Review Article

Impaired Glucose Tolerance and Insulin Resistance in Heart Failure: Underrecognized and Undertreated?

MAMAS A. MAMAS, MA, DPhil, MRCP,[1,2] CHRISTI DEATON, PhD, RN,[1,2] MARTIN K. RUTTER, MD, MRCP,[1,2,4] MARTIN YUILLE, MA, PhD, FRCPath,[6] SIMON G. WILLIAMS, MD, MRCP,[3] SIMON G. RAY, MD, FRCP,[2,3] JOHN NEW, MD, MRCP,[2,5] J. MARTIN GIBSON, MD, PhD, FRCP,[2,5] AND LUDWIG NEYSES, MD, FRCP[1,2]

Manchester, UK; Salford, UK

ABSTRACT

Background: A link between diabetes mellitus (DM) and heart failure (HF) has been well-recognized for more than a century. HF is also closely linked to abnormal glucose regulation (AGR) and insulin resistance (IR) in patients without DM and, similarly, these conditions commonly coexist. In epidemiological studies, each condition appears to predict the other. The prevalence of AGR/IR in HF patients without DM is significantly underrecognized and, as yet, the optimal method for screening for these abnormalities in the outpatient setting is unclear.

Methods and Results: The purpose of this review is to overview the prevalence and prognostic impact of AGR and IR in HF patients without DM and discuss potential pathophysiological pathways that link these conditions with HF. The severity of glucose intolerance in patients with HF correlates with functional and clinical severity of HF and is an independent predictor of an adverse outcome. It is thought that changes in cardiac metabolism, including a switch from glucose metabolism toward fatty acid metabolism, may in part contribute to the pathophysiological processes associated with HF patients with AGR/IR.

Conclusions: We discuss how pharmacological targeting of metabolic pathways in the myocardium of these patients with HF may represent novel therapeutic strategies in these at-risk patients. (*J Cardiac Fail 2010;16:761−768*)

Key Words: Impaired glucose tolerance, insulin resistance, heart failure, mechanisms.

A link between hyperglycemia and heart failure (HF) has been recognized for more than a century.[1] Recently, evidence from epidemiological studies such as the Framingham Heart Study has suggested that the presence of diabetes mellitus (DM) is an independent risk factor for incident HF; in middle-aged diabetic subjects, the risk was 2-fold higher in men and 5-fold higher in women when compared with subjects without DM.[2] Similarly, the Reykjavik Study showed that the age-adjusted odds ratio for incident HF was 2.8-fold higher in patients with DM, compared with patients without DM.[3]

The prevalence of DM in patients with HF is significantly higher than the 4% to 7% prevalence observed in the general population.[3,4] The Euroheart Failure Survey II demonstrated that 33% of patients hospitalized with HF had DM,[5] whereas data from more than 100,000 patients in the Adhere registry indicated a DM prevalence of 44%.[6] Similarly, data from randomized controlled trials in patients with HF have suggested a DM prevalence of 8% to 41%.[7] DM has been shown to be an independent predictor of mortality or hospitalization in several HF studies, including the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM), Beta-Blocker Evaluation of Survival Trial (BEST), and Studies of Left Ventricular Dysfunction (SOLVD) studies.[7−10]

Abnormalities in glucose regulation in HF are not only limited to patients with diabetes. Recent data suggest that impaired glucose tolerance (IGT) and insulin resistance

From the [1]Manchester Royal Infirmary, Biomedical Research Centre, Manchester, UK; [2]Manchester Academic Health Science Centre, University of Manchester, Manchester, UK; [3]University Hospital of South Manchester, Wythenshawe Hospital, Manchester, UK; [4]Manchester Diabetes Centre, Manchester, UK; [5]Salford Royal NHS Foundation Trust, Salford, UK and [6]Centre for Integrated Genomic Medical Research, University of Manchester, UK.

Manuscript received October 2, 2009; revised manuscript received May 12, 2010; revised manuscript accepted May 18, 2010.

Reprint requests: Dr Mamas A. Mamas, Clinical Lecturer in Cardiology, Manchester Heart Centre, Manchester Royal Infirmary, Manchester, M13 9PT, UK. Tel: +44 (0)161 275 5672; Fax: +44 (0)161 275 5669. E-mail: mamasmamas1@yahoo.co.uk

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1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2010.05.027

(IR) are widespread in HF patients without diabetes. Abnormalities of glucose regulation have been shown to correlate with HF severity, and have been shown to be independent risk factors for adverse outcomes (Table 1).[11−15,24,25,28]

The purpose of this review is to provide an overview of the prevalence and prognostic impact of abnormal glucose regulation and IR in HF patients without DM and discuss potential pathophysiological pathways that link these conditions with HF. Finally, we discuss current and novel therapeutic strategies that could be used to target hyperglycemia and IR in HF patients through the target of metabolic pathways.

