Overview of studies of exercise training in chronic heart failure: the need for a prospective randomized multicentre European trial

Chronic heart failure: ‘a major public health problem’

Chronic heart failure is considered a ‘major public health problem’ and is increasing in epidemic proportions. In fact, heart failure is the only common cardiovascular condition that is increasing in incidence, prevalence, and mortality, and remains responsible for major human and economic costs. A study performed among general practitioners in London reported a prevalence of heart failure in four out of every 1000 patients in the general population. The most consistent and striking observation is the dramatic relationship between age and the occurrence of heart failure: in the population above 65 years of age the prevalence is 28 per 1000 patients. Similar findings have been reported in Finland and Sweden.

Patients with chronic heart failure require frequent hospitalization, but also they may need assistance in their daily tasks because of functional disabilities. The social and economic costs of this syndrome are therefore high and are expected to increase further in the future. This is the result of the ageing of the population, because of improved survival following major cardiac events (such as myocardial infarction), and because of progress in the medical and surgical therapy of heart failure.

As a consequence, chronic heart failure places an enormous burden on health care resources. A recent survey has estimated that in Italy each year 190,000 patients need care at hospital cardiology units and about 65,000 are admitted as inpatients. In the U.S.A., in 1993 heart failure was the primary diagnosis listed in 875,000 hospital discharges—a 70% increase since 1983. This accounts for more than 6.5 million days of care. As with other statistics related to heart failure, hospitalizations are more predominant in older patients (78% of hospitalizations are of patients 65 years or older; 53% are of patients 75 years and older). As might be expected from the large number of hospitalizations, the economic cost of heart failure is high. The expenditure on hospitalizations for heart failure were more than twice the expenditure for all types of cancer and substantially more than that spent on myocardial infarction. In addition, chronic heart failure is the second most frequent cardiovascular diagnosis during office visits (an estimated 11.4 million diagnoses in 1990, in the U.S.A., and substantial additional costs accrue from diagnostic testing, medications, and nursing home care.

Although medical interventions, such as ACE inhibitor therapy can be beneficial in heart failure patients, as with any epidemic, prevention is the most effective way to improve outcome. Because the major risk factors for heart failure are hypertension and atherosclerotic vascular disease, it should not be surprising that aggressive antihypertensive and antihyperlipidaemic therapy prevents the onset of heart failure. In patients with manifest disease, medical and surgical strategies for prevention have been proposed with some success, notably ACE inhibitor drugs. The improvement of exercise capacity, which is a major symptomatic limiting factor, associated with reduced quality of life, is less convincing. For example, ACE inhibitor therapy has been proven to induce only limited increases in exercise tolerance: it improves maximal oxygen consumption no more than $1.5 \text{ ml} \cdot \text{ min}^{-1} \cdot \text{ kg}^{-1}$ and exercise time duration less than $1.5 \text{ min}$. No large randomized controlled trial has demonstrated that complex surgical techniques such as dynamic cardio-myoplasty, or cardiac transplantation, can significantly improve exercise tolerance or quality of life. Both medical and surgical treatments for the secondary prevention of heart failure can be extremely expensive.

Physical deconditioning in heart failure

There is objective evidence for similarities between aspects of pathophysiology seen in heart failure and...
the common clinical condition of physical deconditioning (secondary to prolonged forced immobilization): similar changes in peripheral haemodynamics (increased peripheral vascular resistance, impaired oxygen utilization during exercise), in autonomic control (activation of neurohumoral compensatory mechanisms, e.g. the renin/angiotensin system, sympathetic over-activation, vagal withdrawal, reduced baroreflex sensitivity), in functional activity (reduced exercise tolerance, and peak oxygen consumption), in skeletal muscle (reduced mass, composition), and in psychological conditions (reduced activity and well-being)\textsuperscript{[18]}. 

In a series of small trials, a number of groups have now shown that patients with severe left ventricular dysfunction can be safely entered into exercise training programmes and that, by the usual indices of exercise responses in heart rate, ventilation and peak oxygen consumption, achieve a favourable training response\textsuperscript{[17]}. More recently, controlled studies have confirmed the benefit of conditioning in heart failure using a randomized, controlled, cross-over design utilizing a home-based exercise regimen. At the end of the training phase, the patients experienced a significant improvement in symptoms and in exercise capacity; furthermore, exercise training reversed some of the neurohumoral activation, thought to be a major determinant of the rate of progression and of mortality in chronic heart failure patients\textsuperscript{[18]}. 

**Mechanisms of benefit of exercise training in heart failure**

**Left ventricular function**

There has been no evidence of significant changes in left ventricular ejection fraction, end fraction, end-systolic and end-diastolic volumes after training. In the EAMI (Exercise in Anterior Myocardial Infarction) trial, the improvement in exercise tolerance induced by physical training was associated with either no change in left ventricular function or with deterioration and remodelling in post-myocardial infarction patients with ejection fraction less than 40%\textsuperscript{[19]}. These findings are not surprising: in fact there is a lack of correlation between ventricular systolic dysfunction and exercise capacity\textsuperscript{[20]}. More recently, two controlled studies investigated the effect of physical training on central haemodynamics and cardiac function. Dubach and co-workers showed, in a rigorous study using magnetic resonance imaging, that high intensity 2 months physical training resulted in substantial increases in exercise capacity, with no deleterious effect on myocardial remodelling (left ventricular volume, function, or wall thickness) in patients with reduced left ventricular function after myocardial infarction\textsuperscript{[21]}. The absence of changes in cardiac output at rest or during exercise after physical training in post-myocardial infarction patients with left ventricular dysfunction has been confirmed by Ehsani \textit{et al.}\textsuperscript{[22]}. Physical training has been shown, however, to improve left ventricular diastolic function in the presence of both idiopathic dilated and ischaemic cardiomyopathy; the increase in left ventricular diastolic wall stress during exercise was lower after physical training\textsuperscript{[23–25]}, and the improvement in peak oxygen consumption was significantly correlated with an increase in peak early filling rate and reduction in atrial filling rate.

