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Lessons from the trials

PARIS: A good start for exercise in HFPEF

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INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by a constellation of signs and symptoms involving various organ systems. Structural and/or functional cardiac abnormalities form a cornerstone to the pathophysiology of HF. However, extracardiac dysfunction plays an equally important role in its development and progression.[1]

Approximately 50% or more of HF patients have HF with preserved left ventricular ejection fraction (HFPEF), and the proportion is higher among women and the elderly.[2,3] The main symptoms of this entity – similar to HF with reduced ejection fraction (HFREF) – are related to exercise intolerance[4–9] (dyspnea and fatigue) as well as reduced quality of life.[5] However, the pathophysiology of exercise intolerance in this group of patients is not well understood. There is scarcity in HFPEF mechanistic clinical studies and relatively few data regarding its treatment.[10]

Exercise intolerance can be objectively expressed by reduced peak exercise oxygen consumption (VO2) measured by expired gas analysis, a technique that is valid and reproducible in patients with HFPEF.[11,12] According to Fick's equation, reduced peak VO2 results from either reduced cardiac output (CO), peripheral arterial-venous oxygen difference (A-VO2 Diff), or both.

Many studies have reported that endurance exercise training (EET) improves peak VO2 in patients with HFREF,[13,14] and that this improvement results from favorable changes in cardiac,[13,15–17] peripheral vascular,[15] and skeletal muscle function.[16,18–20] These changes increase oxygen delivery to, and utilization by, the active muscles (i.e., increased A-VO2 Diff). In contrast, there are only four studies of such kind in patients with HFPEF[21–24] and the mechanisms of exercise training effects in this group are not known yet.

PARIS STUDY

This study is a randomized, controlled, single-blinded trial that examined the acute and 4-months effect of EET in elderly patients with HFPEF.[22] Its primary endpoint was to detect improvement in peak VO2 after EET, as well as determine the relative contributions of the components of Fick's equation (CO and A-VO2 Diff) in peak VO2.

HFPEF patients were recruited from clinic and hospital discharge records of Wake Forest Medical Center. Cardiopulmonary exercise tests were performed on all patients at baseline and after 4 months in the upright position on an electrically-braked cycle ergometer along with 2-dimensional echocardiography. Peak VO2 was measured – from expired gas analysis – as the highest oxygen consumed in the last 30 seconds of peak exercise. Echocardiograms were performed at rest and during exercise to measure left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV). Patients were randomly assigned after the baseline tests to either 4 months of EET or attention control (AC). EET consisted of walking on a track and cycling for up to 60 min per session with progressive increase in intensity from 40% to 70% heart rate (HR) reserve while the AC subjects were contacted every 2 weeks to collect information and encourage regular attendance of subsequent visits but were not provided with information regarding exercise.

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Stroke volume (SV), HR, CO, and systemic vascular resistance (SVR) were measured. The A-V O2 Diff was calculated using Fick's equation (VO2 divided by CO).[25] Circulatory power was calculated as the product of VO2 and systolic blood pressure.[26]

A mediation analysis was performed to estimate the effect of EET on peak exercise VO2 and measure the relative contributions of CO and any other factor (namely the A-V O2 Diff) to the increase in peak exercise VO2 resulting from EET.[27]

RESULTS

A total of 46 patients completed the 4-month study; but only 40 patients were included in the analysis because of adequacy of the echocardiographic images for volume measurements (22 in the EET group and 18 in the AC group). At baseline, there were no significant differences between the two groups in key demographic or clinical characteristics (e.g. age, female gender, body mass index, NYHA class, anti-HF medications).

After 4 months of intervention, there were still no significant differences between the groups in all variables at rest (HR, LVEDV, LVESV, SV, CO, systolic, diastolic, or mean arterial blood pressures, SVR or estimated A-VO2 Diff).

However, during exercise testing, peak VO2 was significantly higher in the EET group compared to the AC group (16.3 ± 2.6 ml/kg/min vs. 13.1 ± 3.4 ml/kg/min). EET caused a change of +2.3 ml/kg/min in peak VO2 and +6 beats/min in HR. The respiratory exchange ratio was >1.10 in both groups (1.15 ± 0.09 vs. 1.13 ± 0.11; $p = 0.18$), indicating an exhaustive level of effort during exercise. Peak and reserve HR were significantly higher in the EET group compared to AC group (139 ± 16 beats/min vs. 131 ± 20 beats/min, $p = 0.03$; and 69 ± 17 beats/min vs. 57 ± 17 beats/min, $p = 0.01$, respectively).

