



# Cardiorenal syndrome and the association with fitness: Data from a telerehabilitation randomized clinical trial

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## Abstract

**Aims** To investigate the associations of cardiorespiratory fitness with cardiac, vascular, renal and cardiorenal characteristics in chronic heart failure in a telerehabilitation randomized clinical trial. Secondly, to evaluate the associations of cardiorenal syndrome with the effects of exercise.

**Methods and results** Sixty-nine heart failure patients attended baseline examination, and 61 patients were randomly assigned 1:1 to 3-month telerehabilitation or control. Data were collected at baseline and 3-month post-intervention, including echocardiography and vascular ultrasound, laboratory tests, exercise test with peak oxygen consumption ( $VO_{2peak}$ ) measurement and 6-min walk test (6MWT). Baseline  $VO_{2peak}$  and 6MWT distance was  $0.85 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  lower and 20 m shorter per  $10 \text{ mL/min}/1.73 \text{ m}^2$  lower estimated glomerular filtration rate (both  $P < 0.001$ ). Heart failure patients with cardiorenal syndrome had  $3.5 (1.1) \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  lower  $VO_{2peak}$  and diastolic dysfunction grade 2–3, and elevated filling pressure was  $>50\%$  more common compared with those without (all  $P < 0.05$ ). At the 3-month post-intervention follow-up, only the non-CRS patients in the intervention group increased  $VO_{2peak}$  ( $0.73 (0.51) \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ ), whereas  $VO_{2peak}$  in the CRS subpopulation of controls decreased ( $-1.34 (0.43) \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ ). Cardiorenal syndrome was associated with a decrease in  $VO_{2peak}$  in CRS patients compared with non-CRS patients,  $-0.91 (0.31)$  vs.  $0.39 (0.35) \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  respectively,  $P = 0.013$ .

**Conclusions** Cardiorenal syndrome was negatively associated with  $VO_{2peak}$  and 6MWT distance in chronic HF, and the associations were stronger than for heart failure phenotypes and other characteristics. The effect of exercise was negatively associated with cardiorenal syndrome. Exercise seems to be as important in heart failure patients with cardiorenal syndrome, and future studies should include CRS patients to reveal the most beneficial type of exercise.

**Keywords** 6-min walk test; Chronic heart failure; Chronic kidney disease; Echocardiography; Exercise; Intervention;  $VO_{2max}$

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## Introduction

In the chronic cardiorenal syndrome (CRS), chronic heart failure (CHF) coexists with reduced kidney function.<sup>1</sup> Patients with chronic kidney disease (CKD) often develop salt and water retention with increased left ventricular (LV) filling

pressures,<sup>2</sup> which may contribute to an increased risk of cardiovascular diseases. This may also be present in CKD patients without CHF.

Reduced cardiorespiratory fitness is common in both CHF and CKD.<sup>3</sup> Three large randomized controlled trials (RCTs) have investigated the effect of exercise intervention in CHF,

and all found a modest exercise effect by increasing maximal oxygen consumption  $0.6\text{--}1.6\text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ .<sup>4-6</sup> Only one of these investigations performed baseline comparison of cardiorespiratory fitness with CKD classes and found a gradient towards lower  $\text{VO}_{2\text{peak}}$  down to CKD Stage 4 based on creatinine values within the last year of inclusion.<sup>7</sup> The evidence for exercise benefits in CKD patients without CHF is also limited, but a recent review found that physical exercise improved cardiorespiratory fitness and strength in CKD patients.<sup>8</sup> To our knowledge, there is no study investigating the benefits of exercise in CRS, and it is not known if CHF patients can improve cardiorespiratory fitness by attending a telemedical physical exercise programmes.

The current study aimed to investigate the associations of cardiorespiratory fitness with cardiac, renal and vascular characteristics in CHF patients at baseline in a telerehabilitation RCT. Secondly, we aimed to evaluate whether CRS and CKD were associated with a more beneficial effect of exercise training. We hypothesized that CRS and its components were negatively associated with peak oxygen uptake ( $\text{VO}_{2\text{peak}}$ ), walking distance covered during 6-min walk test (6MWT) and LV diastolic function at baseline and that the effect of exercise on  $\text{VO}_{2\text{peak}}$  and 6MWT distance at 3-month post-intervention follow-up was modulated by CRS.

## Methods

### Study design

Patients with stable CHF were recruited to baseline investigations and a 'Living with heart failure' course, before randomization 1:1 to a 3-month telerehabilitation intervention or control group. Randomization was stratified by age ( $</\geq 60$  years old) and LV ejection fraction (EF) ( $</\geq 40\%$ ). Data from baseline and 3-month post-intervention follow-up with data collection from June 2017 to June 2020 are presented.

### Population

Patients  $\geq 18$  years with CHF according to the ESC guidelines<sup>9</sup> with New York Heart Failure Association (NYHA) functional Class II or III from two Norwegian outpatient clinics (St Olavs University Hospital and Levanger Hospital) were eligible for inclusion. Patients were stable on optimal medical treatment for at least 4 weeks prior to inclusion and well compensated at inclusion. Importantly, patients with concurrent CKD were not excluded. Exclusion criteria were participation in an HF rehabilitation programme within the last 6 months, reversible causes of HF like uncontrolled hypertension, not revascularized coronary ischaemia, untreated arrhythmias,

severe valvular disease, severe pulmonary disease and home-based exercise not being considered safe.

### Ethics

All patients provided written informed consents. The study was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (REK 2016/1597) and the institutional board at St Olavs University hospital, Trondheim, Norway. ClinicalTrials.gov Identifier: NCT03183323. All parts of the study were performed according to the Declaration of Helsinki (Br Med J 1964; ii: 177).

### Intervention

All participants underwent a 2-day 'Living with HF' course focusing on knowledge of HF, optimal therapy and lifestyle interventions including recommendations for exercise and safe performance of exercise. Instructions for use of the telecommunication equipment were provided based on the randomization result.

