

**Renal Denervation in Heart Failure with Preserved Ejection Fraction (RDT-PEF): a randomised controlled trial**

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## **Abstract**

### **Aim**

Heart failure with preserved ejection fraction (HFpEF) is associated with increased sympathetic nervous system (SNS) tone. Attenuating the SNS with renal denervation (RD) might be helpful and there are no data currently in humans with HFpEF.

### **Methods and Results**

In this single-centre, randomised, open-controlled study we included 25 patients with HFpEF (preserved left ventricular (LV) ejection fraction, left atrial (LA) dilatation or LV hypertrophy and raised B-type natriuretic peptide (BNP) or echocardiographic assessment of filling pressures). Patients were randomised (2:1) to RD with the Symplicity™ catheter or continuing medical therapy. The primary success criterion was not met in that there were no differences between groups at 12 months for Minnesota Living with Heart Failure Questionnaire score, peak oxygen uptake ( $\text{VO}_2$ ) on exercise, BNP,  $\text{E}/\text{e}'$ , LA volume index or LV mass index. A greater proportion of patients improved at three months in the RD group with respect to  $\text{VO}_2$  peak (56% vs 13%,  $P=0.025$ ) and  $\text{E}/\text{e}'$  (31% vs 13%,  $P=0.04$ ). Change in estimated glomerular filtration rate was comparable between groups. Two patients required plain balloon angioplasty during the RD procedure to treat renal artery wall oedema.

### **Conclusion**

This study was terminated early due to difficulties in recruitment and was underpowered to detect whether RD improved the endpoints of: quality of life, exercise function, biomarkers and left heart remodelling. The procedure was safe in patients with HFpEF though two patients did require intra-procedure renal artery dilatation.

**Keywords: Heart failure with preserved ejection fraction; Renal denervation;  
Sympathetic nervous system; Meta-iodo-benzyl-guanidine; Noradrenaline**

## **Introduction**

Heart failure with preserved ejection fraction (HFpEF) is associated with significant morbidity and mortality. There is currently no effective treatment despite trials of various interventions.<sup>1</sup> The sympathetic nervous system (SNS) is a potential target.

Activity of the sympathetic nervous system (SNS) is elevated in patients with heart failure and it has deleterious effects on the heart, peripheral vasculature, kidneys and skeletal muscle.<sup>2-7</sup> The majority of this evidence relates to heart failure with reduced ejection fraction (HFrEF).<sup>7</sup> In patients with heart failure with preserved ejection fraction (HFpEF) there is also limited evidence of raised SNS activity as measured by heart rate variability,<sup>4, 5</sup> serum noradrenaline levels<sup>3, 6</sup> and muscle sympathetic nerve activity.<sup>2, 8</sup> A dose-response relationship has been demonstrated in patients with HFpEF, such that those with greater sympathetic tone have more symptoms, a lower exercise capacity and higher natriuretic peptide levels.<sup>4, 9</sup> However, treatments known to attenuate the SNS have so far failed to improve outcomes in HFpEF.<sup>1</sup>

Trans-catheter renal denervation (RD) is an investigational technique that can reduce the activity of the SNS.<sup>10, 11</sup> In animal models of HFrEF, RD has been shown to improve natriuresis, diuresis, and cardiac and renal function, which are important endpoints in HFpEF as well.<sup>11, 12</sup> Furthermore, in patients with hypertension, RD reduces left ventricular (LV) mass, stiffness and filling pressures, which are common pathological features of HFpEF.<sup>13</sup> Currently, there are no validated animal models of HFpEF precluding clinical studies to determine the effects of RD.

With this background and the current lack of available treatment options in HFpEF, we have tested the hypothesis that RD will improve haemodynamic and functional outcomes in patients with HFpEF.

## **Methods**

### **Study Design**

The renal denervation in HFpEF (RDT-PEF) trial was a phase II, single-centre, prospective, randomised, controlled, open-label and blinded end point trial. It was investigator initiated and funded by the National Institute of Health Research Cardiovascular Biomedical Research Unit of Royal Brompton Hospital and Imperial College, London. Ethical approval for the study was granted by the National Research Ethics Service. All patients provided written informed consent. The trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01840059): NCT01840059.

### **Study Patients**

Eligible patients were 18-85 years of age and fulfilled the criteria in Table 1 (further details in the supplementary material online).

The protocol was amended four months after the start of the trial to ensure adequate recruitment rate. This removed the requirement of previous heart failure hospitalisation and amended the EF threshold to >40% for trial inclusion (November 2013).

### **Randomisation**

The trial used computer-generated randomisation (2:1; RD:control). Because this was a safety and mechanistic study and because there was limited experience of RD in patients with heart

failure and none in patients with HFpEF, there was no clinician or patient blinding.<sup>12</sup> Instead end points were analysed by observers blinded to patient allocation.

