Islet transplantation is an effective therapy in type 1 diabetes complicated by debilitating hypoglycemia (1). Insulin secretion is a sensitive measure of islet graft function, and measures of insulin resistance may indicate potentially deleterious metabolic stress on islets. How best to monitor insulin secretion, insulin sensitivity (Si), and islet function posttransplantation, has yet to be definitively established. Second phase insulin secretion has not been documented in patients off insulin after an islet transplant, and only five studies have estimated Si after islet transplant, with variable results (2–6). There have been no published euglycemic-clamp studies in islet recipients taking modern immunosuppression, and only one study reports using a 180-min insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT) (2).

We report the results of metabolic monitoring in two successful islet recipients, using noninsulin-modified FSIGT (NIM-FSIGT) (enabling second phase assessment) and euglycemic clamps. Second phase insulin secretion posttransplantation was markedly greater than first phase. We also found that modern immunosuppression regimens did not impair Si in islet recipients by testing the patients before and after transplantation.

Both patients underwent allogeneic-islet transplantation for type 1 diabetes with long-term severe hypoglycemic attacks, hypoglycemia unawarness, and suboptimal glycemia despite insulin-pump therapy. Subject 1 was a 55-year-old woman (body mass index [BMI], 20.6 kg/m²) (diabetes: 28 years) who received 752,328 islet equivalents (IE) (11,629 IE/kg), over two infusions from three donors, attaining insulin independence 4 weeks after the second infusion. Subject 2 was a 50-year-old woman (BMI, 22.7 kg/m²) (diabetes onset, 47 years) who received 580,913 IE (10,279 IE/kg), over two infusions from two donors, attaining insulin independence 6 weeks later. HbA1c normalized 2 to 3 months postinsulin independence (7.6% to 5.2% and 6.7% to 5.4%, respectively). Once exogenous insulin was stopped, both the patients no longer experienced hypoglycemia. Both remained insulin independent 9 months after transplant.

Two-step hyperinsulinemic euglycemic clamps (40 and 100 mU/kg/h insulin) were performed before transplantation and early postinsulin independence, whereas the 180-min NIM-FSIGT (250 mg/kg glucose) was only performed postinsulin independence because stimulated-insulin secretion in our C-peptide-negative subjects was undetectable pretransplant.

Both recipients were taking mycophenolate mofetil and tacrolimus (4–5 mg twice daily). Subjects 1 and 2 underwent the NIM-FSIGT 8 and 14 weeks after the second transplant, respectively (trough tacrolimus, 8.8 and 10.4 μg/L) and the follow-up clamp at 15 and 24 weeks after transplant, respectively (trough: 9.5 and 12.3 μg/L).

To facilitate comparison, clamp and NIM-FSIGT data are expressed as percentages of means derived from historical similarly assessed healthy young controls (two-step clamp group [data from J.E.H., University of Odense], n = 30; mean age, 30.6 years; mean BMI, 26.9 kg/m²; NIM-FSIGT group [data from G.M.W., University of Melbourne], n = 8; mean age, 33.8 years; mean BMI, 23.4 kg/m²).

After islet transplantation, mean NIM-FSIGT first phase insulin secretion was 15% normal and second phase 83% normal. Mean disposition index (DI) for first and second phase was 15% and 108% normal, respectively. Mean clamp Si was 129% normal pretransplant and increased to 211% normal postinsulin independence. Postinsulin independence, mean NIM-FSIGT Si was 116% normal (Table 1). These satisfactory results were obtained despite comparisons with younger controls who might have had greater insulin secretion and sensitivity than an age-matched group.

