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MAGNETIC RESONANCE

# The pathophysiology of the chronic cardiorenal syndrome: a magnetic resonance imaging study

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**Abstract**
*Objective* To study the association of renal function with renal perfusion and renal parenchymal structure ($T_1$ relaxation) in patients with chronic heart failure (HF).
*Methods* After IRB approval, 40 participants were enrolled according to HF and renal function status [10 healthy volunteers<40 years; 10 healthy age-matched volunteers; 10 HF patients eGFR>60 ml/min/1.73 $m^2$; 10 HF patients eGFR< 60 ml/min/1.73 $m^2$] and assessed by MRI. To be eligible for enrolment all HF patients with renal dysfunction (RD) needed to be diagnosed as having chronic cardiorenal syndrome based on current guidelines. Patients with primary kidney disease were excluded.
*Results* Renal cortical perfusion correlated with eGFR values (r=0.52;p<0.01) and was similar between HF patients with and without RD (p=0.27). $T_1$ relaxation correlated negatively with eGFR values (r=-0.41;p>0.01) and was higher in HF patients compared to volunteers (1121±102 ms vs. 1054±65 ms;p=0.03). $T_1$ relaxation was selectively prolonged in HF patients with RD (1169 ms±100 vs. HF without RD 1067 ms±79;p=0.047). In linear regression analyses coronary artery disease (p=0.01), hypertension (p=0.04), and diabetes mellitus (p<0.01) were associated with $T_1$ relaxation.
*Conclusion* RD in HF is not primarily mediated by decreased renal perfusion. Instead, chronic reno-parenchymal damage, as indicated by prolonged $T_1$ relaxation, appears to underly chronic cardiorenal syndrome.
*Key points*
- *The pathophysiology underlying chronic cardiorenal syndrome is not completely understood.*
- *Chronic cardiorenal syndrome is independent of cardiac output or renal perfusion.*
- *Renal $T_1$ relaxation appears to be prolonged in HF with renal impairment.*
- *Renal $T_1$ relaxation is associated with classic cardiovascular risk factors.*
- *Association of renal $T_1$ relaxation with parenchymal damage should be validated further.*

**Keywords** Magnetic resonance imaging · Renal function · Renal perfusion · Cardiac function · Cardiorenal syndrome

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## Introduction

Renal dysfunction is common in patients with HF [1, 2] and has consistently been shown to be one of the strongest predictors of morbidity and mortality in patients with HF [3–7].

On this background of high prevalence and prognostic importance, the co-occurrence of chronic cardiac and renal failure has been termed chronic cardiorenal syndrome [8]. Traditionally, renal dysfunction in HF was thought to be caused by low cardiac output and/or depleted intravascular

volume [9, 10]. However, the adequacy of renal perfusion [10], the degree of venous congestion [11], shared cardiorenal risk factors [8], and drug effects [12] may contribute to the occurrence of renal dysfunction in HF. The relative contributions of these putative factors remain unclear.

Methods for cardiac and systemic haemodynamic evaluation are well established, however the ability to measure renal tissue perfusion in a safe, contrast-free, free-breathing, and readily applicable manner by arterial spin labelling magnetic resonance imaging (ASL-MRI) has only recently become available [13, 14]. ASL-MRI measurements of renal perfusion have susequently been validated against radio-labelled microspheres [15] and para-aminohippurate clearance [16].

Similarly, renal parenchymal structure can be assessed by $T_1$ relaxation time. $T_1$ relaxation time varies for different tissues [17] and changes in disease states of the same organ. In fact, prolonged $T_1$ relaxation times have repeatedly been associated with chronic parenchymal remodelling [18–22] and renal dysfunction [23].

The aim of the present study was to assess these contrast-free MRI parameters in an attempt to delineate the mechanism of renal impairment in patients with chronic HF.