### **Study Procedures**

A detailed description of the methods is provided in the supplementary material online. RD was performed using the Symplicity™ (Medtronic) single-electrode catheter. In all cases this was performed by one of two operators with two years prior experience of RD. Patients randomised to medical therapy were followed-up in the same way at three and 12 months after randomisation (supplementary material Table S1).

### **Efficacy Endpoints**

The endpoints reflected the multiple pathways that are abnormally activated in HFpEF covering symptoms, functional status, biomarkers and cardiac remodelling: The Minnesota Living with Heart Failure Questionnaire (MLWHFQ); peak treadmill exercise oxygen uptake ( $VO_2$  peak); B-type natriuretic peptide (BNP); E/e' (ratio of early mitral outflow velocity to average of medial and lateral mitral annular tissue velocity); left atrial volume index (LAVi from cardiac magnetic resonance (CMR)) and left ventricular mass index (LVMi from CMR).

The primary trial success criterion was defined *a priori* as an improvement in at least three of the six endpoints at 12 months of follow-up, without deterioration in any at  $P < 0.2$ . The use of this probability threshold has precedent from a previous heart failure trial<sup>14</sup> and is supported by the Cardiovascular Cell Therapy Research Network.<sup>15</sup> The risk of excessively inflating a type I error is reduced by the requirement of concordant improvements in all efficacy parameters without worsening of others.

Secondary endpoints included a composite score at the individual patient-level whereby each patient's baseline value was compared with their 3 and 12-month value across the six primary end points and the patients' responses were scored as: +1 for improvement, -1 for deterioration and 0 for no change using the thresholds detailed in the sample size.<sup>14</sup>

Finally, to explore the effects of RD on sympathetic tone, meta-iodo-benzyl-guanidine (mIBG) scintigraphy was performed at baseline and 12 months. This technique permitted the quantification of cardiac sympathetic nerve activity using two derived parameters: washout rate and heart-mediastinum ratio (HMR). Patients with a higher washout rate (indicative of higher adrenergic drive) and lower late HMR (indicative of neuronal function including uptake and release of mIBG) have a worse prognosis in heart failure.<sup>16</sup> Random plasma noradrenaline (the key neurotransmitter of the SNS) and 24 hour urine noradrenaline analyses were also undertaken.

### **Safety Endpoints**

Safety endpoints included vascular access complications, deterioration in eGFR by >30% from baseline and renal artery injury requiring intervention. Renal artery magnetic resonance angiography (MRA) was completed at baseline and 12 months follow-up, to exclude new renal artery stenosis.

### **Statistical analysis**

A sample size of 12 vs. 24 (control vs. RD) would have 85% power to detect an improvement of three or more endpoints with no significant deterioration in any using independent samples statistical tests to compare paired longitudinal differences using a threshold of  $P < 0.2$ .<sup>17</sup>

Clinically relevant changes in the outcomes and their standard deviations (SD) were taken from other studies as:  $\Delta$ MLWHFQ 10 (SD 13);<sup>18</sup>  $\Delta$ VO<sub>2</sub> peak 1.5 ml/kg/min (SD 2.5);<sup>18</sup>  $\Delta$ BNP 50ng/l (SD 130);<sup>19</sup>  $\Delta$ E/e' 2 (SD 3);<sup>19</sup>  $\Delta$ LAVi 4 ml/m<sup>2</sup> (SD 4);<sup>18</sup>  $\Delta$ LWMI 5 g/m<sup>2</sup> (SD 11).<sup>13</sup> A correlation of 0.2 was assumed between the endpoints. After accounting for expected patient attrition we calculated a requirement to enrol 50 patients.

Continuous variables are presented as mean $\pm$ SD and compared using the t-test and analysis of variance. Non-normally distributed data are presented as median (quartile 1, quartile 3) and compared using the Mann-Whitney U test. Categorical data are presented as counts and percentages and compared using the chi-square test. A general linear model was also used to compare changes in the six primary endpoints between the two groups using baseline values as covariates and is presented as analysis of co-variance (ANCOVA) probability values.

For all secondary analyses a P value <0.05 was considered statistically significant. SPSS (IBM v20) was used to perform the statistical analyses.

## **Results**

### **Study Patients**

A total of 25 patients were randomised between July 2013 and December 2014 before the trial was stopped because of difficulty in recruitment despite nationwide screening (Figure 1). Baseline characteristics are shown in Table 2. Sixteen of the 25 patients (64%) had previously been admitted with decompensated heart failure within the preceding 24 months. Right and left heart catheterisation data are presented in supplementary material online Table S2. Fifteen of the 17 patients who were allocated to the RD arm had invasive evidence of raised left ventricular filling pressures at rest (either pulmonary capillary wedge pressure



(PCWP) >15mmHg or left ventricular end-diastolic pressure (LVEDP) >16mmHg). All patients had an EF >50% on CMR.