Judgutt’s study has been the only report to observe a reduction in left ventricular ejection fraction\textsuperscript{[26]}, but this study was criticised for early training intervention and the non-randomized control group. Reviewing all the published studies, there is little, if any, reduction in left ventricular function, and reassurance is offered by the fairly uniform evidence of increased total exercise tolerance (Tables 1 and 2).

**Haemodynamics**

Resting cardiac output shows little, if any, change and little modification is seen in either wedge pressure or left ventricular filling pressures\textsuperscript{[27, 28]}. The major changes in central haemodynamics are increased cardiac output at peak exercise and peak leg blood flow\textsuperscript{[28]}. These studies confirm that the reduction in exercise capacity in heart failure is more significantly determined by factors other than just reduced left ventricular function and central haemodynamics. Training reduces the chronotropic response to exercise, i.e. the same external workload is achieved at a lower heart rate and rate-pressure product, indicating a more efficient utilization of myocardial work and oxygen consumption\textsuperscript{[28]}. 

**Ventilation**

After training, minute ventilation for any given workload is reduced, with a delayed ventilatory anaerobic threshold\textsuperscript{[27]} and the slope that relates minute ventilation to the rate of carbon dioxide production is also reduced, i.e. at a given workload heart failure patients tend to breathe less\textsuperscript{[29]}: this slope has been shown to reflect the severity of heart failure\textsuperscript{[30]} and, in combination with peak oxygen consumption\textsuperscript{[31]}, has important prognostic implications in patients awaiting cardiac transplantation\textsuperscript{[32]}. 

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Table 1 Trials of exercise training in humans with impaired left ventricular function: non randomized and/or non controlled studies

<table>
<thead>
<tr>
<th>No.</th>
<th>LVEF</th>
<th>Peak VO₂</th>
<th>NYHA</th>
<th>Aetiology</th>
<th>Ex. T.</th>
<th>Ex.T. programme</th>
<th>AE peak VO₂</th>
<th>Other findings on exercise tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. 1979</td>
<td>18</td>
<td>18</td>
<td>na</td>
<td>I-III</td>
<td>&gt;6 wk post-MI</td>
<td>18 mo (12-42)</td>
<td>supervised and home-based walking, jogging, cycling, 35-45 min 2-6 d/wk, 70-85% peak HR</td>
<td>na</td>
</tr>
<tr>
<td>Conn et al. 1982</td>
<td>10</td>
<td>20</td>
<td>na</td>
<td>na</td>
<td>&gt;3 mo post-MI</td>
<td>12 mo (4-37)</td>
<td>supervised walking, jogging, 35-45 min 3-5 d/wk</td>
<td>na</td>
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<tr>
<td>Arvan et al. 1988</td>
<td>25</td>
<td>29</td>
<td>22</td>
<td>I-III</td>
<td>&gt;12 wk post-MI</td>
<td>12 wk</td>
<td>supervised cycling, treadmill, handgrip 30-40 min 3 d/wk, 50-85% peak VO2</td>
<td>+7</td>
</tr>
<tr>
<td>Sullivan et al. 1988</td>
<td>12</td>
<td>9-33</td>
<td>10</td>
<td>I-III</td>
<td>CAD-DCM</td>
<td>16-24 wk</td>
<td>cycling, walking, jogging, climbing, 60 min 3-5 d/wk, 75% peak VO2</td>
<td>+3.8</td>
</tr>
<tr>
<td>Jugdutt et al. 1988</td>
<td>7</td>
<td>43</td>
<td>na</td>
<td>na</td>
<td>6-32 wk post-MI</td>
<td>12 wk</td>
<td>Canadian Air force 5Bx 11 min/d calisthenics and jogging</td>
<td>na</td>
</tr>
<tr>
<td>Scalvini et al. 1992</td>
<td>6</td>
<td>32</td>
<td>13</td>
<td>na</td>
<td>&gt;6 mo post-MI</td>
<td>5 wk</td>
<td>supervised cycling, 20 min 5 d/wk, 70% peak workload</td>
<td>-1</td>
</tr>
<tr>
<td>Belardinelli et al. 1995</td>
<td>27</td>
<td>30</td>
<td>&lt;17</td>
<td>II-III</td>
<td>CAD-DCM</td>
<td>8 wk</td>
<td>supervised cycling, 30 min 3 d/wk, 40% peak VO2</td>
<td>+2.8</td>
</tr>
<tr>
<td>Kavanagh et al. 1996</td>
<td>30</td>
<td>22</td>
<td>15</td>
<td>III</td>
<td>CAD-DCM</td>
<td>52 wk</td>
<td>supervised, home-based walking 5 d/wk, 50-60% peak VO2</td>
<td>+2.6</td>
</tr>
<tr>
<td>Wilson et al. 1996</td>
<td>32</td>
<td>23</td>
<td>13</td>
<td>na</td>
<td>CAD-DCM</td>
<td>3 mo</td>
<td>supervised treadmill, stair machine cycling, 45 min 3 d/wk, 50% peak VO2</td>
<td>+1.2</td>
</tr>
<tr>
<td>Demopoulos et al. 1997</td>
<td>16</td>
<td>21</td>
<td>11</td>
<td>II-IV</td>
<td>CAD-DCM</td>
<td>12 wk</td>
<td>supervised cycling 60 min 4 d/wk, 50% peak VO2</td>
<td>+3.5</td>
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<tr>
<td>Single limb training</td>
<td>Kellerman et al. 1990</td>
<td>11</td>
<td>30</td>
<td>na</td>
<td>na</td>
<td>&gt;6 mo post MI or CABG</td>
<td>36 mo</td>
<td>arm ergometry 30 min 2 d/wk, 90% peak workload</td>
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<td>Hertzema et al. 1993</td>
<td>11</td>
<td>31</td>
<td>na</td>
<td>II-III</td>
<td>&gt;2 yr post-MI</td>
<td>60 mo</td>
<td>arm ergometry 30 min 2 d/wk, 80% max HR</td>
<td>NA — Ventr. Arrhythmias</td>
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<tr>
<td>Horning et al. 1996</td>
<td>12</td>
<td>21</td>
<td>17</td>
<td>III</td>
<td>CAD-DCM</td>
<td>4 wk</td>
<td>arm ergometry 30 min/d, 70% max workload</td>
<td>na</td>
</tr>
<tr>
<td>Respiratory Muscle Training</td>
<td>Mancini et al. 1995</td>
<td>14</td>
<td>22</td>
<td>11</td>
<td>I-IV</td>
<td>CAD-DCM</td>
<td>3 mo</td>
<td>isocapnic hyperpnoea, resistive breathing, strength training 90 min 3 d/wk, 70% peak workload</td>
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</tbody>
</table>

