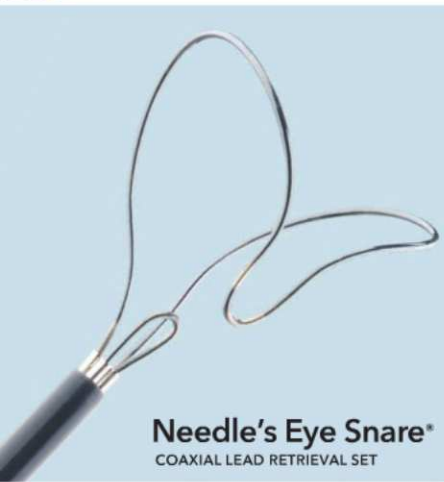




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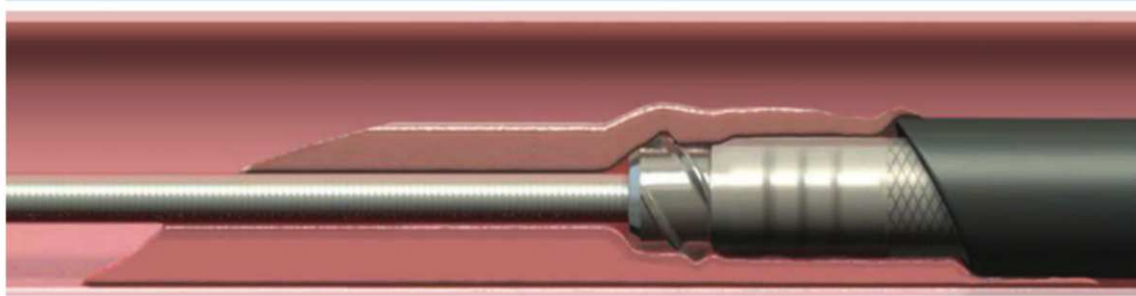
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# Exercise Intervention to Improve Glucose Tolerance in Patients with Heart Failure: A Review

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## Introduction

Heart disease and impaired glucose tolerance (IGT) are often present in the same patient and the combination of both conditions negatively affects prognosis.<sup>1,2</sup> Particularly in chronic heart failure (CHF), current research is focusing on pathophysiology of insulin resistance, and on effective therapeutic strategies to improve glycaemic control. The aim of the present paper is to describe the extent of the problem that the combination of CHF and impaired glucose tolerance (IGT) entails, and to review the impact of exercise intervention.

## Prevalence of Impaired Glucose Tolerance in a CHF Population

The prevalence of impaired glucose regulation in a population of CHF patients has been heavily investigated. Diabetes mellitus type 2 (DMT2) is frequently found in patients with CHF, with percentages varying from 8-41%.<sup>3,4</sup> The suspicion rises that IGT is the rule rather than the exception in patients with severe heart failure. However, the exact prevalence is not known as many patients have undetected or untreated IGT.<sup>4,5</sup> Recently, a study examining glucose tolerance in CHF patients without diagnosed diabetes found that IGT occurred in 23%

and a further 18% had undiagnosed diabetes.<sup>5</sup> Possible explanations for undetected IGT may be the absence of routine screening for IGT in CHF clinics (although European guidelines recommend screening in all cardiovascular patients<sup>6</sup>), and the absence of consensus regarding the correct assessment of glucose tolerance. Although the euglycaemic hyperinsulemic clamp technique is generally considered the gold standard to assess insulin sensitivity, this method is too invasive for screening and hard to perform in large studies. On the other side, fasting glucose levels fail to detect a large group of patients with IGT and sometimes even overt diabetes.<sup>7,5</sup> Therefore, European guidelines state that an oral glucose tolerance test is the recommended screening tool.<sup>6</sup>

In CHF patients, a lower functional NYHA class has been linked to a worse glycaemic control: non-diabetic patients with NYHA III/IV symptoms have a greater chance to develop insulin resistance and diabetes compared to patients with NYHA I/II symptoms.<sup>8,9</sup> Recent studies also suggest a strong link between IGT and diastolic dysfunction.<sup>10,11</sup> The prevalence and severity of diastolic dysfunction are related to the extent of impairment of glucose metabolism along the whole spectrum of metabolic states. The link of non-ischaemic forms of CHF with IGT is yet to be confirmed.<sup>12,13</sup>

Whether glucose intolerance precedes CHF (diabetic cardiomyopathy) or CHF precedes glucose intolerance is also a matter of dispute.