### **Efficacy Endpoints**

At 12 months follow-up the primary trial success criteria were not met and there were no significant changes across any of the six efficacy endpoints (Figure 2, supplementary material online Table S3).

On secondary analysis, there was an improvement in the composite efficacy score at the 3 months in the RD group compared with control (P=0.018) but not at 12 months (P=0.921) (Figure 3). This signal for an early effect was driven by a greater proportion of patients that improved by the pre-specified clinically significant amount in the RD group than in the control group with respect to VO<sub>2</sub> peak (56% vs. 13%, P=0.025) and E/e' (31% vs. 13%, P=0.04) (Figure 2).

### **Safety and hospital admissions**

There were no deaths, strokes or myocardial infarctions during the course of the study. Two patients in the RD group had more than 30% reduction in eGFR at 12 months compared with baseline. There was no evidence of new renal artery stenosis on MRA in these patients. The median change in eGFR at 12 months was not different between the two study groups (-3 ml/min/1.73m<sup>2</sup> [-11, 3] vs. +4 ml/min/1.73m<sup>2</sup> [-8, 5], RD vs. control, P=0.318).

There were no femoral artery complications. Two patients developed intense renal artery spasm/oedema during RD that persisted for 20 minutes after intra-arterial nitrate and were further treated with low pressure angioplasty (without stent deployment), with a visually

satisfactory result. These vessels were patent at 12 months by MRA and both patients had stable renal function.

Three patients developed progression of existing renal artery atheroma that did not require intervention (one in the RDT group, two in the control group). Three patients were admitted with decompensated heart failure (two in the RDT group, one in the control group). Two patients underwent coronary revascularisation between the three and 12 months (one in each group).

### **Number and distribution of ablations**

The number and location of successful ablations are detailed in the supplementary material online Table S4. All patients had a minimum of four (median 5) successful ablations to each attempted artery. No ablation was possible to the left renal artery of one patient because of an acute angle of origin and inability to achieve a stable guide catheter position. Twelve patients had incomplete circumferential ablations, whereby it was not possible to apply radiofrequency energy to all four quadrants successfully.

The five patients who received anatomically complete denervation had no greater improvements at three month or 12 month follow-up compared with the 12 patients who did not (supplementary material online Table S5).

### **Medication Changes**

There were no significant differences between the proportions of patients who had their cardiac medications (limited to angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, alpha-blockers, diuretics, aldosterone antagonists, calcium-

channel blockers and digoxin) altered in either allocation group (supplementary material online Table S6).

### **Blood pressure and heart rate**

At baseline, no patients had 24 hour ambulatory blood pressures greater than 150/90 mmHg. Eight patients had average pressures greater than 135/85 mmHg. There was no difference between groups at 12 months with respect to change in 24 hour ambulatory systolic blood pressure [ $-2.4 \pm 9.7$  vs.  $+1.3 \pm 9.4$  mmHg,  $P=0.410$  (RD vs. control)] or 24 hour mean heart rate [ $-3.4 \pm 7.2$  vs.  $+1.2 \pm 6.4$  beats-per-minute,  $P=0.162$  (RD vs. control)].

### **Autonomic Assessments**

At baseline, 22 patients had evidence of abnormal sympathetic nerve activity: 18 patients had a late heart:mediastinum (HMR) of  $<1.6$ ,<sup>20</sup> 19 had a cardiac wash-out of  $\geq 27\%$ <sup>21</sup> on cardiac mIBG imaging and 12 had a plasma noradrenaline of  $>3.50$  nmol/L (upper limit of normal for our laboratory). RD did not change any of the makers of sympathetic tone (Table 3). There was no difference in the change of autonomic parameters between patients who received anatomically complete RD compared with those who did not (supplementary material online, Table S5).

### **Discussion**

This is the first report of a randomised controlled trial examining the role of RD in patients with HFpEF. The primary efficacy endpoint was not met and there were no significant improvements with RD with respect to heart failure symptoms, peak  $VO_2$  on exercise, BNP,  $E/e'$  on echocardiography, left atrial volume index or left ventricular mass index at 12

months. However, it would be premature to conclude that RD is ineffective in HFpEF for the following reasons:

Firstly, the study was underpowered to detect a difference (85% power required a sample size of 36 patients, compared with 25 actually recruited) and hence is exposed to type II error. Although it might have been ambitious for a single-centre to recruit more patients, eleven heart failure units were involved in identifying patients for this study. Figure 1 shows why this study was underpowered. Of 10,228 patients with a diagnosis of heart failure screened, 124 met the study entry criteria. The reasons for this discrepancy have been discussed previously.<sup>22</sup> Approximately 80% of candidates were excluded because of  $EF \leq 40$  or  $< 50\%$  (depending on timing before or after modification of inclusion criteria). Of the remainder, approximately 90% were excluded because of age  $\geq 85$  years, significant valve disease or  $eGFR < 45$  ml/min/1.73m<sup>2</sup> (supplementary material online, Figure S7). It is likely that stringent eligibility criteria coupled with screening restricted to cardiology clinics and heart failure admissions have made HFpEF a rare condition. A potential method of facilitating future trials is the establishment of national and international heart failure networks capable of diagnosing and identifying such patients. It might be possible to achieve adequate power by pooling our dataset with future trials of renal denervation for HFpEF if similar methods are adopted.

