Heart failure (HF) is a common and often neglected complication of type 2 diabetes mellitus (T2DM). The association is caused by the role of T2DM as a risk factor for coronary artery disease, its comorbidities (eg, hypertension) that themselves cause HF, and the direct effects of T2DM on the myocardium. This diabetic cardiomyopathy arises from multiple causes, including disease of the interstitium (eg, fibrosis), as well as direct myocardial effects, including disturbances of glucose and fatty acid metabolism.

Asymptomatic left ventricular (LV) dysfunction seems to be a precursor to the onset of HF. Although stage B HF has been characterized particularly in ischemic heart disease (based on recognition of impaired ejection fraction, regional wall motion abnormality, and scar), its recognition in non-ischemic heart failure has traditionally depended on the recognition of LV hypertrophy. However, functional disturbances also seem to be a hallmark of stage B HF, and the recognition of stage B HF has been facilitated by the development of sensitive new indices of myocardial function, including the measurement of myocardial deformation. In patients both with and without diabetes mellitus, abnormal myocardial function is a predictor of adverse outcome, including heart failure and death. However, it is not clear how stage B HF should be managed to prevent the progression to HF. As in other situations of asymptomatic LV dysfunction, it seems likely that there is a role for cardioprotective agents, including angiotensin-converting enzyme inhibitors and β-blockers. Given the observation that this entity may reflect disturbance of myocardial metabolism, the question remains as to whether improving glycomic control may improve myocardial function and avoid HF.

In this issue of Circulation: Cardiovascular Imaging, Leung et al report a study of 151 patients with poorly controlled T2DM, who underwent a multifactorial intervention, including targeting of glycemic control, lipids, and blood pressure. There was no correlation between hemoglobin A1c (HbA1c) and cardiac function at baseline. However, the intervention generated a nearly 20% reduction in both HbA1c (9.6%–7.8%) and low-density lipoprotein (2.2–1.8 mmol/L), although there was no change in body mass index or systolic blood pressure. In these patients, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were widely used at baseline and follow-up (respectively, 74% and 79%), and the use of β-blockers increased from 18% to 28%. Similarly, biguanides (75% increasing to 84%) and insulin (54%–66%) were widely used and increased during the study. The interventions were effective for improving both systolic and diastolic function, leading to a 5% ejection fraction improvement, an 18% improvement of global longitudinal strain (GLS; −14.9% to −17.6%), with reduction of end-systolic volume (4 ml) and LV filling pressure (estimated from E/e’). Furthermore, in keeping with previous reports of glucose-lowering agents in poorly controlled T2DM patients with >1% reduction of HbA1c had higher HbA1c at baseline and worse cardiac function at baseline.

In this study, improvements in metabolism appeared to contribute to improvements in function; improvement in GLS was associated with improvement in HbA1c, reduction of body mass index, and use of metformin, independent of baseline GLS, and follow-up GLS was associated with β-blockers. Likewise, change of E/e’ was associated with change in HbA1c, and follow-up e’ was associated with follow-up body mass index. However, in such a multifactorial intervention, the independent contribution of each factor can be difficult to judge. Indeed, previous work (Table) has more commonly shown no association between LV function and glycomic control, albeit in studies over a shorter time frame, better baseline metabolic status, and lesser improvements in glycomic control. Two studies have shown improvement in function with better glycomic control, one limited to diastolic dysfunction—possibly confounded by improvement in BP control—and the other showing improvement with insulin, but not oral agents. In the context of the association of GLS with outcomes, specifically the association of strain with outcomes in T2DM, this is an important observation, but it would be helpful to better understand the underlying mechanism. Furthermore, the lack of a placebo group emphasizes the need for caution against overinterpreting the findings of this nonrandomized study.

