Physical training enhances sympathetic and parasympathetic control of heart rate and peripheral vessels in chronic heart failure.

ALBERTO RADAELLI, ANDREW J.S. CATS *, STEFANO LEUZZI, MASSIMO PIEPOLI, THEO E. MEYER †, ALESSANDRO CALCIAI, GIORGIO FINARDI, LUCIANO BERNARDI and PETER SLEIGHT †.

Department of Internal Medicine, Policlinico S Matteo, IRCCS, University of Pavia, I, cardiac Department John Radcliffe Hospital, University of Oxford †, UK, National Heart and Lung Institute *, London, UK.

ABSTRACT
1. Physical training has been proposed to increase vagal control of heart rate in chronic heart failure. We studied the effects of physical training on cardiovascular control in 6 moderate to severe heart failure (NYH II-III) patients and 6 age matched normal controls in a randomized controlled cross-over trial (Training vs Detraining).

2. Five weeks training (20 min/day, 5 days/week bicycle exercise) increased peak VO2 in both C (from 31.2±1.4 to 37.7±2.4 ml/kg/min p<0.01) and CHF patients (from 12.16±2.2 to 14.13±2 ml/kg/min p<0.05). The sympathetic-vagal control of heart rate and sympathetic control of the resistance vessels was assessed by the power of the oscillations (LF:0.03-0.15 Hz index of sympathetic activity, HF: 0.18-0.35 Hz index of vagal activity) in RR interval, blood pressure (systolic and diastolic by Finapres) and respiration by autoregressive spectral analysis, during free and controlled breathing (15bl/min). In order to increase vagal activity and to avoid the presence of respiratory related oscillations in the LF band, in CHF patients (LF/RR ratio to cb: (D) 1.73±0.35 to 1.19±0.43 p=NS; (T) 2.9±1.2 to 1.13±0.3 (<0.05) and in CHF patients (LF/RR ratio to cb: (D) 2.05±0.56 to 1.24±0.21 p=NS; (T) 2.6±0.89 to 0.87±0.15 p<0.05; and in cb HF%: 36.2±2.7 (D) to 46.2±4.8 (T) p<0.05). Before T, the sympathetic modulation of peripheral vessels (% LF compared to total variability) was depressed in CHF vs C (SBP: 9±2 vs 42±12 % p<0.05; DBP: 29±7 vs 55±31 %, p<0.05), and increased significantly after T in CHF (SBP from 9±2 (D) to 19±5 % (T) p<0.05; DBP from 29±7 to 41±11 % (T) p<0.05). This suggests an overall increase of autonomic control, both vagal on the heart and sympathetic on the peripheral vessels, in CHF by physical training.

INTRODUCTION
Baroreceptors respond to changes in volume and pressure with changes in autonomic nervous activity, i.e. parasympathetic activity to the heart and sympathetic activity to the heart and to the peripheral circulation. In congestive heart failure it has been shown both in animals (1,2) and human studies (3-6) that the baroreceptor control of heart rate and peripheral circulation is altered. Physical training has been proposed to increase vagal control to the heart in congestive heart failure patients (7) but little is known on the effects of physical training on the autonomic control to the peripheral vessels in this disease. Heart rate and blood pressure show non casual oscillations mediated by the autonomic nervous system that can be analyzed by power spectral analysis (8). Low frequency and high frequency oscillatory components have so been recognized in cardiovascular signals; HF (respiratory related) oscillations reflect parasympathetic activity to the heart and sympathetic activity to the peripheral vessels (9-11) mainly through the activity of the arterial baroreceptors (12,13). We then analyzed the fluctuations of RR interval, respiration and blood pressure in order to study the effects of physical training on the autonomic control of both heart rate and peripheral circulation in normal subjects and congestive heart failure patients.