## Why Does IGT Form a Threat in a CHF Population?

Insulin resistance is not merely an innocent bystander, but it appears to be directly involved in the pathophysiology of CHF. In the group of patients with CHF, diabetes mellitus is an independent predictor of mortality. MacDonald *et al.*<sup>14</sup> summarised non-clinical population studies and clinical studies describing the increased risk of mortality with diabetes in patients with CHF. Likewise, prediabetes - or the presence of insulin resistance, hyperinsulinemia, or impaired fasting glucose - is associated with a worse prognosis,<sup>1</sup> and a lower functional status in terms of a



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higher NYHA functional class, lower exercise capacity and muscle strength.<sup>15,12,8,13,9,1</sup> The treatment of IGT is therefore a possible new treatment target in a CHF population.

### Why are CHF Patients Prone to Develop IGT?

From the above-mentioned studies, it has become evident that IGT is omnipresent in CHF patients. However, the underlying reasons have not been clarified yet. In literature, some mechanisms have been proposed to explain the development of insulin resistance in CHF patients: advanced age, sympathetic nervous system overactivity, inflammation, obesity, heart failure medication, hormonal changes, reduced muscle mass and altered muscle metabolism, and physical inactivity.

The prevalence of insulin resistance rises with age.<sup>16,17</sup> In the CHF population comprising a large proportion of elderly patients, a negative correlation between age and insulin sensitivity has been found.<sup>12,18,13</sup> Possible contributors are a reduction in physical activity, poor nutritional habits, as well as muscle atrophy. Whether the development of IGT in CHF patients is related to the ageing process *per se*, or to changes in lifestyle as result of ageing, remains to be elucidated.

A persistent activation of the sympathetic nervous system is characteristic of CHF. Although the interaction between the sympathetic nervous system and glucose metabolism is complex, the insulin-antagonism of catecholamines is established.<sup>19,20,21,22,23,14</sup> The chronic over-activity of the sympathetic nervous system in CHF patients can increase muscle insulin resistance through vasoconstriction in the skeletal muscle<sup>23</sup> and an increased level of free fatty acids due to breakdown of fat stores (through direct activation of adipocyte  $\beta$ -adrenergic receptors). This will lead to a further skeletal muscle insulin resistance and stimulate hepatic glucose production.<sup>23,24,3,25,26,27</sup> The sympathetic overactivity can also increase oxidative stress by promoting proliferation of oxygen free radicals that consume nitric oxide. This interferes with normal insulin-mediated vasodilation.<sup>23,28</sup>

Both heart failure and insulin resistance are associated with increased levels of inflammatory cytokines.<sup>3,29</sup> In fact, it has become evident that "heart failure progresses, at least in part, as a result of the toxic effects exerted by endogenous cytokine cascades on the heart and the peripheral circulation."<sup>30,31</sup> Tumour necrosis factor- $\alpha$  (TNF $\alpha$ ) is an inflammatory mediator stimulating skeletal muscle wasting in chronic diseases, such as CHF. It induces a catabolic state and a reduced skeletal muscle contractility. However, the link between TNF $\alpha$  and insulin resistance in a CHF population has not been confirmed yet.<sup>32</sup>

Body mass index (BMI) is known as a determinant of insulin resistance in a CHF population.<sup>13</sup> In one analysis, BMI could be replaced by fat mass or percentage body fat (assessed by skin fold measures), but not by fat-free mass. On the other hand, body composition data by dual energy X-ray absorptiometry were not related to insulin sensitivity and GLUT4 presentation in the skeletal muscle of CHF patients in another

study.<sup>33</sup> In a general population, obesity, amount and distribution of fat are important regulating factors for glucose and insulin metabolism.<sup>34</sup> Fat tissue can be considered as an endocrine organ, which produces peptide hormones and cytokines (adipokines) that influence insulin sensitivity.<sup>35</sup> Recently, research is focusing on the role of adipokines as adiponectin, leptin and resistin in CHF populations.<sup>36,37</sup> However, we should not forget that not all CHF patients are obese, and that lean or even cachectic CHF patients are often insulin resistant.

Impaired glucose tolerance and insulin resistance are also part of a multiple hormonal deficiency syndrome in CHF, as described by Saccà.<sup>38</sup> Levels of insulin, testosterone, Insulin-like Growth Factor-1 and T3 are out of balance in patients with CHF and changes in each component are associated with impaired functional capacity and poor clinical outcome.

