analysis. A SSFP single breath hold modified Look-Locker (MOLLI) inversion recovery sequence was used for T1 mapping in the LV basal and mid-ventricular short axis levels before and between 15-20 minutes after contrast administration (8mm slice with a 192 read-out matrix, 6/8 phase partial Fourier with 81% phase resolution, FOV 320 x 320, TR 2.4ms, TE 1.01ms, 11 phases (3, 3, 5 scheme), total breath hold 17 R-R intervals). Late gadolinium enhancement imaging (LGE) was performed 7-10 minutes after 0.15 mmol/Kg of gadolinium contrast bolus (Gadovist Bayer Health Care). All patients were consented to receive intravenous gadolinium 0.15mmol/kg.

CMR analysis was performed off-line using CVI<sup>42</sup> software (Circle Cardiovascular Imaging Inc). Myocardial deformation was assessed using Diogenes CMR-FT software (TomTec Imaging Systems, Munich, Germany), a vector-based analysis tool, for subendocardial strain analysis in the LV four chamber SSFP image (Figure 1). Endocardial borders were drawn manually in the enddiastolic frame for each image. The CMR-FT software automatically propagated the contour and followed its through the cardiac cycle. Global longitudinal peak systolic strain (GLS), peak systolic strain rate (GLSR) and early diastolic strain rate (GLSRe) were derived.<sup>5</sup>

Quantitative parametric T1 images were generated using Argus software (Siemens®) with manual contouring to define a region of interest (ROI) in the LV septum at basal and mid myocardial levels. Global native (non-contrast) myocardial T1 time (ms) was calculated from the averaged T1 times in the LV septum basal and mid ventricular ROIs before contrast administration and global ECV after contrast using validated formulae<sup>6.7</sup>:

$$ECV = \lambda * (1 - Hct)]$$

Hct refers to the haematocrit recorded on a venous blood sample at the time of scan,  $\Delta R1 = 1/T1$  time post contrast – 1/T1 time pre contrast. Lambda ( $\lambda$ ) refers to (1/T1 myocardium post contrast – 1/T1 myocardium pre-contrast)/ (1/T1 blood post contrast – 1/T1 blood pre-contrast).

ROIs were drawn to exclude any areas of LGE consistent with previously undiagnosed infarction and RV insertion point LGE, consistent with previous published methodology (Figure 2).<sup>6</sup> Myocardial intracellular volume (ICV) was also calculated as; 1-ECV providing a measure of cell volume which is important when interpreting the composition of the myocardium with LV hypertrophy.<sup>6</sup> All data were analysed by a single experienced observer (NCE).

Continuous variables are expressed as mean  $\pm$  standard deviation (SD) if normally distributed or median (25-75<sup>th</sup> percentile) if non-normally distributed by the Shapiro-Wilk test. Paired group comparisons were performed using independent T-test and one-way analysis of variance with Bonferroni post hoc tests or Kruskal-Wallis Test, as appropriate. Correlations between variables were assessed by bivariate analysis as appropriate. Statistical tests were two tailed and a p-value <0.05 was considered to indicate statistical significance.

#### Results

In total, 129 subjects were studied across the three groups without significant differences in age and gender. The leading aetiologies of renal disease were primary glomerular nephropathy (37%), adult polycystic kidney disease (APKD, 21%), quiescent vasculitis (SLE, Wegeners granulomatosis, 16%). Patient characteristics are presented in Table 1.