A=adrenaline; a-v=arteriovenous; CAD=coronary artery disease; CABG=coronary artery by-pass graft; d=day; DCM=dilated cardiomyopathy; Ex.T=exercise training; HR=heart rate; LVEF=left ventricular ejection fraction (%); MI=myocardial infarction; mo=months; na=not available; NA=noradrenaline; No=number of patients; NYHA=New York Heart Association functional classification; peak VO₂=peak oxygen consumption (ml.min⁻¹.kg⁻¹); PWP=pulmonary capillary wedge pressure; QoL=quality of life; ventr.=ventricular; wk=week.
<table>
<thead>
<tr>
<th>Study design</th>
<th>No.</th>
<th>LVEF</th>
<th>Peak ( V_O_2 )</th>
<th>NYHA</th>
<th>Aetiology</th>
<th>Ex.T. duration</th>
<th>Ex.T. programme</th>
<th>( \Delta ) peak ( V_O_2 )</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-over</td>
<td>17</td>
<td>20</td>
<td>13</td>
<td>II-III</td>
<td>CAD</td>
<td>8 wk</td>
<td>home-based cycling, 20 min 5 d/wk, 70-80% peak HR</td>
<td>+2-4</td>
<td>[HR_{rest} - V_{QoL}]</td>
</tr>
<tr>
<td>Cross-over</td>
<td>12</td>
<td>23</td>
<td>13</td>
<td>II-III</td>
<td>CAD</td>
<td>8 wk</td>
<td>home-based, cycling, 20 min 5 d/wk, 70-80% peak HR supervised walking, jogging, cycling, 85-115 min 5 d/wk, 70-85% peak HR</td>
<td>+1-6</td>
<td>[V_{V}-V_{Symp}-V_{Vagal}]</td>
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<tr>
<td>Parallel</td>
<td>7 vs 8</td>
<td>12</td>
<td>23</td>
<td>&gt;10 wk post MI</td>
<td>CAD</td>
<td>4 wk</td>
<td>home-based, cycling, 20 min 5 d/wk, 70-80% peak HR</td>
<td>+3-6</td>
<td>[V_{workload} +13 W]</td>
</tr>
<tr>
<td>Parallel</td>
<td>7 vs 13</td>
<td>35</td>
<td>na</td>
<td>II-III</td>
<td>&gt;12 wk post-MI</td>
<td>12 wk</td>
<td>home-based, cycling, 20 min 5 d/wk, 70-80% peak HR, walking, rowing, climbing supervised, 60 min 3-5 d/wk, 40-60% peak HR</td>
<td>+1-9</td>
<td>[V_{time}: +3 min]</td>
</tr>
<tr>
<td>Parallel</td>
<td>24 vs 24</td>
<td>30</td>
<td>15</td>
<td>II-III</td>
<td>DCM-CAD</td>
<td>3 wk</td>
<td>home-based, cycling, passive movements, 20 min supervised walking, jogging, cycling, 85-115 min 5 d/wk, 70-85% peak HR</td>
<td>+0-1</td>
<td>[V_{A-V_{02}diff} - tEx.time: +2 min]</td>
</tr>
<tr>
<td>Parallel</td>
<td>5 vs 5</td>
<td>23</td>
<td>13</td>
<td>II-III</td>
<td>CAD</td>
<td>8 wk</td>
<td>home-based, cycling, 20 min 5 d/wk, 70-80% peak HR</td>
<td>+1-3</td>
<td>[V_{workload} +16%]</td>
</tr>
<tr>
<td>Parallel</td>
<td>36 vs 19</td>
<td>26</td>
<td>15</td>
<td>II-III</td>
<td>DCM-CAD</td>
<td>8 wk</td>
<td>supervised cycling, 60 min 3 d/wk, 60% peak ( V_O_2 )</td>
<td>+1-2</td>
<td>[V_{K^+la} - \Delta{\text{lactic acid}}]</td>
</tr>
<tr>
<td>Parallel</td>
<td>12 vs 8</td>
<td>24</td>
<td>20</td>
<td>II-III</td>
<td>CAD</td>
<td>3 mo</td>
