Heart failure and glucose abnormalities: an increasing combination with poor functional capacity and outcome

Diabetes mellitus and pre-diabetic glucose abnormalities are common in patients cared for by cardiologists. It is well established that patients with these abnormalities have an increased morbidity and mortality following an ischaemic event. Recent evidence also indicates that blood glucose is an independent continuous risk factor for cardiovascular disease even when it is below the diabetic threshold. Furthermore, patients with diabetes have not experienced the reduction in cardiac mortality rates that has been observed in non-diabetic people. This, together with the fact that the prevalence of diabetes is likely to double during the next two decades, suggests that the importance of diabetes and gluco-metabolic disorders as a cardiovascular risk factor will increase substantially.

In western society, congestive heart failure is closely related to coronary artery disease. However, there has been an increase in congestive heart failure prevalence despite a decline in coronary artery disease mortality. Thus diabetes and congestive heart failure are a common combination and this is further amplified by the fact that patients with diabetes are more prone to symptomatic heart failure when suffering an ischaemic event, despite equal or even less myocardial damage.

The prevalence of diabetes in the large scale heart failure trials with ACE inhibitors has been approximately 20–25%. However, these trials may underestimate the true problem since most trials have age restrictions and exclude patients with, for example, renal impairment or peripheral vascular disease, features that are common among people with diabetes.

In this issue Suskin and co-workers report on the RESOLVD trial (Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot trial). They found a prevalence of diabetes mellitus of 27% at the time of randomization. The authors did, however, include fasting plasma glucose at the time of randomization, which makes it possible to estimate the true prevalence of glucose abnormalities in this population. Interestingly, they found that 8% had previously unrecognized diabetes mellitus and 9% had impaired fasting glucose (6.1–6.9 mmol. l⁻¹), and in total as many as 43% of the patients had a disturbed glucose metabolism. This number may more accurately reflect the current situation and is similar to a recent report from the U.S.A. which showed that 38% of all congestive heart failure patients admitted to hospital had antidiabetic treatment.

Patients with congestive heart failure also seem to be prone to develop new diabetes. In a recent Italian study the incidence of diabetes was 29% during 3 years follow-up among elderly congestive heart failure patients initially free from this disease, compared to 18% in a group of matched controls. Thus it seems that glucose abnormalities and congestive heart failure are closely interrelated.

Patients with severe chronic heart failure are hyperinsulinaemic and insulin resistant. In RESOLVD, the non-diabetic patients in NYHA class III/IV were more insulin-resistant compared to patients in NYHA class I/II. Furthermore, all patients with gluco-metabolic disturbances (diabetic or non-diabetic patients) were more symptomatic and had a shorter 6-min walk distance compared to patients with normal glucose metabolism. This finding is interesting in the light of the discovery that they all had similar left ventricular systolic function. The end-diastolic volumes were smaller, which may indicate myocardial stiffness and diastolic dysfunction. Early signs of diastolic dysfunction have been the most consistent finding when evaluating heart function in patients with diabetes. Several mechanisms may contribute to the increased signs and symptoms on heart failure among diabetic patients, such as more extensive coronary sclerosis, hypertension, autonomic neuropathy, a shifted myocardial substrate utilization and endothelial dysfunction. However, early signs of abnormalities of cardiac structure and function have been observed not only in diabetic patients but also in those with impaired glucose tolerance and may have an early impact in patients with a low degree of glucose abnormality. It also seems to be a synergistic effect of hypertension, a diagnosis that is common in this patient category.

As discussed by the authors, another possible explanation for the decreased functional capacity in patients with insulin resistance and a defective glucose metabolism could be impaired peripheral adjustment. Increased vascular resistance due to endothelial dysfunction is associated with congestive heart failure but is also a common feature in both type 1 and 2 diabetes. In fact, a recent report from Finland has...
demonstrated that endothelial dependent vasorelaxation is already blunted in patients with impaired fasting glucose and this may be an important explanation for the results since it also may affect the coronary circulation, resulting in impaired diastolic properties[11].

In the present study, patients with diabetes also experienced more events than non-diabetic patients. This is in accordance with previous studies and is interesting since the diabetic patients in the RESOLVD study had similar ventricular function compared to non-diabetic patients. Furthermore, they also had lower levels of markers of neuroendocrine activation than patients with normal glucose metabolism. This is difficult to explain, but really emphasizes the importance of diabetes as a major predictor of future morbidity and mortality.

How should these patients be managed in the future? Since impaired endothelial function with subsequent reduced flow seems to be a common denominator in patients with glucose abnormalities and insulin resistance, action targeted to this abnormality seems to be appropriate. A more widespread implementation of ACE inhibitor use is critical since there are indications that it will improve not only the remodelling process but also insulin resistance and the development of diabetes[12]. Accumulating data also support the view that ACE inhibitors will reduce future vascular events in this patient population. Physical training will also improve insulin resistance and glucose levels and there are also novel drugs under development (insulin sensitizers) that should be tested in this situation. Furthermore, intensive metabolic control, with for example insulin, in patients with diabetes will probably not only decrease insulin resistance but also shift the myocardial metabolism towards more efficient substrate utilization. It is well known from experimental studies that diabetes is characterized by an increased turnover of free fatty acids. Increased free fatty acid levels provoke myocardial oxygen consumption and enhance intracellular accumulation of intermediates, leading to harmful effects that could be prevented by insulin treatment[9]. This could also be achieved by beta-blockade and may be one explanation for the now well documented positive effect of beta-blockade in congestive heart failure patients. Finally, hypertension should be extensively treated since it seems to be a synergistic effect of diabetes and hypertension in developing myocardial morphological alterations[9].

In summary, heart failure and glucose abnormalities are a common and increasing combination that are characterized by low functional capacity together with a high event rate. Existing trial data indicate that patients with these abnormalities and congestive heart failure should be treated extensively with conventional treatment such as ACE inhibitors inhibitors and beta-blockers. Besides this, research on therapies directed towards the metabolic defect is urgently needed. Furthermore it seems that a simple blood glucose test is more than justified in patients with congestive heart failure since it may identify those with low functional capacity and with an increased risk of future events.

A. NORHAMMAR
K. MALMBERG
Karolinska Hospital,
Stockholm, Sweden

References