There were no differences in LV volumes or LVEF between groups (Table 2). LA volumes were increased in CKD compared to controls and hypertensive subjects. Only 2/43 (5%) patients with CKD and 2/43 (5%) patients with hypertension had a LVMI above normal limits for LV hypertrophy. Patients with CKD had reduced GLS, GLSR and GLSRe compared to controls and hypertensive subjects. (Table 2)

CKD was associated with higher native T1 (Table 2 and Figure 3a) and lower post-contrast T1 values ( $419 \pm 52$ ms vs.  $465 \pm 50$ ms vs.  $497 \pm 37$ ms, p<0.01) than controls and hypertensive subjects, respectively. ECV was increased in subjects with CKD compared to controls and hypertensive subjects (Table 2 and Figure 3b) with a clear shift of the ECV histogram to the right. Subjects in the top quartile of ECV (>0.29) had lower ICV, LV mass, GLS and GLSR without a

difference in LVEF or LV volumes. There were no differences in ECV between the stages of CKD or between controls and hypertensive subjects (Table 2). Intra-observer variability of ECV data was low; intra-class correlation 0.96 (95% CI 0.88-0.986).

Thirteen patients (30%) with CKD had evidence of LGE in a non-coronary artery distribution; 6 subjects had mid-wall or epicardial LGE; 7 subjects had LGE at the RV insertion points. None of the foci of LGE were located within the ROIs drawn within the septum and therefore no area of LGE was included in calculation of native T1 times or septal ECV. There was no subendocardial LGE suggestive of previous myocardial infarction. After exclusion of CKD patients with LGE, native T1 times and ECV remained increased in CKD subjects (T1 984ms  $\pm$  40 and ECV 0.27  $\pm$  0.03) compared with controls and hypertensive subjects vs. (T1 957ms  $\pm$  27, p<0.05, ECV 0.25  $\pm$  0.03, p<0.05).

In univariate analysis, native myocardial T1 times were inversely associated with GLS (r = -0.22, p<0.05) and GLSR (r = -0.30, p<0.05). ECV was also associated with reduced GLS (r = -0.43, p<0.01) and GLSR (r = -0.23, p<0.05). There was no association between ECV and LVEF, LVMI, NT-proBNP or eGFR.

#### Discussion

This is the first study to assess diffuse interstitial fibrosis using T1 mapping CMR in patients with early CKD. Longer native T1 times correlate closely with histological quantitation of myocardial fibrosis, based on cardiac biopsy in subjects with aortic stenosis undergoing valve replacement.<sup>8,9</sup> The technique is now well established and has been used to identify adverse clinical outcomes in other disease groups including diabetes<sup>10</sup>, valvular heart disease<sup>9</sup> and amyloidosis.<sup>11</sup> Extracellular volume expansion on CMR also correlates closely with histological quantitation of myocardial fibrosis.<sup>8,9,12,13</sup> The assessment of ECV however, requires administration of intravenous gadolinium contrast (comparing pre-contrast T1 and post-contrast T1 values from the myocardium) whereas measurement of native myocardial T1 times in CKD subjects were consistent with the elevation in ECV and with shorter post-contrast myocardial T1 times than were observed in hypertension subjects or

healthy controls, although the T1-sequence used is more susceptible to differences in relaxivity than newer sequences such as sh-MOLLI.<sup>12</sup> It is clear that T1 mapping has considerable potential in the ESRD population where concerns remain about the risk of nephrogenic systemic fibrosis with gadolinium chelates.<sup>14</sup>

Elevation in ECV is important, since this identifies individuals at greater risk for total and cardiovascular mortality.<sup>15</sup> In population studies, elevation in ECV appears to be of similar but independent adverse prognostic significance to reduction in LVEF.<sup>16</sup> There was no evidence of a reduction in systolic function measured by LVEF in patients with CKD in this study, although both our group and others have shown previously that such a change is not common in CKD.<sup>2,3</sup> Indeed, the prognostic value of EF is limited when in the normal range.<sup>17</sup> There were however, reductions in GLS and GLSR that carry independent, adverse prognostic significance both in CKD<sup>18</sup> and in other populations.<sup>19</sup> Both GLS and GLSR are more sensitive and perform better than LVEF in predicting major cardiac events<sup>19</sup> and all-cause mortality in many cardiac conditions.<sup>20</sup> In our study, subjects with early CKD also had evidence of impaired diastolic relaxation, reflected in reduced GLSRe and increased LA volume (a sensitive marker of increased LV end-diastolic pressure). These reductions in systolic and diastolic function are consistent with previous data in early CKD acquired using tissue Doppler echocardiography.<sup>3</sup> Furthermore, increased LA volume is associated with an adverse prognosis in ESRD.<sup>21</sup> It has been suggested that these changes in myocardial systolic and diastolic deformation are functional markers of diffuse interstitial fibrosis, although it is not possible to identify from our data whether LV dysfunction arises due to the presence of diffuse interstitial fibrosis, or whether both are consequences of damage in CKD that occur as part of the final common pathway to uremic cardiomyopathy (UC) and ultimately heart failure.

