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Renal denervation in patients who do not respond to cardiac resynchronization therapy

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ABSTRACT

Cardiac resynchronization therapy (CRT) reduces the morbidity and mortality in advanced heart failure (HF) in about two-thirds of the patients. Approximately one-third of the patients do not respond to CRT. The overactivity of sympathetic nervous system is associated with advanced HF and deteriorates the hemodynamic state. We tested the hypothesis that controlling sympathetic overactivity by renal denervation (RDN) could be beneficial in nonresponders for CRT. In our HeartF-RDN study (ClinicalTrials.gov. NCT02638324), RDN could not reverse the progression of HF in subjects with New York Heart Association Classification (NYHA) III-IV stage symptoms.

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Cardiac resynchronization therapy; CRT nonresponder; heart failure; renal sympathetic denervation; 6-minute walking test

Introduction

Heart failure (HF) is a pathophysiological state where heart dysfunction causes symptoms and signs of inadequate blood flow and oxygen delivery to metabolizing tissues. The prevalence of HF in developed countries is increasing with age and varies from 1–2% in the whole population to over 10% in the group of ≥ 85 years old [1]. The annual mortality is strongly related to disease severity being about 7% in chronic stable HF [2]. Medication and device therapy aim to retard or prevent worsening of HF and improve survival [3].

Cardiac resynchronization therapy (CRT) is shown to reduce morbidity and mortality in patients with ejection fraction (EF) $< 35\%$, wide QRS complex > 150 ms with left bundle branch block morphology [4]. However, HF does not improve in about one-third of the patients [5]. Moreover, elevated sympathetic tone is present in HF and is associated with excess mortality [6–8]. Renal denervation (RDN) controls sympathetic overactivity [9], but its effect on the prognosis of CRT non-responder is poorly studied [10]. Thus, we aimed to examine RDN as a supportive treatment of severe HF.

Materials and methods

The HeartF-RDN is a single-center open-labeled study conducted between September 2014 and June 2018 in the district of Vaasa Central Hospital in Finland. Based on

literature and power analysis, we aimed to recruit 40 patients [11–13]. The study was prematurely terminated because of the recruiting difficulties caused by restrictions of denervation in clinical use at the completion date.

The patient population consisted of 11 severely diseased adult patients with New York Heart Association Classification (NYHA) III or ambulatory NYHA IV symptoms despite guideline-based CRT implantation [14] between the years 2009–2015. In 50% of patients, CRT was combined with a defibrillator. The etiology of HF was dilatative cardiomyopathy (CM) in six patients, ischemic CM in three patients, and hypertrophic CM in one patient. Eight patients had atrial fibrillation and seven diabetes. All patients used conventional guideline-based maximal tolerated medicine therapy. The criteria for non-responder for CRT was defined by the presence of NYHA III–IV symptoms despite optimal medical therapy, unchanged or worsened EF after CRT, and 6-minute walking test (6MWT) under 440 meters with dyspnea as a walking limiting symptom. The patients with unstable HF and lack of co-operation were excluded from the study.

Patients were randomized 1:1 according to wait list comparison [15,16]. The first group received RDN after enrollment visit and the second group six months after enrollment. The second group served as a control group for the first group during the first six months of the study. After enrollment, one patient from the second group withdrew his informed consent. Thereby, the number of patients

were six in the experimental group and four in the wait list control group.

At every study visit, patients were examined, and two-dimensional transthoracic ultrasound was performed. The quality of life was measured with the Finnish version of the validated EQ-5D test [17]. Basic laboratory tests, electrocardiogram and 6MWT were scheduled. Patients were followed up every third month during the first year, and every sixth month thereafter.

Renal denervation

RDN was performed using the quadripolar second generation ablation catheter Spyral[®] (Medtronic, Dublin, Republic of Ireland) primarily *via* femoral artery, or alternatively, *via* brachial artery. Ablations were performed at the main renal arteries and the accessory renal arteries and side branches with a minimal lumen diameter of 4 mm. Patients received sedation and analgesics when needed. If the subject was on warfarin, the international normalized ratio had to be at therapeutic level during RDN, whereas direct oral anticoagulants were discontinued 24 h before and after RDN. The patients who did not use either anticoagulant received low molecular weight heparin during RDN, and one month antithrombotic medication after RDN.