<td>supervised cycling, 30 min 3 d/wk, 50-60% peak ( V_O_2 )</td>
<td>+3-2</td>
<td>[V_{time}: +12-2 min]</td>
</tr>
<tr>
<td>Parallel</td>
<td>12 vs 10</td>
<td>26</td>
<td>17</td>
<td>II-III</td>
<td>DCM-CAD</td>
<td>6 mo</td>
<td>supervised and home based walking, calisthenics, cycling 40-60 min/d 70% peak ( V_O_2 )</td>
<td>+5-8</td>
<td>[V_{Symp.}, V_{NYHA} - V_{mitochondria}]</td>
</tr>
<tr>
<td>Parallel</td>
<td>21 vs 19</td>
<td>21</td>
<td>16</td>
<td>II-III</td>
<td>DCM-CAD</td>
<td>24 wk</td>
<td>supervised treadmills, arm, cycling, rowing, 40 min 3 d/wk, 60-80% peak ( V_O_2 )</td>
<td>+2-4</td>
<td>[V_{Symp.}, V_{Cardiac Output max}]</td>
</tr>
<tr>
<td>Parallel</td>
<td>12 vs 13</td>
<td>32</td>
<td>19</td>
<td>II-III</td>
<td>CAD</td>
<td>2 mo</td>
<td>supervised 2 hr walking daily, cycling 40 min 4 d/wk, 80% peak ( V_O_2 )</td>
<td>+4-5</td>
<td>[V_{workload} +20 W]</td>
</tr>
<tr>
<td>Parallel</td>
<td>18 vs 21</td>
<td>12</td>
<td>11</td>
<td>II-III</td>
<td>CAD</td>
<td>3 wk</td>
<td>supervised walking, cycling, sitting exercise 3-5 d/wk, 50% peak Ex. capacity</td>
<td>+2-4</td>
<td>[V_{Tl Koch - Tmitochondria}]</td>
</tr>
<tr>
<td>Parallel</td>
<td>8 vs 8</td>
<td>23</td>
<td>13</td>
<td>II-III</td>
<td>DCM-CAD</td>
<td>12 wk</td>
<td>home-based, cycling, 20 min 5 d/wk, 70-80% peak HR</td>
<td>+3-1</td>
<td>[V_{time}: +10 min, V_{Cardiac Output max}]</td>
</tr>
<tr>
<td>Parallel</td>
<td>5</td>
<td>27</td>
<td>15</td>
<td>II-III</td>
<td>CAD-DCM</td>
<td>4 wk</td>
<td>supervised arm ET at fixed workloads, 24 min 6 d/wk, 70-80% peak HR</td>
<td>+0-9</td>
<td>[V_{workload} +10 W]</td>
</tr>
<tr>
<td>Parallel</td>
<td>13 vs 12</td>
<td>26</td>
<td>na</td>
<td>II-III</td>
<td>CAD-DCM</td>
<td>3 mo</td>
<td>small no. of muscle group 90 min 40 sessions</td>
<td>na</td>
<td>[V_{workload} +28 min]</td>
</tr>
<tr>
<td>Parallel</td>
<td>10</td>
<td>na</td>
<td>na</td>
<td>II-III</td>
<td>CAD-DCM</td>
<td>1 mo</td>
<td>forearm ET, 20-30 min 7 d/wk</td>
<td>na</td>
<td>[V_{workload} +20 min]</td>
</tr>
<tr>
<td>Cross-over</td>
<td>9</td>
<td>26</td>
<td>14</td>
<td>II-III</td>
<td>CAD</td>
<td>6 wk</td>
<td>forearm ET, 20-30 min 7 d/wk</td>
<td>+0-7</td>
<td>[V_{workload} +32 min]</td>
</tr>
<tr>
<td>Control Limb</td>
<td>11</td>
<td>21</td>
<td>15</td>
<td>II-IV</td>
<td>CAD-DCM</td>
<td>2 mo</td>
<td>strength or endurance knee extensors — muscle, Quadriceps femoris 3 d/wk</td>
<td>+0-8</td>
<td>[V_{workload} +6 min walk test]</td>
</tr>
<tr>
<td>Parallel</td>
<td>14 vs 7</td>
<td>28</td>
<td>13</td>
<td>II-III</td>
<td>CAD-DCM</td>
<td>8 wk</td>
<td>knee extensors — 15 min 3 d/wk 35-75% peak ( V_O_2 )</td>
<td>+0-1</td>
<td>[V_{workload} +3 min]</td>
</tr>
</tbody>
</table>

