## Highlights

- Cardiac toxicity of tacrolimus is rare, less known but can be serious.
- Tacrolimus cardiotoxicity should be suspected in unexplained cardiomyopathy post kidney transplant.
- Sirolimus can be an effective alternative to preserve or improve cardiac function.

Dr. M.K.Phanish

Corresponding Author

# Dilated Cardiomyopathy in an Adult Renal Transplant Recipient: Recovery upon Tacrolimus to Sirolimus switch: Case Report

*Sorayya Kakhi[1], Mysore Phanish[2], Lisa Anderson[1]*

**[1]Department of Cardiology, St George's University Hospitals NHS Foundation trust, Tooting, London, UK**

**[2]Renal Unit, St Helier Hospital, Epsom and St Helier University Hospitals NHS trust, Carshalton, London, SM5 1AA, UK**

## Abstract

The objective of immunosuppressive drugs used in solid-organ transplantation is to achieve acceptable rejection rates, minimise infections, prolong graft and patient survival. Cardio vascular disease is a major cause of death in kidney transplant recipients. The drugs commonly used to prevent rejection (Calcineurin inhibitors-CNIs and steroids) contribute to cardiac disease seen in transplant patients by increasing the risk of hypertension and diabetes. Direct cardiac toxicity of chemotherapeutic drugs such as Doxorubicin is well-known but potential direct effect of CNIs on myocardium is less explored and understood. Cardiac toxicity, a rare serious adverse effect of Tacrolimus has been observed in patients receiving solid organ transplant such as liver, bowel and kidney. In this report, we describe a case of new onset severe dilated cardiomyopathy after kidney transplantation. Reversal of heart failure occurred after Tacrolimus discontinuation and switch to a mammalian Target of Rapamycin (mTOR) inhibitor; Sirolimus.

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**Author for correspondence: Dr. Mysore Phanish. E mail: m.phanish@nhs.net**

**Telephone: 0044 2082963696**

**Dr. Sorayya Kakhi. E mail: sorayya. kakhi@stgeorges.nhs.uk**

**Dr. Lisa Anderson. E mail: lisa.anderson@stgeorges.nhs.uk**

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**Author for correspondence: Dr. Mysore Phanish. E mail: m.phanish@nhs.net**

**Dr. Sorayya Kakhi. E mail: sorayya. kakhi@stgeorges.nhs.uk**

**Dr. Lisa Anderson. E mail: lisa.anderson@stgeorges.nhs.uk**

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## Introduction

Cardio vascular disease contributes significantly to mortality and morbidity after kidney transplantation. The main contributors are hypertension, diabetes, dyslipidaemia and poor kidney function at least in part driven by the immunosuppressive drugs such as CNIs and corticosteroids. Tacrolimus is a calcineurin inhibitor commonly used post solid organ transplant. It is proven to be superior to Ciclosporine A in improving graft survival and preventing acute rejection in liver and kidney transplants [1].Tacrolimus is better tolerated and is currently the mainstay of immunosuppressive regimes in kidney and other solid organ transplantation. Potential direct toxic effect of CNIs on myocardium is not well studied. Previous reports have predominantly described concentric and hypertrophic cardiomyopathy following solid organ transplant [2, 3]. Mc Leod et al reported a case of dilated cardiomyopathy following liver transplant which did not recover following Tacrolimus withdrawal[4]. In this report, we describe a kidney transplant patient who developed a severe life- threatening dilated cardiomyopathy on Tacrolimus, which reversed after discontinuation of the drug and switch to mTOR inhibitor Sirolimus.

## Case presentation

We present the case of a 66-year-old female patient of Nigerian origin with a background of asthma, osteoarthritis, chronic subdural haemorrhage, microcytic anaemia and end stage renal failure secondary to hypertensive nephropathy, on intermittent unit-based haemodialysis (x 3 times/week) from 2011-2018. Usual medications included Aspirin, Candesartan, Alfacalcidol and Furosemide. Her baseline ECG met the Sokolow-Lyon criteria for left ventricular hypertrophy. PR interval was138ms, QRS duration 94ms and QTc 390ms. Transthoracic echocardiogram in September 2016 before renal transplant showed normal left ventricular (LV) size with mildly impaired systolic function and EF was estimated as 50-55%. Right ventriclular systolic function was normal. The left atrium was mildly dilated and there was no significant valvular disease. The estimated pulmonary pressure was 24mmHg. LV end diastolic diameter was 3.9 cm and end systolic diameter was 3 cm. LV out flow tract diameter was 2.1cm and ejection fraction (EF) was measured as 50-55%.