The 180-min NIM-FSIGT has the advantage of measuring second phase insulin without interference from exogenous insulin, as well as first phase secretion, Si, and DI. Previous studies have demonstrated that the islet recipients maintain normoglycemia despite markedly reduced first phase secretion [39% normal] (3–5). We show that second phase insulin, although diminished (83% normal), is restored to a greater extent than first phase (15% normal) indicating that it is the second phase insulin that principally maintains posttransplant normoglycemia. Therefore, a case can be made that second phase rather than, or in addition to, first phase should be monitored. Earlier studies in steroid-treated islet kidney recipients demonstrated similar reductions in first phase insulin during hyperglycemic clamps but equivocal data regarding second phase insulin (7). Unlike our patients, these steroid-treated recipients additionally had impaired tissue-glucose disposal as measured by one-step euglycemic clamps (7). The smaller than expected first phase insulin secretion in islet recipients could be because of loss of islet innervation (required for first phase coordination) and is unlikely to be secondary to tacrolimus (8).

Our work demonstrates that Si measured longitudinally with the “gold-standard” euglycemic clamp does not deteriorate early posttransplant—confirming the work of Rickels et al. (2,8) who demonstrated cross-sectionally that current immunosuppression regimens do not impair Si when compared with healthy controls.

Our recipients’ improved Si parallels increases in Si seen with intensive insulin therapy (9,10) or whole-pancreas transplantation (9) in type 1 diabetes—postulated causes include reduced glucotoxicity, glucolipotoxicity, and inflammation. Resolution of hypoglycemia might also reduce counter-regulatory hormones that impair Si.

Posttransplant Si is important because improved or preserved Si might slow graft function decline, and because insulin secretion should be interpreted in the context of prevailing sensitivity, that is, DI (= first phase insulin×Si)—a more sensitive indicator of risk for glucose intolerance than first phase or Si alone. Finally, insulin resistance in type 1 diabetes has
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The authors declare no potential conflict of interest.

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**REFERENCES**


**TABLE 1.** Insulin secretion and insulin sensitivity in the islet recipients pretransplantation and posttransplantation, compared with controls

<table>
<thead>
<tr>
<th></th>
<th>Pretransplant</th>
<th>Posttransplant</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin secretion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting C-peptide (nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>Undetectable</td>
<td>0.32</td>
<td>0.37</td>
</tr>
<tr>
<td>Subject 2</td>
<td>Undetectable</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>NIM-FSIGT First phase ([×10^{-2}] mU/mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>Nil</td>
<td>3.16 (20)</td>
<td>15.8 (100)</td>
</tr>
<tr>
<td>Subject 2</td>
<td>Nil</td>
<td>1.45 (9)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Nil</td>
<td>2.31 (15)</td>
<td></td>
</tr>
<tr>
<td>NIM-FSIGT Second phase ([×10^{-2}] mU/mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>Nil</td>
<td>7.56 (50)</td>
<td>15.0 (100)</td>
</tr>
<tr>
<td>Subject 2</td>
<td>Nil</td>
<td>17.19 (115)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Nil</td>
<td>12.38 (83)</td>
<td></td>
</tr>
<tr>
<td>First phase DI [×10^{-6}] [mmol/L]^{-1} min^{-1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>Nil</td>
<td>21.0 (16)</td>
<td>132 (100)</td>
</tr>
<tr>
<td>Subject 2</td>
<td>Nil</td>
<td>18.7 (14)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Nil</td>
<td>19.9 (15)</td>
<td></td>
</tr>
<tr>
<td>Second phase DI [×10^{-6}] [mmol/L]^{-1} min^{-1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>Nil</td>
<td>50.1 (40)</td>
<td>126 (100)</td>
</tr>
<tr>
<td>Subject 2</td>
<td>Nil</td>
<td>221 (176)</td>
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</tr>
<tr>
<td>Mean</td>
<td>Nil</td>
<td>135.6 (108)</td>
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</tr>
<tr>
<td><strong>Insulin sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clamp Si ([×10^{-4}] (mU/L)^{-1} min^{-1})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>3.67 (54)</td>
<td>13.36 (196)</td>
<td>6.80 (100)</td>
</tr>
<tr>
<td>Subject 2</td>
<td>13.84 (204)</td>
<td>15.28 (225)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>8.76 (129)</td>
<td>14.32 (211)</td>
<td></td>
</tr>
<tr>
<td>NIM-FSIGT Si ([×10^{-4}] (mU/L)^{-1} min^{-1})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>—</td>
<td>6.63 (79)</td>
<td>8.40 (100)</td>
</tr>
<tr>
<td>Subject 2</td>
<td>—</td>
<td>12.9 (154)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>—</td>
<td>9.77 (116)</td>
<td></td>
</tr>
</tbody>
</table>

Values in parenthesis represent data normalized as a percentage of mean values from the control groups.

