Treatment of Coronary Artery Fistula Post-Cardiac Transplantation with Covered Stent: A Case Study and Review of Literature

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Abstract
The majority of coronary artery fistulas are congenital and discovered incidentally on coronary angiography. Coronary artery fistulas may also develop after cardiac transplantation as a complication of endomyocardial biopsies. The natural history and optimal management of post-transplant coronary artery fistulas are uncertain. We report the case of a patient who developed symptoms from an early post-transplant coronary fistula, which was treated successfully with a covered stent. We review the literature, discussing current knowledge on incidence, natural history and management.

Introduction
Coronary Artery Fistulas (CAF) have been reported after orthotopic heart transplantation as a possible complication of Right Ventricular (RV) endomyocardial biopsies. Their true incidence, natural history and management have not been well described in the literature. We present a unique case of early detection of CAF at 1-month post-cardiac transplant and serial evaluation by intracoronary hemodynamics to guide management. Post-transplant CAFs are likely a more common complication of endomyocardial biopsies than recognized and routine screening should be considered. We review available data on CAFs in order to better understand the natural history and treatment outcomes.

Case Report
A 53-year-old male with an ischemic cardiomyopathy underwent orthotopic heart transplantation with biatrial anastomosis. He received basilixumab induction therapy and subsequent maintenance immunotherapy of tacrolimus, mycophenolate mofetil and prednisone along with aspirin and a statin. His immediate post-operative course was uncomplicated and he was discharged 12 days after transplant. As part of routine post-transplant rejection surveillance, RV endomyocardial biopsies were performed weekly with a total of 21 samples obtained in the first month. As per current major society guidelines, an average of 4 to 5 endomyocardial samples was obtained at each biopsy. There were no reported complications, however, on the 4th procedure, 4 of 5 biopsy samples contained fibroadipose tissue that was suspicious for epicardial fat sampling. An echocardiogram was performed as the patient complained of shortness of breath. This showed abnormal diastolic flow into the RV apex/apical septum, suggestive of a CAF (Figure 1). Both ventricles were normal in size and systolic function. Coronary angiography confirmed the presence of a mid Left Anterior Descending Artery (LAD) to RV fistula (Figure 2). Concurrent intracoronary hemodynamic evaluation showed reduced LAD coronary flow reserve of 0.5 distal to the fistula compared to a coronary flow reserve of 1.2 proximal to the fistula, suggesting significant coronary steal (Table 1). A right heart hemodynamic study was also performed, which did not demonstrate a step up in oxygen saturation or left to right shunting (Qp:Qs 0.99). As the patient’s symptoms resolved following diuresis, conservative management was pursued with close hemodynamic and imaging monitoring.

At 6 months post-transplant, follow-up surveillance
Figure 1: Reverse apical 4-chamber view 2D image (left) and color doppler (right) demonstrating fistula (single arrow) and diastolic flow (double arrow) into the Right Ventricle (RV).

Figure 2: Angiogram demonstrating the Left Anterior Descending Artery (LAD) to right ventricle fistula (large arrow).

Table 1: Summary of Invasive Coronary Hemodynamic Evaluation of the LAD

<table>
<thead>
<tr>
<th>Time Post-Cardiac Transplant</th>
<th>Distal FFR</th>
<th>CFR Distal to Fistula</th>
</tr>
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<tbody>
<tr>
<td>Week 6</td>
<td>0.76</td>
<td>0.5</td>
</tr>
<tr>
<td>Week 24</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Week 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention #1: covered stent</td>
<td>Pre PCI: 0.67</td>
<td>Post PCI: 6.6</td>
</tr>
<tr>
<td></td>
<td>Post PCI: 0.89</td>
<td></td>
</tr>
<tr>
<td>Week 56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention #2: drug eluting balloon angioplasty</td>
<td>Post PCI: 0.94</td>
<td>Post PCI: 2.7</td>
</tr>
</tbody>
</table>

FFR: fractional flow reserve, CFR: coronary flow reserve, PCI: Percutaneous coronary intervention
are found incidentally during coronary angiography. Patients are usually asymptomatic but occasionally exhibit chest pain, shortness of breath and palpitations. Case series report up to a 21% incidence of acquired CAF in heart transplant patients (Appendix Table 1). The majority of reported CAFs were detected on angiography at 1-year post-transplant, and are believed to be iatrogenic. Interestingly, angiogenesis secondary to the post-cardiac transplant inflammatory state has also been proposed to contribute to the formation of fistulas. This is supported by the detection of CAFs that do not involve the RV, which is unexpected for fistulas complicating RV endomyocardial biopsies [2-5]. The true incidence of CAF post-transplant is likely underestimated as most patients are asymptomatic and surveillance coronary angiography is not routine for all transplant programs. Similarly, our centre utilizes noninvasive echocardiography and nuclear myocardial perfusion imaging for allograft surveillance, which do not enable accurate evaluation for CAF post-transplant.