The telerehabilitation intervention consisted of online group exercise sessions guided by a physical therapist specialized in cardiopulmonary physiotherapy and experienced in cardiac rehabilitation. Online sessions of 60 min with repeated bouts of high intensity were given twice a week in groups of 2–10. Participants were encouraged to carry out at least one extra exercise session per week. In case of absence from training due to disease or injury, the exercise intervention period was prolonged accordingly. After the intervention period, the intervention group was given access to online instruction videos to continue their exercise at home. Participants randomized to the control group were not contacted beyond the planned visits for data collection.

### Data collection

Examinations at baseline and 3-month post-intervention follow-up were performed according to standard operating procedures. Medical history, current medication, exercise habits, demographics and socio-economic status were collected at baseline, and a physical examination including measurements of physical capacity and cardiorespiratory fitness was also performed. Inclusion, classification and evaluation of patients were done jointly by experienced cardiologists and nephrologists. HF severity was graded according to the NYHA class. Electronic medical records were used to verify medication and medical history, including CHF aetiology (categorized as ischaemic, hypertensive, dilated or other), history of prior myocardial infarction and/or revascularization and type of CRS if CKD was present according to the Kidney Disease Improving Global Outcomes guidelines.<sup>10</sup>

The performance of 6MWT was supervised by trained study personnel, with participants walking in the same 30-m corridor at both time points, with marks on the wall for every 5 m. Peak oxygen uptake was measured by direct measures of gas exchange using a direct ergospirometry system (Vyntus CPX, Erich Jaeger GmbH, Hoechberg, Germany). After an initial warm-up on treadmill, the  $VO_{2peak}$  test was performed using a constant, individualized walking speed with incremental inclination every other minute until exhaustion. Testing was performed by experienced researchers blinded to group allocation and surveilled by experienced physicians. Peak oxygen consumption ( $VO_{2peak}$ ) was defined as the average of the highest 30-s oxygen uptake value achieved during testing, regardless of if the criteria for maximal oxygen uptake was fulfilled. The short physical performance battery (SPPB) was performed, and the score (0–4) for each of the three physical tests (balance, walking speed and sit-to-stand time) was summarized to a total score of maximum 12 points.

## Cardiac and vascular ultrasound measurements

All examinations were performed by two experienced operators according to standard operating procedures at baseline and analysed by a cardiologist experienced in echocardiography in EchoPAC SWO (Version 203, GE Ultrasound, Horten, Norway). All personnel were blinded to group assignment and baseline characteristics.

Echocardiography included standard views by grey scale, pulsed, and continuous wave Doppler, and colour and tissue Doppler modalities. LV ejection fraction (LV EF) was calculated from traces of the endocardial border in two-chamber and four-chamber views using the summation of disk method.<sup>11</sup> Peak mitral annular systolic ( $s'$ ) and early diastolic ( $e'$ ) velocities were measured septally and laterally in pulsed-wave tissue Doppler recordings. Left atrial (LA) end-systolic volume (ESV) was calculated from traces of the endocardial border using the summation of disk method in two-chamber and four-chamber views and indexed (LAESVi) for body surface area (BSA). Mitral early (E) and late (atrial) (A) diastolic blood flow velocities were measured in pulsed-wave Doppler recordings. Ratios (E/A and  $E/e'$ ) were calculated. The averaged septal and lateral  $e'$  was used for calculation of  $E/e'$ . LA pressure (LAP) and diastolic dysfunction (DD) grade were estimated according to the latest guidelines,<sup>12,13</sup> based on E, A, E/A,  $E/e'$ , tricuspid regurgitation velocity and LAESVi. The reproducibility of echocardiographic measurements was tested in another study from the same group.<sup>14</sup> Shortly, for the two echocardiographers of this study, the inter-observer coefficients of variation ranged 4–8% for analyses of LV EF, LAESVi, E,  $e'$  and tricuspid regurgitant jet velocity.

Greyscale and pulsed-wave Doppler ultrasound of the carotid and proximal femoral artery were recorded, and the superficial distance from sternal notch to the groin was measured. A fixed measure of 10 cm was used as an estimate of distance from the sternal notch to the carotid artery. Pulse wave velocity was calculated as the time difference between the early systolic steep rise of blood flow velocity recorded from the femoral and the carotid artery, relative to a fixed point in the corresponding ECG, and divided by the difference in distance from the sternal notch to the arteries.

Greyscale and pulsed-wave Doppler ultrasound were recorded at a fixed, image-guided location of the brachial artery above the ulnar and radial branches before and after arterial occlusion using a distal 5 cm paediatric cuff inflated to 250 mmHg for 5 min to enable calculations of flow-mediated dilatation and shear rate. Dimension was measured at the maximal diameter. Blood flow was measured at a <60 degrees angle of insonation, with traces of the Doppler spectrum and calculation of the mean velocity.<sup>15</sup> Post-occlusion recordings were performed 60 s after deflation of the cuff. Flow-mediated dilatation was calculated as peak dilatation after cuff deflation in percentage relative to peak diameter before cuff inflation. The brachial artery systolic shear rate was calculated by mean blood velocity divided by internal diameter of the brachial artery.

## Blood analyses

Fresh venous samples were analysed at St Olavs University Hospital, Trondheim. Creatinine was analysed using enzymatic method (Siemens Advia Chemistry XPT, Siemens Healthcare GmbH, Erlangen, Germany). Glomerular filtration rate (GFR) was estimated using  $CKD-EPI_{creatinine}$  formula.<sup>16</sup> Haemoglobin was analysed by oxidizing iron into a stable pigment for photometric estimation by an automated haematology analyser (Sysmex XN, Germany).

## Cardiorenal severity

A cardiorenal severity score was customized using CHF and CKD severity categories. CHF severity in patients with reduced EF (HF<sub>r</sub>EF; EF ≤ 40%) was scored 1–3 according to tertiles of EF (33.7–40%, 26.0–33.6% and <26.0%, respectively). CHF severity in patients with mildly reduced (HF<sub>mr</sub>EF; EF 41–49%) or preserved EF (HF<sub>p</sub>EF; EF ≥ 50%) was scored 1–3 according to tertiles of  $s'$  (>6.0, 5.3–6.0 and <5.3 cm/s, respectively). Renal severity was scored based on CKD stage,<sup>10</sup> with scores 0 (no CKD), 1 (Stage 1 or 2 CKD), 2 (Stage 3 CKD) or 3 (Stage 4 or 5 CKD). The cardiorenal score for each patient was calculated as the sum of the CHF and renal severity scores (1–6).