## Methods

### Patient population

Forty individuals participated in this study; this included 20 patients with chronic, stable HF, of whom 10 had preserved renal function (eGFR>60 ml/min/1.73 $m^2$) and 10 had impaired renal function (eGFR<60 ml/min/1.73 $m^2$), as well as 20 healthy volunteers (10 age-matched, 10 younger control patients with normal cardiac and renal function). HF patients were recruited during routine visits to the outpatient clinics at the Royal Derby Hospital and the University Hospitals of Leicester. To be eligible for enrolment, all HF patients with renal dysfunction needed to be diagnosed as having chronic cardiorenal syndrome based on current guidelines (i.e. chronic cardiac dysfunction causing progressive chronic kidney disease, representing an eGFR<60 ml/min/1.73 $m^2$) [8]. Patients with a primary kidney disease were excluded. Healthy volunteers were approached through the local clinical research healthy volunteer program. We excluded patients under 18 years of age, those undergoing renal replacement therapy or having any contraindications to MRI. Furthermore, HF patients experiencing an acute deterioration of HF symptoms or having undergone changes in their critical HF medications (diuretics, beta blockers, RAAS-blocking agents) in the month preceding the study were excluded. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all participants.

### Clinical evaluation

Upon enrolment all participants underwent an initial clinical assessment including clinical history, physical examination, blood tests, bioimpendance analysis as well as cardiac and renal MRI. Blood samples drawn at enrolment were centrifuged and frozen at -80 °C before batch analysis in the central laboratory at the lead site. eGFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation [24]. Impaired renal function was defined as an eGFR<60 ml/min/1.73 $m^2$. High-sensitivity troponin-T and NT-proBNP were measured using a multi-channel auto-analyser (Elecsys 2010 system, Roche Diagnostics, Switzerland). Co-morbid conditions were evaluated based on medical history, current medication, and clinical testing.

### Bioimpedence analysis

Bioimpedance analysis (BIA) measurements were taken in the recumbent position after 5 min of rest using a multi-frequency (1, 5, 50, 250, 500, and 1000 kHz), multi-segmental, eight-point contact tetrapolar BIA device (InBody S20; Biospace, Seoul, Korea), previously validated with normal subjects [25, 26] and hemodialysis patients [27]. Total body water (TBW) and extracellular water (ECW) were derived on the basis of the manufacturer's impedance algorithm.

### Magnetic resonance imaging

Images were acquired using a 1.5 Tesla Philips Achieva whole body MR scanner (Philips Healthcare Systems, Best, Netherlands). Subjects were examined in a supine position with a 16-channel coil.

*Phase contrast-MRI* Phase contrast (PC) MRI with through-plane velocity encoding and ECG gating was used to measure the mean area, velocity, and flux in the renal arteries (RA), renal veins (RV), and the ascending aorta (AO). A turbo field echo (TFE) technique was used with the following imaging parameters: slice thickness 6 mm; 15 phases per cardiac cycle (30 for AO); repetition time (TR)/echo time (TE) 6.9/3.7 ms; flip angle (FA) 25°; sensitivity encoding (SENSE) factor 3; number of excitations 2; reconstructed resolution 1.17× 1.17 $mm^2$; the TFE factor depended on the subjects' heart rate (range 4-6); velocity encoding ($V_{ENC}$) 100/50/200 cm/s for RA/RV/AO respectively.

*Cardiac MRI* Serial contiguous short-axis cines were planned from 2- and 4-chamber cines covering the long axis of the left ventricle. A multi-slice TFE sequence was implemented with 30 phases across the cardiac cycle and a 12 slice acquisition (slice thickness 10 mm), TR/TE=2.9/1.45 ms, FA of 60°, and a SENSE factor of 1.8.

*Renal $T_1$ relaxation time* A modified respiratory-triggered inversion-recovery (IR) sequence was used to measure the $T_1$ relaxation time in the renal cortex. Each inversion time ($T_I$) was collected at the same point in the respiratory cycle by introducing an additional delay $T_v$ following the respiratory trigger and prior to the $T_I$ time. The first slice is acquired at $T_I$, with subsequent slice spacing of $T_d$. Data were collected with a field of view of 288×324 mm and voxel size of either 3×3×8 mm (5 slices) or 3×3×5 mm (10 slices). Contiguous coronal-oblique slices were positioned through the long axis of the kidney whilst avoiding the aorta and 9 different inversion times were acquired (100-900 ms in 100-ms steps, with ascending and descending slice order acquisition to increase the dynamic range) using a balanced fast field echo (bFFE) readout (TR/TE=3.4/1.69 ms, FA=60°, SENSE factor 2, and a temporal spacing between slices, $T_d$, of 153 ms).

