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Original Article

Effect of heart failure reversal treatment as add-on therapy in patients with chronic heart failure: A randomized, open-label study☆

Rohit Sane [a], Abhijeet Aklujkar [b], Atul Patil [c], Rahul Mandole [d,*]

[a] MadhavBaug, India
[b] Bhaktivedanta Hospital, Thane, India
[c] Shree Saibaba Heart Institute and Research Center, Nashik, India
[d] Vaidya Sane Ayurved Labs Pvt. Ltd., Thane, India

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ABSTRACT

Objectives: The present study was designed to evaluate effect of heart failure reversal therapy (HFRT) using herbal procedure (*panchakarma*) and allied therapies, as add-on to standard CHF treatment (SCT) in chronic heart failure (CHF) patients.

Methods: This open-label, randomized study conducted in CHF patients (aged: 25–65 years, ejection fraction: 30–65%), had 3-phases: 1-week screening, 6-week treatment (randomized [1:1] to HFRT + SCT or SCT-alone) and follow-up (12-week). Twice weekly HFRT (60–75 min) consisting of *snehana* (external oleation), *swedana* (passive heat therapy), *hrudaydhara* (concoction dripping treatment) and *basti* (enema) was administered. Primary endpoints included evaluation of change in metabolic equivalents of task (MET) and peak oxygen uptake (VO_{2peak}) from baseline, at end of 6-week treatment and follow-up at week-18 (non-parametric rank ANCOVA analysis). Safety and quality of life (QoL) was assessed.

Results: Seventy CHF patients ($n = 35$, each treatment-arm; mean [SD] age: 53.0 [8.6], 80% men) were enrolled in the study. All patients completed treatment phase. Add-on HFRT caused a significant increase in METs (least square mean difference [LSMD], 6-week: 1.536, $p = 0.0002$; 18-week: −1.254, $p = 0.0089$) and VO_{2peak} (LSMD, 6-week: −5.52, $p = 0.0002$; 18-week: −4.517, $p = 0.0089$) as compared with SCT-alone. Results were suggestive of improved functional capacity in patients with HFRT (QoL; Mean [SD] HFRT + SCT vs. SCT-alone; 6-week: −0.44 [0.34] vs. −0.06 [0.25], $p < 0.0001$ and 18-week: −0.53 [0.35] vs. −0.29 [0.26], $p = 0.0013$). Seven treatment-emergent adverse events (mild severity) were reported in HFRT-arm.

Conclusion: Findings of this study highlight therapeutic efficacy of add-on HFRT vs. SCT-alone in CHF patients. The non-invasive HFRT showed no safety concerns.

What is already known?

- Current CHF management guidelines recommend evidence-based treatment and care-modalities. Moreover, there is an emphasis on patient rehabilitation that acknowledge the need for improvement in patient health-related outcome. Add-on therapies based on Ayurveda and/or herbal treatment are known to have the potential to address this lacunae.

What this study adds?

- Present study introduces HFRT, an add-on therapy to SCT that shows promising results for better CHF management.

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* Corresponding author.
E-mail address: drrahul@madhavbaug.org (R. Mandole).

Abbreviations: 2D-ECHO, two dimensional-echocardiogram; ACE, angiotensin converting enzyme; ANCOVA, analysis of covariance; ARBs, angiotensin receptor blockers; CHF, chronic heart failure; DPP, double pressure product; ECG, electrocardiography; EF, ejection fraction; FAS, Full Analysis Set; IHD, Ischemic Heart Disease; HFRT, heart failure reversal therapy; HRR, heart rate recovery; LSMD, least square mean difference; MET, metabolic equivalents of tasks; NYHA, New York Heart Association; PLBS, post lunch blood sugar; PP, Per Protocol Set; QoL, quality of life; SAS, statistical analysis system; SCT, standard CHF treatment; SD, standard deviation; SHS, sampurna hruyday shudhikaran; SS, Safety Set; TEAEs, treatment emergent adverse events; TOI, time to onset of ischemia; VO_{2peak}, peak oxygen uptake.