The patient received a deceased donor kidney transplant in August 2017. Surgery was uneventful with immediate graft function and her Creatinine came down to 80-100 umol/L with eGFR of 51-60

ml/min/1.73m$^2$. She received our low immunological risk immunosuppression protocol with Basiliximab induction, Mycophenolate Mofetil 1 gram twice a day, Tacrolimus 9 mg twice a day (0.1mg/kg BD) and prednisolone 20mg OD (stopped on D7). Tacrolimus levels were initially high. The dose was progressively reduced to achieve a target concentration of 8-12micg/l (first 3m) and 6-8 micg/l (after 3m). The patient was discharged on day five post-transplant, well in herself with no symptoms or signs of cardiac failure. She was under regular transplant clinic follow up with good and stable kidney function (Creatinine 110-130 micmol/l, eGFR 50-60), well controlled blood pressure, normal glucose and HbA1C levels.

In January 2018 the patient presented with symptoms and signs of decompensated heart failure including exertional dyspnoea, orthopnoea and pitting oedema. She was in pulmonary oedema needing admission for intravenous diuretics. Echocardiogram performed in January 2018 showed a dilated LV with severe global LV dysfunction, the EF had declined to 20-25%, severe decline compared to her pre transplant echocardiogram. She had no angina and no evidence of pericarditis. Due to the rapidity of onset of her heart failure, she was thought to have viral myocarditis. A panel of serologies and viral PCRs were performed to look for any infective cause. All the tests were negative including negative CMV, EBV PCRs, negative Lyme, HTLV, HIV and Rickettsia serologies. We considered the adverse impact of her AV fistula on cardiac function and ligated this in March 2018. There was no improvement in her cardiac function following this procedure. She remained short of breath on minimal exertion, NYHA class 3/4 in spite of being on maximum tolerated doses of loop diuretic, Spironolactone and Ramipril. Tacrolimus levels were within the target range of 5-8 mcg/l. The deterioration progressed and by April 2018 the transthoracic echocardiogram showed a dilated left ventricle (mildly dilated by diameter and severely dilated by volume- modified biplane; end-diastolic volume of 135 ml), **(Figure 1)** with severely impaired global systolic function and an LVEF of 11% by modified Simpson's biplane method. There was evidence of restrictive filling pattern of the left ventricle (E/A: 2.16, E/E' average: 19.31). There was no evidence of LV hypertrophy or thrombus (End- diastolic dimension: 5.4 cm, end-systolic dimension: 4.9 cm). LV septum wall diastolic thickness was 1.01 cm and LV posterior wall diastolic thickness was 1.19 cm. The right ventricle (RV) was basally dilated and had impaired systolic function. There was evidence of mild mitral regurgitation and the estimated pulmonary systolic pressure

was 20-25mmHg. At this point she underwent further investigations in search for cause of heart failure; including a coronary angiogram which showed calcified unobstructed coronaries and a cardiac MRI scan which showed a severely dilated LV cavity with severe global LV systolic impairment (EF 17%), mildly dilated RV cavity with moderate RV systolic impairment (EF 34%) and a severely dilated LA. There was no evidence of thrombus, fibrosis or infarction. LV end-diastolic volume: 252 ml (82-162) and LV end-systolic volume: 207 ml (20-57), **(Figure 2)**. LV mass was estimated as 140 g (73-145). The findings were consistent with a non-ischemic dilated cardiomyopathy. The patient had a repeat autoimmune and viral screen for dilated cardiomyopathy, which were all negative. She was started on Bisoprolol, Candesartan and Spironolactone and was discharged home on 80 and 40 mg twice daily dose of Furosemide. After ruling out all other potential causes of heart failure, we agreed that Tacrolimus induced cardiomyopathy was the most likely explanation. Following multidisciplinary discussions between the renal and cardiology teams we decided to withdraw Tacrolimus and switched to Sirolimus. The Sirolimus was started at a dose of 2mg OD and titrated to achieve a target level of 5-7 ng/ml.