*Renal cortical perfusion* Perfusion in the renal cortex was measured using the non-invasive, contrast-free method of respiratory-triggered ASL. We used a flow alternating inversion recovery (FAIR) labelling scheme. To reduce the static tissue signal, in-plane saturation pulses were placed before and after each FAIR inversion pulse, and to maximise the perfusion weighted difference signal, a label delay of 1,100 ms was used. Perfusion data were acquired to match the geometry and slice number used in the $T_1$ measurements with a bFFE readout (TR/TE=3.4/1.69 ms, SENSE factor 2, FA 60°) with a minimal temporal slice spacing and a $T_d$ of 153 ms. An equilibrium base magnetisation $M_0$ image with no inversion was acquired for quantification.

MRI data analysis

*Phase contrast-MRI* Philips Q-flow software (Philips Medical Systems) was used to calculate mean vessel area, velocity and flux of blood flow (ml/s) over the cardiac cycle, across the vessel.

*Cardiac MRI* Philips LV analysis software (Philips Medical Systems) was used to measure left ventricular mass and volumes. Papillary muscles were included in the mass and excluded from the volume calculations. The interventricular septum was included as part of the left ventricle. The basal slice was selected for the end-diastole and the end-systole for the left ventricle when at least fifty percent of the blood volume was surrounded by myocardium. The apical slice was defined as the last slice showing an intra-cavity blood pool.

*Renal cortical $T_1$ relaxation time mapping* Data were fitted on a voxel-by-voxel basis to a 2-parameter model to generate $T_1$ and $M_0$ maps using a least squares non-linear curve fitting algorithm in Matlab® (The MathWorks Inc., Natick,MA). Slices were inspected for any residual motion, and any affected slices were excluded before fitting. A binary mask of the kidney, excluding major vessels, was used to obtain a $T_1$ histogram and segment the cortex from the medulla using a signal intensity threshold.

*Renal cortical perfusion* The time series of the ASL label and control image was motion corrected to the base $M_0$ image using FSL (FMRIB Software Library). Individual perfusion-weighted difference images (control-label) were calculated and then averaged to create a single perfusion-weighted difference map ($\Delta M$). The subjects' $\Delta M$, $M_0$, and $T_1$ were then used in a kinetic model [28] to calculate voxel-wise tissue perfusion (f) maps. The binary mask created from the $T_1$ mapping was applied to the perfusion maps to calculate mean renal cortex perfusion values.

*Volume* Individual total kidney volume was measured using Analyze® 9.0 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). Each kidney was segmented by thresholding each slice in the transverse bTFE localiser, and the volume summed across all slices. This was repeated on the coronal bTFE localiser. The two values were checked for consistency and, subsequently, each direction was averaged. To calculate global kidney perfusion, renal artery flux was divided by the corresponding kidney volume.

Endpoint

The association of renal function as assessed by eGFR with renal perfusion, renal $T_1$ relaxation time, parameters of cardiac function (cardiac output, NT-proBNP), and volume status (extracellular/total body water, renal vein flux and velocity) was evaluated as the primary endpoint of this study.

Statistical analysis

Statistical analyses were performed using SPSS/PC (version 21.0, IBM SPSS Statistics, USA). A statistical significance level of $p<0.05$ was used. Discrete variables are expressed as counts (%) and continuous variables as mean±standard deviation or median and interquartile range [IQR], unless stated otherwise. Comparisons between groups were performed using a chi-square test and Fisher's exact test for categorical variables. Continuous variables were compared using analysis of variance (ANOVA) with Tukey's honest significance post hoc test for multiple comparisons if normally distributed. Homogeneity of variance was tested using Levene's Test of Equality of Variance. Not normally distributed, continuous variables were compared using the Mann-Whitney test. Paired continuous variables (left and right sided measurements) were compared using a t-test for paired samples. Correlations were performed using a Pearson correlation.

Linear regression analysis was applied to identify determinants of $T_1$ relaxation time.