Secondly, it is possible that the Symplicity™ catheter is ineffective at ablating renal innervation. This has been discussed as a possible explanation for the unexpected results of the SYMPPLICITY HTN-3 trial. In the absence of a marker of successful denervation, we used several surrogate markers of sympathetic tone, including mIBG scintigraphy. Despite not forming part of the eligibility criteria all but three patients had evidence of elevated SNS

activity at baseline, however, RDT failed to attenuate any of the surrogate markers. Surprisingly, there was a non-significant trend that patients allocated to control had an improvement in the myocardial noradrenaline concentration (marker of sympathetic nerve integrity) whereas those who received RDT did not change.

SYMPPLICITY HTN-3 used the number of ablations applied and their completeness (covering all four quadrants) as a marker of quality of renal denervation. In that trial, a complete ablation was possible in only 19/364 (5.2%) of patients and these patients experienced the largest reduction in blood pressure.<sup>23</sup> In the RDT-PEF trial, 5/17 (29.4%) patients received a four-quadrant ablation and we found no concordant changes in any of the primary endpoints compared with patients who did not receive complete ablation. It is possible that newer multi-electrode catheters might more readily achieve circumferential ablation pattern.<sup>10</sup>

New findings on human renal nerve anatomy emerged during the conduct of the RDT-PEF trial suggesting that the sympathetic nerves approximate more closely to the distal artery as they pass from the aorta to the renal hilum.<sup>24</sup> With this knowledge, we might preferentially have targeted the distal artery with a greater likelihood of ablating more nerves.<sup>25</sup>

In secondary analyses there was a statistically significant trend improvement at three months in peak  $\text{VO}_2$  and  $\text{E}/\text{e}'$  (Figure 2 &3), but the improvement was not sustained at 12 months. There are three possible explanations for this discrepancy. The first consideration is the Hawthorne effect, whereby patients who are pleased to be allocated to the RD group might make more effort in the cardiopulmonary exercise test thereby increasing the peak  $\text{VO}_2$ .<sup>26</sup> It is likely that this bias would wane with time. Alternatively, the changes seen at three months

might represent a type I error, where a significant difference is seen when one does not truly exist. The final possibility is sympathetic nerve regrowth, i.e. the improvements at three months were genuine. In sheep denervated with the Symplicity™ catheter, functional and anatomical regeneration of the afferent and efferent sympathetic nerves was seen at 11 months.<sup>27</sup> These findings reinforce the importance of blinding and staged analyses to look for early and late benefit.

Consistent with the broader literature, which almost exclusively pertains to the Symplicity™ catheter, RD in patients with HFpEF appears safe up to 12 months of follow-up. However, the procedure is not without risk, with two patients requiring balloon angioplasty to treat intense vessel spasm/oedema, a complication which is usually treated with intra-arterial nitrate alone. Our decision to intervene on these patients was based upon the severity of the vessel reaction (>95% reduction in luminal diameter) and persistence (> 20 minutes); the requirement of balloon angioplasty to treat severe renal artery oedema/spasm following RD has been reported previously.<sup>28</sup> Two other patients had a decline in eGFR>30%; further clinical follow-up data were available to us and these patients' eGFR recovered to pre-randomisation levels after completing treatment for fluid overload. It is important not to automatically extrapolate safety data established in the resistant hypertension population to an HFpEF cohort, which tends to be older and with more co-morbidities.

The role of RD in the treatment of heart failure (regardless of ejection fraction) remains unclear. There exist many uncertainties, firstly- with the technology (multi-electrode versus single electrode systems) and how best to apply it (number and location of ablations in the renal artery); secondly- with trial design and whether sham-blinding should be mandatory; and thirdly, with endpoint selection particularly in phase II heart failure studies, where an

ideal single surrogate endpoint does not exist.<sup>15</sup> Finally, until an approach to accurately quantify the effects of RD on afferent and efferent renal sympathetic nerves is developed, it will remain difficult for future phase II studies to show a ‘dose-response’ effect, which will limit the credibility of any findings.

