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LITERATURE REVIEW

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

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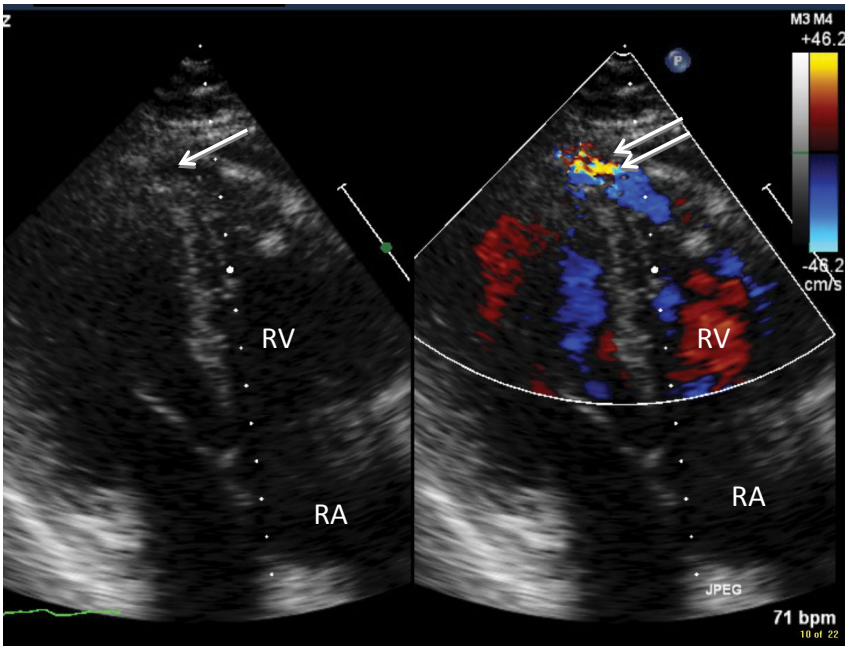

Figure 1: Reverse apical 4-chamber view 2D image (left) and color doppler (right) demonstrating fistula (single arrow) and diastolic flow (double arrow) into the Right Ventricle (RV).

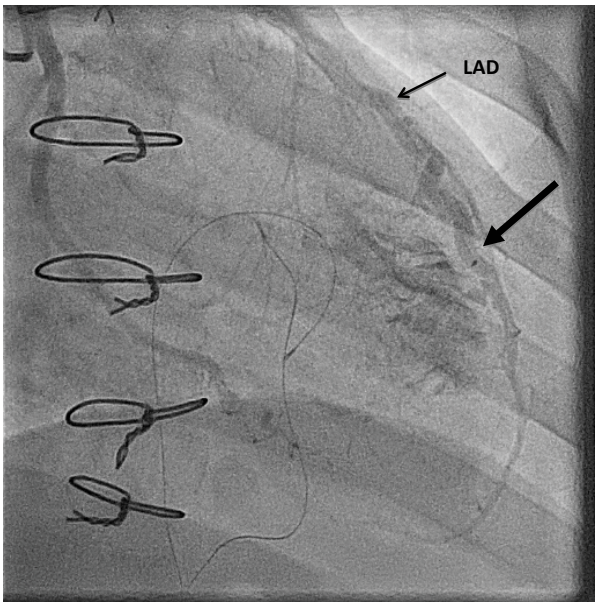

Figure 2: Angiogram demonstrating the Left Anterior Descending Artery (LAD) to right ventricle fistula (large arrow).

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

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

FFR: fractional flow reserve, CFR: coronary flow reserve, PCI: Percutaneous coronary intervention

