ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–6
https://doi.org/10.1093/ehjcr/ytad470

CASE REPORT
Inherited cardiac conditions/cardiomyopathies

Mitochondrial function and coronary flow reserve improvement after autologous myoblast patch transplantation for ischaemic cardiomyopathy: a case report

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Received 27 February 2023; revised 30 August 2023; accepted 19 September 2023; online publish-ahead-of-print 21 September 2023

Background Autologous myoblast patch (AMP) transplantation has resulted in good clinical outcomes for end-stage ischaemic cardiomyopathy, but the mechanisms behind them are unclear. Herein, we report the relationship between mitochondrial function and coronary flow reserve (CFR) before and after AMP transplantation.

Case summary The patient was a 73-year-old man who underwent coronary artery bypass grafting (CABG). At that time, the left ventricular ejection fraction (LVEF) was 53%, but it declined to 25% after 6 years. He was diagnosed with ischaemic cardiomyopathy (ICM). Coronary flow reserve in NH_3-positron emission tomography (NH_3-PET) was impaired to 1.69. In Tc-99m MIBI scintigraphy, the washout rate (WR) was 17%, suggestive of impaired mitochondrial function. He was not a candidate for heart transplantation, and we performed AMP transplantation 6 years after CABG. One year after AMP transplantation, LVEF, CFR, and Tc-99m MIBI WR improved to 36%, 2.07, and 7%, respectively. The Tc-99m MIBI WR improved especially in the anterolateral region, and the CFR increased in almost all segments.

Discussion In this case, AMP transplantation for ICM improved cardiac function, CFR, and mitochondrial function. The mitochondrial transfer from the transplanted myoblasts to the damaged myocardium may have contributed to the mitochondrial function improvement. This probably induced myocardial energy metabolism recovery and decreased oxygen demand. AMP transplantation also has the potential to improve microvascular dysfunction, due to angiogenesis induction. These effects can lead to improved prognoses of ICM after AMP transplantation, highlighting its potential to cure refractory heart failure.

Keywords Regenerative medicine • Coronary artery disease • NH_3-PET • Energy metabolism • Tc-99m MIBI scintigraphy • Case report

ESC curriculum 2.1 Imaging modalities • 2.5 Nuclear techniques • 3.1 Coronary artery disease • 6.5 Cardiomyopathy • 7.5 Cardiac surgery

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Handling Editor: Grigoris Karamasis
Peer-reviewers: Ioannis Skalidis; Doralisa Morrone
Compliance Editor: Franca Morselli

Learning points

- Autologous myoblast patch (AMP) transplantation for ischaemic cardiomyopathy (ICM) can prevent cardiomyocyte damage and improve cardiac function via various mechanisms.
- AMP transplantation for ICM can improve mitochondrial function.
- Coronary flow reserve improved after AMP transplantation for ICM.
- The energy metabolism improved, and the blood supply demand decreased after AMP transplantation for ICM.

Introduction

Autologous myoblast patch (AMP) transplantation for ischaemic cardiomyopathy (ICM) shows promising outcomes.[1] Pre-clinical studies suggest that AMPs secrete cytokines, exerting paracrine effects, and facilitate microvascular network reconstruction to improve myocardial function.[2] However, there is no clinical evidence supporting these mechanisms, leaving their occurrence in humans uncertain. Herein, we identified a patient whose coronary flow reserve (CFR) and mitochondrial function improved after AMP transplantation for ICM.

Summary figure

Time	Event
6 years before	CABG for triple-vessel disease; LVEF, 53%
2 years before	LVEF, 34%; diagnosed with ICM
at AMP transplantation	NYHA III
	LVEF, 25%
	Peak VO_2, 11.4 mL/min/kg
	CFR in NH_3-PET, 1.69
	Tc-99m MIBI washout rate, 17%
	Scar area in MRI, 29.9%
6 months after	No admission for heart failure
	NYHA I
	LVEF, 45%
	Peak VO_2, 13.2 mL/min/kg
	CFR in NH_3-PET, 1.24
	Tc-99m MIBI washout rate, 7.5%
	Scar area in MRI, 26.2%
1 year after	No admission for heart failure
	NYHA I
	LVEF, 36%
	Peak VO_2, 13.8 mL/min/kg
	CFR in NH_3-PET, 2.07
	Tc-99m MIBI washout rate, 7%
	Scar area in MRI, 21.7%

Case presentation

A 73-year-old man with dyslipidaemia, type 2 diabetes mellitus and triple-vessel disease [90%, 50%, 100%, and 99% stenosis in the left anterior descending coronary artery (LAD), proximal left circumflex coronary artery (LCX), distal LCX, and right coronary artery (RCA), respectively] underwent coronary artery bypass grafting (CABG) with left internal thoracic artery (ITA) to LAD, right ITA composite grafting with radial artery to LCX and RCA. The left ventricular ejection fraction (LVEF) was 53% during CABG but decreased to 34% within 4 years, leading to the diagnosis of ICM. Despite optimal medical therapy with a beta-blocker, digoxin, and phosphodiesterase-3 inhibitor, heart failure (HF) symptoms remained consistent at New York Heart Association (NYHA) Class III. Owing to chronic kidney disease, the patient was unable to take the full medication for HF, such as angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, mineralocorticoid receptor antagonist, angiotensin receptor-neprilysin inhibitor, and sodium glucose cotransporter 2.