### **Limitations**

The strengths of the RDT-PEF trial are that it is randomised and controlled and is the first to present data on patients with HFpEF exposed to RD. It is a single centre experience and hence its results may not be generalizable. Furthermore the trial findings are subject to bias as it was a non-blinded trial without a sham procedure. Efforts were undertaken to address this by having observers blinded to allocation analyse the collected data. This is likely to avoid most of the bias reported in the earlier trials of RDT in resistant hypertension but our trial remains susceptible to bias in the subjective endpoints such as symptom questionnaires.<sup>9, 26</sup> Another potential bias is that adherence to prescribed medications may have varied differently during the course of the study between the two treatment groups. This was particularly problematic in the unblinded studies of RD in resistant hypertension.<sup>26</sup> In our HFpEF population, however, the impact of this limitation is likely to be minimal because none of our patients had resistant hypertension and no drugs have been shown to offer persistent benefit in HFpEF, hence changes in adherence should not greatly affect our heart failure related endpoints. The study used a novel trial success criterion based upon multiple primary endpoints; we and others believe that the measure of success of a phase II clinical study should not hinge upon achievement of statistical significance for a small number of primary end-points (this is how phase III studies are designed) but rather to provide a broader mechanistic insight by choosing a selection of endpoints addressing different categories of effects or domains without being overly concerned with suppressing the likelihood of false-

positive findings.<sup>15</sup> Indeed no single endpoint can adequately capture the totality of the patient's experience with HFpEF.<sup>15, 29</sup>

## **Conclusions**

Renal denervation was safe, though not without complication (two patients required renal artery dilatation intra-procedurally), in this cohort of patients with HFpEF. No significant effect of RD was seen on multiple endpoints encompassing quality of life, exercise function, biomarkers and cardiac remodelling, though the study was underpowered for these. A possible signal of effect was seen at three months but this was not sustained at 12 months. A larger study is required, which would benefit from a co-ordinated effort across multiple heart failure networks to overcome the challenges in recruitment, and the use of multiple-electrode catheter systems.



**Figure Legends:**

**Figure 1: Patient flow chart for the RDT-PEF study.** No.- number of; HHF- admissions to hospital with heart failure; RBH: Royal Brompton Hospital; HF: heart failure

**Figure 2: Primary efficacy endpoints for the RDT-PEF trial 3 and 12 months.** The brown dotted lines represent the threshold for a clinically significant change. MLWHFQ- Minnesota Living with Heart Failure Questionnaire; Peak VO<sub>2</sub>- maximum oxygen uptake on exercise treadmill; BNP- B-type natriuretic peptide; LAVi- left atrial volume index; LVMi- left ventricular mass index.

**Figure 3: Changes in composite patient score.** Numbers in each filled circle correspond to an individual patient. Summary lines represent mean with standard error. P values derived from independent samples t-test.

Inclusion Criteria	Exclusion Criteria
NYHA II-III	eGFR <45ml/min/1.73m <sup>2</sup> (MDRD)
Ejection Fraction ≥50%*	Contraindication to CMR
Non-dilated left ventricle (LVEDD <60mm or LVESD <45mm)	Cardiomyopathy (constrictive, restrictive, dilated, previously documented EF <40%)
Either: <ul style="list-style-type: none"> <li>•Dilated left atrium (diameter &gt;38mm (women)/&gt;40mm (men) or area&gt; 20cm<sup>2</sup>)</li> <li>or,</li> <li>•Left ventricular hypertrophy (wall thickness ≥12mm)</li> </ul>	Significant valvular disease (moderate or worse aortic regurgitation/stenosis or mitral stenosis; or severe mitral regurgitation)
Either: <ul style="list-style-type: none"> <li>•E/e' (lateral)&gt;10, E/e' (septal)&gt;15 [7] or,</li> <li>•BNP ≥35 ng/L</li> </ul>	Renal artery diameter >4mm and treatable renal artery segment <20mm
Admission with heart failure in previous 24 months*	Acute coronary syndrome or stroke in previous 6 months

**Table 1: RDT-PEF eligibility criteria.**

\* Criteria that were revised following a protocol amendment. MDRD- Modification of Diet in Renal Disease criteria; eGFR- estimated glomerular filtration rate; LVED- left ventricular

end diastolic dimension; LVEDD- left ventricular end-diastolic dimension; LVEDS- left ventricular end-systolic dimension; BNP- B-type natriuretic peptide; EF- ejection fraction; CMR- cardiac magnetic resonance