NIM-FSIGT, non-insulin-modified frequently sampled intravenous glucose tolerance test; DI, disposition index; Si, insulin sensitivity.

implications for complications and mortality (11). Our data suggest this is not a concern and that preserved or enhanced Si might reduce the risk of complications along with better glycemic control.

In conclusion, we observed greater restoration of second phase insulin secretion compared with first phase after successful islet transplantation. We also observed preserved Si (measured by euglycemic clamp) on modern immunosuppression regimens after islet transplantation. These findings indicate that comprehensive estimates of insulin secretion (first and second phases, and DI) with the NIM-FSIGT have an important role in metabolic surveillance after islet transplantation.

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1292 | www.transplantjournal.com

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Late Airway Anastomotic Dehiscence Associated With Sirolimus and Migratory Staples in a Lung Transplant Recipient

We report a case of late airway anastomotic dehiscence associated with migratory staple and sirolimus use after bilateral lung transplantation. We describe its likely pathophysiology and management.

A 49-year-old white man who underwent lung transplant for 

alpha-1 antitrypsin deficiency in 2004 now presented with 3-month history of dry cough associated with exertional dyspnea and a 4% decline in his forced expiratory volume in 1 sec. He had been taking sirolimus, cyclosporine, and mycophenolate mofetil for immunosuppression after an episode of graft rejection 3 years ago. He was also on atorvastatin for hyperlipidemia for many years. Physical examination was unremarkable. Chest radiograph revealed increased patchy infiltrate over the right lung field. High-resolution chest computed tomography (CT) without contrast demonstrated extra-luminal gas inferomedial to the right mainstem bronchus. A hyperdense lesion is seen spanning across the right mainstem bronchial wall and extending into the lumen. In addition, there was bilateral patchy subpleural consolidation with central ground glass attenuation in the lung parenchyma. Flexible bronchoscopy showed a protruding surgical staple surrounded by mucosal slough at the surgical anastomotic site at the posterior wall of the distal right mainstem bronchus (Fig. 1), confirming partial airway dehiscence grade II. A temporary uncovered ultraflex metallic stent (I) was deployed in the bronchus intermedius extending proximally into the distal right main stem bronchus and overlying the partially dehisced anastomotic line. Pseudomonas aeruginosa was subsequently cultured from the lung tissue obtained from a transbronchial lung biopsy. Histology showed a chronic inflammatory infiltrate with increased eosinophils and organizing pneumonia that could be consistent with an infection or drug reaction. There was no microscopic evidence of cellular rejection. Cultures from both the bronchial lavage and lung tissue were negative for bacterial, viral, or fungal infection. He received 2 weeks of ciprofloxacin, inhaled colistimethate, tobramycin, and empirical voriconazole. Sirolimus and atorvastatin treatments were stopped. A repeat bronchoscopy 4 weeks later showed an intact and patent stent at the bronchus intermedius with overlying well-formed granulation tissue. A follow-up chest CT showed resolved pneumomediastinum and improved parenchymal infiltrates. Unfortunately, the patient developed an acute myocardial infarction requiring coronary stents placement and uninterrupted plavix treatment that preclude removal of the temporary bronchial stent at 8 weeks.

DISCUSSION

Our case is unusual in that the airway dehiscence occurred 4 years after lung transplant, raising the possibility that migration of surgical staple into the anastomotic site precipitated by chronic lung infection with concurrent sirolimus and statin use playing a supportive role had led to this late-onset occurrence. Early bronchial anastomotic dehiscence (<3 months after lung transplant) secondary to defective airway healing has been associated with the use of sirolimus-based immunotherapy regimen during immediate postlung transplant period (1, 2). This has prompted

FIGURE 1. Bronchial wall defect at anastomotic site with surgical staple seen protruding (red arrow).