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Efficacy of heart failure reversal treatment (HFRT) in patients with heart failure with preserved ejection fraction: An observational study

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Abstract
Objective: Heart failure has emerged as global health issue despite multiple treatment options. The present study was conducted to explore the efficacy of heart failure reversal therapy in patients with heart failure with preserved ejection fraction.
Material and Methods: An observational study was conducted in *Madhavbaug Hospital, Khopoli* from January 2015 to December 2017. All elderly male patients aged>60 years with heart failure and ejection fraction>40% were considered eligible. Patients were hospitalized and HFRT was given twice daily for seven days, following which they were discharged and advised to follow-up at 30, 60 and 90 days. The primary efficacy endpoint was improvement in maximal oxygen uptake (VO2 max) and secondary endpoints were changes in body weight, BMI, abdominal girth, heart rate, blood pressure.
Results: A total of 194 patients could complete the entire 90 day treatment and considered for analysis**.** The VO2max measured at day 90 was significantly higher compared to baseline values (26.36 ± 6.88 versus 18.37 ± 5.47, p<0.001). Such improvement was also observed in bodyweight (64.64 ± 9.22 at day 90 versus 68.69 ± 10.31 at baseline) abdominal girth (90.19 ± 8.46 versus 95.06 ± 9.34) BMI (23.76 ± 2.93 versus 25.23 ± 3.15) heart rate (76.61 ± 14.17 versus 80.66 ± 14.59) systolic BP (122.99 ± 12.56 versus 124.55 ± 15.25) and diastolic BP (78.39 ± 7.67 versus 78.15 ± 8.37) (p value <0.001 for all the secondary endpoints).
Conclusion: Our study demonstrated HFRT causes significant improvement in VO2 max in patients with HFpEF which implies better exercise tolerance. HFRT also showed improvement in weight, BMI and abdominal girth, blood pressure of the patients, which could have a positive impact on quality of life**.**

Keywords: Heart failure with preserved ejection fraction, heart failure reversal therapy, Panchakarma, maximal oxygen uptake

1. Introduction
Heart failure (HF) is a disease clinically characterized by the impaired ability of the heart to pump and/or fill with blood [1]. It is escalating in epidemic proportions and has emerged as a major global health issue, with an estimated worldwide prevalence of >37.7 million [2]. It is projected that by 2030, the number of HF patients would rise by 25 % [2]. Heart failure is associated with shorter life expectancy, increased frequency of hospitalization and poor quality of life (QOL), and is a major public health challenge even in India [3]. On the basis of ejection fraction, HF has been classified into three subtypes, namely HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF) and HF mid-range ejection fraction (HFmrEF) [4].Heart failure with preserved ejection fraction (HFpEF) is considered as a primary cause of morbidity and mortality and accounts for approximately 50% of HF cases [5]**.** In Indian context, The Trivandrum Heart Failure Registry (THFR) reported that HFpEF accounted for 25% of the total HF burden, indicating that in Indian clinical practice, HFrEF is predominantly observed [6]. A careful overview of population-based studies revealed that HFpEF is more common in elderly, with associated comorbidities, such as obesity, hypertension, coronary artery disease (CAD), chronic kidney disease, anemia, dyslipidemia, diabetes mellitus [7]. The pathophysiology of HFpEF is poorly understood, and a literature search revealed that no medication trials could demonstrate significant improvement on the primary endpoints of cardiovascular mortality and morbidity.

Consequently, there is an unmet clinical need for new strategies for improving HFpEF quality of life and outcomes.

Ayurveda is a traditional scientific medicinal system indigenous to India. *Ayurveda* means 'knowledge of life', which comprises two Sanskrit words, *Ayu* (life) and *Veda* (knowledge or science). The principal aim of *Ayurveda* is to achieve equilibrium between the physiological and structural entities, which ultimately culminates in good health. Any disparity or unevenness because of external or internal factors may lead to disease development [8]. Ayurvedic treatment aims to restore the equilibrium through the utilization of different techniques, regimens, diet as well as medicines. Ancient Ayurvedic texts mention the clinical features and treatment of heart failure indicating that the knowledge of the disease was present with the Ayurvedic physicians [9].