**Table 2: Baseline characteristics of the RDT-PEF population.**

	<b>Total (n=25)</b>	<b>RD (n=17)</b>	<b>Control (n=8)</b>	<b>P (RD vs Control)</b>
<b>Demographics</b>				
<b>Age</b>	74.3 ± 6.1	74.1 ± 6.8	74.6 ± 4.8	0.852
<b>Male</b>	15 (60%)	11 (64.7%)	4 (50.0%)	0.667
<b>Ethnicity</b>				0.156
<b>Caucasian</b>	19 (76%)	11 (65%)	8 (100%)	
<b>Black</b>	1 (4%)	1 (6%)	0 (0%)	
<b>Asian</b>	5 (20%)	5 (29%)	0 (0%)	
<b>BMI (kg/m<sup>2</sup>)</b>	30.6 ± 5.5	30.5 ± 4.6	30.8 ± 7.4	0.911
<b>BSA (m<sup>2</sup>)</b>	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.3	0.897
<b>Past Medical History</b>				
<b>Hypertension</b>	18 (72%)	14 (82.4%)	4 (50%)	0.156
<b>Diabetes</b>	10 (40%)	8 (47.1%)	2 (25%)	0.402
<b>CVA</b>	1 (4%)	1 (5.9%)	0 (0.0%)	1.000
<b>CHD</b>	6 (24%)	5 (29.4%)	1 (12.5%)	0.624
<b>AF</b>	15 (60%)	10 (58.8%)	5 (62.5%)	1.000
<b>Cardiac Surgery</b>	7 (28%)	4 (23.5%)	3 (37.5%)	0.640
<b>OSA</b>	4 (16%)	3 (17.6%)	1 (12.5%)	1.000
<b>COPD</b>	6 (24%)	4 (23.5%)	2 (25%)	1.000
<b>Cancer</b>	4 (16%)	4 (23.5%)	0 (0.0%)	0.269
<b>Medications</b>				
<b>ACEi/ARB</b>	23 (92%)	16 (94.1%)	7 (87.5%)	1.000
<b>Alpha-blockers</b>	4 (16%)	2 (11.8%)	2 (25%)	0.570

<b>Beta-blockers</b>	18 (72%)	12 (70.6%)	6 (75%)	1.000
<b>CC-blockers</b>	8 (32%)	7 (41.2%)	1 (12.5%)	0.205
<b>Loop diuretics</b>	21 (84%)	16 (94.1%)	5 (62.5%)	0.081
<b>Spirolactone</b>	6 (24%)	6 (35.3%)	0 (0.0%)	0.129
<b>Clinical Assessments</b>				
<b>NYHA Class</b>				1.000
<b>II</b>	14 (56%)	10 (58.8%)	4 (50%)	
<b>III</b>	11 (44%)	7 (41.2%)	4 (50%)	
<b>A SBP (mmHg)</b>	125 ± 13.9	128 ± 15.0	120 ± 9.7	0.190
<b>A DBP (mmHg)</b>	71 ± 8.2	71 ± 9.4	71 ± 5.1	0.866
<b>A HR (b/m)</b>	73 ± 12.2	73 ± 13.7	72 ± 9.0	0.781
<b>Laboratory Tests</b>				
<b>Haemoglobin (g/dl)</b>	131 ± 16	129 ± 16.4	135 ± 15.5	0.455
<b>eGFR (ml/min/1.73m<sup>2</sup>)</b>	61 (49.5-67.5)	61 (50.5-68)	61 (48.5-67.3)	0.887
<b>Primary Efficacy Endpoints</b>				
<b>MLWHFQ</b>	47 (25-54)	48 (27-56)	28 (25-50)	0.351
<b>VO<sub>2</sub> Peak (ml/kg/min)</b>	15.6 ± 3.6	14.7 ± 3.3	17.5 ± 3.8	0.073
<b>BNP (ng/l)</b>	184 (122-287)	210 (137-354)	149 (99-205)	0.124
<b>Average E/e'</b>	13.8 ± 5.3	13.6 ± 5.9	14.4 ± 3.9	0.747
<b>LAVi (ml/m<sup>2</sup>)</b>	62.3 ± 28.1	62.8 ± 29.2	61.3 ± 21.7	0.905
<b>LVMi (g/m<sup>2</sup>)</b>	63.4 ± 10.4	62.9 ± 11.4	64.6 ± 7.1	0.653

Data are presented as mean  $\pm$  standard deviation or median (quartile 1, quartile 3). BMI- body mass index; BSA- body surface area; CVA- cerebrovascular accident; CHD- coronary heart disease; AF- atrial fibrillation; OSA- obstructive sleep apnoea; COPD- chronic obstructive pulmonary disease; MLWHFQ- Minnesota Living with Heart Failure Questionnaire; NYHA- New York Heart Association; A- ambulatory; SBP- systolic blood pressure; DBP- diastolic blood pressure; HR- heart rate; ACEi- angiotensin converting enzyme inhibitor; ARB- angiotensin receptor blocker; CC- calcium channel; eGFR- estimated glomerular filtration rate; BNP- brain-type natriuretic peptide; VO<sub>2</sub>- oxygen uptake; LAVi- left atrial volume index; LVMi- left ventricular mass index