As proposed in this study, there is evidence that improvement of metabolism might be an important means of avoiding HF. In the UK Prospective Diabetes Study (UKPDS), a landmark randomized, multicenter trial of glycomic therapies in over 5000 patients with newly diagnosed T2DM, there was a 19% increase in risk of nonfatal HF with each 1% increase in follow-up mean HbA1c. Although UKPDS showed no

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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association of baseline HbA1c with the risk of CHF, a subsequent study from France showed that each 1% increase in baseline HbA1c was associated with an 18% increased risk of CHF.17 However, it needs to be appreciated that the nature of the agents used for glycemic control may be important for the management of HF and LV dysfunction. For example, a case-control study from a general practice database of 1633 patients with both HF and diabetes mellitus, and 1633 control subjects, sought the effects of metformin and other agents on the development of HF.18 The use of metformin monotherapy (adjusted odds ratio 0.65 [0.48–0.87]), metformin with or without other agents (0.72 [0.59–0.90]), angiotensin-converting enzyme inhibitors and angiotensin receptor blocker (0.55 [0.45–0.68]), and β-blockers (0.76 [0.61–0.95]) were associated with reduced mortality. By contrast, thiazolidinediones are associated with fluid retention and exacerbation of symptomatic HF, a major factor in the reduced mortality.20 Among the secondary end points, HF hospitalization was reduced 35%. A subsequent analysis showed that 0.55 [0.45–0.68], and 

<table>
<thead>
<tr>
<th>N</th>
<th>Agent</th>
<th>Duration</th>
<th>Change HbA1c, %</th>
<th>Systolic BP</th>
<th>Systolic Function</th>
<th>Diastolic Function</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>Pioglitazone 30 mg</td>
<td>6 mo</td>
<td>8.0–7.5</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Small change HbA1c</td>
</tr>
<tr>
<td>39</td>
<td>Other oral agents</td>
<td></td>
<td>7.9–7.5</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Pioglitazone 30 mg</td>
<td>6 mo</td>
<td>8.59–6.73</td>
<td>133–125</td>
<td>No change (EF, s’)</td>
<td></td>
<td>Confounded by ABP</td>
</tr>
<tr>
<td>54</td>
<td>Rosiglitazone 8 mg</td>
<td>6 mo</td>
<td>7.6–6.9</td>
<td>No change</td>
<td>EF 64–66%</td>
<td>Pk filling; No change</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>Placebo</td>
<td></td>
<td>7.6–7.2</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>GLP1 infusion</td>
<td>3 days</td>
<td></td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Under-powered</td>
</tr>
<tr>
<td>66</td>
<td>Gliburide</td>
<td>12 mo</td>
<td>9.5–8.2</td>
<td>No change</td>
<td>EF; No change</td>
<td>Not tested</td>
<td>Insensitive parameter</td>
</tr>
<tr>
<td>21</td>
<td>Insulin</td>
<td>4 mo</td>
<td>6.0–5.3</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not change</td>
<td>Near normoglycemia</td>
</tr>
<tr>
<td>18</td>
<td>Oral agents</td>
<td></td>
<td>5.9–5.1</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not change</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Insulin</td>
<td>3 wk</td>
<td>Reduction 3.8</td>
<td>Not tested</td>
<td>No change</td>
<td>e’ 7.5 to 8.6</td>
<td>Small study</td>
</tr>
<tr>
<td>9</td>
<td>Oral agents</td>
<td></td>
<td>Reduction 3.6</td>
<td>Not tested</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
</tbody>
</table>

BP indicates blood pressure; EF, ejection fraction; and HbA1c, hemoglobin A1c.

of fatty acid uptake and oxidation in HF, with impairment of metabolic flexibility.1 The findings of Leung et al,7 linking glycemic control to LV dysfunction, are part of a larger puzzle pertaining to the metabolic control of the failing heart. We have to hope that the elucidation of these biochemical processes and the impact of new therapeutic interventions will ultimately lead to attenuation of the wave of HF that is likely to follow the current epidemic of diabesity.

Disclosures

Dr Cooper is a consultant for Boehringer Ingelheim.

References


**Key Words:** Editorials ◼ diabetes mellitus ◼ glycemic control ◼ heart failure ◼ left ventricular dysfunction
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Thomas H. Marwick and Mark E. Cooper

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