In June 2018 patient was reviewed at cardiology outpatient clinic and a steady recovery was noted at that point. It was also noted that her NT-pro-BNP fell from 16,124ng/L on 15 April to 4869ng/L by 23$^{rd}$ of May 2018. On physical examination she only had mild pitting oedema up her shins. Transthoracic echocardiogram showed some subtle improvements; Dilated left ventricle (end-diastolic dimension: 5 cm from 5.4 cm, end-systolic dimension: 4 cm from 4.9 cm in April 2018) with global severely impaired systolic function with estimated LVEF of 15-20%. The RV was less dilated and RV longitudinal function has slightly improved. Estimated pulmonary artery systolic pressure was 30 mmHg. There had also been significant improvement in the filling pattern and the deceleration time had increased from 131 to 285ms. As a result, sirolimus was continued.

In March 2019, as part of her regular follow up and nine months after discontinuation of tacrolimus and introduction of sirolimus, the patient had a repeat transthoracic echocardiogram, which showed normal LV cavity size (2.94 cm/m²; 39mL/m²) with mildly increased wall thickness. Overall systolic function

appeared was only mild to moderately impaired with reduced longitudinal function, and EF was measured by Simpson's Biplane was 49%, LV end-diastolic dimension was 5 cm, end-systolic dimension was 3.5 cm and LVOT diameter was 2.1 cm **(Figure 3)**. The right ventricle had normal dimension and systolic function. The echocardiographic findings at various time points are summarised in **table 1**. Renal function was stable with Creatinine of 100 umol/L, eGFR was 45 ml/min/1.73m2. Abdominal ultrasound scan did not show any abnormalities. There were no episodes of rejection following the switch to Sirolimus. On her latest follow up in September 2019, she has remained well with minimal shortness of breath on exertion, mild pedal oedema and stable renal allograft function. She has had no further hospital admissions for heart failure.

**Discussion**

Tacrolimus is a potent immunosuppressant drug which has transformed the outcome of solid organ transplants. It has adverse renal, central nervous system and vascular side effects which have been previously documented. The cardiotoxic effects of Tacrolimus are uncommon and have been most commonly characterized as obstructive or concentric hypertrophic cardiomyopathy described following liver, bowel, renal and heart transplants [2] [3, 5]. McLeod *et al* described development of cardiac hypertrophy shortly after the introduction of Tacrolimus, particularly involving the intraventricular septum, which then rapidly progressed to a dilated cardiomyopathy[4]. In these reports, Tacrolimus withdrawal either had no effect on cardiac function or there was some improvement. Withdrawal of Tacrolimus and switching to an alternative immunosuppressant requires careful consideration of comorbidities, side effect profile and potential risk of rejection. Replacing CNI with an mTOR inhibitor (Sirolimus or Everolimus) is an option to reduce nephrotoxicirty and minimise cardiovascular risks but concerns over efficacy and tolerability has limited their use in clinical practice. However, the recent evidence does support the use of these drugs along with low dose tacrolimus[6] .

The mechanism of Tacrolimus cardiac toxicity has not been fully understood. It is suspected that calcineurin inhibition can alter sympathetic activation or potentially influence calcium release channels, contributing to the development of neurotoxicity, nephrotoxicity, and cardiac toxicity[7]. Indirect

effects on heart through hypertension and diabetes (The risk of both are increased by tacrolimus) contribute to cardiac dysfunction.

Presentation with cardiomyopathy in previous reports occurred between one week and seven years. The majority of Tacrolimus trough concentrations were > 10 ng/mL (range 5–64.4 ng/mL). In general, higher Tacrolimus trough levels were associated with a quicker onset of cardiomyopathy. Modern immunosuppressive regimes, including our protocol; tend to run lower levels, particularly 3 months post transplantation. In our patient apart from few high levels initially, majority of subsequent levels including levels at the time of presentation with heart failure were within target range. Although screening for infectious causes of myocarditis were negative, we cannot totally rule out a possibility of viral myocarditis that recovered upon Sirolimus switch as Sirolimus is known to have anti- viral properties. The presentation with severe heart failure we are reporting here is a rare clinical problem as the majority of patients on Tacrolimus do well. However, direct toxicity of this drug in contributing to cardiac dysfunction following kidney transplantation and the effect of mTOR inhibitors on cardiac structure and function need evaluation in future studies. Our patient made excellent recovery upon sirolimus switch and we could find only one other case report in the literature describing use of Sirolimus for paediatric transplant patients with Tacrolimus induced hypertrophic cardiomyopathy[8]. As far as we are aware, ours is the first report of Tacrolimus induced dilated cardiomyopathy which resolved upon Sirolimus switch.

