Mr S. is a 46-year-old East-Indian male with typical manifestations of the cardiovascular dysmetabolic syndrome of insulin resistance (type II diabetes, obesity, dyslipidemia, hypertension, and elevated levels of high-sensitivity C-reactive protein). His medications include ramipril, simvastatin, entericoated aspirin, metformin, and glyburide. He has no symptoms of cardiac ischemia or congestive heart failure and has preserved left ventricular function. Over the past few months his glycemic control has been inadequate, and a decision to initiate an insulin sensitizer (glitazone) is made. Treatment is initiated with rosiglitazone 4 mg twice daily, with marked improvement in glycemic control and other components of the cardiovascular dysmetabolic syndrome. Approximately 6 months after initiation of therapy, your junior resident receives a phone call from Mr S, who is extremely anxious and distraught about the possibility of developing heart failure on glitazone therapy. The resident and the patient request your expert opinion about the effects of glitazones on cardiac function and associated hemodynamics.

Insulin resistance has been increasingly recognized as a central metabolic disturbance predisposing a patient to hypertension, hyperlipidemia, premature atherosclerosis, left ventricular hypertrophy, and endothelial dysfunction. In addition to being a powerful risk marker for the development of cardiovascular disease, insulin resistance is also closely related to cardiac dysfunction and heart failure. Thiazolidinediones (TZD; glitazones) are peroxisome proliferator-activated receptor (PPAR) agonists that specifically augment insulin sensitivity and counter insulin resistance in patients with the cardiovascular dysmetabolic syndrome. Currently, there are 2 commercially available glitazones, rosiglitazone and pioglitazone. Troglitazone was withdrawn from the market because of hepatic side effects. The PPAR family is composed of 3 subtypes. TZDs bind with high affinity to the PPAR\gamma isoform. The PPAR\gamma isoform is found in the heart, endothelium, vascular smooth muscle (including atherosclerotic lesions and neointima formed after angioplasty), liver, skeletal muscle, monocytes/macrophages, and many other tissues and cell types. Specifically by decreasing insulin resistance, TZDs improve global cardiovascular and metabolic health by improving glucose homeostasis, decreasing plasma insulin levels, improving endothelial function, decreasing vascular inflammation and C-reactive protein levels, and correcting lipid abnormalities. The ability of TZDs to counter the metabolic syndrome has led to widespread use of these drugs in patients with insulin resistance and diabetes.

There has been increasing discussion about whether TZDs affect cardiac function, with evidence suggesting both negative and positive effects on myocardial performance. Consequently, the practicing cardiologist is often faced with a difficult decision about whether to initiate therapy because a large proportion of patients with diabetes often have coexisting ischemic and nonischemic cardiomyopathy. In this article we summarize the available data on glitazones and cardiac function in an attempt to facilitate the decision-making process for a busy clinician.
Effects of Glitazones on Cardiac Function and Hemodynamics

<table>
<thead>
<tr>
<th>Potential Advantages</th>
<th>Potential Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease peripheral vascular resistance</td>
<td>Fluid retention (2%–5%)</td>
</tr>
<tr>
<td>Decrease blood pressure</td>
<td>Peripheral edema (2%–5%)</td>
</tr>
<tr>
<td>Improve cardiac metabolism and glucose uptake</td>
<td>Increased body weight</td>
</tr>
<tr>
<td>Decrease left ventricular end diastolic pressure</td>
<td>Transient decrease in hematocrit</td>
</tr>
<tr>
<td>Positive inotropic effect</td>
<td>Increase in circulating plasma volume</td>
</tr>
<tr>
<td>Coronary vasodilation</td>
<td>Contraindicated in patients with New York Heart Association class III/IV congestive heart failure</td>
</tr>
<tr>
<td>Increase myocardial blood flow</td>
<td></td>
</tr>
<tr>
<td>Attenuate pathological cardiac hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Decrease angiotensin II production</td>
<td></td>
</tr>
<tr>
<td>Decrease angiotensin II receptor I expression</td>
<td></td>
</tr>
<tr>
<td>Increase natriuretic peptide production</td>
<td></td>
</tr>
<tr>
<td>Decrease tumor necrosis factor-α level</td>
<td></td>
</tr>
<tr>
<td>Decrease endothelin-1 level</td>
<td></td>
</tr>
<tr>
<td>Attenuate vascular smooth muscle cells proliferation and migration</td>
<td></td>
</tr>
<tr>
<td>Attenuate ischemia-reperfusion injury</td>
<td></td>
</tr>
<tr>
<td>Decrease myocardial infarction size</td>
<td></td>
</tr>
<tr>
<td>Improve endothelial function</td>
<td></td>
</tr>
</tbody>
</table>

