Emerging concepts in exercise training in chronic heart failure

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There are objective similarities between heart failure and muscular deconditioning. Deficiencies in peripheral blood flow and skeletal muscle function, morphology, metabolism and function are present. The protective effects of physical activity have been elucidated in many recent studies: training improves ventilatory control, metabolism and autonomic nervous system. Exercise training seems to induce its beneficial effects on the skeletal muscle both directly (on function, histological and biochemical characteristics) and indirectly by reducing the activation of the muscle neural afferents (ergoreceptors). On this basis a skeletal muscle origin of symptoms in heart failure has been proposed. The possible metabolic mediators of ergoreceptors are currently being under investigation and they could be a possible target of therapy in heart failure symptoms.

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Physical deconditioning and heart failure

The rationale for the need of physical conditioning in heart failure patients is based on two general concepts. First, these patients are significantly limited and need considerable medical care. They are likely to benefit substantially from even modest improvements in their ability to exercise as many daily tasks push them close to their cardiopulmonary exercise reserve.

On the other hand, there is objective evidence of similarities between aspects of pathophysiology seen in heart failure and the common clinical condition of physical deconditioning (Table I). Both conditions are characterized by similar changes in peripheral hemodynamics (increased peripheral vascular resistance, impaired oxygen utilization during exercise), in autonomic control (activation of neurohumoral compensatory mechanisms, e.g. renin-angiotensin system, sympathetic overactivation, 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)[1].

Table I. Similarity between muscular deconditioning and heart failure.

Hemodynamics
↑ Vascular resistance
↑ Resting heart rate
↓ Max A-VO_2 differences

Function
↓ Exercise tolerance
↓ VO_2 max

Neuroendocrine/autonomic
↑ Renin-angiotensin
↑ Sympathetic
↓ Vagal activity
↓ Baroreflex sensitivity
↓ Heart rate variability

Skeletal muscle
↓ Muscle mass/bulk
Mitochondrial enzymes
↓ Oxidative
↑ Glycolytic
↑ Fiber type IIB/IIA ratio

Psychological
↓ Well-being
↓ Activity scores

Max A-VO_2 differences = maximum artero-venous oxygen differences; VO_2 max = maximum oxygen consumption (ml/kg/min).

Exercise training and heart failure

Traditionally exercise training was contraindicated in patients with heart failure, because of the fear of further precipitating clinical conditions. It was initially thought that significant left ventricular impairment was a contraindication to participation in such programs. In fact, in heart failure, there was a vogue for and reports on the beneficial effects of prolonged bed rest[2].

Despite this prejudice, a few challenging reports emerged in the early 1980s: selected patients with significant left ventricular impairment participating in exercise programs had achieved training responses with increased exercise capacity. However, it was not until the late 1980s that the first reports on training patients with a history of chronic heart failure emerged. Pioneering work by Sullivan et al.[3] showed a significant enhancement in exercise capacity and ancillary physiological benefits, including reduced lactate production, improved use of ventilatory reserve, and increased leg blood flow during progressive exercise. This was immediately followed by the first prospective controlled trial of exercise training in heart failure, an 11-patient crossover study of home-based exercise training using a cycle ergometer for 8 weeks versus a similar period of activity restriction[4]. The result was an improvement in exercise capacity and an improvement in questionnaire-based heart failure-related symptoms. The era of training as a treatment for heart failure had begun.

In the decade following these first reports, there was a profusion of small trials and a long list of impressive physiological gains that could be achieved. These included increased peak oxygen consumption[5,6], an improvement in central hemodynamics[7] and in the autonomic control of the circulation with a reduction in sympathetic nervous system activity and an enhancement in vagal activity[8,9]. These training benefits have been shown against a background of increasing interest in and realization of the importance of secondary peripheral manifestations of heart failure syndrome.

The importance of neurohormonal overactivity has been recognized for a decade, but the importance of other changes, such as altered and wasted skeletal muscle and a host of major metabolic disturbances in heart failure, are only now being appreciated[10]. These include insulin resistance, deficient insulin-like growth factor-1, immune activation and cytokine release, endothelial dysfunction, and baroreflex, chemoreflex[11], muscle ergoreflex (metaboreflex) alterations[12] and autonomic dysfunction, all of which have the capacity of worsening the symptoms and prognosis of heart failure patients and all of which at least in theory might be improved by a customized training program.