## Statistical analyses

Normally and not normally distributed continuous variables are presented as mean (SD) and median (IQR), respectively. Categorical data are presented as numbers (percentages). Baseline differences between CRS and non-CRS patients were tested with independent samples *t*-test, analysis of variance or Mann–Whitney *U* test as appropriate. Proportions were compared by  $\chi^2$  test. For the baseline analysis of 6MWT distance and  $VO_{2\text{peak}}$  vs. cardiac severity, pulse wave velocity, flow-mediated dilatation, shear rate, eGFR, tricuspid regurgitation peak velocity and cardiorenal severity, we used simple and multiple linear regressions, reported as  $\beta$ -coefficient (standard error). Limited by the number of participants, we did not simultaneously adjust for more than three variables in multiple linear regression models.  $VO_{2\text{peak}}$  and pulse wave velocity showed non-normal distribution, but the results from the log-transformed and non-transformed analyses were nearly identical, and we therefore presented the non-transformed results, unless otherwise stated. Exercise effect was measured as change in  $VO_{2\text{peak}}$  from baseline to 3-month post-intervention follow-up and was assessed by analysis of covariance (ANCOVA) with groups per randomization as a fixed factor and cardiorenal syndrome as a random factor and baseline  $VO_{2\text{peak}}$ , age and sex as covariates. Interaction between CRS and randomization group was included in the model.

## Results

### Population

In total, 70 patients were enrolled. *Figure 1* shows the flow of the study participants. After exclusion of one patient not fulfilling the HF criteria, 69 HF participants [13 (19%) females] attended the baseline examination. Further, eight patients were excluded, and 61 were randomized 1:1 to intervention ( $n = 31$ ) or control groups ( $n = 30$ ). Of these, 53 patients attended the 3-month post-intervention follow-up visit.

*Table 1* summarizes the most important baseline differences between CHF patients with or without CRS. Cardiac, renal and vascular characteristics for those attending the baseline examination and those being randomized are presented in Supporting Information, *Table S1*. The disease severity was quite similar in the different groups. Shortly, mean age was 68 years, and most patients were in NYHA Class II. HFrEF was the most common HF type, and the most common aetiology was ischaemia. Atrial fibrillation was common (43–52%), and the majority was on optimal medical therapy, with renin–angiotensin–aldosterone system inhibitors (RAASi) and beta-blockers (BB) used in

$\geq 83\%$  of patients (Supporting Information, *Table 2*). Patients that were included in baseline analyses only ( $n = 8$ ) more often presented with NYHA Class III (33%) and ischaemic aetiology (80%) as well as a lower prevalence of CKD (37%).

CRS patients were  $>50\%$  more likely to have diastolic dysfunction 2 or 3 and elevated left atrial pressure compared with non-CRS patients. Mitral annular systolic and early diastolic velocities were numerically lower in CRS patients, and the peak tricuspid regurgitant jet velocity was higher. Self-reported exercise did not differ with regard to frequency, intensity and duration between CRS and non-CRS (Supporting Information, *Table 3*).

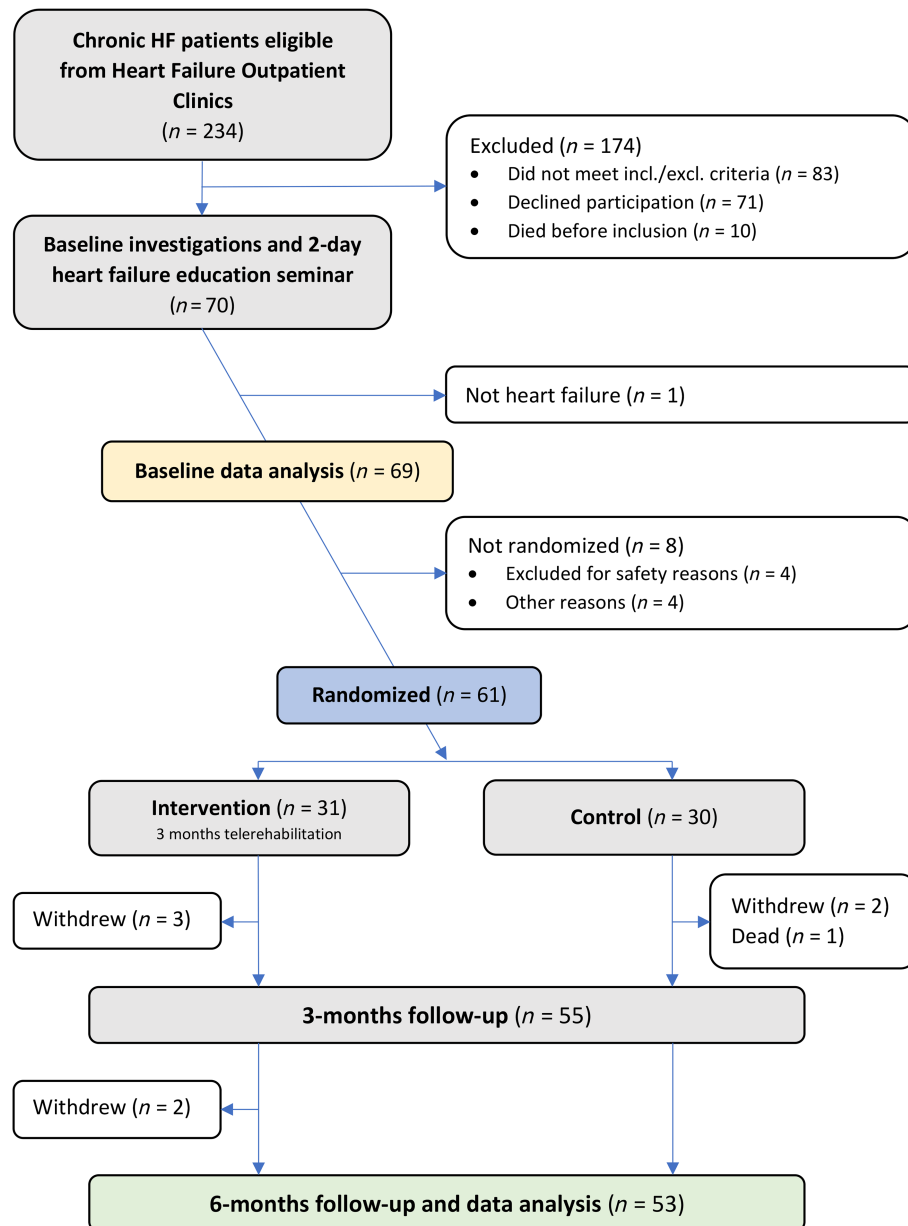
### Cardiac, vascular and renal characteristics associated with physical capacity at baseline