**Table 3: Summary of autonomic assessments in the RDT-PEF trial.**

	RD			Control			Base line	Change from baseline					
	Base line	3 Mo nths	12 Mo nths	Base line	3 Mo nths	12 Mo nths	RD vs Control	3 Months			12 Months		
							P	R D	Con trol	P	R D	Con trol	P
<b>Cardiac mIBG</b>													
<b>Early HMR</b>	1.61 (1.50, 1.80)		1.58 (1.45, 1.77)	1.56 (1.46, 1.72)		1.73 (1.67, 1.89)	0.66 9				+0.01 (-0.13, 0.11)	+0.00 (-0.01, 0.33)	0.1 66
<b>Late HMR</b>	1.49 ± 0.18		1.49 ± 0.17	1.52 ± 0.19		1.65 ± 0.19	0.73 0				-0.00 ± 0.11	+0.10 ± 0.11	0.0 59

<b>Washout rate (%)</b>	36.7 ± 15.2		32.8 ± 19.7	33.0 ± 16.6		30.0 ± 12.5	0.59 1		- 3.8 ± 19.1	+0.8 ± 8.8	0.5 52		
<b>Noradrenaline Assays</b>													
<b>Plasma (nmol/l)</b>	3.91 ± 1.29	3.86 ± 2.22	3.87 ± 1.58	3.34 ± 0.85	4.25 ± 2.29	3.05 ± 0.91	0.27 0	- 0.05 ± 2.37	+0.9 1 ± 1.62	0.3 13	- 0.0 4 ± 1.7 8	- 0.03 ± 0.91	0.9 91
<b>24hr Urine (nmol/24hr)</b>	248 ± 98		228 ± 125	245 ± 68		203 ± 41	0.92 0				-28 ± 36	-20 ± 85	0.7 62

RD- renal denervation; HMR- heart-mediastinum ratio. Parametric data are presented as mean±standard deviation. Non-parametric data are presented as median (quartile 1, quartile 3).

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## References

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Jung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**(8):803-69.
2. Verloop WL, Beeftink MM, Santema BT, Bots ML, Blankestijn PJ, Cramer MJ, Doevendans PA, Voskuil M. A systematic review concerning the relation between the sympathetic nervous system and heart failure with preserved left ventricular ejection fraction. *PLoS One* 2015;**10**(2):e0117332.
3. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002;**288**(17):2144-50.
4. Patel H, Ozdemir BA, Patel M, Xiao HB, Poole-Wilson PA, Rosen SD. Impairment of autonomic reactivity is a feature of heart failure whether or not the left ventricular ejection fraction is normal. *Int J Cardiol* 2011;**151**(1):34-39.
5. Arora R, Krummerman A, Vijayaraman P, Rosengarten M, Suryadevara V, Lejemtel T, Ferrick KJ. Heart rate variability and diastolic heart failure. *Pacing and clinical electrophysiology : PACE* 2004;**27**(3):299-303.
6. Vinch CS, Aurigemma GP, Hill JC, Gaasch WH, Volturo G, Tighe DA, Meyer TE. Usefulness of clinical variables, echocardiography, and levels of brain natriuretic peptide and norepinephrine to distinguish systolic and diastolic causes of acute heart failure. *Am J Cardiol* 2003;**91**(9):1140-3.
7. Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. *Eur Heart J* 2015;**36**(30):1974-1982.
8. de Souza SB, Rocha JA, Cuoco MA, Guerra GM, Ferreira-Filho JC, Borile S, Krieger EM, Bortolotto LA, Consolim-Colombo FM. High muscle sympathetic nerve activity is associated with left ventricular dysfunction in treated hypertensive patients. *Am J Hypertens* 2013;**26**(7):912-7.
9. Sugiura M, Yamamoto K, Takeda Y, Takeda Y, Dohmori T, Ogata M, Kondo H, Suzuki S, Fukutomi T. The relationship between variables of 123-I-metaiodobenzylguanidine cardiac imaging and clinical status of the patients with diastolic heart failure. *Int J Cardiol* 2006;**113**(2):223-8.
10. Patel H, Dhillon P, Mahfoud F, Lindsay A, Hayward C, Ernst S, Lyon A, Rosen S, di Mario C. The biophysics of renal sympathetic denervation using radiofrequency energy. *Clin Res Cardiol* 2014;**103**(5):337-344.
11. Bohm M, Ewen S, Kindermann I, Linz D, Ukena C, Mahfoud F. Renal denervation and heart failure. *Eur J Heart Fail* 2014;**16**(6):608-13.
12. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, Hamady M, Hughes AD, Sever PS, Sobotka PA, Francis DP. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. *Int J Cardiol* 2013;**162**(3):189-92.
13. Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Bohm M, Hoppe UC. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol* 2012;**59**(10):901-9.