In keeping with this idea, exercise training (given its diverse and metabolically powerful effects) is being viewed as an exciting potential therapy for stable heart failure patients.

An overview of randomized controlled trials of physical training in heart failure patients has been performed which supports the concept of the beneficial effect of exercise conditioning in heart failure[13]. The patient population included 134 patients with stable moderate to severe heart failure. Only 8 patients did not complete the program. 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/kg/min, +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. Among the following baseline data not one was a significant predictor of training response: clinical characteristics, indexes of neurohumoral, autonomic, left ventricular function, and exercise capacity. The presence of non-sustained ventricular tachycardia did not preclude a training effect and neither did older age. There was a significant positive correlation between the level of the training effect and the duration of physical training. A tailored, moderate, home-based, combined bicycle plus calisthenic physical training seemed safe and beneficial in a large cohort of heart failure patients.

Beneficial mechanisms of exercise training in heart failure

Ventilation. The clear indication of a training effect is the increase in peak oxygen consumption: this objective and reproducible marker of improved exercise tolerance was clearly demonstrated even in the first original reports[3,4].

A more recent acquisition was the finding that training generates a more efficient ventilation. In fact it reduces minute ventilation for any given work load with a delayed ventilatory anaerobic threshold. The slope that relates minute ventilation to the rate of carbon dioxide production is also reduced, i.e. at a given work load heart failure patients tend to breathe less[14]. This slope has been shown to reflect the severity of heart failure and, in combination with peak oxygen consumption, has important prognostic implications in patients awaiting for cardiac transplantation[15,16].

The mechanism that reduces ventilation after training is unclear: whether reduced lactate levels, which reflect improved blood flow to exercising muscle, or enhanced oxygen extraction by the muscle or improved metabolism within the muscle. It was proposed that this index may not only be determined by hemodynamic and functional impairments but it more reflects the neurohumoral abnormality characteristics of this syndrome, caused by enhanced chemo- and ergoreflexes and concomitant impaired baroreflex[11,12]. It was not surprising that augmented chemoreflex was associated with higher ventilation/carbon dioxide output slope, reduced left ventricular ejection fraction, worse NYHA functional class, and higher incidence of non-sustained ventricular tachycardia[17].

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. By power spectral analysis, the effect of physical conditioning on the balance of sympathetic and

vagal tone was assessed as described by the low and high frequency peaks of R-R interval variability respectively. Before training the predominance of sympathetic over vagal tone was dramatically modified by training, which induced a predominance of the vagal rhythm[18]. When the effect of physical training on the circadian pattern of heart rate variability (recorded over 24 hours in relation to both time and frequency) was assessed, it was evident that physical training maintained and improved circadian variations of the sympatho-vagal balance[19]. These beneficial changes may lessen the predisposition to ventricular arrhythmia by reducing the indices of ventricular repolarization dispersion[20].

All these findings are in keeping with the results of a recent study which showed that training reduces resting levels of hormones related to the progression of heart failure syndrome (angiotensin; aldosterone, vasopressin, atrial natriuretic peptide)[8].

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 a better quality of life. It could be expected that heart failure patients could benefit also from a small increase in exercise tolerance because most of their daily tasks will push them above their anaerobic threshold. Physical conditioning improves scores for breathlessness, fatigue, and general well-being and eases normal daily activity in heart failure[4]. However the benefit of a short-term exercise training program should always be considered to be the beginning of a continuous lifestyle change.

A more recent study has observed that also localized leg training (knee extensor muscle 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[21].

Central hemodynamics. Only one preliminary report observed a reduction in left ventricular ejection fraction[22], but this study was criticized for an 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.

Dubach et al.[23] showed in a rigorous study using magnetic resonance imaging that a high intensity 2-month physical training program resulted in substantial increases in exercise capacity, with no deleterious effect on myocardial remodeling (left ventricular volume, function, or wall thickness) in patients with reduced left ventricular function after myocardial infarction. 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[24,25].

Physical training has been shown, however, to improve left ventricular diastolic function in the presence of both idiopathic dilated and ischemic cardiomyopathy; the increase in left ventricular diastolic wall stress during exercise was lower after physical training, and the improvement in peak oxygen consumption was significantly correlated with an increase in peak early filling rate and a reduction in atrial filling rate[26,27].