In our study, ECV was not elevated and GLS/SR were not reduced in subjects with hypertension. These findings are in contrast to a previous study which showed reduced LV systolic strain in hypertensive subjects who had uncontrolled BP (mean 161/101mmHg) and LV hypertrophy.<sup>22</sup> Our findings are consistent with those of Narayanan et al. who found similar myocardial strain values in hypertensive subjects and healthy controls.<sup>23</sup> In both our study and that of

Narayanan, mean BP was better controlled 137/82mmHg and neither study recruited patients with LV hypertrophy. The elevation in ECV in our study in early CKD compared to those with hypertension is important, suggesting that the mechanisms driving the development of diffuse interstitial fibrosis and the alteration in myocardial function are not BP dependent. Histological studies do indicate that reactive interstitial fibrosis can be found in hypertension but this is due to accumulation of type I and type III collagen fibres in advanced disease.<sup>24</sup> In contrast biopsies from patients with ESRD have shown severe myocyte hypertrophy, myocyte disarray and extensive interstitial fibrosis.<sup>25</sup> Subjects in this study with in the highest quartile of ECV and hence lower intracellular volume (a marker of myocardial cellular composition), had a lower LV mass and impaired global longitudinal strain. This observation might support a role of cellular regression with an associated impairment of LV systolic function in the presence of increasing myocardial fibrosis.

This study does not address mechanisms for the development of diffuse fibrosis in CKD but factors likely worthy of further investigation include: aldosterone<sup>26</sup>, the phosphaturic hormone fibroblast growth factor 23 (FGF-23)<sup>27</sup> and high intracellular phosphate levels which actively promote transformation of vascular smooth muscle cells.<sup>28</sup> There is also an association between urinary protein and sodium excretion and LV mass on CMR, independent of blood pressure which requires explanation.<sup>29</sup> Further work to examine associations and investigate possible mechanisms is required.

This was a cross-sectional, observational study and while we have shown associations between ECV and myocardial T1 times with markers of LV function, this does not prove any causative relationship. Longitudinal studies are needed to define whether LV dysfunction arises as a result of progressive fibrosis or not. We acknowledge the lower haematocrit levels in CKD compared to other subjects which might influence calculation of ECV. These data would not affect native myocardial T1 times and indeed are consistent with haematocrit data published in studies of ECV in both diabetics<sup>10</sup> and systemic sclerosis.<sup>30</sup> Subjects did not undergo angiography to exclude coronary artery disease, thus a contribution of ischaemia cannot be completely excluded. No biomarkers for the turnover of extracellular cardiac matrix proteins were measured. The small numbers of patients with each stage of CKD meant that it was not possible to investigate the relationship between severity of

CKD and ECV. Future study of the natural history of myocardial fibrosis using T1 mapping are warranted, together with collection of structural and functional (exercise parameters) data to confirm association with adverse cardiovascular consequences in CKD.

Acknowledgements: James Hodson & Peter Nightingale for statistical support.

Conflict of Interest: None

Funding sources: None

**Contributorship statement:** All authors have made substantial contributions to the conception, design, acquisition, analysis or interpretation of data. NE, RPS, JNT and CF conceived this study. NE, WEM, MY and MK were responsible for the data acquisition and analysis. NE and RPS were responsible for the first version of the manuscript but all authors have contributed to subsequent versions and have approved the final version of the submitted manuscript.