Of note, there were no significant differences between groups in peak exercise LVEDV (77 ± 18 ml vs. 77 ± 17 ml, $p = 0.51$), LVESV (30 ± 11 ml vs. 31 ± 13 ml, $p = 0.58$), SV (48 ± 9 ml vs. 46 ± 9 ml, $p = 0.83$), CO (6.6 ± 1.3 l/min vs. 5.9 ± 1.5 l/min, $p = 0.32$), systolic (187 ± 22 mm Hg vs. 178 ± 28 mm Hg, $p = 0.19$), diastolic (89 ± 10 mm Hg vs. 84 ± 8 mm Hg, $p = 0.43$) or mean arterial pressures (122 ± 12 mm Hg vs. 116 ± 14 mm Hg, $p = 0.22$), or SVR (1,499 ± 303 dynes.s/cm^5 vs. 1631 ± 440 dynes.s/cm^5, $p = 0.32$). The percent reduction in SVR from rest to peak exercise was also similar in the 2 groups (44 ± 13% vs. 45 ± 14%, $p = 0.46$). However, the calculated peak and reserve A-VO2 Diff were significantly higher in EET group (19.8 ± 4.0 ml/dl vs. 17.3 ± 3.7 ml/dl, $p = 0.03$; and 10.5 ± 4.2 ml/dl vs. 7.2 ± 3.3 ml/dl, $p = 0.01$) (Figure 1). Finally, peak and reserve circulatory power were significantly higher in the EET (3080 ± 712 ml/kg/min.mmHg vs 2295 ± 687 ml/kg/min.mmHg; $p = 0.002$ and 2596 ± 670 ml/kg/min.mmHg vs 1817 ± 608 mml/kg/min.mmHg; $p < 0.001$).

Mediation analysis showed a 19.8% increase in peak VO2 in the EET group compared to AC group. The magnitude of this increase that was explained by the effect of training on CO was only 3.2% (i.e. 16% of the total improvement in peak VO2). Thus, 84% of the training-related improvement in peak VO2 was due to factors other than CO (i.e., improved A-VO2 Diff).

DISCUSSION

This study sheds more light on the value of EET as a non-pharmacologic intervention method in treatment of HFPEF that is still underutilized in our daily practice. It showed that 4 months of EET in elderly compensated HFPEF patients caused an improvement in peak exercise capacity. This was mainly attributed to increased peak A-VO2 Diff. Surprisingly, the CO was not affected by training. These findings imply that EET improves peripheral vascular, microvascular, and/or skeletal muscle functions and causes an increase in oxygen transport or greater oxygen utilization by the active skeletal muscle. This could introduce a new concept in the understanding of the process of exercise intolerance in HFPEF patients that may direct future treatment.

However, the results of this study should be taken cautiously. The study recruited elderly patients; an age group that is known to have lower skeletal muscle mass as a part of the aging process. This may explain the improvement that happened with EET and the rise in the peak A-V O2 Diff. Moreover, the effect of EET on peak VO2 could be gender-specific. The majority of patients were females; which reflects the gender distribution of HFPEF in the general population. Previous studies on healthy elderly women reported an increase in peak VO2 after EET that was entirely due to an increase in A-V O2 Diff. In contrast, healthy elderly men had an increase in peak VO2 that was attributed to increased peak SV and CO and -to a less extent- increased A-V O2 Diff.[28,29]