We considered the progression of coronary artery lesions and a newly developed valvular disease as causes of HF. However, none were confirmed through cardiac workup.

At 6 years post-CABG, echocardiography revealed the LV end-diastolic diameter (LVDd), LV end-systolic diameter (LVDs), and LVEF were 60, 53 mm, and 25%, respectively (*Figure 1A*). The peak VO_2 was 11.4 mL/min/kg (*Figure 1B*). Coronary flow reserve in NH_3-positron emission tomography (NH_3-PET) was impaired in each region (total, 1.69; LAD, 1.67; LCX, 1.64; RCA, 1.83) (*Figure 2*). In Tc-99m MIBI scintigraphy, the washout rate (WR) was 17% and was especially high in the anterior to lateral region (*Figure 3*), suggesting impaired mitochondrial function. In magnetic resonance imaging (MRI) with late gadolinium enhancement (LGE), the enhanced area [scar area (SA)] percentage was 29.9%, distributed in the lateral to inferior region but not transmurally (*Figure 4*).

As the patient was ineligible for heart transplantation, AMP transplantation was performed 6 years after CABG. Muscle specimens were harvested from the vastus medialis and cultured in a sheet as previously reported.[1] Five patches were transplanted to the anterolateral LV wall via left thoracotomy. The patient required inotropic support for 3 days post-surgery, which was smoothly weaned off and he was discharged 30 days after surgery.

The patient had an uneventful course after discharge, without HF-related hospitalizations. One year post-AMP transplantation, the LVDs decreased from 53 to 47 mm; the LVEF improved from 25 to 36% (*Figure 1A*). Physical activity showed improvements, with peak VO_2 increasing from 11.4 to 13.8 mL/min/kg, and NYHA classification improving from Class III to Class I (*Figure 1B*). NH_3-positron emission tomography indicated a decline in myocardial blood flow (MBF) both at rest and in stress conditions (*Figure 2*). Coronary flow reserve declined from 1.69 to 1.24 at 6 months after treatment but significantly improved to 2.07 at 1 year after treatment (*Figure 2*). Coronary flow reserve improvement was observed in all coronary regions (*Figure 2*). The Tc-99m MIBI WR improved from 17 to 7% 1 year after treatment, especially in the anterolateral region (*Figure 3*). Coronary flow reserve increased in all 17 American heart association segments. The Tc-99m MIBI WR improved in most segments, except 4 and 10 (see Supplementary material online, *Figure S1*). Magnetic resonance imaging with LGE revealed a reduction in the percentage of the SA from 29.9 to 21.7% after treatment (*Figure 4*, Supplementary material online, *Video S1*). The percentage of the SA in each coronary region also decreased after treatment (*Figure 4*). Consequently, there was an improvement in LVEF on echocardiography and a reduction in SA on MRI after treatment, along with the improvements in CFR and Tc-99m MIBI WR (*Figure 5*).

The bull's eye image demonstrates local changes in CFR, Tc-99m MIBI WR, and SA on MRI (*Figures 2–4*). CFR improved globally;