In our institute (Madhavbaug Hospital, Khopoli) the Ayurvedic physicians are using a multi-faceted management treatment protocol [Heart Failure Reversal Therapy (HFRT)] to treat heart failure, which includes a combination of herbal treatment with Panchakarma and allied therapies. HFRT uses various decoctions and oils and constitutes of a 4-step procedure namely: a. *Snehana* / external oleation or massage b. *Swedana* / passive heat therapy c. *Hrudaydhara* / variation of shirodhara technique and *Basti* / per rectal drug administration.

However, a literature search revealed that there is a dearth of published literature to show the efficacy of HFRT in HFpEF patients. In this backdrop, the present study was conducted to demonstrate the efficacy of HFRT on HFpEF patients. The primary efficacy endpoint was improvement in maximal oxygen uptake (VO2 max) and secondary endpoints included was reduction in Weight, BMI, Abdominal Girth, Heart Rate (HR), SBP and DBP.

2. Material and Methods:

2.1 Study setting and patient selection:

A prospective observational study was conducted in *Madhavbaug Hospital, Khopoli* for a period of two years, extending from January 2015 to December 2017 to address the study objective. All elderly male patients with age greater than sixty years with clinical evidence of heart failure (NYHA 1-IV) and ejection fraction greater than 40% were considered eligible to participate in the study.

2.2 Study procedure

Eligible patients with heart failure were hospitalized in the clinic after initial screening. On day 1 of the study, baseline clinical status of the patient was determined by measuring blood pressure, weight, BMI, Abdominal Girth, ejection fraction (as measured by 2D Echo) and Stress test. Following this, HFRT therapy is applied twice daily (morning and evening) to the patients. This pattern is followed in the next seven days during the hospitalization with a diet plan of 1000-1200 kcals. On Day 7, the same tests performed on day 1 were repeated and the patient was discharged from the hospital. At the time of discharge, patients were advised to follow-up at 30-days, 60-days and 90-days. During each follow-up visit, blood pressure, weight, BMI, abdominal Girth, ejection fraction were measured and Stress test was performed. In this context, it is prudent to share the details of HFRT procedure. The HFRT therapy is a combination of Panchakarma and allied therapies. HFRT uses various decoctions and oils and constitutes of a 4-step procedure namely:

a. *Snehana* / external oleation or massage (~30 -35 minutes): An oil-based decoction was used to administer external massage to the HF patients. This massage technique uses centripetal or upward strokes directed towards the heart.
b. *Swedana* / passive heat therapy (~10 -20 minutes): To administer this therapy HF patients were asked to lie in a supine position inside a sudation box and their head was positioned outside the box. *Dashmoola* (group of ten herbs) steam of temperature not more than 40 was then passed steadily for 10-15 minutes. After the treatment, patients were asked to relax for 3-4 minutes.
c. *Hrudaydhara* / variation of shirodhara technique (~ 15 minutes): During this technique, luke-warm *dashmoola* decoction was allowed to drip at a constant speed from a fixed height on the medial mediastinum region of the HF patients demarked by a hrudayapatra.
d. *Basti* / per rectal drug administration (~ 15 minutes): A drug was administered to HF. that remains inside the body ≥ 15 minutes for maximum absorption.

Each cycle of HFRT is about 60-75 minutes duration.. The detailed schedule of HFRT is described below in Table 1.

