Cilostazol Is Useful for the Treatment of Sinus Bradycardia and Associated Hemodynamic Deterioration Following Heart Transplantation

Tomoki Uchikawa,1 MD, Takeo Fujino,2 MD, Taiki Higo,1 MD, Kisho Ohtani,1 MD, Akira Shiose,3 MD and Hiroyuki Tsutsui,1 MD

Summary

Bradycardia is a common complication at the early postoperative period after heart transplantation (HT). The heart rate (HR) usually recovers within a few weeks; however, several patients need a temporary pacemaker or chronotropic agents to stabilize their hemodynamics. Here, we report the first case of transient bradycardia associated with hemodynamic deterioration following HT, which was successfully treated with cilostazol, a phosphodiesterase-3-inhibiting agent. A 59-year-old man received HT for advanced heart failure due to ischemic cardiomyopathy. General fatigue persisted even after the HT. His HR was around 60 beats per minute (bpm) with sinus rhythm. Echocardiography showed no abnormal findings. Right heart catheterization showed that the cardiac index (CI) was 1.9 L/minute/m². Continuous intravenous infusion of isoproterenol (0.003 μg/kg/minute) increased the HR to 80 bpm and CI to 2.7 L/minute/m² and improved his symptoms. Isoproterenol was switched to oral administration of cilostazol (100 mg, twice a day), which maintained the HR at around 80 bpm and CI of 2.5 L/minute/m². The patient’s HR gradually recovered and cilostazol could be discontinued three months after the HT. Oral administration of cilostazol can be a therapeutic option for patients with sinus bradycardia following HT, who need positive chronotropic support.

Key words: Advanced heart failure, Phosphodiesterase 3 inhibitor, Complication

Orthotopic heart transplantation (HT) is an established strategy for advanced heart failure refractory to medical therapy.12 Bradycardia is a common complication during the early period following HT, which is reported to occur among 14-44% of patients.13 This is mainly due to sinus node dysfunction and usually recovers spontaneously within a few weeks.12 However, several patients need a temporary pacemaker or positive chronotropic agents to stabilize their hemodynamics.

Here, we report the first case of sinus bradycardia associated with hemodynamic deterioration following HT, which was successfully treated with cilostazol, a phosphodiesterase-3- (PDE3-) inhibiting agent.

Case Report

A 59-year-old man with advanced heart failure due to ischemic cardiomyopathy received HT using the bicaval technique following mechanical support with a continuous-flow left ventricular assist device. The donor was a male in his late 50s with hypoxic encephalopathy, who did not have any history of cardiac diseases; the donor’s heart rate (HR) just before the harvest was around 70 beats per minute (bpm) with normal sinus rhythm. The total ischemic time was 261 minutes. After HT, immunosuppressive therapy with our standard regimen using tacrolimus, mycophenolate mofetil, and prednisolone was started. The recipient was taking esomeprazole before HT, and we continued it after HT to prevent gastrointestinal damage due to perioperative stress, prednisolone, and antithrombotic drugs. A temporary epicardial pacemaker was needed following the reperfusion of the donor’s heart.

Even after HT, general fatigue and shortness of breath persisted, classified as New York Heart Association (NYHA) class III. Two weeks after the HT, the HR was around 60 bpm and the plasma brain natriuretic peptide (BNP) concentration was 292 pg/mL (Table). Chest X-ray showed cardiomegaly and slight pulmonary congestion (Figure 1A). Electrocardiogram showed sinus rhythm with HR of 68 bpm (Figure 1B). Echocardiography showed normal left ventricular systolic function with end-diastolic diameter of 41 mm and ejection fraction of 70%. Right heart catheterization (RHC) under intravenous milrinone infusion showed cardiac index (CI) of 1.9 L/minute/m².
with HR of 60 bpm (Figure 2, blue arrows). The mean right atrial pressure was 5 mmHg and mean pulmonary capillary wedge pressure was 9 mmHg. Endomyocardial biopsy showed grade 1A acute cellular rejection with no evidence of antibody-mediated rejection. Coronary angiography showed no significant lesions on the coronary arteries. On the basis of these findings, sinus bradycardia was considered to be the main cause of the low cardiac output in this patient. Intravenous infusion of isoproterenol (0.003 μg/kg/minute) was started, and the CI markedly increased to 2.7 L/minute/m², associated with the increase of the HR to 85 bpm (Figure 2, red arrows). As a result of hemodynamic improvement, he achieved symptomatic relief (NYHA class II).