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1. Introduction

The management of chronic heart failure (CHF) is a topic, broadly discussed since eons, and has well-established treatment regimens emphasizing the goal of reduction in symptoms and improvement of prognosis. The worldwide growing prevalence of CHF shows an annual incidence of 0.5–1.8 million in India.[1] As a result, plethora of research is performed to identify newer therapeutic targets for better management of CHF.[2] A contemporary physician is mindful of crucial objective of maximizing function in everyday life and strives to achieve the highest level of quality of life (QoL) within the limitations imposed by the disease. Along with symptoms of CHF, an array of undesirable emotions including fear and anxiety of health status lead to deterioration in the patient's morale and a progressive decline in QoL. Despite improvement in therapeutic drugs and devices, CHF has poor prognosis. The critical therapeutic advantages are those that maintain and stabilize the patient's limited functional abilities and, also improve the comfort of the patient for remaining life-span.[3]

The standard CHF treatment (SCT) includes β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), digoxin, anti-platelets and diuretics.[4] However, majority of CHF patients require complex management due to growing age, comorbidities, multiple medications, and depression or reduced coping skills.[5] Considering these exigencies, a search is ongoing for preferably non-invasive add-on therapies with SCT. Historical data have reported that β-blockers, ARBs have antioxidant, and/or anti-inflammatory properties, which may attribute to their therapeutic effects.[6,7] Several herbs are known to possess antioxidant, anti-inflammatory, antiplatelet or hypolipidemic properties.[8–14] It would, therefore, be interesting to explore if these herbs have an additional cardioprotective effect in CHF patients.

Ayurvedic physicians advocate use of conventional treatment in the acute disease phase and in chronic condition subsequent use of panchakarma therapy (a 5-step procedure for internal purification of the body) as an add-on, for providing maximum benefit to the patient.[15] Heart failure reversal therapy (HFRT) formerly known, sampurna hruyday shudhikaran (SHS) therapy is a combination of herbal treatment with panchakarma and allied therapies.[16–18] The techniques used in panchakarma namely snehana (massage), swedana (fomentation therapy) and basti (type of enema) are known to eliminate toxins.[15,19]

The primary objective of this randomized, open-label, comparative study was to evaluate the effect of HFRT as an add-on therapy to SCT on metabolic equivalents of tasks (METs) and peak oxygen uptake (VO_{2peak}) in CHF patients. The effect on ejection fraction (EF), time to onset of ischemia (TOI), double pressure product (DPP), heart rate recovery (HRR) and quality of life (QoL) were also evaluated.

2. Methods

2.1. Study population

Study participants included patients (both gender, aged 25–65 years) with CHF (New York Heart Association, NYHA Class I–III), history of CHF irrespective of angioplasty and coronary artery bypass graft on SCT, having MET values: 3–7 (inclusive), and EF between 30–65% (inclusive) on a standard two dimensional-Echocardiogram (2D-ECHO) test (6 months prior to screening). Additional inclusion criteria were systolic blood pressure not >150 mmHg and diastolic blood pressure not >90 mmHg, hemoglobin levels ≥10 g/dL, blood sugar level (fasting not <60 mg/dL and PLBS not >250 mg/dL).

Patients with suspected hypersensitivity to study therapy, acute heart failure, decompensated heart failure attack (last 3-months), irritable bowel syndrome, bleeding piles or fistula (grade-I or II piles), 2nd/3rd degree hemorrhoids, asthma or chronic obstructive pulmonary disease, abnormal thyroid function test, hepatic or renal insufficiency, cancer, physical disability (any form) leading to immobilization, participation in another study 30-days prior to screening were excluded. Patients not on stable dose of SCT (last 3-months), needing upward dose titration were excluded and also pregnant or lactating women.

The Independent Ethics Committee approved the protocol. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki, consistent Good Clinical Practices, and applicable regulatory requirements. All patients or their legally acceptable representatives provided written informed consent to participate in the study.

2.2. Study design

Open-label, randomized study, conducted from 2014 to 2015 in outpatients at two centers (Bhaktivedanta Hospital, Mumbai and Shree Saibaba Heart Institute and Research Center, Nasik) was divided into 3-phases: screening (up to 1-week), treatment (6-week) and follow-up phase (12-week). At treatment phase, patients enrolled after screening were randomized (1:1) to either groups: (1) HFRT, twice/week plus SCT (like β-blockers, ACE inhibitors, digoxin, anti-platelets and diuretics) or (2) SCT-alone. Randomized and treated patients were evaluated at end of the treatment (6-week) and at 18-week in the follow phase (Fig. 1).

Permuted block randomization was performed to allot either treatment: HFRT + SCT or SCT-alone based on next available number as per the randomization chart.

2.3. Study therapy

The HFRT, a 4-step procedure *(snehana, swedana, hrudaydhara, basti)* requiring 65–75 min was performed after a light breakfast (Fig. 2; Supplementary material[15,19]).

