Cardio DIGEST
The easy way to stay up to date with developments in cardiovascular care

Editorial

Jiten Vora
Editor, Cardio Digest

HEART FAILURE AND DIABETES: ARE WE DOING ENOUGH?

While epidemiological studies have established the importance of heart failure (HF) in people with diabetes, the aetiology remains less clearly understood. Undoubtedly there is a contribution of myocardial ischaemia, hypertension and a specific diabetic cardiomyopathy. These may contribute to the biochemical, anatomical and functional alterations in cardiac myocyte function. The myocardial ischaemia may, of course, result from coronary artery disease but also potentially diabetic microangiopathy and abnormal endothelial function.

Diabetic cardiomyopathy, associated with mild cellular hypertrophy and fibrosis, is associated with reduced ejection function and electrophysiological abnormalities, altered cellular calcium transport and, as a consequence, contraction. These all produce sub-clinical systolic and diastolic dysfunction. The presence of ischaemia and cardiomyopathy together with hypertension results in a fibrotic, non-compliant myocardium with initial diastolic and later systolic dysfunction. With reducing function there is a progressive activation of the renin-angiotensin and sympathetic nervous systems, leading to remodelling to include compensatory changes in cardiac structure and function. These changes will potentially increase cardiac muscle mass and will result in further alteration of ventricular function. Further basic biochemical changes result in alteration of gene expression, potentially through beta-adrenergic signal transduction abnormalities, resulting in a 'foetal gene programme'. Altered foetal isoforms of myosin chains are expressed leading to a more foetal-like pattern, and resulting in further abnormalities of ventricular function (Bristow, 1998).

Treating heart failure in patients with diabetes

Treatments for HF in patients with diabetes include improvement in glycaemic control, angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. Improved glycaemic control may be beneficial for cardiac function, by improving cardiac metabolism and therefore performance, predominantly by decreasing myocardial-free fatty acid oxidation and increasing glucose utilisation. While the benefit of glycaemic control in improving the outcome of patients with diabetes with HF remains to be further examined, it should remain a part of the holistic management strategy for HF. ACE inhibitors and angiotensin-receptor antagonists (ARAs) predominantly work by reducing abnormal cardiac remodelling, which consequently produces improvement of left ventricular function. ACE inhibitors may reduce mortality and HF in patients with diabetes with or without systolic dysfunction. This effect is greater in patients with diabetes compared to those without. Blockade of the renin-angiotensin system, with ARAs, was particularly effective in reducing progression of HF in patients with diabetes and overt hephropathy, as witnessed in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial (Brenner et al, 2000) and the Irbesartan Diabetic Nephropathy Trial (IDNT; Berl et al, 2003). HF is associated with chronic sympathetic nervous stimulation, and the situation is further exacerbated by the presence of insulin resistance and hyperinsulinaemia. Increased catecholamines cause direct myocardial toxicity and

'While the benefit of glycaemic control in improving the outcome of patients with diabetes with heart failure remains to be further examined, it should remain a part of the holistic management strategy for heart failure.'

Editorial

'As rising HbA_{1c} is associated with increasing heart failure in patients with diabetes, the importance of tight glycaemic and also blood pressure control cannot be understated.'

stimulate altered gene expression and remodelling. Increased angiotensin 2 levels may further produce increases in catecholamine production. The cardiac remodelling effects of the abnormal sympathetic nervous system can be avoided by beta blockade, particularly using third generation beta-blocking agents. In HF clinical trials, particularly using carvedilol, patients with diabetes make up to a third of participants. Indeed, the mortality and morbidity outcomes in patients with diabetes were at least as good as those controlled subjects without diabetes. These treatments have resulted in major decreases in overall mortality. While ACE inhibition has been readily accepted by physicians treating patients with diabetes, the use of beta-blockers has been less than uniformly accepted on grounds of potential masking of or prolongation in duration of hypoglycaemia and possible adverse effects on peripheral circulation. There is evidence of these adverse effects being less with third generation beta-blockers.

Given this high prevalence in mortality of HF in patients with diabetes, identification and management of risk factors and delivery of appropriate therapy for HF per se appear obvious. Clearly, while treatment reduces complications of HF by approximately half in individuals with left ventricular dysfunction, a large number of patients remain undiagnosed and untreated. Of the risk factors, the most prominent are the presence of ischaemic heart disease, previous myocardial infarction and angina, together with hypertension. Diabetes is a significant contributor by itself but particularly with increasing age, longer duration of diabetes, use of insulin and increasing body mass index. As rising HbA_{1c} is associated with increasing HF in patients with diabetes, the importance of tight glycaemic and also blood pressure control cannot be understated.

While careful history may detect symptoms of HF, patients with left ventricular systolic function may not present with typical symptoms. Further detailed physical examination may not identify patients with reduced ejection fraction and HF. Therefore, further investigations are necessary. An electrocardiogram and chest X-ray may assist, but two-dimensional and pulsed Doppler echocardiography may be required. Clearly, this presents logistic and economical pressures and consequently additional screening may be necessary to pre-select patients with HF and left ventricular dysfunction. One may be able to utilise plasma levels of brain natriuretic peptide, which is elevated with increased cardiac filling pressures. Utilising this for screening patients aged above 55 has a reported sensitivity of 92 % and a specificity of 72 % (McDonagh et al, 1998).

Thus, it may be time for physicians to incorporate plasma brain natriuretic peptide measurements as a regular method of assessment.

Berl T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, et al (2003) Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Annals of Internal Medicine* **138**(7): 542–9

Brenner BM, Cooper ME, Zeeuw Dd D, Grunfeld JP, Keane WF, Kurokawa K, et al (2000) The losartan renal protection study – rationale, study design and baseline characteristics of RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan). *Journal of the Renin Angiotensin Aldosterone System* **1**(4): 328–35

Bristow MR (1998) Why does the myocardium fail? Insights from basic science. *Lancet* **352**(Suppl. 1): SI8–SI14

McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE et al (1998) Biochemical detection of left-ventricular systolic dysfunction. *Lancet* **351**: 9–13