Table 1: Study Treatment: Heart Failure Reversal Therapy (HFRT)

Step of HFRT	Type of Therapy	Herbs used for therapy	Duration of Therapy
Snehana	Massage or external oleation centripetal upper strokes directed towards heart)	10 grams T. arjuna, 10 grams *Dashamoola* and 5 grams *V. negundo* [100 ml extract processed in sesame oil]	30-35 minutes
Swedana	Passive heat therapy	*Dashmoola* (group of ten herbal roots) with steam at ≤ 40 degrees Celsius)	10-15 minutes + 3-4 minutes of relaxation after procedure
Hrudaydhara	Decoction dripping therapy from a height of 7-8 cm	Luke-warm *dashmoola* decoction	15 minutes
Basti	Drug administered per rectal, should be in body for ≥ 15 minutes for maximum absorption	1.88 grams *T. arjuna*, 0.42 grams *B. diffusa* and 0.18 grams *A. calamus* [10 ml aqueous extract]	10 minutes

2.3 Statistical analysis:

Data was entered in MS excel and analyzed using R Version 3.5.0 software. The data of only those patients who could complete the entire treatment (hospitalized for 7 days and attended all follow-up visits) were considered for analysis. One way ANOVA was used to test statistical significance for changes in the primary endpoint (improvement in VO2max) and secondary endpoint (Reduction in Weight, BMI, abdominal Girth, Heart Rate, blood pressure) at all-time points, namely baseline i.e. Date of admission(DoA), date of discharge (DoD), 1st follow up, 2nd Follow up, 3rd

Follow up. A two tailed p-value<0.05 was considered to be statistically significant for all the variables.

3. Results

During the study period, a total of 575 patients were considered eligible for participation in the study. However, 194 patients could complete the entire treatment and were considered for analysis. The baseline characteristics of the study population are shown in Table 2. The medical history of the patients was also assessed for the presence of co-morbidities.It may be noted that put of 194 subjects, hypertension was the most common co-morbidity followed by ischemic heart disease, diabetes mellitus, coronary artery disease and myocardial infarction. Most of the patients were of Class II 137 (70.62%) and Class III 30 (15.46%) as per NYHA functional class. Only 3 respondents belong to class IV.

Table 2: Baseline characteristics of the study subjects (n= 194)

Variable	Mean ± SD
Gender (M)	194/0
Age (Years)	64.88±3.92
Height (cm)	164.83±6.48
Past medical history Frequency (%)	
CAD	82 (42.27)
HTN	139 (71.65)
DM	97 (50.00)
IHD	130 (67.01)
MI	19 (9.79)
NYHA functional class Frequency (%)	
Class I	17 (8.76)
Class II	137 (70.62)
Class III	30 (15.46)
Class IV	3 (1.55)

3.1 Primary endpoint

Assessment of improvement in VO2 max: The VO2 measured at day 90 was significantly higher when compared to the mean value on day 1 which was considered as the baseline value (26.36 ± 6.88 vs 18.37 ± 5.47, p<0.001) [Table 3, Figure 1.1].This signifies a positive impact of HFRT on cardiorespiratory fitness.