There is currently no consensus on the ideal management of post-cardiac transplant CAF as their natural history is unclear. Theoretical concerns include: [1] coronary steal leading to ischemia and arrhythmia, [2] a source of embolization, and [3] the risk of infectious endocarditis. A conservative management approach is common, but follow-up data is short ranging from 2 to 4 years after initial diagnosis [6-8]. Variable outcomes have been reported with some fistulas increasing in size, some remaining unchanged in appearance and others resolving spontaneously. Furthermore, despite the abovementioned theoretical complications of CAFs, few have been confirmed in the literature.

Data on treatment intervention for CAF is relatively sparse. The majority of available long-term data is for
congenital CAF. Congenital CAFs that are found incidentally in adulthood have been treated with ligation, coils, occluder devices, vascular plugs and even bypass. Invasive surgical intervention is difficult to justify in asymptomatic patients. In a case series of 58 patients with treated congenital CAFs, all patients’ survived surgery but 8 patients had ischemia in the peri-operative period and 1 had a significant arrhythmia leading to a stroke [9].

Appendix Table 2 summarizes published outcomes of treatment interventions for post-cardiac transplant CAF. The decision to treat was based on the development of symptoms for the majority of patients. Oreglia, et al. reported a case of a LAD to RV fistula noted on 1-year surveillance angiogram [10]. The patient was initially asymptomatic with a normal echocardiogram. At 10 years post-transplant the patient developed apical hypokinesis on echocardiogram, a continuous murmur and a dilated LAD. A Jo stent was inserted in the distal LAD to cover the fistula. Allograft function remained preserved before and after the procedure and 1-year follow-up angiography showed a patent stent. A similar successful treatment strategy with a Jo stent to cover a LAD CAF was reported in a patient presenting with an acute myocardial infarction immediately post-endomyocardial biopsy (Figure 4) [11]. Other percutaneous options have also been explored including detachable balloons and coils [12,13]. Uchida, et al. reported a single case of coronary artery surgical bypass for a CAF post-transplant [14]. A saphenous vein graft was performed on the LAD with suturing of the fistula. Long-term data was not reported for any of the above studies.

Post-transplant CAFs are potentially a more common complication of endomyocardial biopsies than recognized and routine screening should be considered. In our patient, the decision to intervene was based on the presence of symptoms, demonstrable coronary steal on hemodynamic evaluation and progressive reduction of distal coronary flow on serial angiograms. To our knowledge, this is the first reported case of post-transplant CAF with detailed longitudinal hemodynamic, angiographic and cardiac imaging evaluation before and after treatment. The rapid development of in-stent restenosis 5 months postcoronary intervention may be related to the pro-inflammatory state post-cardiac transplantation. Alternatively, underlying pathogenic mechanisms of early cardiac allograft vasculopathy in our patient may have played an important role in early restenosis. The long-term outcome of this clinical approach remains to be determined. Long-term data on CAFs is needed to better understand the natural history of this unique post-transplant phenomenon, and to guide recommendations for screening, monitoring and management.

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Disclosures

The authors have no disclosures.

References

1. Sandhu JS, Uretsky BF, Zerbe TR, Goldsmith AS, Reddy


<table>
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<tr>
<th>Study</th>
<th>Patients with fistulas N (%)</th>
<th>Location</th>
<th>Signs and symptoms</th>
<th>Other diagnostic investigations</th>
<th>Time of detection by diagnostic angiogram (Post-Transplant)</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Wei, et al. [1]</td>
<td>432</td>
<td>89 (21%)</td>
<td>Coronary Artery Origin: RCA 54%, LAD 39%, Cx 6% Non-coronary artery origin: RA 30%, L. Thoracic Vessels 12%, RV 5%, PA 5%, LA 4%, LV 4%, SVC 1%, Ao 2%, Cx 6% [112 fistulas]</td>
<td>N/A</td>
<td>1-year surveillance</td>
<td>96% noted at 1-year surveillance</td>
</tr>
<tr>
<td>Saraiva, et al. [2]</td>
<td>175</td>
<td>5 (3%)</td>
<td>Coronary artery to RA (n = 1) and RV (n = 10) [1 fistulas]</td>
<td>N/A</td>
<td>1-year surveillance</td>
<td>None</td>
</tr>
<tr>
<td>Lazar, et al. [3]</td>
<td>480</td>
<td>14 (3%)</td>
<td>Coronary artery to RA (n = 1) and RV (n = 17 fistulas)</td>
<td>None</td>
<td>1-year surveillance</td>
<td>None</td>
</tr>
<tr>
<td>Paede, et al. [4]</td>
<td>160</td>
<td>3 (2%)</td>
<td>RCA (n = 2), LAD (n = 1) to RV [3 fistulas]</td>
<td>None</td>
<td>1-year surveillance</td>
<td>None</td>
</tr>
<tr>
<td>Henzlová, et al. [5]</td>
<td>74</td>
<td>4 (5%)</td>
<td>RCA (n = 2), LAD (n = 3) to RV [5 fistulas]</td>
<td>None</td>
<td>2- and 3-year surveillance</td>
<td>None</td>
</tr>
<tr>
<td>Fitchett, et al. [6]</td>
<td>35</td>
<td>5 (14%)</td>
<td>RCA (3), LAD (2) to RV [5 fistulas]</td>
<td>None</td>
<td>&gt; 1 year</td>
<td>1 continuous murmur</td>
</tr>
<tr>
<td>Sandhu, et al. [7]</td>
<td>176</td>
<td>14 (8%)</td>
<td>RCA (52%, LAD (43%), Cx (5%) to RV [21 fistulas]</td>
<td>None</td>
<td>2 and 3 years</td>
<td>None</td>
</tr>
</tbody>
</table>