ADP/ATP = adenosine diphosphate/triphosphate; diast.funct. = diastolic function; PC = phosphocreatinine; Vagal = vagal activity; \([K^+]_a\) = arterial potassium concentration. For other abbreviations, please refer to Table 1.
It is not clear what the mechanism is that reduces ventilation after training: reduced lactate levels, which reflect improved blood flow to exercising muscle; enhanced oxygen extraction by the muscle; or improved metabolism within the muscle? Barlow attributed the improvement in the ventilatory response to exercise to a reduced arterial potassium release, the pathophysiological implications of which are still unclear. Recently, decreased activity in a neural signal coming from the exercising muscle to the ventilatory centres in heart failure patients was observed after physical training. The metabolic and haemodynamic improvement induced by training seems to reduce the activity of the ergoreceptors and consequently the excessive ventilation, seen during exercise.

**Autonomic control and neurohumoral activation**

Physical training improves autonomic control in heart failure with a reduction in sympathetic tone and an increase in vagal tone. A reduction in noradrenaline spillover is accompanied by a decrease in the standard deviation of R-R intervals, an index correlated with respiratory sinus arrhythmia and consistent with a depressed vagal tone. By power spectral analysis, the effect of physical conditioning on the balance of sympathetic and vagal tone was assessed as described by the low frequency and high frequency peaks of the R-R interval variability, respectively. Before training, the predominance of sympathetic tone over vagal was dramatically modified by training, which induced a predominance of the vagal rhythm. On the peripheral circulation an overall increase in autonomic control was observed in both vagal and sympathetic limbs.

When the effect of physical training on the circadian pattern of heart rate variability (recorded over 24 h in relation to both time and frequency) was assessed, it was evident the physical training maintained and improved circadian variations of sympatho-vagal balance: these beneficial changes may lessen the predisposition to ventricular arrhythmia.

**Skeletal muscle function**

A leading role has been proposed for the acquired abnormalities of skeletal muscle in the genesis of symptoms of exercise limitation in heart failure, including impaired peripheral blood flow, defective oxidative metabolism, and alterations in enzymatic activity and mitochondrial function.

**Peripheral blood flow**

Exercise conditioning induces an increase in leg blood flow. Sullivan first showed that after physical training there was an increased exercise capacity associated with improvement in the peak leg blood flow, leg oxygen delivery, reduced leg vascular resistance, and increased oxygen arterio-venous differences (increased oxygen extraction) at peak exercise (although these variables were unchanged at rest). But the more interesting observations were made at the submaximal exercise level after training where Sullivan showed a decrease in lactate production, i.e. reduced anaerobic metabolism, while no changes were observed at peak exercise. Thus, although early lactate appearance in heart failure can be due in part to inadequate skeletal muscle blood flow, Sullivan showed that anaerobic metabolism has been delayed after exercise conditioning, independent of improvement in leg blood flow and oxygen delivery at a submaximal exercise level. Thus physical training in heart failure can lead to a significant improvement in exercise capacity mediated by both haemodynamic and metabolic adaptations.

**Skeletal muscle metabolism**

Sullivan et al. in their uncontrolled trial in humans showed that exercise training decreased lactate accumulation and reduced anaerobic metabolism. In an animal model of heart failure, physical training can partially prevent or even improve metabolic abnormalities. The decrease in phosphocreatinine depletion and the increase in adenosine triphosphate resynthesis indicated a correction of the impaired oxidative capacity of the skeletal muscle. These positive effects were subsequently confirmed in humans with heart failure by using 31P magnetic resonance spectroscopy: the training effect was associated with a reduction in early and excessive acidosis and phosphocreatinine depletion on exercise. This suggested an increased capacity for oxidative synthesis of adenosine triphosphate.

**Skeletal muscle ultrastructural changes**

Intrinsic changes of the muscle (mitochondria, fibre size, capillary density, endothelium) have also been described in heart failure and may be improved by physical training. Hambrecht et al. have recently demonstrated that after 6 months of aerobic training not only the total volume density of the mitochondria increased by almost 20%, but in particular the volume density of cytochrome oxidase-positive mitochondria increased by 41%, and that this increase was
significantly correlated with the improvement in exercise tolerance (as assessed by oxygen consumption at the anaerobic threshold)\textsuperscript{44,45}. After physical training, changes in femoral venous lactate during submaximal exercise were unrelated to changes in submaximal leg blood flow, but were inversely correlated with changes in volume density of mitochondria\textsuperscript{45}. These findings confirm that factors other than haemodynamics are likely to be involved in local muscle intolerance, and that the increases in aerobic enzyme activity in skeletal muscle may play an important role in improving exercise tolerance after physical training. Exercise conditioning at 40% of peak oxygen uptake was associated with increased exercise tolerance, reduced lactic acidosis as well as significant increases in muscle fibre size, in capillary density (not significant), and in the volume density of mitochondria\textsuperscript{46}. The increase in volume density of mitochondria was significantly correlated with the increase in peak oxygen uptake. Horning reported that heart failure is associated with endothelial dysfunction, including impaired endothelium-mediated flow-dependent dilatation and that physical training restores endothelium-mediated vasodilatation. This seems to be mediated by endothelial release of nitric oxide: after infusion of N-mono methyl arginine, an inhibitor of nitric oxide production and release, the response was blunted, particularly after physical training\textsuperscript{47}.