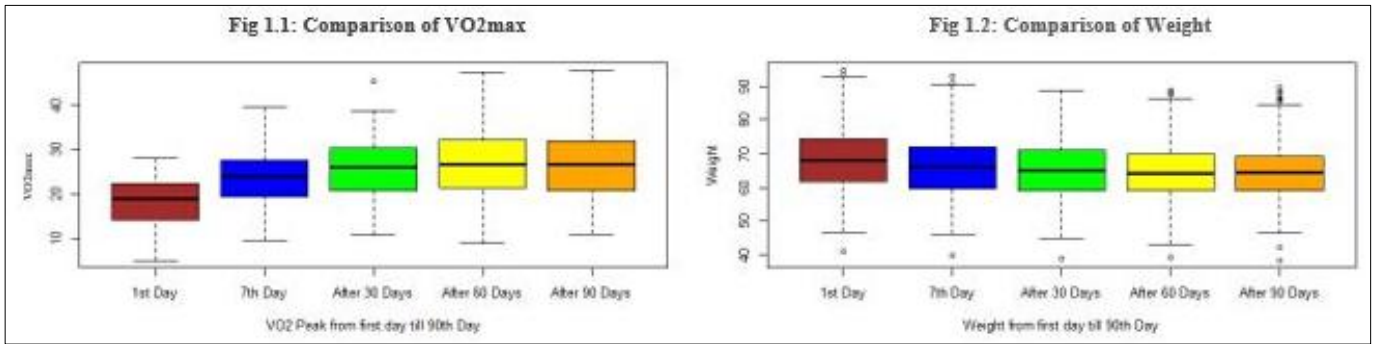
3.2 Secondary endpoints

a. Body weight: The body weight of the patients reduced significantly in the follow-up visits from their baseline values. The mean decrease in bodyweight measured at third follow-up was 64.64 ± 9.22 as compared to the baseline value on Day 1 i.e. day of admission (68.69 ± 10.31; p <0.001).(Table 3, Figure 1.2)
b. BMI: The mean BMI underwent significant reduction on day 90 when compared to the mean BMI recorded at the baseline (23.76 ± 2.93 vs 25.23 ± 3.15, p<0.001) [Table 3, Figure 1.3].
c. Abdominal girth: The abdominal girth was also significantly reduced on day 90 compared to the baseline mean abdominal girth (90.19 ± 8.46 vs 95.06 ± 9.34, p<0.001) [Table 3, Figure 1.4].
d. Hemodynamic parameter: At the third follow-up visit, there was significant reduction in the basal heart rate from baseline value (76.61 ± 14.17 versus 80.66 ± 14.59, p<0.001, Table 3, Figure 1.5).Such reduction in also noticed in SBP, DBP at third follow-up as compared to baseline (SBP 122.99 ± 12.56 versus 124.55 ± 15.25, p<0.001) and DBP (78.39 ± 7.67 versus 78.15 ± 8.37, p<0.001).(Table 3, Figure 1.6 and 1.7)

Table 3: Effect of HFRT treatment on improvement of various body parameters according to overall and NYHA subjects

Variable	Sample size	Mean ± SD					P-value
		DOA	DOD	1 f/u	2 f/u	3 f/u	
VO2 max	194	18.37 ± 5.47	23.44 ± 6.14	25.85 ± 6.77	26.79 ± 7.24	26.36 ± 6.88	<0.001
Weight	194	68.69 ± 10.31	66.62 ± 9.98	65.57 ± 9.68	65 ± 9.52	64.64 ± 9.22	<0.001
BMI	194	25.23 ± 3.15	24.48 ± 3.08	24.09 ± 2.97	23.89 ± 2.95	23.76 ± 2.93	<0.001
Abdominal Girth	194	95.06 ± 9.34	92.89 ± 9.02	91.03 ± 8.55	90.53 ± 8.47	90.19 ± 8.46	<0.001
Heart Rate	194	80.66 ± 14.59	73.51 ± 12.88	76.62 ± 13.02	77.97 ± 13.92	76.61 ± 14.17	<0.001
SBP	194	124.55 ± 15.25	118.27 ± 12.31	120.27 ± 13.87	120.49 ± 13.02	122.99 ± 12.56	<0.001
DBP	194	78.15 ± 8.37	75.21 ± 6.99	76.53 ± 8.15	76.27 ± 7.7	78.39 ± 7.67	<0.001

Effect of HFRT treatment on improvement of body parameters is summarized in Table 2. For all 203 cases, HFRT treatment showed significant improvement in all the parameters.