2.4. Study evaluations

2.4.1. Cardiac function measures

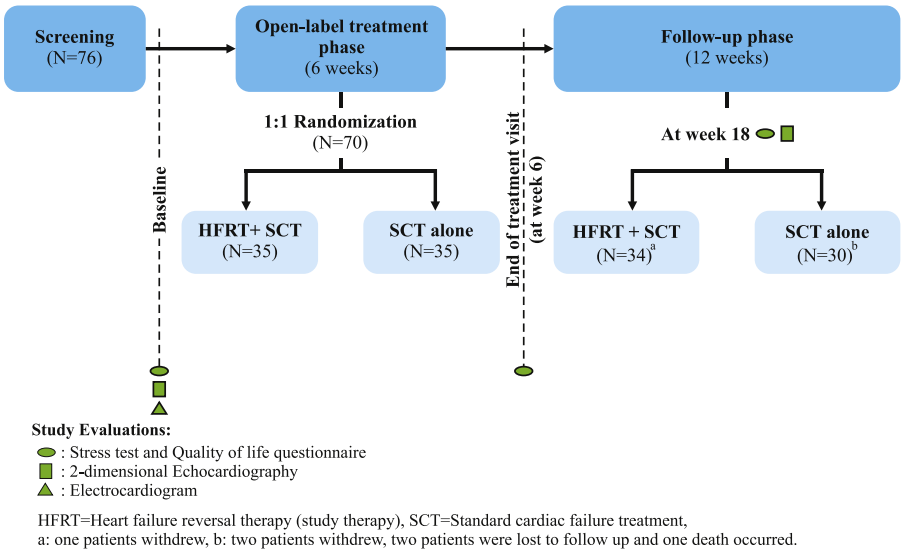
Primary endpoints were improvement in MET and VO_{2peak} as evaluated by cardiac stress test with modified Bruce protocol and 12-lead electrocardiography (ECG) at baseline, 6 and 18-week. MET is ratio of metabolic rate (the rate of energy consumption) during a specific physical activity to a reference metabolic rate (3.5 ml O_2 kg^{-1} min^{-1}). VO_{2peak} is the measurement of the volume of oxygen that the body can utilize during physical exertion (VO_{2max} = MET value × 3.6).

Secondary endpoints (monitored at 6 and 18-week) included improvement in QoL: assessed by questionnaires (adapted from validated questionnaires[20–23]), EF, improvement in TOI and DPP and HRR as assessed by monitoring heart rate.

HRR is time taken to return to normal heart rate at end of stress test. TOI (time to onset 1 mm of ST segment change in more than 2 leads) and DPP (product of maximum heart rate and systolic blood pressure) were recorded during stress test.

2.4.2. Safety and tolerability

Safety was assessed throughout the study and evaluated by frequency, severity and intensity of treatment-emergent adverse events (TEAEs), serious TEAEs, physical examinations, vital signs and laboratory tests (biochemistry, hematology, and urine analysis).



HFRT=Heart failure reversal therapy (study therapy), SCT=Standard cardiac failure treatment,
a: one patients withdrew, b: two patients withdrew, two patients were lost to follow up and one death occurred.

Fig. 1. Study design and patient flow.

Heart failure reversal therapy	Type of technique	Duration	Herbs used	Additional information
Snehana[15]	External oleation or massage	30–35 minutes	100 mL extract (processed in sesame oil): 10 gm *T. arjuna,* 5 gm *V. negundo* and 10 gm *Dashamoola*	It uses centripetal or upward strokes directed towards the heart
Swedana[15]	Passive heat therapy	10-15 minutes + 3-4 minutes of relaxation after procedure	*Dashmoola* (group of ten herbal roots) steam (temperature not > 40°C)	During the procedure, patients were asked to lie down inside a sudation box in supine position with head positioned outside
Hrudaydhara	Decoction dripping treatment (constant speed, from 7-8 cm height over the medial mediastinum region)	15 minutes	Luke-warm *dashmoola* decoction	Variation of *shirodhara* technique[19]
Basti[15]	Medicated enema	10 minutes	10 mL aqueous extract of: 1880 mg *T. arjuna*, 420 mg *B. diffusa* and 180 mg *A. calamus*	Administered per rectal solution had to remain inside the body ≥15 minutes for maximum absorption

Fig. 2. Study therapy.

2.5. Statistical methods

2.5.1. Analysis set

Analysis sets were as follows: Safety Set (SS) randomized patients who received treatment at least once; Full Analysis Set (FAS) – patients who had primary efficacy parameters assessed post-baseline; Per Protocol Set (PP) – patients who completed the study with no protocol deviations.