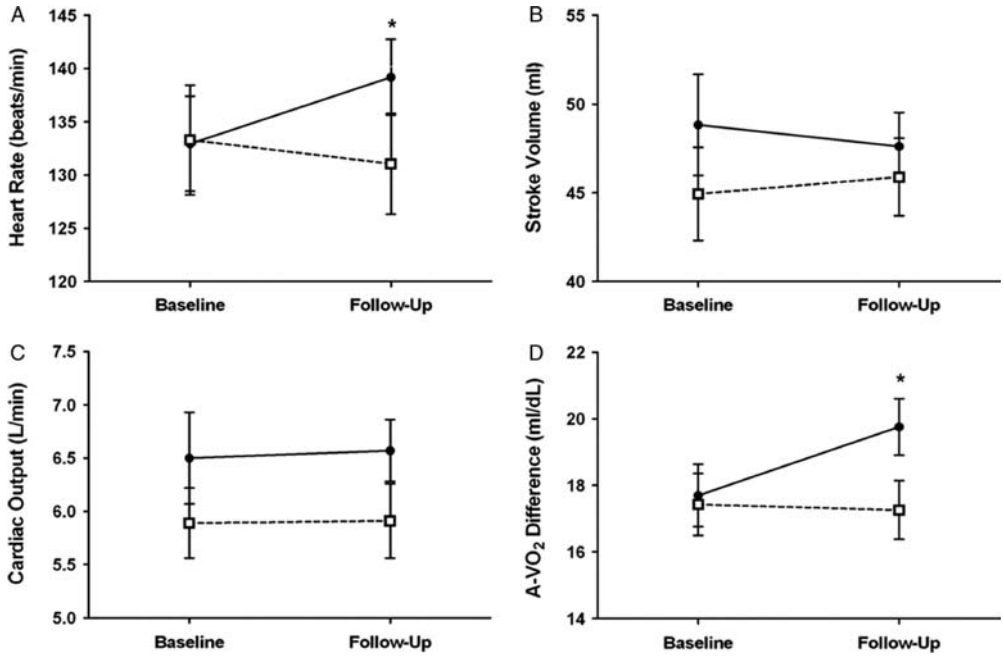

Figure 1. Peak Exercise Data at Baseline and 4-month Follow-up. Peak exercise data at baseline and 4-month follow-up for (A) heart rate, (B) stroke volume, (C) cardiac output, and (D) arterial-venous oxygen (A-VO2) difference. Solid circles and solid lines represent the group randomly assigned to exercise training; open squares and dashed lines represent patients randomly allocated to the attention control group. Values displayed at each time point are raw mean ± SE. *$p = 0.03$. All p values are from the analysis of covariance model based on comparison of least-square means at follow-up after adjustment for baseline values.

In addition, the EET group was trained for only 4 months. There is no available data on the effects of extending training to longer periods or using training protocols other than the endurance training; alone or in combination with it.

In this study, A-V O2 Diff was not measured directly but was rather derived from Fick's equation. The authors stated that this method was used in a number of physiologic studies investigating mechanisms of exercise intolerance that had included HFPEF patients[25,30–33] and that they analyzed changes in reserve capacity (rest minus peak values) within individual subjects and not absolute values, so that comparisons of CO and estimated A-VO2 Diff between the 2 groups were valid. However, the main outcome of the study has to be measured directly in order to obtain valid and reliable results. In addition, the authors did not mention anything about the power of the study and the difference in estimated A-V O2 Diff between the 2 groups that they considered significant.

The authors concluded that EET caused an increase in peak VO2 after 4 months and suggested that this effect was attributed to changes in peak A-V O2 Diff; after excluding the other variable in the Fick's equation "the unchanged CO". Thus, they postulated that these findings could imply that EET improved peripheral vascular, microvascular, and/or skeletal muscle functions and caused an increase in oxygen transport and/or greater oxygen utilization by the active skeletal muscle. In a more recent extension of the PARIS study,[34] they showed that the change in peak A-V O2 Diff was not attributed to a change in endothelial function or arterial stiffness, thus they excluded these two components of the A-V O2 Diff variable and concluded that effect of EET may be explained by changes in skeletal muscle perfusion and/or oxygen utilization.

WHAT HAVE WE LEARNED?

HFPEF is still an incompletely understood disease entity. The underlying pathophysiologic mechanisms of the disease process are yet to be determined. EET can improve exercise capacity of the patients, possibly by an effect on peripheral circulation and skeletal muscle function. More clinical trials are needed to improve our understanding of the underlying mechanisms, select the type of exercise training, design the optimal training protocols and the optimal duration to produce considerable effects in this disease entity.

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