14. Jessup M, Greenberg B, Mancini D, Cappola T, Pauly DF, Jaski B, Yaroshinsky A, Zsebo KM, Dittrich H, Hajjar RJ. Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase in patients with advanced heart failure. *Circulation* 2011;**124**(3):304-13.
15. Hare JM, Bolli R, Cooke JP, Gordon DJ, Henry TD, Perin EC, March KL, Murphy MP, Pepine CJ, Simari RD, Skarlatos SI, Traverse JH, Willerson JT, Szady AD, Taylor DA, Vojvodic RW, Yang PC, Moyer LA. Phase II clinical research design in cardiology: learning the right lessons too well: observations and recommendations from the Cardiovascular Cell Therapy Research Network (CCTRN). *Circulation* 2013;**127**(15):1630-5.
16. Carrio I, Cowie MR, Yamazaki J, Udelson J, Camici PG. Cardiac sympathetic imaging with mIBG in heart failure. *JACC Cardiovasc Imaging* 2010;**3**(1):92-100.
17. Davison BA, Cotter G, Sun H, Chen L, Teerlink JR, Metra M, Felker GM, Voors AA, Ponikowski P, Filippatos G, Greenberg B, Teichman SL, Unemori E, Koch GG. Permutation criteria to evaluate multiple clinical endpoints in a proof-of-concept study: lessons from Pre-RELAX-AHF. *Clin Res Cardiol* 2011;**100**(9):745-53.
18. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, Binder L, Topper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Loffler M, Hasenfuss G, Halle M, Pieske B. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol* 2011;**58**(17):1780-91.
19. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, Dungen HD, Tschope C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013;**309**(8):781-91.
20. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, Agostini D, Weiland F, Chandna H, Narula J. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J Am Coll Cardiol* 2010;**55**(20):2212-21.
21. Ogita H, Shimonagata T, Fukunami M, Kumagai K, Yamada T, Asano Y, Hirata A, Asai M, Kusuoka H, Hori M, Hoki N. Prognostic significance of cardiac (123)I metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: a prospective study. *Heart* 2001;**86**(6):656-60.
22. Patel HC, Hayward C, di Mario C, Cowie MR, Lyon AR, Rosen SD. Heart failure with preserved ejection fraction: the impact of stricter definitions. *Eur J Heart Fail* 2014;**16**(7):767-771.
23. Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, Flack JM, Katzen BT, Lea J, Lee DP, Leon MB, Ma A, Massaro J, Mauri L, Oparil S, O'Neill WW, Patel MR, Rocha-Singh K, Sobotka PA, Svetkey L, Townsend RR, Bakris GL. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 2015;**36**(4):219-227.
24. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, Kolodgie FD, Virmani R, Joner M. Anatomic Assessment of Sympathetic Peri-Arterial Renal Nerves in Man. *J Am Coll Cardiol* 2014;**64**(7):635-643.
25. Patel HC, Otero S, Moser JB, Hayward C, Rosen SD, Lyon AR, Mohiaddin R, di Mario C, Padley S. A cross-sectional imaging study to identify organs at risk of thermal injury during renal artery sympathetic denervation. *Int J Cardiol* 2015;**197**:235-240.
26. Patel HC, Hayward C, Ozdemir BA, Rosen SD, Krum H, Lyon AR, Francis DP, di Mario C. Magnitude of Blood Pressure Reduction in the Placebo Arms of Modern Hypertension Trials: Implications for Trials of Renal Denervation. *Hypertension* 2015;**65**:401-406.
27. Booth LC, Nishi EE, Yao ST, Ramchandra R, Lambert GW, Schlaich MP, May CN. Reinnervation of renal afferent and efferent nerves at 5.5 and 11 months after catheter-based radiofrequency renal denervation in sheep. *Hypertension* 2015;**65**(2):393-400.

28. Scheurig-Muenkler C, Weiss W, Foert E, Toelle M, van der Giet M, Kroncke TJ, Zidek W, Powerski MJ. Renal denervation for refractory hypertension - technical aspects, complications and radiation exposure. *Rofo* 2013;**185**(6):550-7.

29. Zannad F, Garcia AA, Anker SD, Armstrong PW, Calvo G, Cleland JG, Cohn JN, Dickstein K, Domanski MJ, Ekman I, Filippatos GS, Gheorghiade M, Hernandez AF, Jaarsma T, Koglin J, Konstam M, Kupfer S, Maggioni AP, Mebazaa A, Metra M, Nowack C, Pieske B, Pina IL, Pocock SJ, Ponikowski P, Rosano G, Ruilope LM, Ruschitzka F, Severin T, Solomon S, Stein K, Stockbridge NL, Stough WG, Swedberg K, Tavazzi L, Voors AA, Wasserman SM, Woehrle H, Zalewski A, McMurray JJ. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. *Eur J Heart Fail* 2013;**15**(10):1082-94.