Standard medications in the treatment of heart failure are known to have an influence on the glucoregulatory mechanism. The increases in glycaemia induced by thiazides are small and appear to attenuate over time,<sup>14</sup> but opinion leaders have raised concerns about the potential for long-term adverse effects of the observed dysglycaemia.<sup>39,40</sup> Most beta-blocking agents have deleterious effects on insulin sensitivity, carbohydrate and lipid metabolism.<sup>41</sup> The newer third-generation vasodilating  $\beta$ -blockers, such as Carvedilol and Nebivolol have shown a better metabolic profile.<sup>41,42</sup> Vasodilating  $\beta$ -blockers may reduce the risk for promoting new-onset diabetes in patients with CHF.<sup>23</sup> Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can reduce the incidence of diabetes in CHF patients,<sup>14</sup> possibly by reducing the SNS activation.<sup>23</sup>

As the skeletal muscle is the major site of glucose disposal, the defects that are located at the level of the skeletal muscle in CHF patients are of major importance to explain the elevated risk for the development of IR. The 'muscle hypothesis' proposes that exertional dyspnoea and fatigue in CHF are mainly resulting from skeletal muscle abnormalities.<sup>43</sup> A loss of muscle mass and muscle strength is a common problem in CHF,<sup>44,45</sup> as well as changes in muscle fiber type. CHF patients have a relative preponderance of type II muscle fibers, which are less sensitive for insulin. These muscle fibers have reduced blood flow, and thus a reduced uptake of glucose by muscle.<sup>46,3,47</sup> The expression of the glucose transporter isoform 4 (GLUT4) in skeletal muscle is reduced in CHF patients when compared with healthy subjects.<sup>33</sup> The degree of GLUT4 reduction directly relates to the severity of whole body insulin resistance, and the reduction is parallel to the severity of CHF.<sup>33</sup> Explanations for a reduced expression of GLUT4 protein in CHF could be found in physical inactivity, reduced muscle fiber contractions (which are a stimulus for GLUT4 translocation from the inside of the cell to the plasma membrane), and tissue hypoxia (which can reduce GLUT4 translocation by 50%).<sup>48</sup> It has been proposed that the skeletal muscle can also be viewed as an endocrine organ. Cytokines and other peptides that are produced, expressed, and released by muscle fibers and exert paracrine or

endocrine effects should be classified as “myokines”.<sup>49,50</sup> When the skeletal muscle is relatively inactive, these myokines can interfere with the glucose metabolism.

In final, physical inactivity *per se* has been described as an independent predictor for insulin resistance in CHF.<sup>13</sup> Apart from the central role of inactivity and deconditioning in the skeletal muscle hypothesis, inactivity may lead, through a cascade of events, to transcriptional changes to metabolic and mitochondrial genes, thereby influencing oxidative phosphorylation.<sup>51</sup>

### Exercise as a Treatment of IGT

In the general population, physical activity is a means to prevent a deterioration of glucose metabolism.<sup>52</sup> According to the Standards of Medical Care in Diabetes 2011, moderate physical activity should be performed for at least 150 minutes per week in order to prevent or delay DMT2.<sup>53</sup> In the Finnish Diabetes Prevention study, lifestyle intervention had greater effect in preventing DMT2 compared to metformin and placebo. It was concluded that lifestyle changes with diet and exercise training involve considerable benefits in the prevention of diabetes. These treatment methods, however, are seriously underused.<sup>54,55</sup>

Despite the high prevalence of diabetes and prediabetes in CHF patients, consensus regarding treatment is not reached. The use of glucose-lowering medication is not evident, as metformin and thiazolidinediones may be contra-indicated in CHF patients because of negative effects regarding lactic acidosis and fluid retention.<sup>3</sup> However, other treatment modalities for IGT are already components of recommended CHF treatment: diet, physical exercise and carvedilol among  $\beta$ -blockers.<sup>38</sup> Recent recommendations of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation for exercise therapy include endurance training (20-60 minutes, 3-5 days per week at moderate-to-high intensity), interval training and resistance training (as a complement to increase muscle endurance and muscle mass).<sup>56</sup>

In addition to beneficial effects on exercise tolerance, health-related quality of life and self-care, there are many reasons to believe that exercise therapy may improve glucose tolerance in CHF patients.