## Results

### Baseline characteristics

Detailed baseline characteristics of the study population are summarized in Table 1, and Table 3 of the Appendix. As per the study design, the two healthy volunteer groups differed primarily in age, while the two HF groups differed in renal function. As expected, all parameters of cardiac function and geometry were significantly different between healthy volunteers and HF patients. Systolic blood pressure was higher in HF patients with impaired renal function compared to HF patients with preserved renal function (p=0.04). Parameters of cardiac function (cardiac output p=0.61, NT-proBNP p=0.90), ventricular mass (left ventricular mass p=0.06, left ventricular mass index p=0.10), and volume status (extracellular/total body water p=0.45, renal vein flux p=0.64, and velocity p=0.52) did not differ between patients with HF with or without renal impairment.

### Phase contrast MRI and volume adjusted global kidney perfusion

Initially, volume and flux parameters were assessed for similarity in left and right kidney. Renal volume and renal flux parameters were similar in the left and right kidneys for the overall population and within the groups. Consequently, we decided to use the average of the left and right kidney values for further calculations. In the overall study population, renal artery flux (r=0.70; p<0.01), renal vein flux (r=0.46; p=0.02), and volume-adjusted global kidney perfusion (r=0.36; p=0.04) correlated with eGFR.

In patients with HF, renal artery flux (3.8±1.2 ml/s vs. 6.2±1.9 ml/s; p<0.01), renal vein flux (4.4 ±1.6 ml/s vs. 6.1 ±1.8 ml/s; p=0.02), and volume adjusted global kidney perfusion (179±73 ml/100 g/min vs. 304±101 ml/100 g/min; p<0.01) were decreased compared to healthy volunteers. Renal vein flux, indicative of renal congestion (3.3±1.8 ml/s vs. 4.2±1.9 ml/s, p=0.35), and volume adjusted global kidney perfusion (147±49 ml/100 g/min vs. 208±80 ml/100 g/min; p=0.10) were similar between HF patients with and without renal impairment.

### ASL-MRI and renal function

Renal ASL cortex perfusion values were similar between left and right kidneys for the overall population (252±72 ml/100 g/min vs. 230±85 ml/100 g/min; p=0.21) and within the groups. Consequently, we used side-averaged ASL values for subsequent calculations. Renal ASL cortex perfusion values showed weak, albeit significant, correlations with parameters of cardiovascular function (cardiac output r=0.35, p=0.05; cardiac index r=0.39, p=0.03), a highly significant correlation with eGFR (r=0.52; p<0.01) (Fig. 1), and a negative correlation

**Table 1** Baseline Characteristics

| Variable | Young Volunteers | Age-Matched Volunteers | HF with preserved renal function | HF with impaired renal function |
|---|---|---|---|---|
| Age (year) | 30.8±4.8 | 64.7±8.7 | 69.7±7.9 | 70.3±5.4 |
| Female | 5 (50 %) | 5 (50 %) | 2 (20 %) | 3 (30 %) |
| eGFR (ml/min/1.73 $m^2$) | 101±17 | 75±16 | 73±8 | 38±11 |
| Medical History | | | | |
| Arterial Hypertension | 0 | 1 (10 %) | 10 (100 %) | 10 (100 %) |
| Diabetes mellitus | 0 | 0 | 2 (20 %) | 6 (60 %) |
| Coronary Artery Disease | 0 | 0 | 7 (70 %) | 5 (50 %) |
| Signs and Symptoms | | | | |
| NYHA functional class>2 | 0 | 0 | 4 (40 %) | 7 (70 %) |
| Systolic BP (mmHg) | 115±4 | 130±14 | 120±17 | 144±26 |
| Diastolic BP (mmHg) | 75±7 | 76±10 | 73±12 | 71±12 |
| Extracellular Water/Total Body Water | | 0.382 [0.379-0.388] | 0.388 [0.379-0.392] | 0.391 [0.388-0.403] |
| Magnetic Resonance Imaging Results | | | | |
| Cardiac output (L) | 5.6±1.3 | 5.3±1.0 | 4.5±0.5 | 4.7±1.3 |
| Cardiac index ($L/m^{2)}$ | 3.0±0.5 | 2.8±0.2 | 2.1±0.2 | 2.4±0.7 |
| ASL-MRI renal cortex perfusion (ml/100 g/min)* | 278±59 | 274±65 | 171±31 | 146±50 |
| $T_1$ relaxation time (ms)* | 1,080±68 | 1,030±55 | 1,067±79 | 1,169±100 |