Statistics

Based on the existing literature [11,12,13], we calculated that with α -error 0.05, 20 patients in each group would produce 80% power to find 45 meters difference in 6-minute walking test (6MWT) with standard deviation 50 meters. Repeated measures ANOVA was planned to be used to evaluate long term effects of RDN. However, due to the small sample size in our study, the data cannot be taken as normally distributed, and the mean differences between two groups at 6 months were calculated using Mann–Whitney U-test. After six months, we revised the study protocol and combined the groups. In the revised protocol, the time point 0 was when RDN was performed. Wilcoxon matched-pair signed-rank was used to compare the statistical significance of differences in results at different time points compared to the screening visit. The revised primary end point was 6MWT at 24 months. The secondary endpoints were the mortality rate, EF, and NT-proBNP at 24 months. The results are expressed as means with range. P -value < .05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics for Windows version 26 (Armonk, NY, USA).

Ethics

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK:146/1801/2013) and was conducted in accordance with the Declaration of Helsinki. The registration number in

ClinicalTrials.gov. was NCT02638324. All patients gave a written informed consent.

Results

The mean age of the study participants was 75 years (range 68–80 years). All patients were men. The mean interval between the implantation of CRT and RDN was 3.9 years.

Approximately 10 ablations per renal artery were delivered for each patient. Because of occlusion of right iliac artery, RDN was successfully performed *via* brachial artery in one patient nine months after enrollment. This patient's data have been calculated at different time points, counting the data from the successful RDN. Two patients died during the study, one from each group. The cause of death in both cases was advanced HF. No immediate or late RDN-related complications occurred.

As shown in the Table 1, the results in six months after the screening visit did not show any difference between the groups.

After combining the results of both groups, the RDN did not affect primary or secondary endpoints at 6, 12 or 24 months. At 24 months, 6MWT was 73 meters shorter as compared with the result at the screening visit being statistically significant deterioration. Further, serum creatinine increased significantly at 24 months. In addition, NT-ProBNP tended to rise. The detailed results at 24 months are presented in Table 2. The data at 12 months are not shown.

Discussion

According to the HeartF-RDN study, the subjects with NYHA III-IV stage HF who are non-responders to CRT do not benefit from RDN. Indeed, in our view, the deterioration in 6MWT by 73 meters and the rising tendency of serum creatinine and NT-ProBNP reflect the progression of the disease despite RDN rather than a deleterious effect of RDN.

A meta-analysis suggested that RDN may improve heart dysfunction and exercise capacity in patients with NYHA II-IV symptoms [18]. However, the only previous study evaluating RDN in non-responders to CRT did not demonstrate improvements in exercise capacity, EF or NT-ProBNP [10]. Notably, the patients in that study had NYHA II and III symptoms, whereas in our study patients were more morbid.

In our study, HF had lasted on average 14 years before the implantation of CRT, which may entail some survival bias in our group. Speculatively, the results could have been different if all evidence-based medicines had been up-titrated to target dose, CRT been implanted, and RDN performed in a shorter period.

The main limitation of our study is the small sample size. However, analyzing groups apart at six months and combining the groups in final analysis at 24 months showed

Table 1. Difference between the groups at six months.