The main cardiac, vascular, renal and cardiorenal associations with  $VO_{2\text{peak}}$  and 6MWT distance are shown in *Table 2*. CHF severity was negatively, though not significantly, associated with  $VO_{2\text{peak}}$ , with  $-1.3$  and  $-1.4 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  per unit higher score of CHF severity in unadjusted and adjusted analyses ( $P \geq 0.06$ ). The log-transformed analyses showed similar results (data not shown). Similarly, HF severity was numerically, but not significantly, associated with 6MWT distance, with  $-23$  and  $-13 \text{ m}$  per unit higher score of CHF severity in unadjusted and adjusted analyses ( $P \geq 0.20$ ).

The differences in  $VO_{2\text{peak}}$  between types of CHF are shown in *Figure 2*. In post hoc (log-transformed) analyses, HFrEF patients had lowest  $VO_{2\text{peak}}$  (difference  $P = 0.01$  vs. HFpEF,  $P = 0.03$  vs. HFmrEF). There was a significant difference in  $VO_{2\text{peak}}$  between patients with different grades of diastolic dysfunction ( $P = 0.047$ , log-transformed), where diastolic dysfunction grade 2 patients had lower  $VO_{2\text{peak}}$  than grade 1,  $P = 0.02$  (*Figure 2B*). At baseline, patients with elevated filling pressure had significantly lower  $VO_{2\text{peak}}$  (*Figure 2C*; difference  $-3.2(1.2) \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ,  $P = 0.01$ ) and shorter 6MWT distance ( $-74$  (32) m,  $P = 0.03$ ). The significant associations of  $VO_{2\text{peak}}$  and 6MWT distance with peak tricuspid regurgitant jet velocity are shown in *Table 2* and Supporting Information, *Figure S1*. In unadjusted and adjusted analyses,  $VO_{2\text{peak}}$  was  $3.7$  and  $3.8 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  lower, and 6MWT distance was  $106$  and  $79 \text{ m}$  shorter per  $1 \text{ m/s}$  higher peak tricuspid regurgitant jet velocity.

None of the vascular measures, that is, pulse wave velocity, flow-mediated dilatation or shear rate, were significantly associated with  $VO_{2\text{peak}}$  or 6MWT distance (all  $P \geq 0.06$ ) (*Table 2*).

$VO_{2\text{peak}}$  was significantly associated with renal characteristics (*Table 2* and *Figure 3*).  $VO_{2\text{peak}}$  was  $0.85 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  lower per  $10 \text{ mL/min}/1.73\text{m}^2$  lower eGFR at baseline

**Figure 1** CONSORT flow diagram of the study population.

( $P < 0.001$ ). Adjustment for sex and age did not alter the results ( $P < 0.001$ ); neither did adjustments for diabetes mellitus and/or body mass index (data not shown). eGFR was significantly associated with 6MWT distance, with 20 m shorter distance per 10 mL/min/1.73m<sup>2</sup> lower eGFR ( $P < 0.001$ ). Adjustment for sex and age did not alter the results ( $P < 0.001$ ).

Further adjustments for haemoglobin level and heart failure (HF) medication did not alter the associations of cardiac, vascular and renal characteristics with  $VO_{2peak}$  and 6MWT at baseline (data not shown).

### CRS and the associations with cardiac characteristics, physical capacity and training effect

Cardiorenal syndrome patients had (by definition) a higher CRS severity score with mean (SD) 4.1 (1.1) compared with 2.0 (0.8) points in those without CRS,  $P < 0.001$ . There were otherwise no significant differences in clinical cardiac characteristics and no difference between patients with or without CRS with respect to CHF etiology, NYHA class, prevalence of previous myocardial infarction and/or revascularizations,