* ASL-MRI and $T_1$ relaxation time values represent averages of left and right kidney measurements;

with age (r=-0.60, p<0.01) and parameters of HF severity (NT-proBNP r=-0.59, p<0.01; NYHA classes r=-0.75, p<0.01). There was a significant correlation between volume adjusted global kidney perfusion measured by PC-MRI and renal cortex perfusion measured by ASL (r=0.76, p<0.01). The association of renal cortex perfusion values with HF and renal function status is displayed in Fig. 2.

### $T_1$ relaxation and renal function

$T_1$ relaxation time was similar between left and right kidneys for the overall population (1,081±88 ms vs. 1,085± 91 ms; p=0.29) and within the groups. Consequently, side-averaged $T_1$ relaxation time values were used for subsequent calculations. $T_1$ relaxation times correlated negatively with eGFR in the overall study population (r=-0.41, p= 0.02) (Fig. 3), but was not correlated to age (r=0.04, p= 0.81), markers of cardiovascular function (cardiac output r=-0.14, p=0.42; cardiac index r=-0.14, p=0.43; NT-proBNP r=0.31, p=0.08) or renal perfusion (Renal ASL cortex perfusion: r=-0.22, p=0.20; PC-MRI volume adjusted global kidney perfusion: r=-0.29, p=0.11). The association of $T_1$ relaxation time with HF and renal function status is displayed in Fig. 4. $T_1$ relaxation time was only prolonged in HF patients with renal dysfunction compared to HF patients with normal renal function (1,169±100 ms vs. 1,067±79 ms; p=0.047).

Factors showing univariate association with $T_1$ relaxation time via regression analysis are displayed in Table 2.

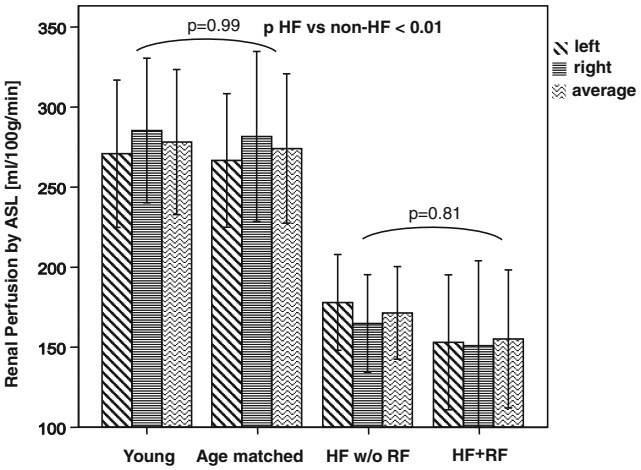


**Fig. 2** Bar chart displaying renal perfusion measured by arterial spin labelling according to HF and renal function groups. Whisker bars represent 95 % confidence intervals. Statistical analysis by ANOVA analysis with Tukey's honest significance post hoc test for multiple comparisons

## Discussion

In this study, we simultaneously evaluated parameters of cardiovascular function, renal tissue perfusion, and renal parenchymal structure to assess the pathophysiology underlying the occurrence of renal dysfunction in patients with stable chronic HF. The current study contains multiple key findings. First, our study suggests, that renal impairment in stable chronic HF patients is not related either to low cardiac output or reduced renal perfusion; parameters of cardiac function and renal perfusion were similar in HF patients with or without renal impairment. Second, in this observational study, renal $T_1$ relaxation