	Treatment group at the baseline (n = 6)	Control group at the baseline (n = 4)	Treatment group six months after RDN (n = 6)	Control group at six months (n = 4)
Systolic blood pressure (mmHg)	115 (100–130)	111 (90–135)	113 (105–123)	115 (93–148)
Diastolic blood pressure (mmHg)	69 (56–80)	66 (60–70)	66 (58–70)	62 (57–74)
Heart rate (/min)	70 (60–77)	72 (70–77)	69 (60–75)	70 (70–70)
Body mass index (kg/m ²)	28.5 (24.1–35.0)	29.7 (26.0–38.3)	28.9 (22.6–35.9)	28.9 (24.0–36.8)
6-minute walk test (m)	289 (187–394)	301 (268–335)	274 (70–420)	330 (245–398)
Quality of Life index (EQ-5D)	62 (50–90)	63 (20–86)	63 (29–90)	70 (49–90)
Global ejection fraction (%)	29 (22–34)	31 (20–41)	26 (16–36)	29 (24–38)
Left ventricular end-diastolic diameter (mm)	72 (61–78)	72 (64–78)	74 (62–80)	72 (65–79)
Hemoglobin (g/L)	138 (115–150)	146 (105–172)	131 (110–149)	146 (100–174)
Erythrocytes (10 ¹² /L)	4.8 (4.2–5.4)	4.6 (3.2–5.3)	4.4 (3.8–5.2)	4.6 (3.2–5.6)
Leucocytes (10 ⁹ /L)	6.3 (4.6–8.4)	7.0 (3.9–10.9)	6.6 (5.6–8.8)	7.2 (3.4–10.1)
Thrombocytes (10 ⁹ /L)	178 (141–215)	171 (154–196)	176 (129–251)	180 (129–221)
B-type natriuretic peptide (ng/L)	4904 (1395–7959)	1517 (517–2874)	4748 (793–9631)	1589 (602–2566)
Sodium (mmol/L)	141 (131–148)	139 (137–141)	142 (138–146)	141 (136–143)
Potassium (mmol/L)	3.9 (3.4–4.4)	4.1 (3.6–4.8)	4.1 (3.7–4.5)	3.9 (3.6–4.3)
Creatinine (μmol/L)	132 (113–150)	116 (86–142)	126 (98–146)	122 (92–192)

The results are expressed as means with (range). Mann–Whitney U-test was used to compare the statistical significance of differences between the groups and was performed by using IBM SPSS Statistics for Windows version 26 (Armonk, NY, USA). None of the *p*-values was under statistically significance limit .05.

Table 2 Results in combined groups at six and 24 months.

	At the baseline (n = 10)	Six months after renal denervation (n = 10)	<i>p</i> -value for difference from baseline	24 months after renal denervation (n = 8)	<i>p</i> -value for difference from baseline
Systolic blood pressure (mmHg)	114 (93–148)	115 (92–163)	.95	111 (88–135)	.55
Diastolic blood pressure (mmHg)	67 (56–80)	67 (55–82)	.78	64 (57–80)	.48
Heart rate (/min)	70 (60–77)	70 (60–75)	.46	73 (70–79)	.59
Body mass index (kg/m ²)	28.7 (24.0–36.8)	28.9 (22.6–35.9)	.59	27.2 (21.6–36.0)	.78
6-minute walk test (m)	305 (187–398)	283 (70–420)	.31	232 (129–340)	.01
Quality of Life index (EQ-5D)	64 (49–90)	59 (29–90)	.74	55 (45–70)	.73
Global ejection fraction (%)	29 (22–38)	28 (16–36)	.68	27 (20–39)	.21
Left ventricular end-diastolic diameter (mm)	72 (61–79)	72 (61–80)	.39	72 (60–85)	.44
Hemoglobin (g/L)	141 (100–172)	128 (84–149)	.06	139 (113–168)	.18
Erythrocytes (10 ¹² /L)	4.7 (3.2–5.5)	4.2 (2.6–5.2)	.01	4.7 (3.8–5.4)	.326
Leucocytes (10 ⁹ /L)	6.7 (3.4–10.1)	6.7 (5.6–8.8)	.95	7.0 (4.8–10.2)	.674
Thrombocytes (10 ⁹ /L)	178 (129–221)	195 (129–325)	.31	173 (147–239)	.674
B-type natriuretic peptide (ng/L)	3587 (602–7959)	3631 (457–9631)	.44	6499 (996–20714)	.07
Sodium (mmol/L)	141 (131–148)	142 (138–146)	.80	141 (135–144)	.14
Potassium (mmol/L)	3.9 (3.4–4.4)	4.0 (3.7–4.5)	.51	4.1 (3.4–4.7)	.21
Creatinine (μmol/L)	128 (92–192)	123 (74–161)	.34	134 (98–173)	.02

The results are expressed as means with (range). Wilcoxon matched-pair signed-rank was used to compare the statistical significance of differences and was performed by using IBM SPSS Statistics for Windows version 26 (Armonk, NY, USA).

only a progression of the disease irrespective of the treatment group.