A recent study by Hambrecht et al.[7] has demonstrated that a well controlled training program could beneficially affect both central hemodynamics at rest (left ventricular ejection fraction) and exercise (peak exercise stroke volume); this was associated with a reduction in left ventricular end-diastolic volume and peripheral vascular resistance. These results are in keeping with those presented in the pioneering work of Coats et al.[4].

Skeletal muscle. The leading role of peripheral abnormalities in the genesis of symptoms of exercise limitation in heart failure, is supported by the finding that the training effect seems to be mainly mediated by an improvement in peripheral skeletal function (Table II).

Table II. Adaptations to physical training in chronic heart failure humans.

Ventilation	↑ Peak VO_2
	↓ VE/VCO_2 slope
Neuroendocrine	↓ Resting catecholamine
	↓ Sympathetic activity
	↑ Vagal tone
	↑ Baroreflex sensitivity
	↓ Resting and submaximal heart rate
Quality of life	↑ Well-being
	↑ Activity scores
Central hemodynamics	↑ Resting and exercise stroke volume
	↓ Left ventricular diastolic wall stress
	↓ Left ventricular end-diastolic volume
	↓ Peripheral vascular resistance
Skeletal muscle	↑ Blood flow
	Ultrastructural changes
	Fiber size and composition
	Capillary density
	Endothelial function
	Mitochondria
	Metabolism
	↑ Enzyme for aerobic metabolism
	↓ Ergoreflex

VE/VCO_2 = ventilation/carbon dioxide output.

Peripheral blood flow. Exercise conditioning induces an increase in leg blood flow: increased exercise capacity is associated with improvement in peak leg blood flow, leg oxygen delivery, reduced leg vascular resistance, and increased oxygen artero-venous differences (increased oxygen extraction) at peak exercise (although these variables were unchanged at rest). At submaximal exercise level after training there is a decrease in lactate production, i.e. reduced anaerobic metabolism[3]. Although early lactate appearance in heart failure can be due in part to inadequate skeletal muscle blood flow, physical training in heart failure can lead to a significant improvement in exercise capacity mediated by both hemodynamic and metabolic adaptations. More recently Wang et al.[28] have observed that in animal models, after acute myocardial infarction during the development of heart failure, exercise training can prevent hemodynamic abnormalities, i.e. it preserves endothelium-mediated vasodilation.

Skeletal muscle ultrastructural changes. The dominant role of ultrastructural and metabolic modifications over the circulatory changes in the functional improvement induced by exercise training has been further confirmed. After physical conditioning the reduction in femoral venous lactate during submaximal exercise was inversely correlated with changes in volume density of mitochondria but unrelated to changes in submaximal leg blood flow[29]. This finding confirms that hemodynamic factors are involved in local muscle intolerance and that the increase in aerobic enzyme activity in the skeletal muscle may contribute significantly to exercise tolerance. Intrinsic changes of the muscle (mitochondria, fiber size, capillary density, and endothelium) have also been described in heart failure and may be improved by physical training.

• Fiber size and composition. Exercise conditioning is associated with increased exercise tolerance and increased muscle fiber size[6]. Physical training seems to reverse abnormalities in fiber composition: there is an increase in the proportion of slow-twitch fibers and a reduction in fast-twitch glycolytic fibers in the skeletal muscle[29,30].

• Capillary density. Exercise conditioning is associated with increased exercise tolerance, and increased capillary density[6].

• Endothelial function. Hornig et al.[31] reported that heart failure is associated with endothelial dysfunction, including impaired endothelium-mediated flow-dependent dilation, which can be restored by physical training. This seems to be mediated by endothelial release of nitric oxide: after infusion of N-monomethyl arginine, an inhibitor of nitric oxide production and release, the response was blunted, particularly after physical training. In animal models of heart failure, exercise training prevented hemodynamic changes at rest and maintained the endothelium-mediated vasodilation function and gene-expression of endothelial constitutive nitric oxide synthase[28]. Recently Varin et al.[32] have observed that the benefit of exercise training on blood flow is mediated by increasing the expression of endothelial nitric oxide synthase and by preventing the production of vasoconstrictor prostanoids and free radicals.