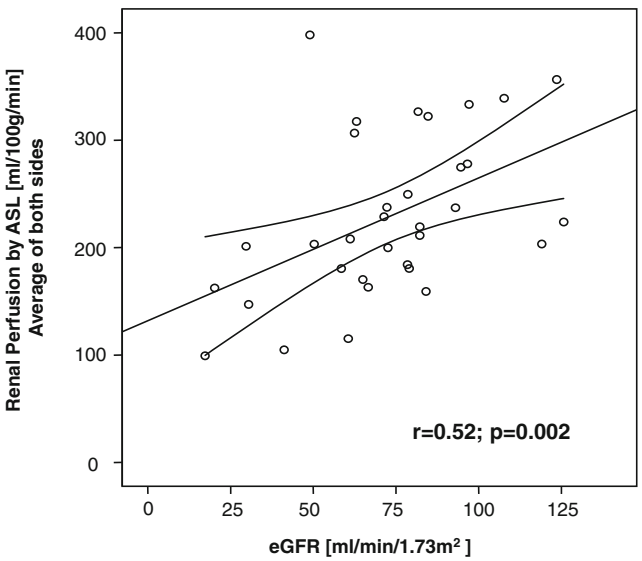


**Fig. 1** Scatter plot showing the Pearson correlation between the estimated glomerular filtration rate (eGFR) and renal perfusion measured by arterial spin labelling (ASL). The middle line depicts the correlation coefficient; outer lines depict its 95 % confidence interval

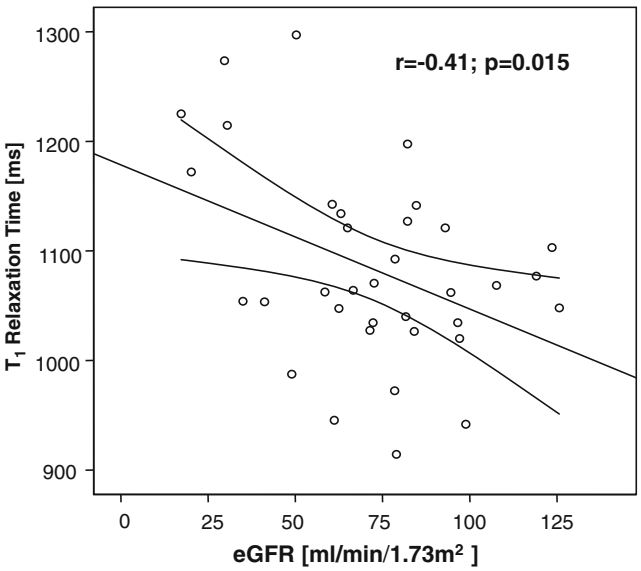


**Fig. 3** Scatter plot showing the Pearson correlation between the estimated glomerular filtration rate (eGFR) and renal microstructure measured by $T_1$ relaxation time. The middle line depicts the correlation coefficient; outer lines depict its 95 % confidence interval

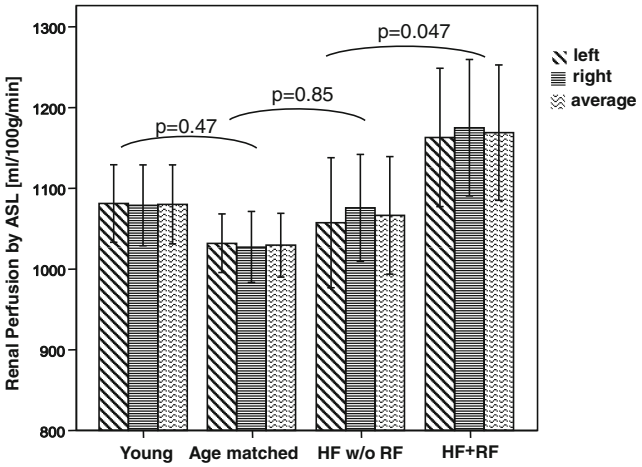


**Fig. 4** Bar chart displaying renal microstructure measured by $T_1$ relaxation time according to HF and renal function groups. Whisker bars represent 95 % confidence intervals. Statistical analysis by ANOVA analysis with Tukey's honest significance post hoc test for multiple comparisons

time was prolonged only in stable chronic HF patients with renal impairment. Finally, renal $T_1$ relaxation time appeared to be associated with classic cardiovascular risk factors.