2.5.2. Sample size determination

The sample size ($N = 27$, each treatment group) was pre-specified to the minimal detectable differences of 1.5 in MET and 3.0 in VO_{2peak} levels (mean change from baseline) between the two treatment groups at week 12 with 80% power and a 0.05, two-sided significance level and standard deviation of 1.9 in MET and 3.8 in VO_{2peak} levels. Assuming 20% dropout rate, 35 CHF patients were required to be enrolled in each group.

2.5.3. Statistical analyses

Demographic and baseline characteristics of SS were summarized descriptively. The mean change in efficacy endpoints between groups was analyzed using non-parametric rank analysis of covariance (ANCOVA), with baseline values as covariates. Wilcoxon Rank Sum test was used to compare QoL data. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., USA).

3. Results

3.1. Study population

Total 70/76 screened CHF patients were enrolled and randomized in open-label treatment-phase to either groups: HFRT + SCT ($n = 35$, 50%) or SCT-alone ($n = 35$, 50%). The study population (mean [SD] age: 53.0 [8.6]) comprised of 80% men (HFRT + SCT group, $n = 27$ [77%]; SCT-alone group, $n = 29$ [83%]). The baseline

Table 1
Baseline and clinical characteristics (Safety Set).

Parameters	HFRT + SCT ($N = 35$)	SCT alone ($N = 35$)	Total ($N = 70$)
Age, years			
Mean (SD)	53.5 (8.1)	52.5 (9.1)	53.0 (8.6)
Men, *n* (%)	27 (77)	29 (83)	56 (80)
Baseline weight, (kg)			
Mean (SD)	67 (11.3)	69 (13.1)	68 (12.1)
Smoking, n (%)			
Yes	1 (3)	1 (3)	2 (3)
Tobacco consumption, n (%)			
Yes	1 (3)	1 (3)	2 (3)
Alcohol consumption, n (%)			
Yes	3 (9)	4 (11)	7 (10)
History of allergy, n (%)			
Yes	0	1 (3)	1(1)
Medical history, n (%)			
Hypertension	18 (51)	19 (54)	37 (53)
Diabetes	8 (23)	12 (34)	20 (29)
Hypercholesterolemia	2 (6)	2 (6)	4 (6)
Intervention			
PTCA	11 (31)	12 (34)	23 (33)
NYHA Class, n (%)			
I	9 (26)	5 (14)	14 (20)
II	25 (71)	30 (86)	55 (79)
III	1 (3)	0	1 (1)
Concomitant medicines, n (%)			
Anti-platelets drugs	15 (43)	17 (49)	33 (47)
NSAIDs	5 (14)	5 (14)	10 (14)
Statins	5 (14)	5 (14)	10 (14)
β-Blockers	3 (9)	3 (9)	7 (10)

HFRT, heart failure reversal therapy; NSAID, non-steroidal anti-inflammatory drug; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty; SCT, standard chronic heart failure treatment.

demographic and clinical characteristics were comparable between the groups (Table 1).

All randomized patients completed the 6-week treatment-phase in both groups. A total of 34 (97%) patients in HFRT + SCT and 30 (86%) in SCT-alone group completed the follow-up (Fig. 1).

3.2. Efficacy measurements

Efficacy parameters were analyzed at 6 and 18-week. Patients in HFRT + SCT group showed significant improvement in MET and VO_{2peak} values from baseline, at 6-week (least square mean difference [LSMD], MET: −1.536, $p = 0.0002$; VO_{2peak}: −5.52, $p = 0.0002$) and 18-week (LSMD, MET: −1.254, $p = 0.0089$; VO_{2peak}: −4.517, $p = 0.0089$) as compared to SCT-alone group. The percent change for MET and VO_{2peak} values was higher in HFRT + SCT vs. SCT-alone group from baseline, at 6-week (MET: 45.33 vs. 15.44; VO_{2peak}: 45.34 vs. 15.49) and 18-week (MET: 51.48 vs. 26.03; VO_{2peak}: 51.49 vs. 26.03). Results obtained from PP population confirmed findings from FAS population (Table 2).