In conclusion, our case demonstrates an adult renal allograft recipient who developed a dilated cardiomyopathy following kidney transplantation whilst on Tacrolimus therapy. Almost full recovery was achieved by conversion from Tacrolimus to Sirolimus. High index of suspicion is required in patients with new diagnosis of heart failure and worsening of existing heart failure after being treated with Tacrolimus. If tacrolimus cardiotoxicity is suspected multidisciplinary discussions are needed to decide the best available alternatives and to monitor response to the intervention.

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## Figures

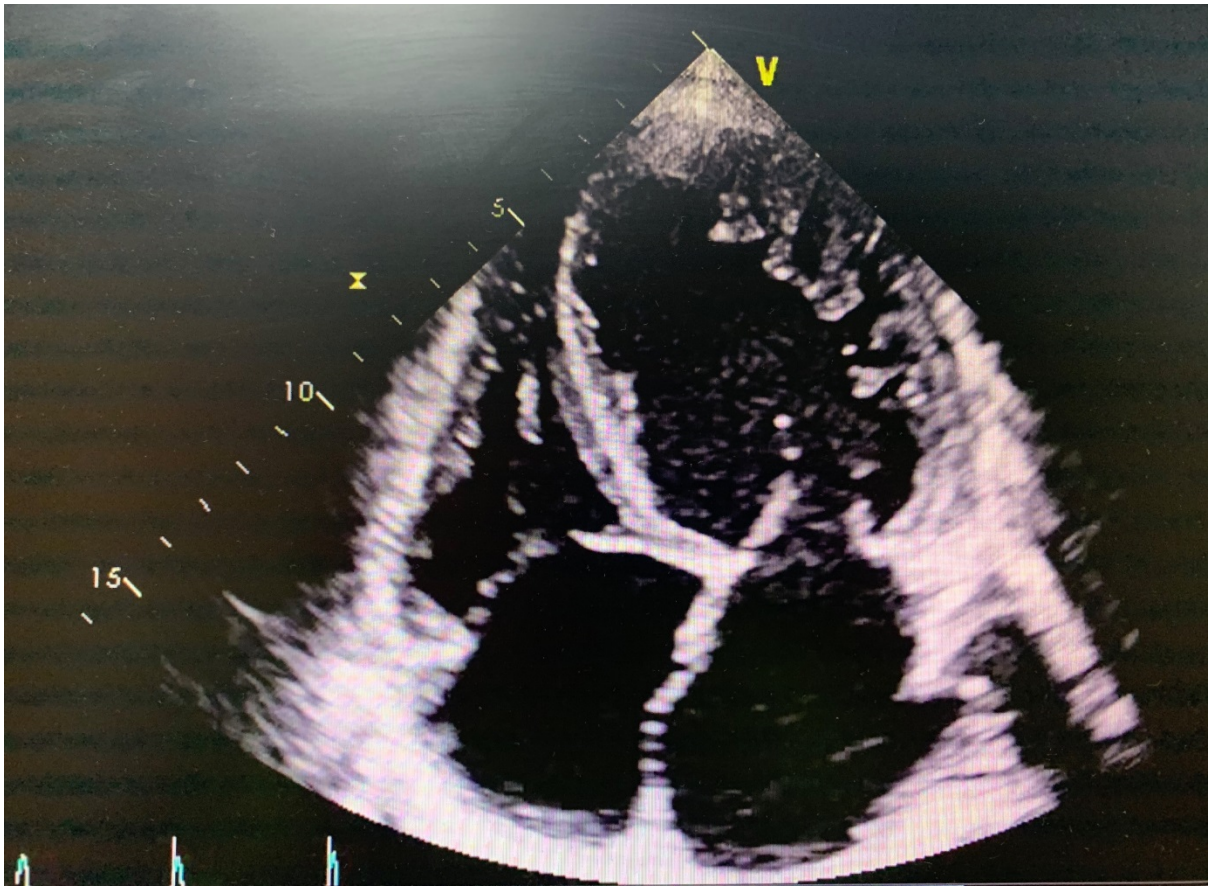


**Figure 1:** Four-chamber view on 2D transthoracic echocardiogram showing aneurysmal dilation of the left ventricular mid/apical segments, in end-diastole of cardiac cycle, patient was on Tacrolimus. Ejection fraction by Simpson's biplane method 11%.