METHODS AND PROTOCOL
Six moderate to severe heart failure patients (males, mean age 55±3 yrs, NYHA II-III) and six age matched control subjects (males, mean age 50±2 yrs) were included in a randomized cross-over study comparing physical training vs detraining. Exclusion criteria for heart failure patients were: clinically unstable heart failure, inability to perform a cycloergometer exercise test, exercise-induced cardiac ischemia, the presence of major arrhythmias. All the subjects underwent at least two maximal exercise tests at the beginning of the study. During the exercise tests VO2, VCO2 anaerobic threshold and pulmonary ventilation were measured. The training consisted in a home-based training program. Stationary bicycles were given to the patients for the training period. All the subjects were instructed to cycle at home on a cycloergometer at 60-70 % of the VO2max for five weeks, for 5 days/week, for 30 min/ day. During the detraining period all the subjects were asked to return the bicycles and to avoid any regular physical activity. At the beginning and at the end of each period (T and D) the subjects underwent a maximal exercise test with expired gases analysis. Moreover continuous recordings of RR interval (ECG), respiration (by means of impedance method) and non invasive blood pressure (by Finapres Ohmeda 2300, Englewood, USA.) were performed for five minutes in supine position, after at least twenty minutes of rest, both during free and controlled breathing, in order to increase vagal activity and to avoid the presence of respiratory related oscillations in the LF band. On the day of the study the subjects were asked not to smoke, to have a light meal at twelve, and not to drink coffee, tea, chocolate or alcohol. Studies were carried out always at the same hour (15:30) in a quiet room at a stable temperature (24-26 °C). Informed consent was obtained from all volunteers and patients. The data were recorded on a frequency modulated tape recorder and then analyzed by means of autoregressive power spectral analysis.

Power spectrum analysis
The power spectrum analysis program was written in our laboratory as previously described using an autoregressive algorithm (14). The respiratory signal obtained by the impedance pneumograph was expressed in absolute arbitrary values (mV output from the device). Total variability of each signal has been expressed as standard deviation (SD), as variance does not have a normal distribution (11,14,15). Spectral analysis allowed to identify the low frequency peak (between 0.03-0.14 Hz), reflecting mainly the sympathetic nervous activity both at the cardiac and vascular level (11,13) and the respiration related oscillations on the RR interval and blood pressure spectra which were identified by their correspondence with the oscillations of the respiratory spectrum. The high frequency peak, identified on the different signals by correspondence with the peak on the respiratory spectrum, reflects at the cardiac level the efferent parasympathetic activity (11,16) while at the vascular level it reflects the mechanical activity of the heart vessels and on the cardiac output. The LF/RR ratio reflects at the cardiac level the sympatho/vagal balance. At the vascular level the % of LF vs total variability was used as an index of the % of autonomic modulation vs all fluctuations.

Statistical analysis
Table 1: Effects of physical training on RR interval and blood pressure.
(each value represent the means±SEM)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Control</th>
<th>CHF</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>detraining</td>
<td>training</td>
<td>detraining</td>
<td>training</td>
</tr>
<tr>
<td>RR (msec)</td>
<td>1088±65</td>
<td>1119±65</td>
<td>809±41**</td>
<td>801±50</td>
</tr>
<tr>
<td>RR var (msec)</td>
<td>2159±493</td>
<td>2512±683</td>
<td>293±45**</td>
<td>181±25</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>129±7</td>
<td>127±6</td>
<td>118±9</td>
<td>115±9</td>
</tr>
<tr>
<td>SBP var (mmHg)</td>
<td>39±11</td>
<td>39±6</td>
<td>14±2</td>
<td>14±6</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>67±5</td>
<td>71±5</td>
<td>81±7</td>
<td>78±7</td>
</tr>
<tr>
<td>DBP var (mmHg)</td>
<td>13±2</td>
<td>12±2</td>
<td>9±2</td>
<td>5±1^</td>
</tr>
</tbody>
</table>

** : p<0.005 HF vs control.
^ : p<0.02 T vs D.

Data are expressed as mean ± SEM. Paired t test was used for comparisons within groups, unpaired t test was used for comparisons between groups.

RESULTS
During the detraining period mean RR interval and RR interval variance were significantly lower in heart failure patients than in control subjects (p<0.005, table 1).

Mean systolic blood pressure (SBP) was lower in heart failure patients but the difference was not statistically significant. On the contrary mean diastolic blood pressure (DBP) tended to be higher in heart failure patients than in control subjects, but this was not statistically significant. Systolic and diastolic blood pressure variabilities (variance) were lower, even if not significantly different, in heart failure patients with respect to control subjects (table 1).

During bicycle exercise, all subjects reached the anaerobic threshold, and the exercise tests were stopped because of leg fatigue. Training increased peak VO2 both in control subjects (from 31.2±1.4 to 37.7±2.4 ml/kg/min p<0.01) and in heart failure patients (from 12.16±2.2 to 14.13±2 ml/kg/min p<0.05).

RR interval and RR interval variability did not change significantly with physical training nor in control subjects or in heart failure patients. Nevertheless in control subjects RR interval and RR interval variability tended to increase after physical training (table 1). Blood pressure did not change significantly in both groups even if systolic blood pressure showed a tendency to decrease (table 1). Blood pressure variability did not change in control subjects while diastolic blood pressure variability decreased significantly in heart failure patients (p<0.02, table 1).