• Mitochondria. Together with increased exercise tolerance, reduced lactic acidosis, after exercise conditioning, the volume density of mitochondria increases significantly[26]. The increase in volume density of mitochondria was significantly correlated with the increase in peak oxygen uptake.

The mitochondrial ultrastructure has been analyzed in detail before and after training by Hambrecht et al.[29]: 6 months of aerobic training increased the total volume density of mitochondria by almost 20%. This was associated with increased activity of oxidative enzymes: in particular the volume density of cytochrome c oxidase-positive mitochondria, and of the surface density if mitochondrial cristae, and the surface density of the mitochondrial inner border membrane were increased. These changes were correlated with enhanced exercise tolerance but seem to be unrelated to changes in peripheral perfusion, as changes in leg blood flow were unrelated to changes in volume density mitochondria.

Skeletal muscle metabolism. Sullivan et al.[3] 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[33]. 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 heart failure humans by using ^{31}P nuclear 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[34]. Direct evidence has been obtained by needle biopsies in humans which have demonstrated a significant increase in oxidative enzyme activity > 50%, whereas glycolytic enzyme activity was unaltered or reduced[35].

Recently a study by Kiilavouri et al.[36] has questioned these beneficial effects of training: they observed that exercise training had no effect on the percentage distribution of slow-twitch and fast-twitch muscle fibers, or capillary density or oxidative enzyme activity in heart failure. However, in this study the observed findings were probably affected by the fact that the exercise training program used was probably not enough intensive to produce a proper training effect. In fact the Ki-

ilavouri et al. patients were unable to increase strength, endurance, in contrast for example to the Hambrecht et al.[29] studies.

Muscle ergoreflex system: the missing link between peripheral abnormalities and symptom generation

On the basis of the current studies, there is a uniform consensus on the pivotal role of peripheral skeletal muscle abnormalities in symptoms of reduced exercise tolerance in heart failure: the response to exercise is characterized by overventilation and sympathetic vasoconstriction. The link between muscle changes and the abnormal ventilatory and hemodynamic responses to exercise remains object of debate.

The role of muscle afferents (ergoreflex) in the hemodynamic, ventilatory and autonomic responses to exercise has been recognized for long time both in experimental[37] and human[38] studies. The ergoreceptors are small myelinated and unmyelinated neural afferents sensitive to the metabolic products of skeletal muscle work. We have hypothesized that the increased and early acidification observed in the exercising muscle in heart failure may constitute a stimulus for an overactivation of these afferents as compensatory mechanisms to maintain peripheral circulation and to protect the muscle work. An overactivation of this afferents may contribute to the sympathetic, vasoconstrictive responses observed in heart failure[39]. The stimulation of the ergoreflex induced an increase in ventilation/carbon dioxide output slope in normal controls: the abnormal respiratory response to exercise typical of heart failure patients may be induced by stimulation of the ergoreflex[40].

The hypothesis of an increased stimulation of muscle ergoreflex in heart failure patients has been confirmed[12]. At baseline and after detraining an abnormal overactivity of this reflex was evident in patients: the increased ventilation, sympatho-excitation 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. Physical training increased exercise capacity and tolerance, and by improving peripheral metabolism of the muscle with reduced acidification, it decreased the overactivity of muscle receptors. Therefore the reduction in the ventilatory drive, sympathetic response and vasoconstriction induced by physical training may all be mediated by a reduced ergoreceptor activation. The severity of heart failure symptoms correlates with the activation of the ergoreflex activity and the ergoreflex system has been proposed as a neural link between peripheral muscle abnormalities and exercise limitation[41].

Recently Notarius et al.[42] have demonstrated in heart failure patients that peak oxygen consumption is inversely related to resting muscle sympathetic nerve activity consistent with the concept of a peripheral neurogenic limit to exercise in heart failure.

Unanswered questions

The published data seem to support exercise conditioning as a real therapeutic option in heart failure; however three major questions still remain unanswered by the predominantly single-center studies published to date: i) whether the training effects could be maintained over the long term, ii) whether training is practicable in multiple medical settings other than enthusiastic specialist clinics, and iii) whether training would have an effect on mortality or morbidity, either adverse or beneficial.

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

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