The inability of cardiac dysfunction to explain the occurrence of renal dysfunction in HF patients observed in our study corroborates and extends previous findings. For example, in a study of pulmonary artery catheter-guided acute HF therapy, Nohria et al. found no correlation between baseline renal function and cardiac index. Importantly, improvements in cardiac function during HF therapy were not accompanied by concurrent improvements in renal function [29].

Another factor previously associated with the occurrence of renal dysfunction in HF is elevated renal venous pressure, which is thought to induce renal dysfunction by diminishing the pressure gradient across the glomerulus and subsequently reducing renal perfusion [11, 30]. However, the current study found no differences in parameters of renal venous stasis/congestion (renal vein flux, renal vein flow velocity, renal vein area, extracellular/total body water) in stable chronic HF patients with or without renal impairment. Similarly, two studies assessing central venous pressure in patients with acute HF syndromes failed to show an association between central venous pressure and simultaneously measured renal function [9, 31]. Therefore, renal venous congestion does not appear to be the primary determinant of renal function in stable chronic HF.

**Table 2** Factors showing univariate association with $T_1$ relaxation time

| Determinants of $T_1$ Relaxation Time in Univariate Linear Regression | Coefficient Beta | *p*-value |
|---|---|---|
| History of Diabetes | 113 (95 % CI 47-179) | 0.01 |
| History of CAD | 82 (95 % CI 18-147) | 0.01 |
| Dyslipidemia | 77 (95 % CI 16-138) | 0.01 |
| History of Hypertension | 59 (95 % CI 1-117) | 0.04 |
| Cardiac output (L) | -0.15 (95 % CI -38.7-16.3) | 0.41 |
| ASL Renal Perfusion (ml/100 g/min) | -0.22 (95 % CI -0.63-0.14) | 0.20 |
| Extracellular Body Water/Total Body Water | -0.48 (95 % CI -178-140) | 0.83 |

In a study of chronic HF patients, Smilde et al. found renal blood flow (RBF) measured by 131I-Hippuran clearance to be the strongest determinant of renal function [32]. In agreement with their observations, our study also found a significant, albeit weaker, correlation between renal perfusion and function. However, renal perfusion was similar in HF patients with or without renal impairment. Differences in study populations between the two reports are likely to explain the contrasting results. While the previous study recruited patients with relatively preserved renal function (mean GFR 74 ml/min/1.73 $m^2$) [32], the current report compared patients with and without renal impairment. Additionally, despite significant differences in renal perfusion, we found no difference in renal function between age-matched healthy volunteers and HF patients with preserved renal function. Our data suggest that a reduction in renal perfusion is not the main trigger of renal dysfunction in stable HF patients.

Importantly, our results suggest renal $T_1$ relaxation time to be only prolonged in HF patients with impaired renal function. In agreement with our results, a study evaluating ten hypertensive patients undergoing single kidney glomerular filtration rate (SKGFR) measurements for suspected renovascular disease found $T_1$ relaxation time to negatively correlate with SKGFR [23]. Similarly, a study assessing $T_1$ relaxation in 12 native and 15 transplanted kidneys [33] found $T_1$ relaxation time to be prolonged in patients with impaired renal function (eGFR< 60 ml/min/1.73 $m^2$) independent of transplantation status. Reassuringly, $T_1$ relaxation times obtained for healthy volunteers (1,057±94 ms in [33] vs. young: 1,080 ms±68 vs. age-matched: 1,030 ms±55) and patients with renal impairment (1,204±113 ms in [33] vs. 1,169 ms±100 in this study) were very similar to our study. Indeed, a historic study using 0.15 Tesla MRI found prolonged $T_1$ relaxation times in patients with chronic kidney disease [34]. Importantly, this older study also assessed three patients with acute renal failure and biopsy-proven acute tubular necrosis in which $T_1$ relaxation times were not prolonged. In addition, $T_1$ relaxation time has been associated with chronic parenchymal remodelling in animal models of post infarct myocardial scarring [18], knee cartilage in osteoarthritis [19], and biopsy-proven liver cirrhosis [20–22].