**Muscle ergoreflex activation**

The contribution of muscle afferents (ergoreflex) to the haemodynamic, ventilatory and autonomic responses to exercise has been studied in normals and patients with heart failure\textsuperscript{34,35}. The ergoreceptors are small myelinated and unmyelinated neural afferents sensitive to the metabolic state of the muscle. The activity of this reflex in the responses to exercise in heart failure has been compared with respect to controls before and after training. At baseline and after detraining, an abnormal overactivity of this reflex was evident in patients. The increased ventilation, sympathoexcitation and vasoconstriction of heart failure on exercise seemed to be, at least partially, mediated by the overactivity of muscle receptors due to abnormal metabolism of the exercising muscles. The stimulation of the ergoreflex induced in normal controls an increased ventilation/carbon dioxide output slope: the abnormal respiratory response to exercise typical of heart failure patients was induced by stimulation of the ergoreflex. Physical training increased exercise capacity and tolerance, and by improving peripheral metabolism of the muscle with reduced acidification, reduced the overactivity of muscle receptors. Therefore the reduction of the ventilatory drive and sympathetic response and vasoconstriction induced by physical training may all be mediated by reduced ergoreceptor activation.

A correlation between the severity of the symptoms and the activation of the ergoreflex contribution to the ventilatory response to exercise has been recently demonstrated; the ergoreflex system has been proposed as a neural link between peripheral muscle abnormalities and exercise limitation\textsuperscript{48}.

**Effects on quality of life**

The negative effects of limiting exercise are well-known while physical training improves quality of life, and the patients can become fitter and feel consequently more comfortable in performing their daily tasks, with increased independence and less illness behaviour. It could be expected that heart failure patients could also benefit from a small increase in exercise tolerance because most of their daily tasks will stress them above their anaerobic threshold. Physical conditioning improves scores for breathlessness, fatigue, and general well-being and the ease of normal daily activity in heart failure\textsuperscript{18}. However the benefit of a short-term exercise training programme should always be considered as the beginning of a continuous life-style change.

Tyni-Lenné et al\textsuperscript{49} in 21 heart failure patients recently observed that localized leg training (knee extensor muscles physical training) for 8 weeks not only increased exercise tolerance but also health-related quality of life. The improvement was more pronounced in the two-leg training group as compared to the one-leg training group: therefore the effects on quality of life appear to be exercise-related, in addition to a possible placebo-related effect. Also, the effect appears to be related to the volume of muscle trained at any one time.

**The missing link between peripheral abnormalities and symptoms generation**

It has been proposed that a vicious circle exists in heart failure that presents the peripheral abnormalities as responsible for some of the exercise intolerance symptoms of the syndrome because they lead to physical deconditioning\textsuperscript{50}. In fact, although left ventricular dysfunction is the initial factor responsible for the syndrome, complex pathophysiological changes develop in response to reduced cardiac
left ventricular dysfunction, after participation in

In 1979, a first uncontrolled study showed improvements in exercise tolerance in patients with severe failure.

and the common prescription of resting and inactivity leading to increased vasoconstriction and consequently reduced blood flow, inactivity, malnutrition, and a catabolic state, and subsequently skeletal and respiratory myopathy which lead to physical deconditioning. Moreover, in the past, exercise in heart failure patients was believed to be harmful, further comprising left ventricular function and the common prescription of resting and inactivity was given by the physicians augmenting the physical deconditioning. Deconditioning itself can be detrimental, inducing peripheral alterations and central abnormalities (such as in the muscular and vascular structure, in autonomic tone, and muscle ergoreflex) which are responsible for vasoconstriction, sympathoexcitation, vagal withdrawal, further comprising left ventricular function (Fig. 1). With physical training we might be able to slow or block this circle and start to reverse some of the consequences of heart failure.

**Uncontrolled studies (Table 1)**

In 1979, a first uncontrolled study showed improvements in exercise tolerance in patients with severe left ventricular dysfunction, after participation in rehabilitation programmes; subsequently Conn et al. and Arvan observed the beneficial effect of generalized physical training in patients with left ventricular dysfunction using a non-randomized design. Sullivan and co-workers, in a series of studies, evaluated the central and peripheral haemodynamic and metabolic adaptations to physical training. A significant increase in peak oxygen uptake (+23%) was observed; a subgroup of these patients showed a non-significant improvement in cardiac output. The increase in systemic exercise performance seemed to rely heavily on improvements in the peripheral mechanisms: increases in leg arteriovenous oxygen difference and in peak exercise leg blood flow were observed. The training-induced decrease in lactate production was associated with a decrease in carbon dioxide production, respiratory exchange ratio, and ventilation during submaximal exercise. Thus a close link between the ventilatory and metabolic responses to exercise in skeletal muscle was first hypothesized.

The report by Judgutt et al. was the only study that observed a deterioration of left ventricular function with a further increase in the amount of asynergy after physical training (measured from the echocardiographic short-axis view). In another trial, with a scantily defined training programme, physical training improved exercise load but not peak oxygen consumption; only patients with a less depressed left ventricular function had an improved peak oxygen consumption.
Kavanagh et al. evaluated the benefit of a longer term physical training programme. The benefit of exercise conditioning persisted over one year and was associated with improved left ventricular ejection fraction\[42\].

With the aim of establishing the most suitable physical training for a high risk group of patients such as those with heart failure, physical training at low workload\[25,46\] and localized arm training have been proposed\[58,59\]. These exercise protocols produced positive systemic results not only in terms of exercise tolerance, but also concerning cardiac function, reduction in ventricular arrhythmias and of indexes of sympathetic activation, such as plasma noradrenaline and adrenaline. Belardinelli’s study in particular\[46\] described the modification in skeletal muscle fibre size and mitochondrial volume density induced by low intensity physical training, with no changes in central haemodynamics (cardiac output, stroke volume). A significant correlation was reported between peripheral changes and increases in peak oxygen uptake.