### Acute Exercise

It is well established that an acute bout of exercise is followed by a substantial increase in glucose uptake in skeletal muscle via insulin-independent mechanisms.<sup>52,57</sup> Muscle contractions provide a stimulus for insulin-independent translocation of GLUT4 protein to the cell surface. Furthermore, the acute effect of exercise on glucose transport is mediated by enhanced insulin receptor signalling, activation of AMP-activated protein

kinase pathway,<sup>58</sup> Akt/protein kinase B-phosphorylation, NO production and Ca-mediated mechanisms.<sup>52</sup>

### Chronic Exercise: Exercise Therapy

The factors linking CHF and IGT, on which exercise training has a beneficial influence, are summarised and highlighted in figure 1.

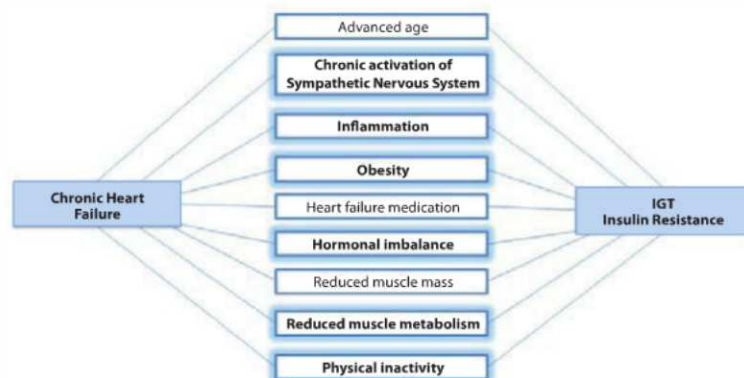
#### Changes in Skeletal Muscles

The skeletal muscle hypothesis constitutes the physiological basis for the benefit of exercise therapy in CHF patients.<sup>45</sup> It is suggested that exercise training with resistance exercises in CHF may improve underlying skeletal muscle abnormalities and neuromuscular function, rather than simply increasing muscle mass.<sup>59</sup> Exercise therapy enhances the trafficking and translocation of GLUT4 protein towards the cell surface<sup>60,51</sup> and may promote a shift towards insulin-sensitive type I fibers.<sup>47</sup> Furthermore, the expression and activity of proteins involved in insulin signal transduction are increased. Some proposed sites of enhanced postreceptor signal transduction are insulin receptor substrate (IRS) proteins, PI3kinase and AS160.<sup>51,58</sup> Mitochondrial biogenesis in skeletal muscle is enhanced by exercise training, thereby enhancing the oxidative capacity.<sup>51,46</sup> This results in an improved lipid utilization in terms of enhanced lipid oxidation and turnover, increased use of plasma FFA, and an increased whole-body fat oxidation at rest and during exercise.

A decrease in local muscle inflammatory factors as TNF-alpha,<sup>61,62</sup> interleukine-1-beta,<sup>61,62</sup> interleukine-6 (61) has been described in CHF training studies.

#### Change in Hormonal Status

Changes in hormonal status may improve insulin resistance and reduce neuro-hormonal activation. Most training studies in CHF patients report a decrease of sympatho-excitation at rest,<sup>63,64</sup> but no changes in cortisol.<sup>55,66</sup> No influence of training on IGF-I in venous blood has been reported,<sup>66</sup> while local IGF-I expression was improved after training.<sup>67</sup> Finally, raised adiponectin levels are reduced following exercise training in patients with CHF.<sup>68</sup>



**Figure 1.** Factors linking heart failure and impaired glucose tolerance and effect sites of exercise training. Factors that can be positively influenced by exercise training are highlighted. IGT: impaired glucose tolerance.