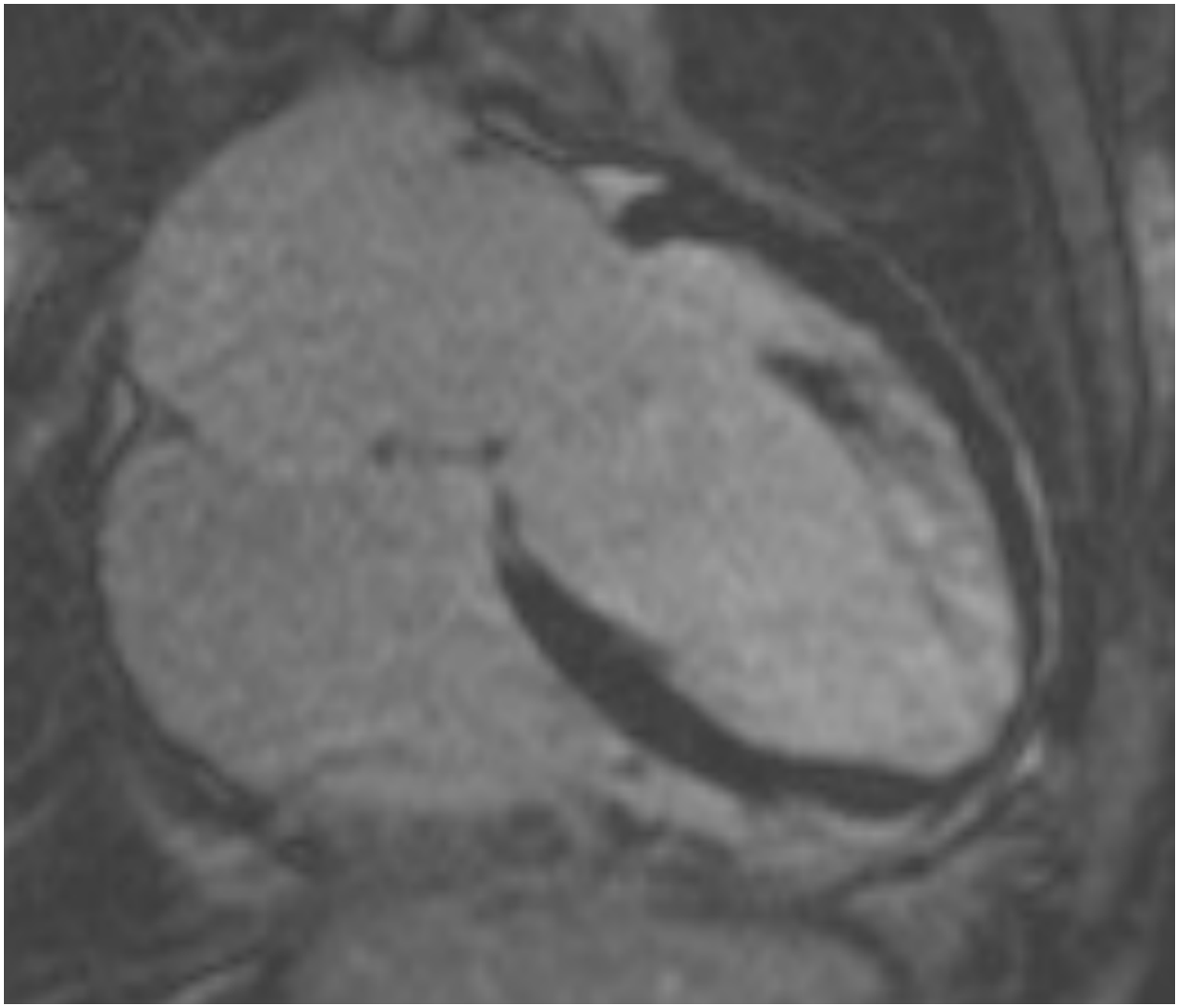

**Figure 2:** Four-chamber view on late gadolinium enhancement (LGE) cardiac MRI; showing a severely dilated left ventricle, and dilated atria. No myocardial enhancement is seen and the appearances are compatible with a dilated cardiomyopathy.