The important contribution to peripheral adaptation induced by physical training has also been described by Hornig et al.; the significant improvement in endothelial function observed after localized 4 week arm training was related to the release of nitric oxide\[47\].

Meyer et al. have specifically evaluated physical responses to different modes and levels (50%, 70% and 80% of predetermined maximal capacity) of interval cycle ergometer exercise; all three interval modes resulted in a physical response in an acceptable range of values, and thus could be recommended as a training protocol in heart failure patients\[60\].

Mancini et al. more recently proposed a rigorously standardized localized training programme of selective respiratory muscle training\[61\]. Small muscle group training that does not stress the cardiovascular system might have the added advantage of inducing peripheral muscle changes without possible adverse cardiac effects.

Wilson and colleagues\[62\] found that training was less effective in patients with a more abnormal function, and an abnormal cardiac output response to exercise. However, the training programme in the study was aggressive. A more tailored programme may have benefited these patients as well.

Table 1 summarizes the main findings of the uncontrolled studies above mentioned.

**Randomized controlled trials (Table 2)**

Coats et al.\[18,28\] confirmed the benefits of physical training in 17 patients with heart failure by using, for the first time, a randomized, controlled design and a home exercise regimen; training also reversed the heightened neurohumoral activation seen in heart failure and improved symptoms.

Minotti et al.\[63\] was the first to examine the ability of the skeletal muscle of congestive heart failure patients to adapt to chronic exercise (wrist flexor training). Inorganic phosphate and phosphocreatinine were monitored by magnetic response spectroscopy. Localized forearm physical training improved muscle energetics during exercise independent of limb blood flow, or a central cardiovascular response during training.

In the studies by Minotti et al.\[61\] and Adamopoulos et al.\[41\], the changes in muscle pH and concentrations of phosphocreatinine and adenosine triphosphate were measured in phosphorus-31 spectra of calf muscle obtained at rest, throughout incremental workload plantar flexion until exhaustion and during recovery from exercise. Training increased exercise tolerance; the rate of phosphocreatinine resynthesis after exercise and the inferred maximal rate of mitochondrial adenosine triphosphate synthesis were significantly increased by training, so that they were not significantly different from values in control subjects. Using the same methodology as Adamopoulos et al., Stratton et al.\[42\] investigated whether forearm metabolic responses to exercise were improved by 1 month’s training in 10 males with heart failure. During incremental exercise, the increase in duration was associated with an improvement in pH and an increased phosphocreatinine resynthesis rate.

The substantial contribution of physical training to improving exercise tolerance mediated by peripheral changes has been confirmed by other controlled studies. Kayanakis et al.\[64\] observed a reduced vascular resistance, and Hambrecht et al.\[44,45\] that improved aerobic exercise capacity is closely linked to an exercise-induced increase in oxidative capacity of the working skeletal muscle. In 22 patients, an ambulatory physical training programme improved exercise tolerance and peak oxygen consumption associated with increases in the total volume density of mitochondria and the volume density of cytochrome c oxidase-positive mitochondria. Cardiac output and peak leg oxygen consumption increased significantly. Changes in cytochrome c oxidase-positive mitochondria were significantly related to changes in oxygen\[46\]. More recently\[65,66\] it has been confirmed that improvement in exercise tolerance induced by physical training was independent of changes in central haemodynamics.

The beneficial effects of physical training on autonomic control have been confirmed\[38,67\].
Physical training maintains and improves circadian variations in heart rate variability measures.

Meyer reported the training effect to be additive to the influence of ACE-inhibitor therapy, suggesting that the long-term effects of these drugs may be at least partially independent of physical conditioning effects[68]. Demopoulos et al. have recently reported that long-term, non-selective beta-adrenergic blockade (with carvedilol and propranolol) does not prevent heart failure patients from deriving systemic and regional benefits from physical training: increase in peak oxygen uptake was associated with improvements in peripheral haemodynamics[69].

In contrast with a previous uncontrolled study[26] Dubach et al. reported that physical training does not cause further myocardial damage in heart failure with ischaemic aetiology, i.e. wall thinning, infarct expansion, changes in ejection fraction, or increase in ventricular volume[21].

Other authors investigated the effect of activation of just one muscle group at a time, to avoid the potential adverse effect on cardiac function by systemic training in heart failure. Magnusson et al. investigated the skeletal muscle adaptations in high intensity knee extensor strength and/or endurance training[70]. After training, the maximal exercise intensity tolerated rose and there were increases in the cross-sectional area of muscle quadriceps femoris, and of the capillary per fibre ratio of muscle vastus lateralis. The oxidative enzyme activity in muscle vastus lateralis also rose. Gordon et al.[71] evaluated the effects of local physical training, designed as one- or two-legged knee extensor training: exercise capacity and strength increased in both one- or two-legged exercise groups and were associated with an increase in quality of life and improved ventilatory response at the submaximal exercise level[49,72]. The depressed activity of citrate synthase estimated in tissue samples from the quadriceps femoris muscle increased by 25–35%[71,72].