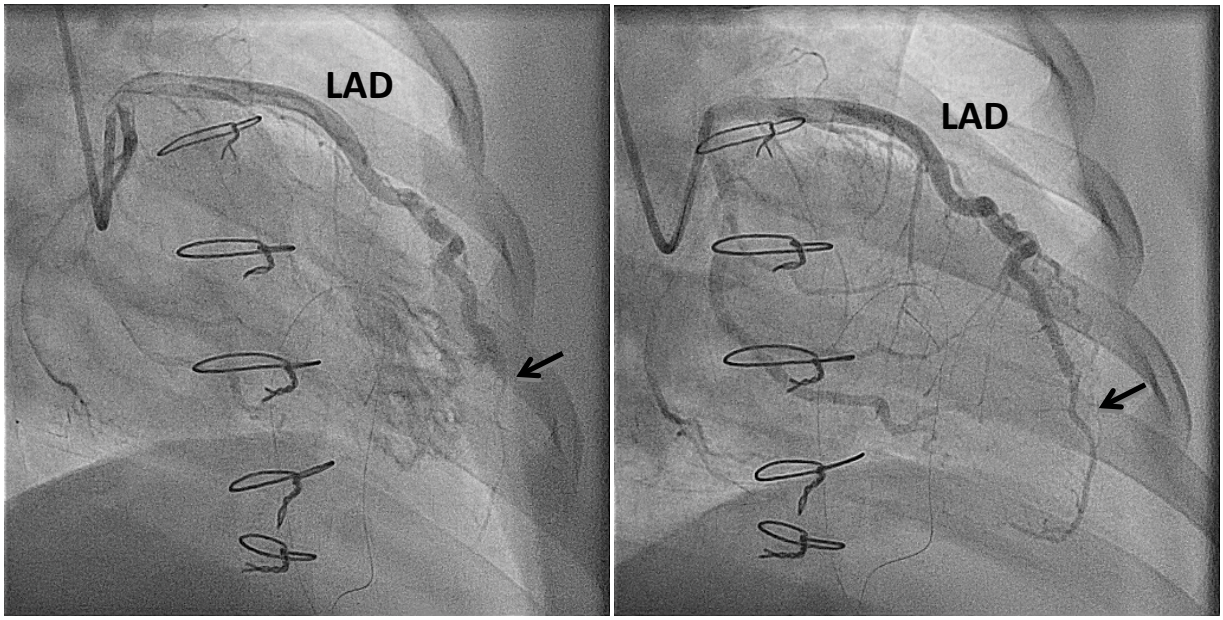

Figure 3: A) Occlusion of distal Left Anterior Descending Artery (LAD) at fistula (arrow); B) Improved flow in distal LAD following insertion of covered stent (arrow).

coronary angiography showed negative remodeling and occlusion of the LAD distal to the fistula. Filling of the distal LAD occurred after administration of intracoronary glyceryl trinitrate and intravenous adenosine. Coronary flow reserve was again reduced distal to the fistula, measuring 0.6. Dipyridamole rubidium-82 cardiac positron emission tomography showed mildly reduced myocardial flow reserve at the left ventricular apex. Due to these findings, elective percutaneous coronary intervention was scheduled and undertaken 8 months after transplant. A covered bare-metal stent was placed to seal off the fistula (Figure 3). Subsequent surveillance echocardiograms and myocardial perfusion/flow imaging did not demonstrate recurrence of abnormal flow. However, on follow-up coronary angiography at 13 months post-transplant (5 months after stenting), there was 90% in-stent restenosis and evidence of early cardiac allograft vasculopathy with non-obstructive disease evident in the all three major coronary arteries. The LAD in-stent restenosis was treated by drug eluting balloon angioplasty. Sirolimus was added to his immunosuppression regimen to delay progression of cardiac allograft vasculopathy. The patient remains well, currently at 30 months post-transplant.

Discussion

Coronary Artery Fistulas (CAF) occur in the general population but are rare with a reported 0.2% incidence [1]. Large, hemodynamically significant fistulas are detected at an early age and usually treated by surgical intervention. Congenital CAF occur due to embryologic arrest leading to additional communications within the heart or major vessels. Acquired CAF are commonly due to trauma or iatrogenic, related to endomyocardial biopsies or less commonly, inadvertent bypass of the vein instead of the artery during coronary bypass. Most CAFs 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

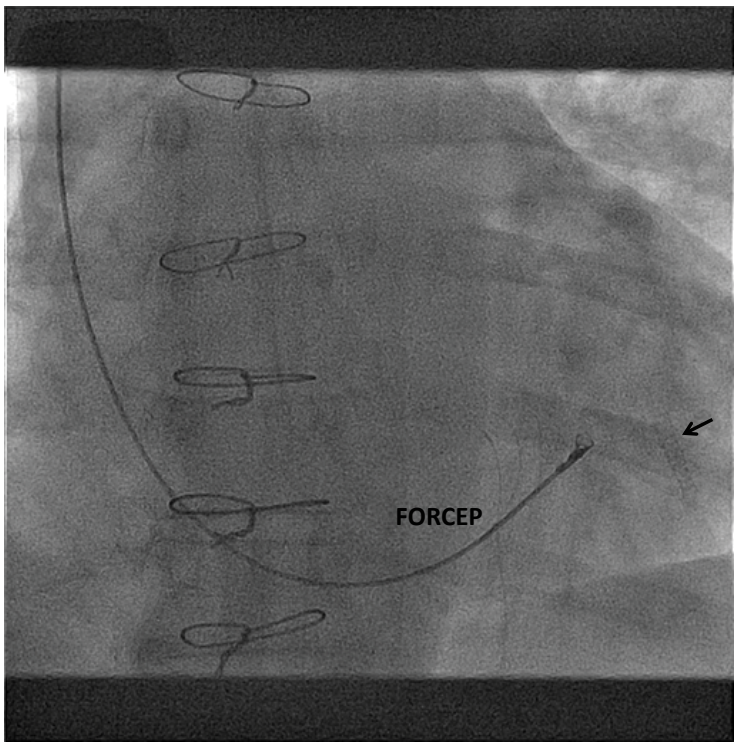

Figure 4: Fluoroscopic image obtained during subsequent endomyocardial biopsy demonstrating the close proximity of the biopsy forceps to the inserted covered stent in left anterior descending artery (arrow).

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.