Abnormalities of Glucose Regulation in HF

Abnormalities in glucose regulation are commonly observed in nondiabetic patients with HF. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study,[11] 23% of nondiabetic patients had impaired fasting glucose (IFG), 11% had fasting glucose concentrations in the diabetic range, whereas 33% had IR as assessed by Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Similarly, Witteles et al[12] demonstrated that 48% of nondiabetic patients with idiopathic dilated cardiomyopathy had abnormal glucose tolerance as assessed by oral glucose tolerance test (OGTT). Other studies have demonstrated that nondiabetic patients with HF of mixed etiology have up to 58% lower insulin sensitivity when compared with control subjects assessed by intravenous glucose tolerance test.[13] In a community-based HF clinic of 970 nondiabetic patients, 58% of patients had an HbA_{1c} of $>6\%$, whereas 11% had an HbA_{1c} of $>6.7\%$.[14] In this study, although the authors maintain that these were patients though to be nondiabetic from the history and random blood glucose measured at baseline, it is possible that a proportion of those with HbA_{1c} $>6.7\%$ represented patients with undiagnosed diabetes. Nevertheless, close to 50% of patients still had an HbA_{1c} level of between 6% and 6.7%. In 454 consecutive patients presenting with acute HF syndrome, 24% of the patients studied had known DM or an admission plasma glucose level >11 mmol/L, whereas a further 13% of patients had a plasma glucose in the abnormal glucose tolerance range (8.0 to 10.9 mmol/L).[15]

Many of these studies investigating the prevalence of dysglycemia in HF have used fasting or random plasma glucose levels. Fasting plasma glucose has limited sensitivity for detecting IGT in patients with cardiovascular disease.[12,16,17] For example, in the small study by Witteles[12] cited previously, only 14% of patients with HF who were found to have ''abnormal glucose tolerance'' had abnormal fasting glucose levels. Similarly, in cohorts of patients with macrovascular disease, abnormal glucose tolerance is also a common finding that is seldom detected by measuring fasting glucose alone. For example, in a large study assessing the utility of preoperative OGTT for risk stratification in 404 vascular surgery patients, only 25% of those found to have IGT also had IFG,[16] with similar observations recorded in a cohort of patients undergoing diagnostic cardiac catherization.[17]

Some data suggest that HbA_{1c} measurement may have even lower performance than fasting glucose for detecting IGT or new DM in the setting of heart disease. In patients with acute myocardial infarction, HbA_{1C} was less strongly related to the 2-hour OGTT glucose level than fasting plasma glucose (r^2: 0.34 versus 0.50).[18] This study also showed that in the diagnosis of IGT or new DM using OGTT as gold standard, the area under the ROC curve was 0.76 for fasting glucose and 0.71 for HbA_{1c}. Other studies have shown only 17%[19] and 25%[20] of patients with IGT have abnormal HbA_{1c}, and that HbA_{1c} is ineffective for screening for IGT.[21] Consequently, it seems likely that the true prevalence of IGT and DM in HF populations will be greatly underestimated by IFG or abnormal HbA_{1c}, and that the gold standard should remain the OGTT.

Severity of HF and Abnormalities in Glucose Regulation

Insulin resistance and abnormalities in glucose regulation appear to correlate with functional, clinical, and biochemical severity of heart failure in nondiabetic HF cohorts studied. Data from the RESOLVD study in patients without known DM have shown that NYHA Class III/IV patients compared with Class I/II patients were more likely to have IFG (32% versus 18%, $P < .005$), hyperinsulinemia (45% versus 28%, $P < .005$), or IR assessed by HOMA-IR (44% versus 28%, $P < .005$).[11]

In a prospective study of 105 male HF patients, IR was higher than in age-matched controls, and IR measured in the HF group was positively related to NYHA class.[22] IR in HF patients has been shown to strongly correlate with brain natriuretic peptide (BNP) levels[23] and peak oxygen consumption.[13]

Abnormalities of Glucose Regulation and Prognosis

Recent data suggest that IGT or IR in HF patients are independent predictors of adverse outcomes (Table 1). Data from 2412 CHARM study subjects showed that HbA_{1C} was an independent predictor of CV death, hospitalization for worsening HF, and total mortality.[24] Similarly, in the Reykjavik study, IGT was an independent predictor of all-cause mortality (OR 1.9; 95% CI 1.5−2.5) that was of similar magnitude to that associated with the presence of DM (OR 2.1; 95% CI 1.5−2.9).

In the study of Doehner et al[22] in HF patients, IR predicted 2-year mortality in multivariable-adjusted models. Other studies suggest that IGT is only associated with an adverse effect on mortality in those patients with a left ventricular (LV) ejection fraction of $<45\%$ with no effect on mortality in those patients with HF and preserved systolic function.[14] IGT has been shown to be a predictor of mortality in acute HF syndrome. In 454 consecutive patients admitted with HF, abnormal glucose tolerance predicted in hospital mortality (HR 5.90; 95% CI 1.03−34.0) and