**Table 1** Basic characteristics in patients with and without cardiorenal syndrome

	Without CRS (n = 29)	With CRS (n = 40)	P-value
Age at inclusion, years, mean (SD)	65 (13)	71 (9)	<0.05
Females	7 (24%)	6 (15%)	0.34
Heart failure characteristics			
NYHA II	25 (89%)	29 (74%)	0.13
NYHA III	3 (11%)	10 (26%)	
HF reduced EF	19 (66%)	28 (70%)	0.39
HF mildly reduced EF	9 (31%)	8 (20%)	
HF preserved EF	1 (3%)	4 (10%)	
Renal characteristics			
eGFR, mL/min/1.73 m <sup>2</sup>	78 (12)	44 (22)	<0.001
ACR, mg/mmol, median (IQR)	1 (0.7–1.5)	2.6 (1.2–7.7)	<0.001
Haemoglobin, g/dL, mean (IQR)	14.2 (13.1–15)	12.9 (11.3–14.5)	<0.05
SBP, mmHg, mean (SD)	122 (18)	118 (21)	0.40
DBP, mmHg, mean (SD)	76 (14)	70 (11)	<0.05
Diabetes mellitus I or II	3 (11%)	15 (39%)	<0.05
Diabetic nephropathy	0	9 (23%)	<0.01
Anthropometry			
BMI, kg/m <sup>2</sup> , mean (SD)	28.1 (4.9)	28.4 (4.9)	0.78
BSA, m <sup>2</sup> , mean (SD)	2.0 (0.2)	2.0 (0.2)	0.81
Waist-to-hip ratio, cm, mean (SD)	1.01 (0.1)	1.05 (0.1)	<0.05
Physical capacity tests			
6MWT, distance, m, mean (SD)	523 (91)	427 (118)	<0.01
SPPB, total score, median (IQR)	11 (10–12)	10 (8–12)	0.10
CPET, VO <sub>2peak</sub> , mL*min <sup>-1</sup> *kg <sup>-1</sup> , mean (SD)	19.5 (4.7)	16.0 (3.8)	<0.01
Echocardiographic features			
LV EDV, mL, mean (SD)	167 (67)	182 (81)	0.32
LV EF, %, mean (SD)	35 (10)	34 (12)	0.625
Mean septal/lateral s', cm/s, mean (SD)	5.2 (1.6)	4.6 (1.4)	0.08
LAESVi, mL/m <sup>2</sup> , mean (SD)	46 (12)	60 (25)	<0.05
LAESV/LVEDV ratio, median (IQR)	0.6 (0.4–0.7)	0.6 (0.4–0.9)	0.53
Mean septal/lateral e', cm/s, mean (SD)	6.0 (2.7)	5.7 (2.5)	0.28
E/e' ratio, median (IQR)	11 (9–13)	15 (10–18)	<0.05
TR V <sub>max</sub> , m/s, mean (SD)	2.6 (0.4)	2.9 (0.5)	0.06
Elevated LAP	16 (55%)	35 (87%)	<0.01
DD Grade 1	12 (41%)	4 (10%)	<0.05
DD Grade 2	14 (48%)	30 (75%)	
DD Grade 3	3 (10%)	6 (15%)	

6MWT, 6-min walk test; ACR, albumin-to-creatinine ratio; BMI, body mass index; BSA, body surface area; cm, centimetres; cm/s, centimetres per second; CPET, cardiopulmonary exercise test; DBP, diastolic blood pressure; DD, diastolic dysfunction; e', basal left ventricle early diastolic velocity by tissue Doppler; EF, ejection fraction; EF, ejection fraction; g/dL, grams per decilitre; HF, heart failure; IQR, interquartile range; kg, kilograms; L, litre; SBP, systolic blood pressure; LAESVi, indexed end systolic left atrial volume; LAP, left atrial pressure; LVEDV, left ventricle end diastolic volume; m/s, metres per second; m<sup>2</sup>, square metres; mg, milligrams; mL, millilitres; s', basal left ventricle systolic velocity by tissue Doppler; mmHg, millimetres of mercury; mmol, millimole; NYHA, New York Heart Association (functional class); SD, standard deviation; SPPB, short physical performance battery.

Data are presented as number and percentage, n (%), if not stated elsewhere.

arrhythmias, hypertension, hyperlipidaemia and smoking status, nor in the prevalence of cerebrovascular disease, peripheral artery disease, chronic obstructive pulmonary disease or cancer (data not shown, all  $P \geq 0.35$ ).

Patients with CRS had significantly lower VO<sub>2peak</sub> [difference 3.5 (1.1) mL\*min<sup>-1</sup>\*kg<sup>-1</sup>,  $P = 0.002$ ] and shorter 6MWT distance [difference 96 (27) m,  $P = 0.001$ ] at baseline compared with non-CRS patients (Table 1). The cardiorenal severity score was significantly associated with VO<sub>2peak</sub> and 6MWT distance (Table 2 and Figure 3). Per unit higher cardiorenal severity score (1–6), VO<sub>2peak</sub> was 1.5 mL\*min<sup>-1</sup>\*kg<sup>-1</sup> lower ( $P < 0.001$ ) and 6MWT distance approximately 35 m shorter ( $P < 0.001$ ) in unadjusted and adjusted analyses. We did not find significant differences in short physical performance battery results between CRS groups ( $P = 0.10$ ).

The change in VO<sub>2peak</sub> from baseline to 3-month post-intervention follow-up in CRS patients was  $-1.379$  (0.432) mL\*min<sup>-1</sup>\*kg<sup>-1</sup> in the control group and  $-0.434$  (0.407) mL\*min<sup>-1</sup>\*kg<sup>-1</sup> in the intervention group. The corresponding changes in VO<sub>2peak</sub> in non-CRS patients were 0.055 (0.497) mL\*min<sup>-1</sup>\*kg<sup>-1</sup> and 0.729 (0.512) mL\*min<sup>-1</sup>\*kg<sup>-1</sup> in the control and intervention group, respectively. Overall, the change in VO<sub>2peak</sub> was  $-0.907$  (0.305) mL\*min<sup>-1</sup>\*kg<sup>-1</sup> in the CRS patients compared with 0.392 (0.354) mL\*min<sup>-1</sup>\*kg<sup>-1</sup> in the non-CRS patients ( $P = 0.013$ ) after adjustment for sex, age, and baseline VO<sub>2peak</sub>.

Further adjustments for haemoglobin level and HF medication did not alter the associations of cardiorenal characteristics with VO<sub>2peak</sub> and 6MWT at baseline or change until 3-month post-intervention follow-up (data not shown).