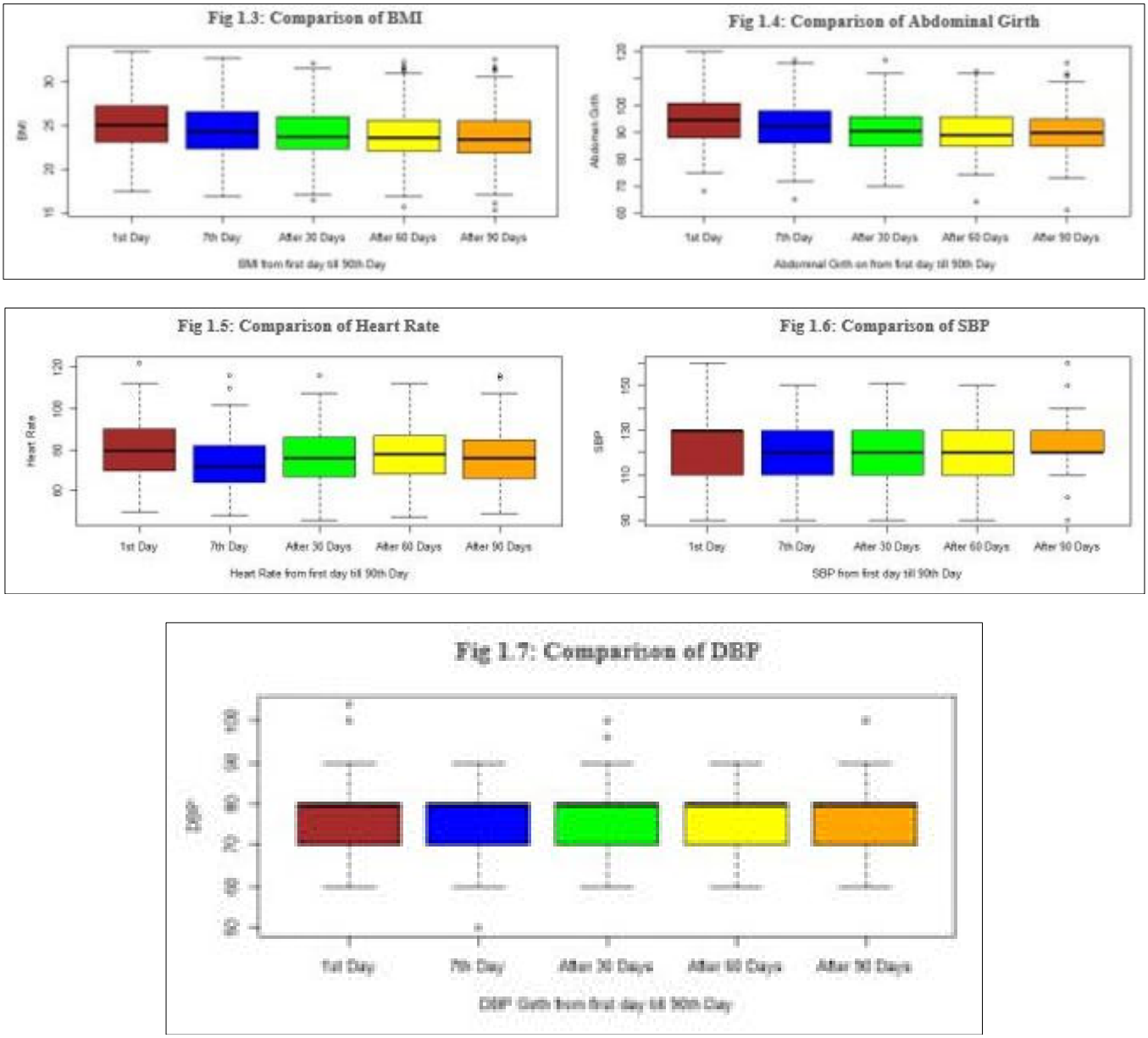


Fig 1: Comparison of study endpoint at all time period (DoA, DoD, 1st follow up, 2nd Follow up and 3rd Follow up).