Hemodynamic Effects of Glitazones as They Relate to Cardiac Function

Effects on Vascular Resistance and Afterload

There is accumulating evidence to suggest that insulin stimulates endothelium-dependent nitric oxide-mediated vasodilatation, and that this effect is closely associated with the overall effects of insulin on glucose disposal. Importantly, insulin-mediated vasorelaxation is blunted in patients with insulin resistance (also known as vascular insulin resistance). In addition to decreased NO-mediated vasorelaxation, patients with insulin resistance often have coexistent hyperinsulinemia, which is a stimulus for enhanced endothelin production, thereby further impairing endothelial function and increasing vascular tone.

Improving insulin sensitivity with glitazones may counter vascular insulin resistance and reduce hyperinsulinemia-induced endothelin-1 production, resulting in improved tonic vasodilator response to insulin and reduction in peripheral vascular resistance and blood pressure. By reducing plasma insulin levels, these agents may reduce the blood-pressure-raising actions of insulin such as renal sodium retention and increased sympathetic activity.

The aforementioned vascular effects of glitazones may offer an advantage to patients with heart failure by decreasing afterload and peripheral vascular resistance. Indeed, in troglitazone-treated patients, decreased peripheral resistance produced an increase in stroke volume and cardiac output. Earlier studies with troglitazone demonstrated a significant reduction in diastolic blood pressure by 6.5 mm Hg (8%). Likewise, rosiglitazone (4 mg twice a day over 52 weeks) is associated with a significant decrease in systolic blood pressure (3.5 mm Hg) and diastolic pressure (2.7 mm Hg). Although reductions in afterload and blood pressure would theoretically be beneficial to diabetic patients with heart failure, this remains to be carefully evaluated.

Effects on Left Ventricular Mass and Contractility

Left ventricular hypertrophy is an important risk factor for coronary heart disease and cardiac-related mortality. The growth factor actions of insulin, acting via insulin-like growth factors, may lead to an exaggerated hypertrophic response of the left ventricle in response to arterial hypertension. In fact, the potent effects of angiotensin-converting enzyme inhibitors on regression of left ventricular hypertrophy are related, in part, to their ability to improve insulin sensitivity.

Yamamoto et al demonstrate that PPARγ activators inhibit cardiac hypertrophy in cardiac myocytes and regulate cardiomyocyte hypertrophy, mediated in part through the nuclear factor-κB pathway. Asakawa et al report that the PPARγ-dependent pathway plays a critical role in the inhibition of cardiac hypertrophy in response to in vitro and in vivo physiological and pharmacological stimulation.

Experimental studies suggest that glitazones may exert inotropic effects, but the exact nature of this response remains unclear. Studies with troglitazone suggest that the response is transient and that the main hemodynamic effect of long-term treatment with glitazone treatment is vasodilation, not inotropy. Indeed, troglitazone treatment results in increased myocardial blood flow, which in turn may lead to an increase in myocardial performance. However, clinical and echocardiographic studies with glitazones in patients with type-2 diabetes show a neutral effect on cardiac structure and function.

Effects on Neurohumoral Regulation

Insulin and insulin resistance have complex and inter-related effects on components of the neurohumoral cascade activated in patients with heart failure. It is well accepted that increased sympathetic tone can induce insulin resistance, and conversely, hyperinsulinemia and insulin resistance promote increased sympathetic discharge. The renin-angiotensin system is activated progressively as cardiac function deteriorates, and inhibition of angiotensin-
converting enzyme favorably remodels the myocardium in patients with heart failure. A growing body of evidence suggests that glitazones counter angiotensin activation, thus having a beneficial effect on ventricular remodeling in diabetic patients with heart failure. Evidence suggests that glitazones significantly reduce the production of tumor necrosis factor-α (TNF-α), a key factor in the development and progression of heart failure. PPARγ activators inhibit the cardiac expression of TNF-α in part through attenuating nuclear factor-κB activation. In chronic heart failure, plasma levels of endothelin are increased and are of prognostic value. Preliminary studies indicate that glitazones may reduce endothelin-1 production, which in turn may benefit diabetic patients with heart failure.

Effects on Myocardial Metabolism

Insulin resistance adversely affects myocardial metabolism and bioenergetics. Because glucose uptake and metabolism are dependent on insulin, resistance to its effects is particularly detrimental in the failing heart. Improving insulin sensitivity prevents the heart’s reliance on free fatty acids as the primary source of energy production by improving myocardial glucose use. Glucose provides a greater amount of ATP for a given rate of oxygen consumption, and hence correcting myocardial insulin resistance has important implications for myocardial metabolic function.

