



## Supplementary material

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### Inspiratory Muscle Training and Functional Electrical Stimulation for Treatment of Heart Failure With Preserved Ejection Fraction: The TRAINING-HF Trial

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#### SUPPLEMENTARY MATERIAL

##### METHODS

###### Procedures

###### *Cardiopulmonary Exercise Testing*

Maximal functional capacity was evaluated with incremental and symptom-limited cardiopulmonary exercise testing (CORTEX Metamax 3B) on a bicycle ergometer, beginning with a workload of 10 W and increasing stepwise at 10-W increments every 1 minute. During exercise, patients were continuously monitored with 12-lead electrocardiogram and blood pressure measurements every 2 minutes. Gas exchange data and cardiopulmonary variables were averaged every 10 seconds. Peak exercise oxygen uptake (peak  $\text{VO}_2$ ) was considered the highest value of  $\text{VO}_2$  during the last 20 seconds of exercise. The  $\text{VE}/\text{VCO}_2$  slope was determined by measuring the slope across the entire course of exercise.<sup>1</sup> Physical effort was assessed by respiratory exchange ratio.

###### *6-minute Walk Test*

Patients were instructed to cover the maximum distance possible in 6 minutes, at a self-graded walking speed, pausing to rest when needed. Each patient underwent 4 tests. The goal of the first test was to allow patients to familiarize themselves with the test.

*Inspiratory Muscle Strength Test*

Maximal inspiratory pressure was obtained using a hand-held respiratory mouth pressure meter (electronic manometer-ELKA, PM15). With a noseclip on, patients were instructed to breathe through a mouthpiece only during inspiration. The maximal inspiratory pressure values were obtained in standing position by inspiration from residual volume. At each visit, the maximal inspiratory pressure was repeated, at least, within a 1-minute interval until 3 technically satisfactory and reproducible measurements were obtained (variation of -10%).

*Echocardiography*

Doppler echocardiogram examinations were performed under resting conditions using 2-dimensional echocardiography (iE33, Philips). All parameters, including tissue Doppler parameters were measured according to current guidelines of the European Society of Echocardiography.<sup>2</sup>

*Health Related Quality of Life*

Quality of life was assessed with the Minnesota Living with Heart Failure Questionnaire.

*Serum Biomarkers*

N-terminal pro-B-type natriuretic peptide and serum carbohydrate antigen 125 were analyzed.

**REFERENCES**

1. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure. *Chest*. 2003;124:720-727.
2. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J*. 2007;28:2539-2550.

**FIGURE LEGENDS OF THE SUPPLEMENTARY MATERIAL**

**Figure 1 of the supplementary material.** Illustrative figures of training procedures. A,B: inspiratory muscle training. C,D: functional electrical stimulation of the lower limb muscles.

**Figure 2 of the supplementary material.** Change from baseline in echocardiogram parameters (A, B) and biomarkers (C, D) among treatments and visits. FES, functional electrical stimulation; IMT, inspiratory muscle training; Tx, treatment; UC, usual care;  $\Delta$ -CA125, delta serum carbohydrate antigen 125;  $\Delta$ -E/E'ratio, delta E/E' ratio;  $\Delta$ -LAVI, delta left atrial volume index;  $\Delta$ -NT-proBNP, delta N-terminal pro-B-type natriuretic peptide.

**Figure 3 of the supplementary material.** Change from baseline in ventilatory efficiency among treatments and visits. FES, functional electrical stimulation; IMT, inspiratory muscle training; Tx, treatment; UC, usual care;  $\Delta$ -VE/VCO<sub>2</sub> slope, delta ventilatory efficiency.

**Figure 4 of the supplementary material.** Change from baseline in the 6-minute walk test among treatments and visits. FES, functional electrical stimulation; IMT, inspiratory muscle training; Tx, treatment; UC, usual care;  $\Delta$ -6-MWT, delta distance walked in 6-minute walk test.