4. Discussion

The global problem of heart failure is on escalation at an alarming rate worldwide as well as in India. Researchers and policymakers have repeatedly highlighted the need for new treatment options to manage heart failure, which turned our attention towards *Ayurveda*, the ancient form of alternative medicine widely used in India. Ayurvedic practitioners have been treating heart failure since ancient times.

Heart Failure Reversal Therapy (HFRT) is one such treatment used to treat heart failure in India, which includes a combination of herbal treatment with Panchakarma and allied therapies. In the present study, we have assessed the efficacy of this treatment technique on cardiovascular parameters like VO2 max, abdominal girth, BMI, blood pressure, body weight. All these parameters were significantly reduced in the patients on HFRT management, at the end of 90 days.

The primary endpoint of our study was VO2 max. Exercise intolerance constitutes one of the hallmark symptoms of heart failure. The main reason of reduced exercise capacity in HF patients is systolic and/or diastolic left ventricular dysfunction, which results in impaired hemodynamic response to exercise [11].Other pathophysiological mechanisms postulated are impaired muscle blood flow caused by increased vasoconstriction, and/or decreased local vasodilatory capacity, muscle mitochondrial dysfunction, an augmented ventilatory response to exercise, autonomic imbalance [11]. American Heart Association (AHA) in a recent statement (2016) mentioned that low levels of cardiorespiratory fitness (CRF) are associated with a high risk of cardiovascular disease (CVD) and all-cause mortality [12]. Although CRF is now recognized as an important marker of cardiovascular health, it is rarely assessed in clinical studies and practice. Researchers have opined that VO2 is a reliable indicator of the severity of heart failure and a strong predictor of the prognosis in HF patients [13]. Hence, we considered V02 max as the primary study endpoint. Our study revealed that HFRT causes a significant improvement in VO2 max from baseline value which implies better exercise tolerance of HF patients. This improvement in exercise tolerance could translate into a decrease in cardiovascular mortality, morbidly and quality of life of the patients.

Snehana is provided using *Neem* (*Azadirecta indica*) oil all over the body. Oleation is an anxiolytic procedure which decreases the sympathetic stress. The reduced sympathetic action decreases the vasoconstriction, which can be helpful to improve the hemodynamic status. *Swedana* is a process wherein patients are allowed to sleep inside a wooden box full of steam with head and neck outside the box, temperature being maintained around 40-45-degree Celsius. After 15-20 min patient is asked to come outside the box. It is hypothesized that hot fomentation, which is a relaxing process, induces sweating and decreases the excess of sodium and water which comprehensively helps to decrease fluid retention and improve hemodynamic status of HF patients. This helps in the reduction of edema in the patient thus alleviating the congestive symptoms of heart failure [10].
In *Basti*, mild purgation will occur which help in reducing the sodium retention and thus controlling the BP as evidenced in the earlier study [14]. Besides this mechanism, *Lekhana Basti* was found to have a significant effect in reducing the symptoms of *Medodushti* (dyslipidemia) and in reduction of objective parameters like weight, body mass index (BMI), body fat percentage [15].
Infact, the four basic elements of HFRT namely *Snehana*, *Swedana*, *Hrudaydhara* and *Basti* are postulated to act in synergism to alleviate the symptoms of heart failure [10]. This synergistic action ultimately resulted in the improvement of both primary and secondary endpoints.
The present study was however not free from limitations. It was single-arm study due to which the results could not be compared with the standard care. Quality of life (QoL) variables was beyond the scope of our study. Future clinical trials with large sample size are required to generate stronger evidence.

5. Conclusion
The present study demonstrated HFRT causes significant improvement in VO2 max from baseline value which implies better exercise tolerance of HF patients. This improvement in exercise tolerance could translate into a decrease in cardiovascular mortality, morbidity. HFRT also showed improvement in the metabolic parameters of weight, BMI and abdominal girth of the heart failure patients which have a positive impact on their quality of life However, multicentric clinical trials with adequate sample size could generate stronger evidence on effectiveness of HFRT in HFpEF patients.

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