**Table 2** Regression analyses of  $VO_{2peak}$  and 6MWT distance versus cardiac, vascular, renal, and cardiorenal characteristics at baseline

	$VO_{2peak}$ ( $mL \cdot min^{-1} \cdot kg^{-1}$ )		6MWT distance (m)	
	Simple $\beta$ (SE), P-value	Adjusted $\beta$ (SE), P-value	Simple $\beta$ (SE), P-value	Adjusted $\beta$ (SE), P-value
Chronic heart failure severity (per unit)	-1.4 (0.73), P = 0.06	-1.3 (0.70), P = 0.08	-23 (18), P = 0.20	-16 (17), P = 0.34
Tricuspid regurgitation peak velocity (per m/s)	-3.7 (1.7), P = 0.03	-3.8 (1.7), P = 0.03	-106 (41), P = 0.02	-79 (40), P = 0.05
Pulse wave velocity (per cm/s)	-0.22 (0.16), P = 0.17	-0.14 (0.17), P = 0.41	-7.7 (4.1), P = 0.07	-5.3 (4.2), P = 0.22
Flow-mediated dilatation (per %)	-0.072 (0.046), P = 0.13	-0.087 (0.046), P = 0.06	-1.8 (1.2), P = 0.14	-1.6 (1.2), P = 0.19
Share rate (per 1/s)	0.019 (0.016), P = 0.25	0.022 (0.017), P = 0.18	0.19 (0.42), P = 0.65	0.59 (0.41), P = 0.15
eGFR (per mL/min/1.73 m <sup>2</sup> )	0.085 (0.020), P < 0.001	0.082 (0.020), P < 0.001	2.0 (0.51), P < 0.001	2.2 (0.48), P < 0.001
Cardiorenal syndrome severity (per unit)	-1.53 (0.35), P < 0.001	-1.52 (0.36), P < 0.001	-34 (9), P < 0.001	-35 (9), P < 0.001

6MWT, 6-min walk test; eGFR, estimated glomerular filtration rate;  $VO_{2peak}$ , peak oxygen consumption.

Data are presented as  $\beta$  coefficients (standard error (SE)) and P-value for simple and multiple (adjusted for age and sex) regression analyses.

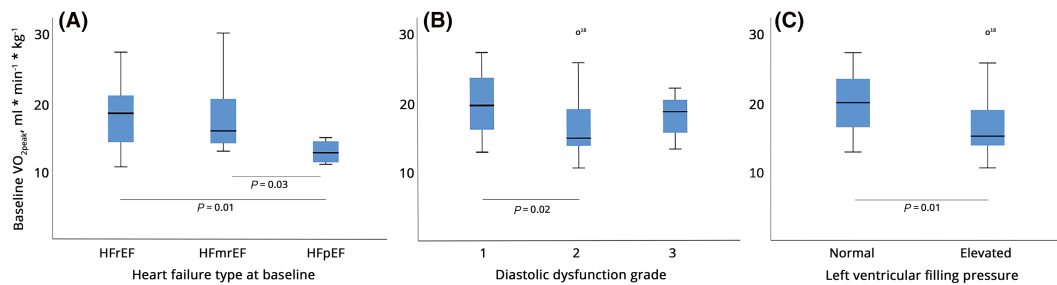
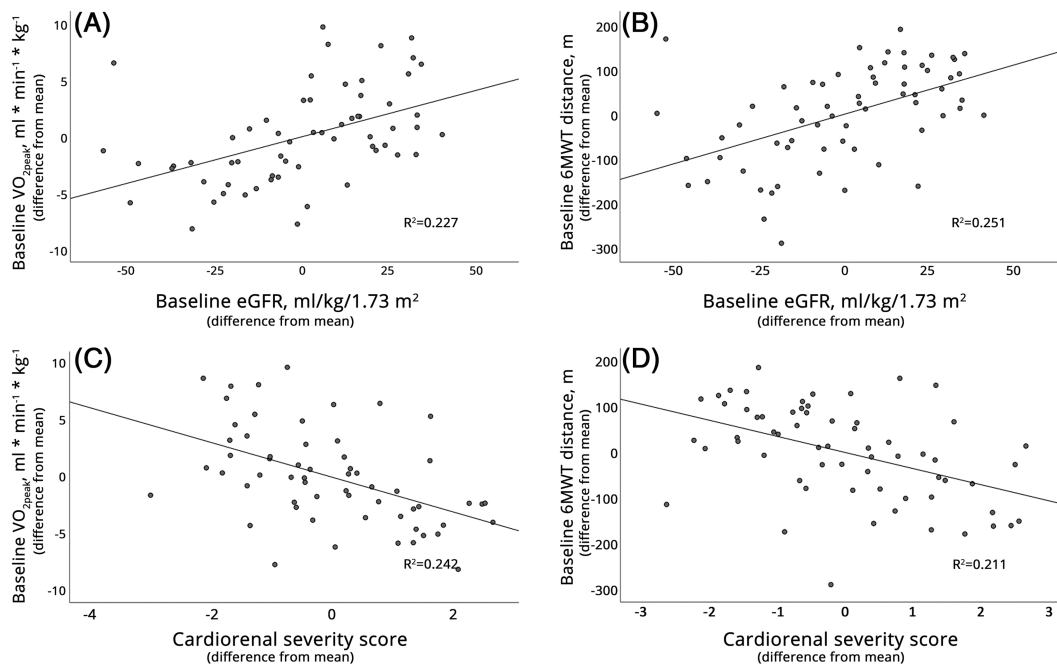
## Discussion

In this RCT evaluating telerehabilitation in CHF patients, patients with CRS had lower cardiorespiratory fitness, more severe diastolic dysfunction and higher prevalence of elevated left atrial pressure at baseline. Furthermore, CRS status was associated with change in cardiorespiratory fitness. Only non-CRS patients in the intervention group increased their cardiorespiratory fitness, whereas CRS patients in the control group decreased cardiorespiratory fitness at 3-month post-intervention follow-up.

