EDITORIAL COMMENT

Time to Address the Cardiac Metabolic “Triple Whammy”

Ischemic Heart Failure in Diabetic Patients*

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The prevalence of congestive heart failure (CHF), chronic ischemic heart disease, and diabetes mellitus is increasing in most societies, and it is not surprising that in most large clinical trials of CHF at least 75% of patients have underlying ischemic heart disease while approximately 20% to 35% of patients have diabetes (1,2). There is strong evidence that the presence of diabetes in patients with CHF is an independent marker of adverse prognosis (3), and it has also been suggested that outcomes tend to be worse in patients with ischemic, as distinct from non-ischemic, cardiomyopathy (4).

Intriguingly, 2 studies (5,6) have taken this association one step further by evaluating the possibility of differential prognostic impact of diabetes in ischemic versus non-ischemic CHF. In the SOLVD (Studies of Left Ventricular Dysfunction) trials, adjusted analyses suggested that diabetes was associated with a 37% increase in all-cause mortality in patients with ischemic cardiomyopathy as well as with increased risks of progression of symptoms, whereas there was no similar association in non-ischemic subjects (5). A similar analysis of patients in the BEST (Beta-Blocker Evaluation of Survival) trial reached remarkably similar conclusions (6). Although it might be suggested that these findings might simply reflect an increased risk of (re)infarction in the diabetic/ischemic patient cohort, this did not appear to explain the overall excess mortality (6). An alternative hypothesis, raised by the investigators who initially documented this association (5), is that myocardial metabolism and energetics may be differentially perturbed, depending on the presence/absence of ischemia in patients with heart failure.

There is considerable evidence that the failing heart is in a state of energy deficit. For example, in both animal models and humans, CHF is associated with reductions in cardiac phosphocreatine (PCr), adenosine triphosphate (ATP), and PCr:ATP ratios (7,8).

Moderate to severe CHF is also associated with changes in myocardial substrate utilization (9), which may modulate this energetic deficit, in part by impairment of efficiency of myocardial oxygen utilization. The majority of human studies have demonstrated increased myocardial utilization of fatty acids in class II to III CHF of both ischemic (10) and non-ischemic origin (11), although in very advanced non-ischemic cardiomyopathy there is down-regulation of fatty acid metabolism, with increased uptake of glucose (12,13). Similarly, animal studies have demonstrated relatively normal myocardial substrate metabolism in moderate heart failure with fatty acid utilization predominating (14,15), whereas down-regulation of fatty acid oxidation and enhanced glucose utilization characterizes more severe decompensated heart failure (15). Enhanced glucose utilization in late-stage heart failure appears to be a consequence of the reduced fatty acid oxidation rather than due to a direct enhancement of the glucose pathway, because some enzymes of the carbohydrate metabolic pathway are down-regulated, not up-regulated (16,17).

Myocardial responsiveness to insulin is potentially of pivotal importance as a determinant of the extent of myocardial glucose oxidation. Whole body and skeletal muscle insulin resistance is characteristic of diabetes and has also been documented extensively in patients with CHF both of ischemic and non-ischemic origin (11,18–20) and also in the presence of ischemic heart disease without either diabetes or CHF (18). However, a previous carefully conducted study by Utriainen et al. (21) in diabetic and control subjects without CHF demonstrated no evidence of myocardial, as distinct from skeletal, muscle, or whole body, insulin resistance. This study, which corrected for determinants of myocardial work under normoglycemic hyperinsulinemic conditions, concluded that in the absence of myocardial ischemia (or CHF), the myocardium is unlikely to develop an energetic deficit related to impaired glucose uptake. Nevertheless, there is some evidence for a myocardial energy deficit in diabetic hearts. Scheuermann-Freestone et al. (22) demonstrated reduced PCr/ATP in hearts from patients with type 2 diabetes without evidence of cardiac dysfunction, PCr/ATP correlating negatively with plasma non-esterified fatty acid concentrations, and, therefore, potentially reflecting impairment of glucose utilization.

In this issue of the Journal, Dutka et al. (23) have investigated the impact of diabetes on myocardial insulin sensitivity in a group of patients with CHF secondary to multivessel coronary artery disease who were undergoing myocardial positron emission tomographic evaluation of myocardial viability as a screening test for possible surgical revascularization. During hyperinsulinemic glucose clamp, myocardial glucose utilization, measured via uptake of $^{18}$F-fluorodeoxyglucose was significantly lower in diabetic than in non-diabetic patients, indicating the presence of

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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insulin resistance at the myocardial level. Given that insulin sensitivity in non-diabetic CHF patients was self-impaired (in comparison with historical control subjects), this finding implies that CHF per se and diabetes contribute incrementally to myocardial insulin resistance in patients with concomitant myocardial ischemia.

These important findings beg 3 further questions. First, is there any available information regarding the impact of diabetes on myocardial insulin resistance in patients with CHF but no coronary disease? This important experiment, which would offer a possible explanation for previous clinical findings (5,6), unfortunately has not yet been performed by any group in the clinical setting.

Second, what is the signal transduction mechanism whereby diabetes increases myocardial insulin resistance? One likely possibility is that expression of the myocardial Glut-4 glucose transporter, or translocation of Glut-4 to myocardial cell membranes in response to insulin, may be impaired. In the absence of diabetes, reduced expression of Glut-4 has been observed in the rat infarction model of heart failure (24), whereas reduced translocation of Glut-4 has been observed in a canine model of advanced heart failure (25). In the current study, left ventricular biopsy samples in a subset of patients showed no variation in Glut-4 protein expression in the diabetic patients compared with those without diabetes, but this does not exclude a defect in Glut-4 translocation. Alternatively, as suggested by the authors, it is possible that the somewhat higher concentrations of free fatty acids in the subjects with diabetes during the hyperinsulinemic euglycemic clamp-induced inhibition of glucose uptake.

The final issue raised by the current report by Dutka et al. (23) is whether specific therapeutic avenues should be considered for patients with concomitant ischemic heart disease, diabetes, and CHF. The crucial issue here remains one of “chicken and egg”: can we be completely confident that the energetic deficit seen in patients with CHF, and presumably particularly in the diabetic/ischemic subset, actually contributes directly to the impairment of contractility and to poor outcomes, or might it represent a consequence of “myocardial hibernation”? Importantly, therapeutic avenues are now opening up to test this hypothesis. Although the therapeutic potential of thiazolidinediones in CHF is limited by the risk of aggravation of symptoms (26), a number of “metabolic” agents are now showing promise for the management of CHF. Peroxelaxine, an inhibitor of the carnitine palmitoyltransferase system responsible for the uptake of long-chain fatty acids across mitochondrial membranes (27), markedly improved functional status and hemodynamics in patients with moderately severe CHF (28). However, peroxelaxine appeared to have similar beneficial effects in both ischemic and non-ischemic CHF. Furthermore, preliminary studies with trimetazidine, which acts largely as a partial inhibitor of mitochondrial fatty acid oxidation (29) in patients with class II to III CHF, indicated improvement in left ventricular systolic function (30,31). Fragaasso et al. (30) showed that these benefits were also seen in a small diabetic/CHF/ischemic cohort. The current study by Dutka et al. (23) suggests that it may be time to perform adequately powered therapeutic trials to test the Koch’s postulates for this group of high-risk patients.

**References**