QoL improved significantly from baseline (Mean [SD] HFRT + SCT vs. SCT-alone at 6-week: −0.44 [0.34] vs. −0.06 [0.25], $p < 0.0001$ and 18-week: −0.53 [0.35] vs. −0.29 [0.26], $p = 0.0013$). At 6-week, TOI (LSMD: −97.202, $p = 0.002$) and DPP (LSMD: −2242.404, $p = 0.0116$) was improved significantly from baseline in HFRT + SCT as compared to SCT-alone group. However, the values were not statistically significant at 18-week. The EF was significantly improved from baseline, at 18-week (LSMD: −3.205, $p = <0.0001$) in patients of HFRT + SCT as compared with SCT-alone group (Table 2).

3.3. Safety and tolerability

Total 15 TEAEs in either treatment group (HFRT + SCT: $n = 7$ [20%] and SCT-alone: $n = 8$ [23%]) were reported with mild severity and resolved by end of the study. The TEAEs were mainly of cardiac or respiratory organ class. One death was reported in the SCT group during follow-phase (Table 3).

Overall, no TEAEs of abnormal laboratory results, vital signs, or ECG values were reported from baseline to follow-up.

4. Discussion

This randomized, open-label study of HFRT as add-on therapy for CHF management, yielded significant improvements in MET and VO_{2peak} values in comparison with SCT-alone, from baseline to 6-week. Interestingly, the improved status was maintained even 12-weeks after the therapy. Significant improvements in secondary endpoints, EF and QoL were also demonstrated in HFRT treated patients. Furthermore, the HFRT group showed a better safety profile vs. SCT-alone.

The CHF patients have a decreased rate of O_2 uptake compared to healthy individuals, leading to fatigue and slow recovery after exertion. Therefore improvement in VO_{2peak}; a validated indicator of O_2 uptake can help to improve CHF prognosis.[24] Consistent with our results, increased VO_{2peak} in CHF patients was noted in other studies, although the intervention was different.[25,26] Further, our observations of enhanced MET from baseline to 18-week are corroborated by another report evaluating the relationship between exercise volume and clinical events in CHF patients wherein 3–7 MET showed a clinical benefit.[27] Previous studies conducted for HFRT (or SHS) also showed improvement in MET and VO_{2peak} values.[18]

A retrospective study in coronary heart disease patients reported that 1-unit (mL/kg/min) increase in VO_{2peak} is associated with ~15% decrease in risk of death.[28] A patient's capacity for exercise as measured by VO_{2peak} was thus considered as a strong predictor of mortality. In the current study, a significant enhancement of VO_{2peak} by 45.34% at the end of HFRT therapy possibly reflects a decline in the risk of mortality in CHF patients.

The CHF patients experience a progressive decline in QoL as their ability to perform routine physical activities is compromised due to early onset of dyspnea and fatigue. Exercise training is known to substantially increase VO_{2peak} and MET and is currently recommended to improve QoL in these patients as they become more tolerant to exertion, experience less fatigue and dyspnea and become comfortable in performing routine activities.[29–31] The significantly enhanced QoL post HFRT reflected a remarkable improvement in these features, sleep pattern, memory and routine lifestyle. The 4-elements of the HFRT treatment: *Snehana, Swedana, Hrudaydhara* and *Basti* mostly act in cohesion to alleviate the detrimental effects of CHF. The improvement in QoL with HFRT treatment by 6-week was maintained till 12-weeks after treatment. In a retrospective-cohort study in CHF patients, SHS therapy caused a remarkable improvement from NYHA Class II and III to Class I in 72% patients.[18]

The TOI and DPP are associated with Ischemic Heart Disease (IHD). The HFRT was efficacious with respect to these parameters for 6-week but not in long-term. Therefore, the role of HFRT in IHD treatment requires further investigation. HRR is an effective prognosis parameter at constant workload and MET-value. In this study, workload and MET-values were variable and hence, HRR could not be a reliable measure. This explains the erratic HRR results obtained in both arms of the study.

Although this study had a small sample size, there was 100% compliance in both treatment arms and the protocol deviations

Table 2
Analysis of change from baseline in study parameters (Full Analysis Set).