With this background, our data might indicate that the $T_1$ relaxation time alterations observed in HF patients with renal dysfunction reflect chronic reno-parenchymal damage such as fibrosis, tubulointerstitial disease, and vascular pathology. These chronic changes are likely induced by classic cardiovascular risk factors and appear to be the primary cause of renal dysfunction in HF.

There are several limitations to this study. First and foremost, no renal biopsies were performed during this study, prohibiting us from describing the association of prolonged $T_1$ relaxation times with histopathological findings. Nevertheless, based on the results obtained for other organs [18–22] and the lack of $T_1$ alterations during acute kidney injury [34], prolonged relaxation times appear to correspond to more severe tissue fibrosis and scaring. Further studies are needed to verify the association of renal $T_1$ relaxation with parenchymal damage. Secondly, we only enrolled patients with stable HF and cannot comment on the pathophysiology of acute renal impairment during episodes of acute HF. However, one patient experienced an episode of acute HF with worsening renal function during the study period and agreed to undergo an additional MRI examination. During acute HF, renal perfusion was reduced below the steady state perfusion of the individual patient, while $T_1$ relaxation time remained unchanged from steady state values.

In conclusion, based on our small sample, renal dysfunction in HF does not appear to be primarily mediated by decreased renal perfusion. Instead, a prolonged $T_1$ relaxation time reflecting chronic reno-parenchymal damage appears to be the primary culprit in the pathophysiology of chronic cardiorenal syndrome. The association of renal $T_1$ relaxation with parenchymal damage should be validated further in future studies.

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## Appendix

**Table 3** Baseline Characteristics extended

| Variable | Young Volunteers | Age-Matched Volunteers | HF with preserved renal function | HF with impaired renal function |
|---|---|---|---|---|
| Body Mass Index (kg/m$^2$) | 23.4±2.7 | 25.9±2.6 | 31.6±6.1 | 31.7±4.7 |
| Signs and Symptoms | | | | |
| Rales | 0 | 0 | 2 (20 %) | 4 (40 %) |
| Peripheral Edema | 0 | 0 | 3 (30 %) | 6 (60 %) |
| Hepato-Jugular Reflux | 0 | 0 | 2 (20 %) | 3 (30 %) |
| NT-proBNP (pg/ml) | 52±59 | 55±39 | 1,083±1,230 | 1,140±600 |
| Troponin T (ng/L) | n.d. | n.d. | 12.7±4.5 | 33±35 |
| Medication | | | | |
| RAAS Blockade | 0 | 0 | 10 (100 %) | 9 (90 %) |
| Percentage of Maximal Daily Dose | | | 88 % ±21 | 75 % ±35 |
| Betablocker | 0 | 0 | 10 (100 %) | 6 (60 %) |
| Percentage of Maximal Daily Dose | | | 50 % ±31 | 40 % ±38 |
| Diuretic | 0 | 0 | 8 (80 %) | 10 (100 %) |
| Daily Dose Furosemide Equivalent (mg) | | | 42±35 | 106±117 |
| Magnetic Resonance Imaging Results | | | | |
| Stroke volume (ml) | 89±10 | 87±15 | 80±7 | 86±30 |
| Stroke volume index (ml/m$^{2)}$ | 50±4 | 47±4 | 38±5 | 44±14 |
| Left ventricular mass (g) | 70±20 | 83±31 | 144±26 | 109±35 |
| Left ventricular mass index (g/m$^{2)}$ | 39±7 | 44±12 | 68±12 | 56±18 |
| Renal Artery Mean Flux (ml/s)* | 6.8±1.9 | 4.9±1.2 | 4.5±1.7 | 2.8±0.9 |
| Renal Vein Mean Flux (ml/s)* | 6.7±2.0 | 5.9±1.0 | 4.1±1.8 | 5.1±1.7 |
| Renal Vein Mean Velocity (cm/s)* | 8.6±1.2 | 8.1±1.1 | 7.1±1.3 | 7.7±1.7 |
| PC-MRI volume adjusted global kidney perfusion (ml/100 g/min)* | 278±85 | 334±114 | 208±80 | 147±49 |

Renal Vein Mean Flux, Renal Vein Mean Velocity, Renal Artery Mean Flux, PC-MRI values represent averages between left and right kidney measurements

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