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#### Legends

## Figure 1. Examples of global longitudinal myocardial deformation analysis in CKD and healthy controls

Four chamber SSFP cine image in 2a) CKD with adult polycystic kidney disease healthy control and 2b) healthy volunteer. The subendocardium is traced round by manual contouring. The CMR-FT software automatically propagated the contour throughout the cardiac cycle allowing derivation of global longitudinal subendocardial peak systolic strain (S), peak systolic strain rate (SR) and early diastolic strain rate (SRe') in each myocardial segment and globally for the ventricle.

#### Figure 2. Examples of CMR imaging for function and myocardial characterization

1a-c. Three images from a subject with CKD; a) Standard steady-state free precession image at the mid left and right ventricular level, 1b) Native T1 map (MOLLI sequence) at the same ventricular level as figure 1a. Manual contouring within the septum and blood pool allows calculation of the myocardial and blood T1 times which are used to calculate extracellular volume. Areas of higher signal are noted within the mid wall of the septum (green) indicative of higher T1 times which reflect diffuse fibrosis, 1c) Inversion recovery image performed 7-10 minutes after intra-venous gadolinium administration. Two focal areas of late enhancement (white) are seen at the insertion of the RV into the LV but are not included in the calculation of ECV. The significance of this pattern remains debatable but is not thought to reflect fibrosis.

1d-f. Three images from a subject with CKD; 1d) Standard steady-state free precession image at the mid left and right ventricular level, 1e) Native T1 map (MOLLI sequence) at the same ventricular level as figure 1d with an area of high T1 signal in the infero-septal segment, 1f) Inversion recovery

image with no evidence of LGE. The technique is not sensitive enough to pick up subtle areas of diffuse fibrosis seen in with the native T1 map in 1e.

#### Figure 3a. Box scatter plot of native myocardial T1 times

Error bars are standard error of the mean x2. Myocardial T1 time were assessed in the left ventricular septum from the basal and mid ventricular levels and averaged to yield a "global T1 time". Measurements excluded RV insertion point late gadolinium enhancement. \* p < 0.05 CKD vs. control,

† CKD vs. hypertension.

#### Figure 3b. Frequency histogram of myocardial extracellular volume

The histogram for CKD is shifted rightward with a higher mean septal ECV in the left ventricle but with greater scatter

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Variable	СКД	Controls	Hypertension
	n = 43	n = 43	n = 43
Age (years)	$57 \pm 10$	$57 \pm 10$	57 ± 10
Men	24 (56%)	24 (56%)	24 (56%)
Body Surface Area (m <sup>2</sup> )	$1.9\pm1.2$	$1.9 \pm 1.2$	$1.9 \pm 1.2$
Body Mass Index (Kg/m <sup>2</sup> )	$26 \pm 3*$	26 ± 5	28 ± 5
Haemoglobin (g/L)	$127 \pm 16^{*}$ †	138 ± 11	136 ± 14
Haematocrit (%)	$0.38\pm0.04*\ddagger$	$0.41 \pm 0.04$	$0.41\pm0.04$
Serum creatinine (mg/dL))	1.38 (0.78-2.09)*	$0.9\pm0.16$	$0.95\pm0.18$
N-terminal pro B Natriuretic peptide (ng/L) #	76 (47-187)*	3 (3-173)	7 (5-20)
Glomerular Filtration Rate (ml/min/1.73m <sup>2</sup> )#	50 ± 22*†	$80 \pm 11$	$81\pm8$
Stage 2 n	16	-	-
Stage 3 n	16	-	-
Stage 4 n	11	-	-
Total cholesterol (mg/dL)	$185\pm31$	$201\pm43$	$189\pm35$
Systolic blood pressure (mmHg)	$127 \pm 12$ †	$126\pm11$	$143\pm17$
Diastolic blood pressure (mmHg)	$69 \pm 11$ †	$77\pm 8$	$93\pm11$
Medications			
Angiotensin converting enzyme inhibitor or	37 (86%) *†	0 (0%)	11 (26%)
angiotensin receptor blocker			
Diuretic	9 (21%)*	0 (0%)	7 (16%)
Beta blocker	4 (9%)	2 (5%)	2 (5%)
Calcium channel blocker	9 (21%)*	1 (2%)	11 (26%)‡