**Appendix Table 1:** Post-Transplant CAF Case Series (N ≥ 5).

*Congenital patients (D-TGA, HLH); RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; Cx: Circumflex Artery; RA: Right Atrium; RV: Right Ventricle; R. Thoracic Vessels: Right Thoracic Vessels; L. Thoracic Vessels: Left Thoracic Vessels; N/A: No Data Available.*
<table>
<thead>
<tr>
<th>Study</th>
<th>Location of fistula</th>
<th>Time of detection by diagnostic angiogram (Post-Transplant)</th>
<th>Intervention method/device</th>
<th>Signs and symptoms</th>
<th>Other diagnostic investigations</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keifer, et al. [8]</td>
<td>AscAo to PA</td>
<td>Few months</td>
<td>Amplatzer duct occlude</td>
<td>Right heart failure</td>
<td>None</td>
<td></td>
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<tr>
<td>Zoghi, et al. [9]</td>
<td>RCA to PA</td>
<td>6 years</td>
<td>Coil embolization</td>
<td>None</td>
<td>Echocardiogram: Normal right ventricle function</td>
<td></td>
</tr>
<tr>
<td>Oreglia, et al. [10]</td>
<td>Serial LAD to RCA</td>
<td>1st year</td>
<td>PTFE stent x 2</td>
<td>Fatigue</td>
<td>Echocardiogram: Normal</td>
<td></td>
</tr>
<tr>
<td>Lee, et al. [11]</td>
<td>LAD to RV</td>
<td>Acute ASTEMI 2 hours post 2 month routine biopsy</td>
<td>PTFE stent x 4</td>
<td>Fatigue</td>
<td>Echocardiogram: Normal left ventricular function</td>
<td></td>
</tr>
<tr>
<td>Furniss, et al. [12]</td>
<td>LAD to RV</td>
<td>LAD to RV (6 months post fistula)</td>
<td>4 coils to distal fistula</td>
<td>Fatigue</td>
<td>Echocardiogram: Normal left ventricular function</td>
<td></td>
</tr>
<tr>
<td>Uchida, et al. [13]</td>
<td>LAD to RCA</td>
<td>4 years post</td>
<td>Suture fistula and LAD bypass surgery</td>
<td>Shortness of breath on exertion</td>
<td>Echocardiogram: Normal left ventricular function</td>
<td></td>
</tr>
</tbody>
</table>

**Diagnosis:**
- Right ventricular strain
- Elevated pulmonary pressures
- Right ventricular systolic pressure
- Myocardial Perfusion study: Ischemia in apex, inferior and anterolateral walls
- Qp:Qs: 1.2
- 2. Qp:Qs = 1.12
- Normal right ventricle function
- Moderate apical akinesis with normal ejection fraction
- Normal left ventricular function
- Normal RV systolic pressure
- Normal left ventricular function
- Normal right ventricular function
- Normal biventricular function on echocardiogram
- Normal biventricular function on echocardiogram
- Normal RV systolic pressure
- Normal Qp:Qs: 1.48
- Increased murmur Intensity

**Intervention:**
- Amplatzer duct occlude
- Coil embolization
- PTFE stent
- 4 coils to distal fistula
- Suture fistula and LAD bypass surgery

**Post-Procedural:**
- Resolved symptoms
- Decreased murmur intensity
- Normal Qp:Qs: 1.48

**Signs and Symptoms:**
- Chest pain (2 hours post-biopsy)
- Continuous murmur on exam
- Continuous murmur after eating
- Fatigue
- Shortness of breath on exertion
- Shortness of breath on exertion
- Fatigue
- Fatigue

**Other:**
- Right heart failure
- None
- None
- None
- Fatigue
- Fatigue
- Fatigue
- Fatigue

**Notes:**
- RCA: Right Coronary Artery
- LAD: Left Anterior Descending Artery
- Cx: Circumflex Artery
- RA: Right Atrium
- RV: Right Ventricle
- SVC: Superior Vena Cava
- Ao: Ascending Aorta
- Aoa: Descending Aorta
- LV: Left Ventricle
- PTFE: Polytetrafluoroethylene
- Qp:Qs: Ratio Of Flow Through The Pulmonary Circulation And Flow Through The Systemic Circulation
- N/A: No Data Available
Appendix References