Do Glitazones Precipitate Heart Failure?

It is unclear whether glitazones have a direct detrimental effect on cardiac function. The majority of mechanistic and experimental studies would suggest that glitazones might favorably influence cardiac hemodynamics in heart failure. However, large-scale clinical trials have reported fluid retention and increase in plasma volume (6% to 7%) with glitazone therapy, with an increased incidence of peripheral edema occurring in 2% to 5% patients. Although the mechanistic basis remains elusive, some evidence suggests that this effect may be related to increased endothelial cell permeability induced by glitazone therapy. Others report that glitazones may interfere with renal hemodynamics. Glitazone-induced peripheral edema and fluid retention seem to be refractory to diuretics but promptly respond to withdrawal of therapy. An increase in preload with resultant pulmonary edema may contribute to worsening cardiac function in patients with brittle heart failure, and hence these agents are contraindicated in the setting of New York Heart Association class III and IV functional status. The Canadian Adverse Reaction Monitoring Program (CADRMP) received 8 reports of heart failure related to rosiglitazone between March 2000 and February 2001, and 2 similar reports for pioglitazone between August 2000 and August 2001. Previously reported cases of glitazone-related pulmonary edema occurred 4 to 13 months after starting therapy, although pulmonary edema has been reported as early as 3 days after treatment. Scattered reports indicate that glitazone-induced pulmonary edema may occur in patients with normal left ventricular systolic function after remarkable increase of body weight, although this seems to be an isolated observation.

Concluding Remarks

You ask your junior resident to discuss the following issues with Mr S.

Insulin resistance affects a large number of North Americans and consists of a cluster of cardiovascular...
and metabolic risks that include diabetes, hypertension, obesity, dyslipidemia, and atherosclerotic cardiovascular disease. Countering insulin resistance with glitazones holds promise for cardiovascular risk reduction in patients with the metabolic syndrome. However, because a large number of diabetic patients develop heart failure, there has been increasing discussion about the role of these agents in modulating cardiac function. Insulin resistance may play an important role in the development of adverse cardiac remodeling and facilitate the expression of heart failure. This may be caused directly by the effect of insulin resistance on myocardial angiotensin regulation, cytokine production, sympathetic nervous system activity, and altered myocardial metabolism. In addition, insulin resistance adversely affects vascular hemodynamics, and resistance to the vascular actions of insulin may serve to augment peripheral and coronary vascular tone and to raise blood pressure. From this standpoint, glitazone therapy may afford protection against the development and progression of heart failure if initiated early in the course of the disease (Table and Figure). On the other hand, glitazone therapy is associated in 2% to 5% of patients with increases in fluid retention, increased plasma volume, and pulmonary edema and may predicate heart failure in patients with poor ventricular function. It is possible that early intervention with glitazones in patients with the metabolic syndrome and preserved heart function may delay the development of heart failure. However, in patients with established heart failure, the beneficial effects of glitazones may be offset by an increase in fluid volume and pulmonary edema. In such patients, glitazone therapy should be initiated with caution and promptly withdrawn with worsening heart failure.

You inform the resident that because Mr S has no evidence of ischemic cardiomyopathy and has preserved left ventricular function, treatment with a glitazone is safe and not likely to precipitate heart failure. Furthermore, early and aggressive intervention with a glitazone in patients with the metabolic syndrome may delay the onset of heart failure in this patient and offer benefits in terms of cardiovascular risk reduction. Lastly, you remind the resident that PPARγ agonists (glitazones) have pleiotropic anti-atherogenic and antiinflammatory effects that may contribute to improved systemic vascular homeostasis in patients with diabetes.

**Note Added in Proof**

During the review process, an important paper by Shioi et al. was published evaluating the effects of glitazones on left ventricular remodeling and failure after a myocardial infarction. The authors report that pioglitazone improved left ventricular remodeling and function in mice with postinfarction heart failure, in part, via attenuated expression of inflammatory cytokines and chemokines, and hence may hold promise as preventative strategies, in heart failure.

**Acknowledgment**

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Glitazones and Heart Failure: Critical Appraisal for the Clinician
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Correction

In the Clinician Update “Glitazones and Heart Failure: Critical Appraisal for the Clinician” by Chao-Hung Wang et al, which appeared in the March 18, 2003, issue of the journal (Circulation. 2003;107:1350–1354), reference 37 was inadvertently omitted during revision. Reference 37 appears below.