#### Table 1.Patient Characteristics

Mean  $\pm$  standard deviation, # median (25-75<sup>th</sup> percentile),

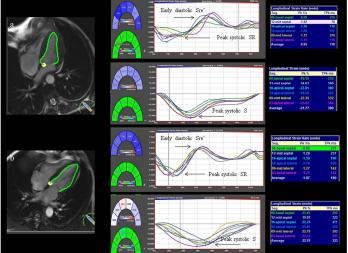
\*p<0.05 CKD vs. Controls, † p<0.05 CKD vs. hypertension, ‡p<0.05 hypertension vs. controls,

Variable	CKD	Controls	Hypertension
Left ventricular ejection fraction (%)	71 ± 6	$73\pm 6$	$71\pm 6$
Left ventricular end-diastolic volume index (ml/m <sup>2</sup> )	66 ± 14	$62 \pm 10$	$59 \pm 12$
Left ventricular end-systolic volume index (ml/m <sup>2</sup> )	$20\pm7$	$17 \pm 7$	17 ± 4
Left ventricular mass index (g/m <sup>2</sup> )	$61\pm15$	58 ± 10	63 ± 13
Native septal T1 time (ms)	$986 \pm 37*$ †	$955\pm30$	$956 \pm 31$
Septal extracellular volume	$0.28 \pm 0.04*$ †	$0.25\pm0.03$	$0.25\pm0.02$
Presence of late gadolinium enhancement, n	13* †	0	1
RV insertion point	7	-	1
Mid wall / epicardial	6	-	-
Left atrial volume index (ml/m <sup>2</sup> )	45 ± 14 * †	$31\pm7$	$32\pm9$
Mitral annular plane systolic excursion (mm)	13 ± 2*	$15\pm3$	$12\pm3$
Global longitudinal strain (%)	$19.8 \pm 4.6^{*}$ ‡	$22.7\pm5.0$	$25.1\pm7.4$
Global longitudinal strain rate (s <sup>-1</sup> )	$1.09 \pm 0.22$ *‡	$1.33\pm0.39$	$1.43\pm0.48$
Global longitudinal early diastolic strain rate (s <sup>-1</sup> )	$0.95 \pm 0.31^{*}$ ‡	$1.21\pm0.35$	$1.22\pm0.39$

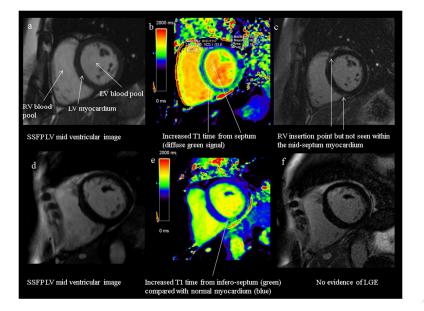
#### Left ventricular functional and morphological data on cardiac MRI Table 2.

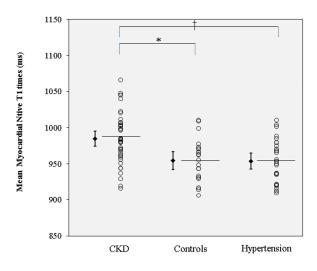
Mean (SD), \*p<0.05 CKD vs. Controls, † p<0.05 CKD vs. hypertension, ‡p<0.05 hypertension vs. 

controls,

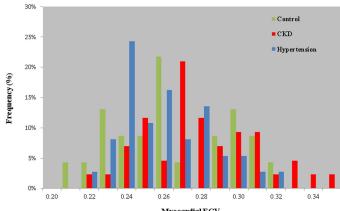


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