Three weeks after the HT, his cardiac output remained low, with CI of 1.7 L/minute/m² and HR of 63 bpm without isoproterenol. We then switched the intravenous infusion of isoproterenol to an oral administration of cilostazol, a selective inhibitor of PDE3, to maintain his HR. Cilostazol (100 mg, twice a day) successfully maintained his HR around 80 bpm, and his symptoms did not exacerbate even after the discontinuation of isoproterenol infusion. RHC showed that the CI was 2.5 L/minute/m², and his BNP concentration decreased to 77 pg/mL (Table and Figure 2). He was discharged 62 days after the HT. We continued cilostazol after the discharge, and his HR gradually increased up to 90 bpm. We then discontinued cilostazol at three months after the HT, under close in-hospital monitoring. His HR was maintained around 75 bpm and he remained asymptomatic. Four months after the HT, RHC showed that the CI was 2.4 L/minute/m² and BNP concentration was 46 pg/mL (Figure 2). He did not suffer from any bleeding event during the course.

**Discussion**

This is the first case report claiming that cilostazol is safe and effective for treating sinus bradycardia during the early period after HT. In our patient, his HR was about 60 bpm after HT and he experienced symptoms due to low

---

**Table.** Laboratory Data at Two and Eight Weeks after HT

<table>
<thead>
<tr>
<th></th>
<th>Two weeks</th>
<th>Eight weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBCs (μL)</td>
<td>13,160</td>
<td>5,970</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.3</td>
<td>9.8</td>
</tr>
<tr>
<td>Platelets (10^4/μL)</td>
<td>15.7</td>
<td>12.4</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>5.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.1</td>
<td>0.6</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>69</td>
<td>15</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>283</td>
<td>14</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.44</td>
<td>1.04</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>126</td>
<td>140</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.9</td>
<td>4.0</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.31</td>
<td>0.24</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>292</td>
<td>77</td>
</tr>
</tbody>
</table>

WBCs indicates white blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; and BNP, brain natriuretic peptide.
Figure 2. Time-dependent change of the HR, CI, and plasma BNP concentration after HT. The blue and red arrows indicate the HR and CI before and after starting isoproterenol, respectively. HR indicates heart rate (beats per minute); CI, cardiac index; and BNP, brain natriuretic peptide.

Cardiac output. HR under 70 bpm is considered significant bradycardia in HT recipients.5) In the current era of extended donor criteria such as older age and longer ischemic time, bradycardia is still a serious problem after HT.5) Bradycardia occurs among 14-44% of HT recipients and the majority of them are due to sinus node dysfunction during the early period after HT, which spontaneously recovers within a few weeks.2,3) However, several patients need chronotropic support or pacemaker implantation to stabilize their hemodynamics. Jones, et al. reported that only 32% of HT recipients who had received permanent pacemaker implantation were pacemaker-dependent during long-term follow-up.7) Therefore, less invasive but effective therapy other than permanent pacemaker implantation is required. The guideline from International Society for Heart and Lung Transplantation recommends positive chronotropic agents, such as isoproterenol or theophylline, to increase the HR in such cases.6) Theophylline, an adenosine receptor antagonist, is reported to be effective for bradycardia after HT.7) However, it may interact with other drugs, such as antibiotics, and careful monitoring of drug concentration is required. Furthermore, because our patient suffered from tacrolimus-induced tremor, we were hesitant to start an oral administration of theophylline or β-adrenergic receptor agonists which could exacerbate his symptoms.

Cilostazol is a PDE3-inhibiting agent and is effective for peripheral arterial diseases4) and the secondary prevention of cerebral infarction.8,11) Because it increases the HR via upregulating cyclic adenosine monophosphate in the myocardium and sinus node,8) it is also known to be effective against sinus bradyarrhythmia.10) In our case, we used cilostazol to treat symptomatic bradycardia and showed its positive chronotropic effect in a transplanted heart. We then successfully switched from intravenous isoproterenol to oral cilostazol. The major side effect of cilostazol is bleeding, due to its antiplatelet activity, although its risk is low.8) Our patient did not suffer from any side effects from cilostazol during the course.

We here reported the first case of bradycardia after HT, which was successfully treated with cilostazol. Although the role of theophylline and β-adrenergic receptor agonists is established in this situation, cilostazol can be an alternative option for HT recipients who need positive chronotropic support.

Disclosures

Conflicts of interest: None.

References