Training induced a significant decrease in RR interval LF/HF ratio during controlled respiration both in control subjects (LF/HF ratio fb to cb: (D) 1.73±0.35 to 1.19±0.43 p=NS; (T) 2.9±1.2 to 1.13±0.3 p<0.05) and heart failure patients (LF/HF ratio fb to cb: (D) 2.05±0.56 to 1.24±0.21 p=NS; (T) 2.6±0.89 to 0.87±0.15 p<0.05), and a significant increase in cb HF% in heart failure patients: 36.2±2.7 (D) to 46.2±4.8 (T) (p<0.05).

Before training the % of LF with respect to total blood pressure variability was depressed in heart failure patients vs control subjects (SBP: 9±2 % vs 42±12 % p<0.05; DBP: 29±7 % vs 55±31 %, p<0.05). The % of LF in blood pressure increased significantly after training in heart failure patients (SBP from 9±2 % (D) to 19±5 % (T) p<0.05; DBP from 29±7 % (D) to 41±11 % (T) p<0.05) indicating a restored autonomic modulation to the vessels.

DISCUSSION
Abnormalities in baroreceptor sensitivity represent a major feature in congestive heart failure patients. The altered baroreceptor control is evident both at the heart and at the vascular level. At the heart level a reduced chronotropic response to nitrupressive infusion and a reduced bradycardic response to phenylephrine infusion are present (3). At the vascular level it has been shown that animals with experimental low-output heart failure (1,17) show an impaired vasoconstrictor response to carotid occlusion, while patients with heart failure show an impaired response to both carotid and cardiopulmonary receptor stimulation (18-19). The reduced baroreceptor sensitivity is accompanied by an increased overall sympathetic activity and a reduced parasympathetic activity (20,21). Physical conditioning has been shown to improve vagal control to the heart in human healthy subjects and in subjects with an impaired sensitivity of the baroreceptors like hypertensive subjects (22). Moreover a recent study (7) performed in heart failure patients showed, by means of PSA, that physical training was able to increase respiratory sinus arrhythmia. Nevertheless heart failure patients are known to breathe in an irregular way. In these patients RSA could not be entirely reflected in RR interval HF oscillations, as slow breaths induce slow (LF) frequency RR interval oscillations as well (23). Changes in the power of HF oscillations could therefore be due both to changes in the pattern of breathing and in autonomic activity. In order to avoid the confounding effect of respiration, we recorded also...
the respiratory signal and performed recordings also during controlled respiration (15 b/min). Our results confirm the previous data showing that physical training increases respiration-related RR interval oscillations (RSA) in control subjects and in heart failure patients. Then we extended our study to analyze the autonomic components to the peripheral circulation. Low frequency (LF) non casual blood pressure oscillations are thought to reflect mainly sympathetic activity. It has been shown that this oscillatory component does not follow the increase in sympathetic nerve activity during physical exercise. However the presence of saturated adrenergic receptors during massive sympathetic activation such as during strenuous exercise could be partially responsible for a discrepancy between the increase in sympathetic activity and in LF power (24). The fact that LF oscillations in blood pressure are the result of a cyclic firing of the sympathetic nervous system has conducted to the hypothesis that they reflect a modulation of the nerve activity more than an absolute level of the nerve activity per se. In this view baroreceptors have been shown to be involved in RR interval LF oscillations (12). In this study we show that under basal condition in heart failure patients, known to have an overall increase in sympathetic activity and decreased baroreceptor sensitivity, the low frequency component of total blood pressure variability is reduced with respect to control subjects. This component increases after physical training in parallel with the increase in the vagal control to the heart and the decrease in sympathetic activity to the peripheral vessels, as shown also in a recent paper by NE spillover (7). Therefore this increase is unlikely to reflect an increase in sympathetic nerve activity to the vascular bed. It is possible that a reduction in sympathetic activity increases the availability of adrenergic receptors, so increasing the net effect of sympathetic stimulation to the vascular bed. Nevertheless heart failure patients show a normal vasconstrictor response to phenylephrine (19). An alternative hypothesis that can be in agreement with these findings could be that the improvement in the autonomic modulation of the peripheral vessels is brought about by more sensitive baroreceptors.

In conclusion the present data indicate that in CHF, after a home-based training program, there is a restoration of the overall autonomic modulation to the heart and to the peripheral vessels which can be unmasked by both an increase in the vagal components of heart rate variability and by an increase in the autonomic (LF) vs mechanic (HF) proportion of fluctuations in blood pressure. The ultimate significance of this restored modulation of the cardiovascular system is unknown, however one may speculate that it could improve cardiac output distribution both at rest and during exercise, so contributing to the overall increase in exercise tolerance.

REFERENCES