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

Study	N	Patients with fistulas N (%)	Location	Time of detection by diagnostic dngiogram (Post-Transplant)	Signs and symptoms	Other diagnostic investigations	Outcomes
Wei, et al. [1]	432	89 (21%)	Coronary Artery Origin: RCA 54%, LAD 39%, Cx 6% Non-coronary artery origin: RA 30%, R. thoracic vessels 12%, RV 5%, PA 5%, LA 4%, LV 4%, SVC 1%, Ao 2%, L.Thoracic vessels 3% [112 fistulas]	96% noted at 1-year surveillance	None	N/A	Follow-up: 5.2 years Progression: no change
Saraiva, et al. [2]	175	5 (3%)	N/A	1-year surveillance	N/A	N/A	Follow-up: 2 years Progression: 20% resolved, 20% no change Lack of data in 60%
Lazar, et al. [3]	480	14 (3%)	Coronary artery to RA (n = 1) and RV (n = 16) [17 fistulas]	17 (74%) at 1-year surveillance, 4 (17%) at 2-year surveillance, 2 (9%) at 3-year surveillance	None	None	Follow-up: 6 years Progression: 71% resolved 21% no change
Pande, et al. [4]	160	3 (2%)	RCA (n = 2), LAD (n = 1) to RV [3 fistulas]	2- and 3-year surveillance	None	None	N/A
Henzlova, et al. [5]	74	4 (5%)	RCA (n = 2), LAD (n = 3) to RV [5 fistulas]	1-year surveillance	None	None	Follow-up: 2 and 3 years Progression: - Year 2: 25% no change - Year 3: 25% increased dilation with new fistula, 25% decreased in size
Fitchett, et al. [6]	35	5 (14%)	RCA (3), LAD (2) to RV [5 fistulas]	> 1 year	1 continuous murmur	Echocardiogram showed apical akinesis in 1 out of 5 patients	N/A
Sandhu, et al. [7]	176	14 (8%)	RCA (52%), LAD (43%), Cx (5%) to RV [21 fistulas]	19 (11%) 1-year surveillance	1 continuous murmur	None	Follow-up: 2.25 years Progression: no change

*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; LA: Left Atrium; LV: Left Ventricle; SVC: Superior Vena Cava; Ao: Aorta; L. Thoracic Vessel: Left Thoracic Vessels; N/A: No Data Available.

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Appendix Table 2: Case reports of intervention in post-transplant CAFs.

Study	Location of fistula	Time of detection by diagnostic angiogram (Post-Transplant)	Intervention method/ device	Signs and symptoms	Other diagnostic investigations	Outcomes
Keifer, et al. [8]	AscAo to PA	Few months	Amplatzer duct occlude	Right heart failure	Echocardiogram: • Right ventricular strain • Elevated pulmonary pressures 2. Qp:Qs = 1.2	Symptoms: • Improved at 4 months post-intervention Investigations: • Normalized right ventricular functions
Zoghi, et al. [9]	RCA to PA	6 years	Coil embolization	None	Echocardiogram: • Normal right ventricle • Mild hypokinetic inferior and anterior septal wall and inferior wall • Elevated right ventricle systolic pressure Myocardial Perfusion study: • Ischemia in apex, inferior and anterolateral walls	Symptoms: • Remain none Investigations: • Normalized biventricular function on echocardiogram • Myoview negative for ischemia
Oreglia, et al. [10]	Septal LAD to RCA	1st year	PTFE stent x 2	At Detection (1st year): • None At Intervention (10 years): • Vasovagal symptoms after eating • Continuous murmur on exam	Echocardiogram: • At detection (1 year): normal • At intervention (10 years): moderate apical akinesis with normal ejection fraction	Symptoms: • None, however, peri-procedure myocardial infarction noted biochemically alongside occluded septal branch seen on angiogram Investigations: • Normalized biventricular function on echocardiogram post-procedure
Lee, et al. [11]	LAD to RV	Acute ASTEMI 2 hours post 2 month routine biopsy	PTFE stent x 1	Chest pain (2 hours post-biopsy)	Echocardiogram: • Apical and distal septal hypokinesis,	N/A
Furniss, et al. [12]	LAD to RV (5 fistulas)	6 months post	4 coils to distal fistula	• Fatigue • Shortness of breath on exertion • Murmur and thrill	Echocardiogram: • Normal	Symptoms: • Resolved symptoms • Decreased murmur intensity
Uchida, et al. [13]	LAD to RCA	4 years post	Suture fistula and LAD bypass surgery	• Shortness of breath on exertion • Fatigue	Echocardiogram: • Normal left ventricular function • Qp:Qs: 1.48	Symptoms: • Resolved symptoms

RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; Cx: Circumflex Artery; RA: Right Atrium; RV: Right Ventricle; R. Thoracic Vessels: Right Thoracic Vessels; LA: Left Atrium; LV: Left Ventricle; SVC: Superior Vena Cava; Asc. Ao: Ascending Aorta; Ao: Aorta; L. Thoracic Vessel: Left Thoracic Vessels; PA: Pulmonary Artery; ASTEMI: Anterior ST Elevation Myocardial Infarction; PTFE: Polytetrafluoroethylene; Qp:Qs: Ratio Of Flow Through The Pulmonary Circulation And Flow Through The Systemic Circulation; N/A: No Data Available.

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