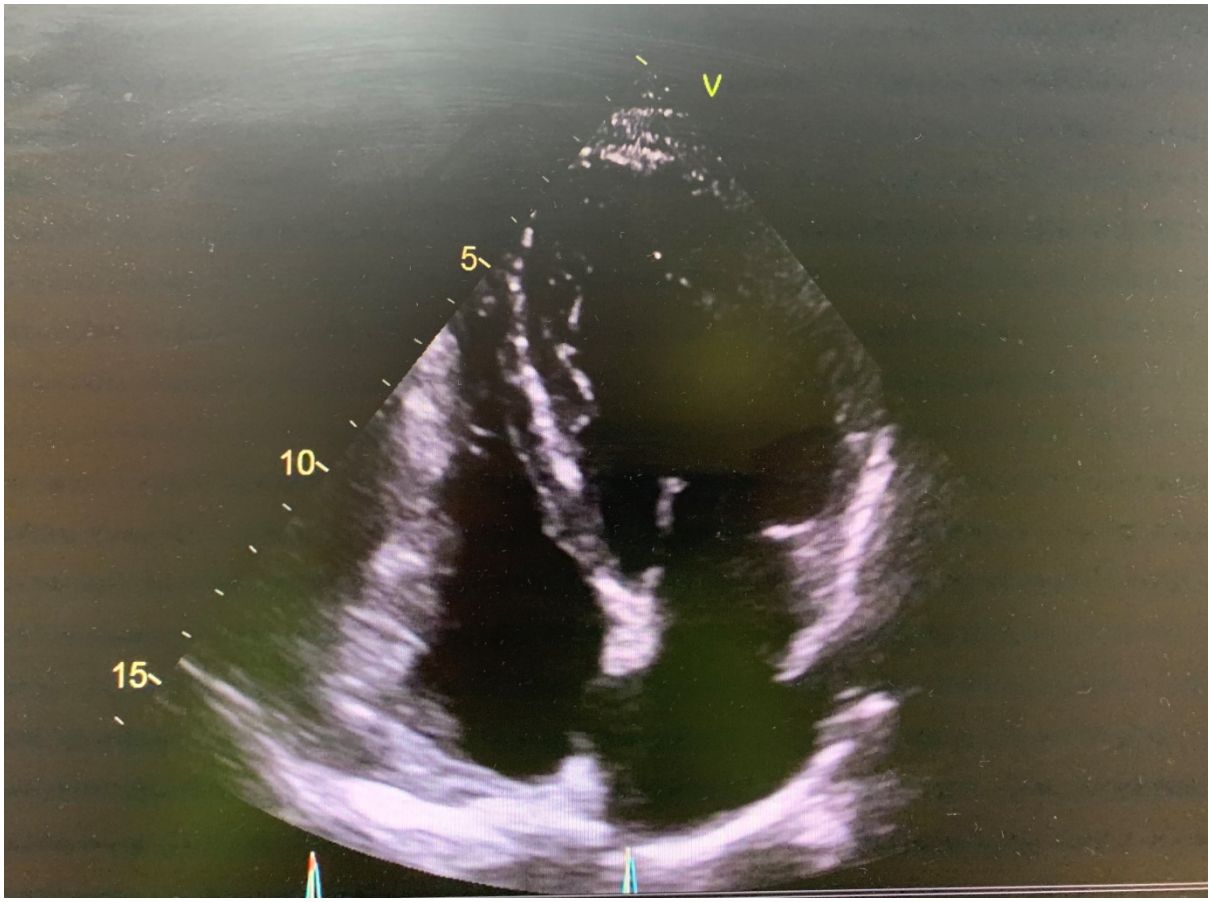


**Figure 3:** Two-chamber view on 2D transthoracic echocardiogram in end-systole; patient left ventricle has remodeled significantly with reduction in LV and RV volume, and decreased size of atria after discontinuation of Tacrolimus and switch to Sirolimus. Ejection fraction by Simpson's biplane method 49%.

| Echocardiographic findings | Pre-Transplant | 5m post Transplant | 8m post transplant | 10m post transplant<br>(2m after discontinuation of Tacrolimus and Sirolimus switch | 19m post transplant<br>(9-10m after discontinuation of Tacrolimus and Sirolimus switch) |
|---|---|---|---|---|---|
| EF | 50-55% | 20-25% | 11% | 15-20% | 49% |
| LV end diastolic diameter | 3.9 cm | | 5.4 cm | 5 cm | 5 cm |
| LV end systolic diameter | 3 cm | | 4.9 cm | 4 cm | 3.1 cm |
| LV outflow tract diameter | 2.1 cm | | | | 2.1 cm |
| NT-pro-BNP | | | 16,124ng/L | 4869ng/L | |

**Table 1:** Echocardiographic findings and NT-pro-BNP before transplantation, at presentation with heart failure and after tacrolimus discontinuation/Sirolimus switch.