Conclusion

In our study, RDN did not show benefit for patients with severe heart failure (NYHA III and IV) who were non-responders to CRT.

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Disclosure statement

No potential competing interest was reported by the authors.

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- [1] Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93(9):1–1146.
- [2] Maggioni AP, Dahlström U, Filippatos G, Heart Failure Association of the European Society of Cardiology (HFA), et al. EURObservational research programme: Regional differences and 1-year follow-up results of the heart failure pilot survey (ESC-HF pilot). *Eur J Heart Fail*. 2013;15(7):808–817.
- [3] Ponikowski P, Voors AA, Anker SD, ESC Scientific Document Group, et al. 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(27):2129–2200.
- [4] Priori SG, Blomström-Lundqvist C, Mazzanti A, ESC Scientific Document Group, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). endorsed by: Association for European paediatric and congenital cardiology (AEPC). *Eur Heart J*. 2015; 36(41):2793–2867.
- [5] Brugada J, Delnoy PP, Brachmann J, RESPOND CRT Investigators, et al. Contractility sensor-guided optimization of cardiac resynchronization therapy: Results from the RESPOND-CRT trial. *Eur Heart J*. 2017;38(10):730–738.
- [6] Böhm M, Ewen S, Linz D, et al. Therapeutic potential of renal sympathetic denervation in patients with chronic heart failure. *EuroIntervention*. 2013;9(R):R122–R126.
- [7] Kaye DM, Lefkowitz J, Jennings GL, et al. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol*. 1995;26(5):1257–1263.
- [8] Kaye DM, Lambert GW, Lefkowitz J, et al. Neurochemical evidence of cardiac sympathetic activation and increased central nervous system norepinephrine turnover in severe congestive heart failure. *J Am Coll Cardiol*. 1994;23(3):570–578.
- [9] Recordati G, Moss NG, Genovesi S, et al. Renal chemoreceptors. *J Auton Nerv Syst*. 1981;3(2-4):237–251.
- [10] Drożdż T, Jastrzębski M, Moskal P, et al. Renal denervation in patients with symptomatic chronic heart failure despite resynchronization therapy – a pilot study. *Postępy Kardiologii Interwencyjnej*. 2019;15(2):240–246.
- [11] Cahalin LP, Mathier MA, Semigran MJ, et al. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest*. 1996;110(2):325–332.
- [12] O’Keeffe ST, Lye M, Donnellan C, et al. Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. *Heart*. 1998;80(4):377–382.
- [13] Shoemaker MJ, Curtis AB, Vangnes E, et al. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. *Cardiopulm Phys Ther J*. 2013;24(3):21–29.
- [14] Glikson M, Nielsen J, Kronborg M, ESC Scientific Document Group, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: Developed by the task force on cardiac pacing and cardiac resynchronization therapy of the European society of cardiology (ESC) with the special contribution of the European heart rhythm association (EHRA). *Eur Heart J*. 2021;42(35):3427–3520.
- [15] Kinser PA, Robins JL. Control group design: Enhancing rigor in research of Mind-Body therapies for depression. *Evidence-Based Complementary and Alternative Medicine*. 2013;2013: 1–10.
- [16] Cunningham JA, Kypri K, McCambridge J. Exploratory randomized controlled trial evaluating the impact of a waiting list control design. *BMC Med Res Methodol*. 2013;13(1):150.
- [17] Dyer MTD, Goldsmith KA, Sharples LS, et al. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes*. 2010;8:13.
- [18] Fukuta H, Goto T, Wakami K, et al. Effects of catheter-based renal denervation on heart failure with reduced ejection fraction: a Meta-analysis of randomized controlled trials. *Heart Fail Rev*. 2022;27(1):29–36.