Publication	Sample Size** Patient Population NYHA Score	Method for Assessing Glucose Metabolism	Programme Duration (Weeks)	Resistance Training	Effect on Glucose Uptake	Effect on FG	Effect on FI	Effect on HbA <sub>1c</sub>
Dylewicz 2000	20 HFrEF post-CABG	Fasting blood measurements	3	No	ND	↓	↑ ns	ND
Kemppainen* 2003	7 vs 7 Idiopathic dilated CMP NYHA 1.4	Euglycaemic hyperinsulinemic clamp	21	Yes	25% ↑ in whole-body insulin-stimulated glucose uptake (to level comparable with healthy control subjects)	↑ ns	↓ ns	ND
Kemppainen 2003	9 vs 7 Idiopathic dilated CMP NYHA 1.6	Euglycaemic hyperinsulinemic clamp  PET scan: whole-body and regional glucose uptake	21	Yes	23% ↑ in whole-body insulin-stimulated glucose uptake 53% ↑ skeletal muscle glucose uptake in the resting muscle 55% ↑ skeletal muscle glucose uptake in the exercising muscle	↑ ns	↓ ns	ND
Sabelis* 2004	36 vs 25 HFrEF NYHA II-III	Euglycaemic hyperinsulinemic clamp  HOMA	26	Yes	Insulin sensitivity ↑ ns HOMA ↑ ns	↑ ns	↑ only in IR-patients	ND
Nishiyama 2006	14 vs 6 HFrEF NYHA II-III	Fasting blood measurements	3	No	HOMA ↓, only in IR-patients	ND	↓ ns	ND
Prescott 2009	52 HFrEF NYHA II-III	Fasting blood measurements	8	Yes	ND	↓ ns	↑ ns	No effect
Prescott* 2009	20 vs 23 HFrEF NYHA II-IV	Fasting blood measurements	8 + 12 months	Yes	ND	Smaller ↑ in exercise group	↓ ns	Smaller ↑ in exercise group

\*: randomised controlled trial, \*\*: exercise vs. control, HFrEF: heart failure with reduced ejection fraction, CABG: coronary artery bypass grafting, CMP: cardiomyopathy, HOMA: homeostasis model assessment, FG: fasting glucose, FI: fasting insulin, ND: not described, ns: not significant

**Table 1.** Studies describing the effect of exercise intervention on glucose metabolism in a heart failure population.

### Changes in Inflammatory Markers in Blood Serum

Long-term exercise training has an anti-inflammatory effect in the general population.<sup>69</sup> However, serum levels of inflammatory markers TNFα,<sup>70,61,62,66,71</sup> IL-1β,<sup>61,62</sup> IL-6,<sup>70,61,44,66,71</sup> and IL-8<sup>44</sup> were not reduced after exercise training in a CHF population. Other studies described reduced peripheral inflammatory markers associated with endothelial dysfunction,<sup>72,73</sup> reduced TNFα<sup>74</sup> and reduced IL-6<sup>73</sup> after exercise therapy.

### Effect of Exercise Intervention on Glucose Metabolism in Patients with CHF

There is a limited number of exercise intervention studies in patients with CHF that investigate the effects on glucose metabolism. The studies that described effects of an exercise intervention on whole-body glucose metabolism<sup>75,76,77,78,66,71,79</sup> are summarised in Table 1. Sample sizes are relatively small, and methods for assessing glucose metabolism, exercise capacity and the exercise intervention are very heterogeneous. All studies included endurance training, but training duration varied from 20 to 90 minutes, endurance training intensity is described in various ways and training frequency varied from 3 to 7 times a week. All studies, except from Dylewicz *et al.*<sup>75</sup> and Nishiyama *et al.*<sup>80</sup> included home-based training sessions. The results of Kemppainen

*et al.*<sup>76</sup> are encouraging, although the beneficial effects of exercise on insulin resistance could not be confirmed in other studies. Along with a modestly improved glucose homeostasis, Prescott *et al.*<sup>71</sup> found a decrease in C-reactive protein and markers of endothelial damage. The changes in whole-body and skeletal glucose uptake in rest and in exercise were not accompanied by changes in muscle perfusion, suggesting improvements of glucose extraction at cellular level.

Although evidence points to a possible beneficial effect on whole body glucose uptake, no conclusive answer can be derived to the question whether exercise is an effective therapy for IGT in CHF patients. There is a great need to standardise methods of IGT assessment and exercise interventions.

### Clinical Implications

The prevalence of impaired glucose tolerance is high in CHF patients, and there are sound arguments for a standard screening for glycaemic abnormalities in this population. Exercise training may be an effective tool to prevent further deterioration of glycaemic control into DMT2. Cardiac rehabilitation with exercise therapy is recommended as a standard treatment in CHF, but it is poorly implemented, with only 42% of the CHF clinics incorporating an

exercise component in their CHF management programmes.<sup>81</sup> Also when an exercise component is present, recruitment and adherence

is low.<sup>82</sup> This is a missed opportunity, both from the viewpoint of heart failure and glycaemic control.

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