Reduced cardiorespiratory fitness in chronic kidney disease is well known,<sup>3,17,18</sup> and various mechanisms have been suggested. Volume overload and systemic venous congestion is a frequent problem in both CHF and CKD.<sup>19–21</sup> In CRS, this problem is amplified by the kidneys' limited ability to excrete sodium and by the heart's limited ability to cope with increased levels of extracellular fluid.<sup>22</sup> Neurohormonal activation and endothelial dysfunction caused by CKD and other non-cardiac diseases may contribute to the left ventricular stiffening typically found in HFpEF by cross-bridging fibrosis and less compliant isoforms of the giant spring protein titan within cardiomyocytes.<sup>23,24</sup> Our findings of elevated pulmonary artery pressure (shown by the higher tricuspid regurgitant velocities) in CRS patients support that diastolic dysfunction with higher volume states and a higher proportion of elevated left atrial pressure may be another important mechanism in CRS. Some authors suggest CKD-associated HFpEF to be a separate subgroup.<sup>24</sup>

CKD patients typically have a high number of risk factors that could influence cardiorespiratory fitness. Diabetes mellitus, a major cause of CKD, is previously shown to be independently associated with reduced LV function.<sup>25</sup> Furthermore, various metabolic changes, including anaemia, reduced mitochondrial function and altered fatty acid metabolism, will also reduce their cardiorespiratory fitness.<sup>26</sup> Immunosuppressive drugs in renal transplant recipients may also limit exercise tolerance.<sup>3</sup> There may be CKD-related factors not measured or not controlled for in our study, but further adjustments for diabetes mellitus did not explain the presented associations of CKD and eGFR with reduced  $VO_{2peak}$  and 6MWT distance (data not shown). Additional adjustments for HF medication or haemoglobin did not alter the presented associations of cardiac, renal or cardiorenal characteristics with cardiorespiratory fitness or 6MWT distance at baseline or 3-month post-intervention follow-up.

In our trial, HF phenotype and echocardiographic parameters only showed modest associations with physical capacity. The customized overall cardiorenal severity score, but not the cardiac sub-dimension, was significantly associated with  $VO_{2peak}$  and 6MWT distance. In general, echocardiographic indices of type and severity of HF presented weaker associations with cardiorespiratory fitness than renal indices. Previous studies have shown conflicting results regarding

**Figure 2** Associations of HF characteristics and  $VO_{2peak}$  at baseline. Significant *P*-values from log-transformed analyses are annotated.**Figure 3** Associations of renal characteristics and cardiorenal severity score with physical capacity. Panels A and B show the associations of eGFR (in difference from mean) with  $VO_{2peak}$  and 6MWT distance by linear regression analyses controlled for age and sex. Panels C and D show the associations of cardiorenal severity score (in difference from mean) with  $VO_{2peak}$  and 6MWT distance adjusted for age and sex.

the relationship between vascular health and CKD,<sup>19,27</sup> even though the endothelium is affected by the sodium retention in HF.<sup>21</sup> We found no significant associations of any vascular measure with CRS status.

We found lower physical fitness in HF patients with CRS, and further, a linear relationship between eGFR and  $VO_{2peak}$  and 6MWT distance. Reduced eGFR was closer associated with  $VO_{2peak}$  than age and sex. The linear relationship between  $VO_{2peak}$  and eGFR is previously shown in non-HF patients.<sup>28</sup> In the HF-ACTION trial, the correlation of CKD stage and  $VO_{2peak}$  in HFrEF patients with available measures of creatinine within 1 year of inclusion was evaluated. The study found lower  $VO_{2peak}$  and more risk factors at higher CKD stages.<sup>7</sup> We measured creatinine within

1 day of exercise testing, and the presented results confirm the close association of eGFR with cardiorespiratory fitness.

The effect size of exercise, although not significant, is in line with findings in other large, randomized trials.<sup>4–6</sup> In these trials, exercise increased maximal oxygen consumption by 0.6–1.6  $mL \cdot min^{-1} \cdot kg^{-1}$ , despite these trials did not include CRS patients with severely reduced kidney function. Reduced cardiorespiratory fitness may occur as the results of acute complications.<sup>29</sup> However, our findings are more consistent with a gradual deterioration of cardiorespiratory fitness over time. Thus, the findings of this study indicate a potential for modifying cardiorespiratory fitness, and subsequently prognosis, in CHF patients with and without CRS.



## Strengths and limitations

The main strengths of our investigations are the comprehensive and standardized data collection including gold standard measurements of cardiorespiratory fitness on a treadmill and comprehensive echocardiography. Furthermore, unlike in other trials, we included CKD patients at Stages 1 and 2 according to KDIGO classification, based on the presence of albuminuria or other indicators of kidney disease.<sup>1,10</sup> However, the limited sample size reduced the ability to simultaneously control for more than three variables. Iron levels were not included in our investigations. As adjustment for haemoglobin did not alter the presented results, we find it unlikely that between-group differences in iron status would have changed the results.

## Conclusions

By evaluating baseline data in this RCT of exercise intervention in CHF patients, we found a strong linear association of eGFR with  $VO_{2peak}$  and 6MWT distance. The association of renal function with cardiorespiratory fitness was stronger than for HF phenotype and other characteristics. This may be due to higher volume states in CRS patients. We found a gradient in training effect where control patients with CRS had a significant decrease until 3-month post-intervention follow-up, while non-CRS patients in the exercise group significantly increased their cardiorespiratory fitness. The results highlight the importance of including and stratifying for renal function in future exercise trials and indicate a treatment potential of physical exercise for CRS patients. Exercise seems to be as important in CHF patients with CRS as in those without, but future studies are needed to find the most beneficial type of training.

## References

- House AA, Anand I, Bellomo R, Cruz D, Bobek I, Anker SD, Aspromonte N, Bagshaw S, Berl T, Daliento L, Davenport A, Haapio M, Hillege H, McCullough P, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P, Ronco C, Acute Dialysis Quality Initiative Consensus Group. Definition and classification of cardio-renal syndromes: Workgroup statements from the 7th ADQI consensus conference. *Nephrol Dial Transplant* 2010; **25**: 1416–1420.
- Jain A, Scott C, Chen HH. The renal-cardiac connection in subjects with preserved ejection fraction: A population based study. *ESC Heart Fail* 2017; **4**: 266–273.
- Zelle DM, Klaassen G, van Adrichem E, Bakker SJL, Corpeleijn E, Navis G. Physical inactivity: A risk factor and target for intervention in renal care. *Nat Rev Nephrol* 2017; **13**: 152–168.
- O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL, HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301**: 1439–1450.
- Mueller S, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, Pieske-Kraigher E, Beckers P, Bobenko A, Hommel J, Van de Heyning CM. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: A randomized clinical trial. *JAMA* 2021; **325**: 542–551.
- Ellingsen O, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, Larsen A-I, Hole T, Mezzani A, Van Craenenbroeck EM, Videm V, Beckers P,

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## Conflict of interest

All authors declare that they have no conflict of interest.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Basic characteristics of the study population at baseline.