Parameters	HFRT + SCT		SCT alone		LS mean change between groups[a]	95% CI	ANCOVA *p*-value	Non-parametric rank ANCOVA *p*-value
	LS mean CFB (SE)	95% CI	LS Mean CFB (SE)	95% CI				
	N = 34		*N* = 33					
Week-6								
METs	2.33 (0.27)	1.78, 2.88	0.79 (0.28)	0.23, 1.35	−1.54	−2.32, −0.75	0.0002	<0.0001
VO_{2peak}	8.38 (0.99)	6.40, 10.35	2.86 (1.00)	0.85, 4.86	−5.52	−8.34, −2.70	0.0002	0.0001
TOI	200.41 (21.09)	158.29, 242.54	103.21 (21.41)	60.45, 145.97	−97.20	−157.50, −36.90	0.002	0.0016
DPP	1977.51 (604.1)	770.68, 3184.35	−264.89 (613.24)	−1489.98, 960.20	−2242.40	−967.16, −517.65	0.0116	0.016
HRR	24.25 (16.48)	−8.67, 57.17	−24.29 (16.73)	−57.70, 9.13	−48.54	−95.46, −1.62	0.0428	0.0695
QoL	Mean (SD) −0.44 (0.34)		Mean (SD) −0.06 (0.25)				<0.001	
Parameters	LS Mean CFB (SE)	95% CI	LS Mean CFB (SE)	95% CI	LS Mean Change between groups[a]	95% CI	ANCOVA *p*-value	Non-parametric rank ANCOVA *p*-value
	N = 34		*N* = 30					
Week-18								
METs	2.63 (0.32)	2.0, 3.27	1.38 (0.34)	0.70, 2.05	−1.25	−2.18, −0.33	0.0089	0.0016
VO_{2peak}	9.48 (1.14)	7.20, 11.77	4.96 (1.22)	2.53, 7.40	−4.52	−7.86, −1.18	0.0089	0.0016
TOI	3.28 (0.48)	2.33, 4.24	0.08 (0.51)	0.94, 1.10	−3.21	−4.64, −1.77	<0.0001	<0.0001
DPP	194.68 (25.34)	144.01, 245.35	134.73 (26.98)	80.78, 188.68	−59.95	−134.08, 14.19	0.111	0.0608
HRR	2236.71 (807.92)	621.17, 3852.24	474.33 (860.49)	−1246.33, 2194.99	−1762.38	−4131.25, 606.50	0.142	0.0694
	26.87 (15.6)	−4.33, 58.07	18.55 (16.61)	−14.67, 51.77	−8.33	−53.93, 37.28	0.7164	0.984
QoL	Mean (SD) −0.53 (0.35)		Mean (SD) −0.29 (0.26)				0.013	

[a] LS Mean change between groups is calculated as SCT-alone − HFRT + SCT.
ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; DPP, double pressure product; HRR, heart rate recovery; HFRT, heart failure reversal therapy; LS mean, least square mean, MET, metabolic equivalents of task; QoL, quality of life; TOI, time to ischemic onset; VO_{2peak}, peak oxygen uptake.

Table 3
Treatment-emergent adverse events (Safety Set).

	HFRT + SCT	SCT alone
	N = 35	*N* = 35
	n (%)	*n* (%)
Number of patients		
With at least one TEAE	5 (14.3)	2 (5.7)
With at least one severe TEAE	0	2 (5.7)
With at least one serious TEAE	0	2 (5.7)
TEAEs		
Lower respiratory tract infection	1 (2.9)	0
Upper respiratory tract infection	1 (2.9)	0
Pain in cubital fossa	1 (2.9)	0
Dengue fever	1 (2.9)	0
Chest pain	1 (2.9)	0
Cough	0	1 (2.9)
Hemoptysis	0	1 (2.9)
Breathlessness	0	1 (2.9)
Breathlessness secondary to cardio-myopathy with left ventricular failure	0	1 (2.9)
Dysphagia	0	1 (2.9)
Elevated hypertension	1 (2.9)	0
Vertigo	0	1 (2.9)
Weakness	1 (2.9)	0
Serious TEAE		
Death	0	1 (2.9)

HFRT, heart failure reversal therapy; SCI, standard chronic heart failure treatment; TEAE, treatment-emergent adverse event.

were minimal. Future studies involving HFRT with a larger sample-size and long-term follow-up in patients with different levels of CHF severity can shed more light on understanding this novel treatment option.

5. Conclusion

Add-on therapy with HFRT demonstrated significant therapeutic effects with improvement in METs, oxygen uptake and cardiac measures as compared with SCT-alone and no safety concerns were observed. The HFRT therapy augments the beneficial effects of SCT thereby improving the exercise tolerance, aerobic capacity, prognosis and QoL of CHF patients. Hence, the non-invasive HFRT therapy can be a viable option for planning the modus operandi for better CHF management

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Conflicts of interest

Dr. RM is an employee of Vaidya Sane Ayurved Labs Pvt. Ltd. Drs. RS, AA and AP has received honoraria from Vaidya Sane Ayurved Labs Pvt. Ltd.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ihj.2016.10.012.

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