Numerous investigators have confirmed the benefit of different supervised physical training programmes in heart failure patients, with both ischaemic and idiopathic aetiology, low baseline exercise tolerance and depressed left ventricular ejection fraction[73–77]. Localized arm training not only improved exercise tolerance but also reduced the activity of the muscle afferents in the forearm more in heart failure than in controls, in terms of ventilation dia­stolic pressure and leg vascular resistance[34]. All the findings from published trials confirm that skeletal muscle changes in stable, moderate, chronic heart failure are not entirely irreversible; depressed skeletal muscle oxidative capacity adapts to such physical training with increased activity to an extent similar to that of healthy volunteers. There is a maintained plasticity of skeletal muscle in heart failure patients. A major factor contributing to these changes and to exercise limitation is deconditioning.

Table 2 summarises the main findings of the controlled studies above mentioned.

### Overview of physical training programme

Recently an overview of randomized controlled trials of physical training in heart failure patients has been performed[78]. The patient population included 134 patients who entered the trial with stable, moderate-to-severe heart failure of at least 3 months’ duration, with no changes in medication, stable sinus rhythm, limitation of exercise by breathlessness or fatigue on exercise. Only eight patients did not complete the programme. The remaining 126 patients completed the trials without adverse events and with no change in drug therapy. Physical training significantly increased exercise tolerance (exercise duration improved by +17%, peak oxygen consumption +1.8 ml. min⁻¹. kg⁻¹, +13%, P<0.01), while the ventilation/carbon dioxide output slope was reduced (−8.0%, P<0.01). There was a general improvement in symptoms of breathlessness. No baseline data were significant predictors of training response out of: clinical characteristics, indexes of neurohumoral, autonomic left ventricular function, exercise capacity. The presence of non-sustained ventricular tachycardia did not preclude a training effect, nor did older age. There was a significant positive correlation between the size of the training effect and the duration of physical training. A tailored, moderate, home-based, combined bicycle plus calisthenic physical training programme seemed safe and beneficial in a large cohort of heart failure patients.

### Unsolved questions on physical training programmes

Although deconditioning may not be the only cause of peripheral changes, it is apparent that training reverses many abnormalities, resulting in increased exercise performance. These observations suggest that patients with heart failure in a proper environment could benefit from a cardiac rehabilitation programme similar to those prescribed for patients with coronary heart disease.

It is important to notice that several studies have confirmed a mean increase in exercise duration
of more than 2 min and of peak oxygen uptake of around 2 ml min\(^{-1}\) kg\(^{-1}\). These increases exceed the 0.5–1.5 min increase in exercise tolerance that have been previously observed in clinical trials evaluating ACE inhibitors or digoxin\(^{[79]}\).

The benefits of physical training assume added importance in the light of previous reports that exercise capacity may be one of the most powerful predictors of survival in heart failure\(^{[80]}\). Bittner et al.\(^{[81]}\), examining the prognosis of the patients recruited in the Studies of Left Ventricular Dysfunction (SOLVD)\(^{[13,82]}\), demonstrated that patients with a better 6-min walk test performance had lower mortality/morbidity (hospital admission) rates. The relation between the 6-min walk test and the mortality/morbidity rate was independent of left ventricular function and only moderately correlated with functional classification. Nonetheless, the message of the potential benefit of regular physical training in heart failure is not well established. Consideration of such patients for referral to a cardiac rehabilitation exercise programme has not become a current option, as is in the case for patients recovering after myocardial infarction, coronary artery bypass grafting, PTCA, or cardiac transplantation.

The growing literature on exercise and muscle physiology in heart failure supplies some answers, as well as raising a number of important questions. Because cardiac rehabilitation can be expensive, and could involve a certain risk, the idea that effort, expenditure and risk could be avoided if a low likelihood of benefit were predicted on the basis of initial patient data is crucial. Although previous findings provide some baseline data, only larger studies could determine whether any factors may predict the success or failure of physical training. The identification of patients who might benefit most from an exercise programme, or be at risk of harm, would have important clinical implications, particularly in relation to disability and reimbursement.

Other unsolved questions on physical training in heart failure include the effect on prognosis or morbidity, who should be treated, patients' compliance with long-term programmes, and the relative safety of patients with mixed heart failure and angina, the interaction between training and concomitant therapy.

The HEART project, 'Heart failure, European Action, Rehabilitation Trial'

Thus there remains the need for a large controlled prospective trial to assess the value of medically prescribed and supervised physical training in this group of patients. We are proposing The HEART project, 'Heart failure, European Action, Rehabilitation Trial', a multicentre randomized trial of rehabilitation in heart failure patients. The general aim of the study is to establish the feasibility of physical training in heart failure patients as an effective means of secondary prevention, for patients coming from different European areas, and to develop harmonized methods, procedures, and common research instruments between different centres. In particular, it will be evaluated as to whether physical training improves the functional status, morbidity and mortality of selected stable heart failure patients compared to detraining. The study design consists of two phases. The first phase is a 6-month non-randomized pilot phase to facilitate new centre preparation, standardization of test protocols and training procedures, and testing of patient recruitment rates. The second phase will be a prospective, randomized, unblinded, parallel group 3 year evaluation of patients submitted to a physical training programme vs patients in the detraining group. Patients will remain in this phase until completion of the study, and until they meet specific inclusion/exclusion criteria and choose to take part in the study.

The questions that this study aims to answer are complex and the need exists, therefore, to establish a collaboration between European teams of researchers involved in cardiac rehabilitation in heart failure. Among other pharmacological and non-pharmacological treatment, it is now the time to establish physical training as a further step in heart failure treatment.

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