**Table S2.** Additional baseline characteristics.

**Table S3.** Supplementary baseline characteristics in patients with and without cardiorenal syndrome.

**Figure S1.** Associations of tricuspid regurgitation peak velocity with physical capacity.

- Christle JW, Winzer E, Mangner N, Woitek F, Höllriegel R, Pressler A, Monk-Hansen T, Snoer M, Feiereisen P, Valborgland T, Kjekshus J, Hambrecht R, Gielen S, Karlsen T, Prescott E, Linke A. SMARTEX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure) Group. High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation* 2017; **135**: 839–849.
7. McCullough PA, Franklin BA, Leifer E, Fonarow GC. Impact of reduced kidney function on cardiopulmonary fitness in patients with systolic heart failure. *Am J Nephrol* 2010; **32**: 226–233.
8. Nakamura K, Sasaki T, Yamamoto S, Hayashi H, Ako S, Tanaka Y. Effects of exercise on kidney and physical function in patients with non-dialysis chronic kidney disease: A systematic review and meta-analysis. *Sci Rep* 2020; **10**: 18195.
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
10. KDIGO CKD Work Group. KDIGO 2012 guidelines CKD. Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements*. 2013: 1–150.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt J-U. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 233–270.
12. Nagueh SF. Left ventricular diastolic function: Understanding pathophysiology, diagnosis, and prognosis with echocardiography. *JACC Cardiovasc Imaging* 2020; **13**: 228–244.
13. Nagueh SF. Non-invasive assessment of left ventricular filling pressure. *Eur J Heart Fail* 2018; **20**: 38–48.
14. Letnes JM, Eriksen-Volnes T, Nes B, Wisløff U, Salvesen Ø, Dalen H. Variability of echocardiographic measures of left ventricular diastolic function. The HUNT study. *Echocardiography* 2021; **38**: 901–908.
15. Thijssen DHJ, Bruno RM, van Mil A, Holder SM, Fata F, Greyling A, Zock PL, Taddei S, Deanfield JE, Luscher T, Green DJ, Ghiadoni L. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur Heart J* 2019; **40**: 2534–2547.
16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612.
17. Alexandrou ME, Theodorakopoulou MP, Boutou A, Pella E, Alexandrou M-E, Patoulas D, Kassimatis E, Dipla K, Papagianni A, Sarafidis PA. Cardiorespiratory fitness assessed by cardiopulmonary exercise testing between different stages of pre-dialysis chronic kidney disease: A systematic review and meta-analysis. *Nephrology (Carlton)* 2021; **26**: 972–980.
18. Pella E, Boutou A, Theodorakopoulou MP, Sarafidis P. Assessment of exercise intolerance in patients with pre-Dialysis CKD with cardiopulmonary function testing: Translation to everyday practice. *Am J Nephrol* 2021; **52**: 264–278.
19. Essig M, Escoubet B, de Zuttere D, Blanchet F, Arnoult F, Dupuis E, Michel C, Mignon F, Mentre F, Clerici C, Vrtovsnik F. Cardiovascular remodelling and extracellular fluid excess in early stages of chronic kidney disease. *Nephrol Dial Transplant* 2008; **23**: 239–248.
20. Harjola VP, Mullens W, Banaszewski M, Bauersachs J, Brunner-La Rocca HP, Chioncel O, Collins SP, Doehner W, Filippatos GS, Flammer AJ, Fuhrmann V. Organ dysfunction, injury and failure in acute heart failure: From pathophysiology to diagnosis and management. A review on behalf of the acute heart failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail*. 2017; **19**: 821–836.
21. Nijst P, Verbrugge FH, Grieten L, Dupont M, Steels P, Tang WW, Mullens W. The pathophysiological role of interstitial sodium in heart failure. *J Am Coll Cardiol* 2015; **65**: 378–388.
22. Rangaswami J, Bhalla V, Blair JEA, Chang TJ, Costa S, Lentine KL, Lerma EV, Mezue K, Molitch M, Mullens W, Ronco C. Cardiorenal syndrome: Classification, pathophysiology, diagnosis, and treatment strategies: A scientific statement from the American Heart Association. *Circulation* 2019; **139**: e840–e878.
23. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013; **62**: 263–271.
24. Fang JC. Heart failure with preserved ejection fraction: A kidney disorder? *Circulation* 2016; **134**: 435–437.
25. Vinereanu D, Nicolaidis E, Tweddel AC, Mädler CK, Holst B, Boden LE, Cinteza M, Rees AE, Fraser AG. Subclinical left ventricular dysfunction in asymptomatic patients with type II diabetes mellitus, related to serum lipids and glycated haemoglobin. *Clin Sci (Lond)* 2003; **105**: 591–599.
26. Hallan S, Sharma K. The role of mitochondria in diabetic kidney disease. *Curr Diab Rep* 2016; **16**: 61.
27. Wang MC, Tsai WC, Chen JY, Huang JJ. Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. *Am J Kidney Dis* 2005; **45**: 494–501.
28. Leikis MJ, McKenna MJ, Petersen AC, Kent AB, Murphy KT, Leppik JA, Gong X, McMahon LP. Exercise performance falls over time in patients with chronic kidney disease despite maintenance of hemoglobin concentration. *Clin J Am Soc Nephrol* 2006; **1**: 488–495.
29. Canada JM, Trankle CR, Buckley LF, Carbone S, Abouzaki NA, Kadariya D, Shah K, Cooke R, Kontos MC, Patel J, Mankad P. Severely impaired cardiorespiratory fitness in patients with recently decompensated systolic heart failure. *Am J Cardiol* 2017; **120**: 1854–1857.