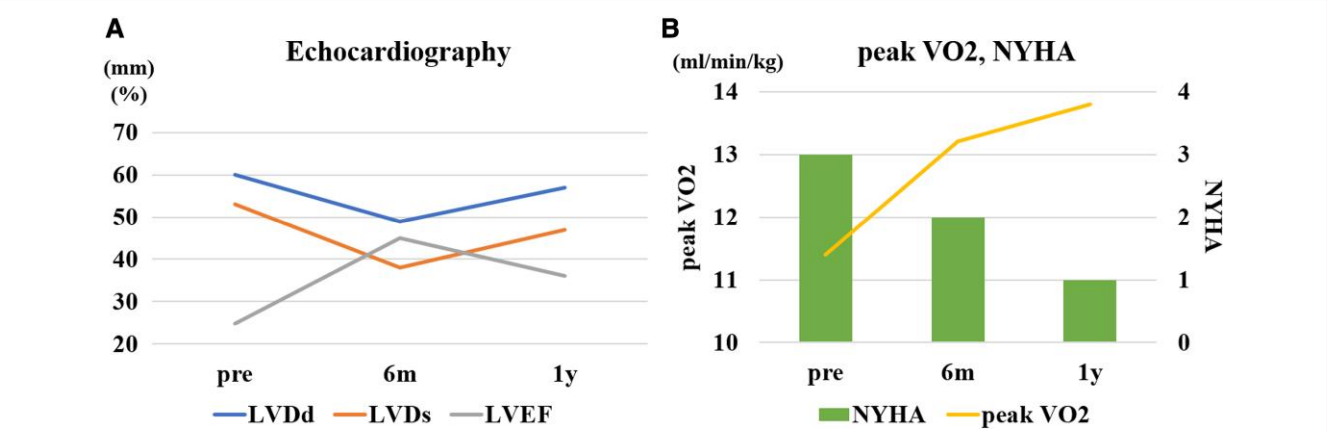

Figure 1 Serial data of echocardiography, peak VO_2, and NYHA classification. (*A*) Echocardiographic changes observed in LVDd, LVDs, and LVEF. (*B*) Changes in peak VO_2, and NYHA classification. LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

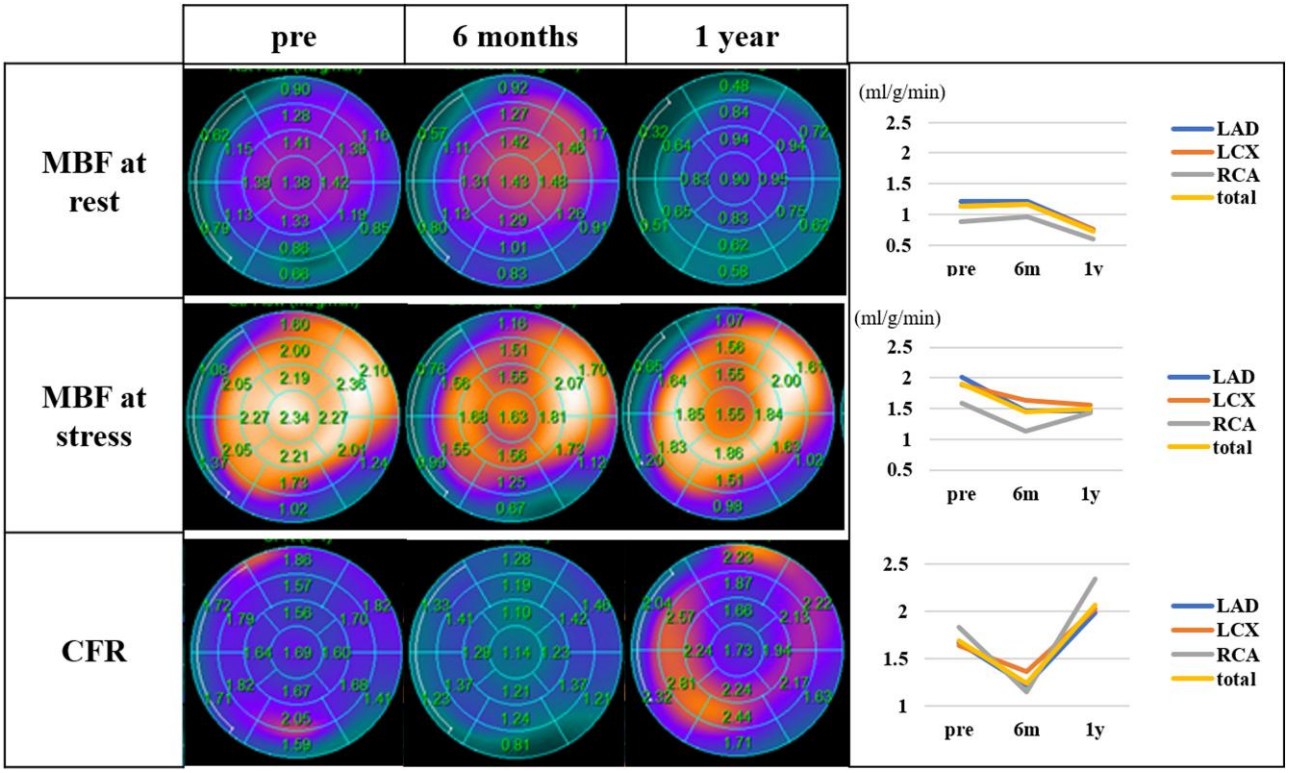

Figure 2 Changes in CFR and MBF in NH_3-PET. In the bull's eye images, MBF at rest and at stress declined 1-year after treatment, but CFR improved 1-year after treatment. The chart depicts changes in MBFs (at rest and stress) and CFRs in total and each coronary artery region. CFR, coronary flow reserve; MBF, myocardial blood flow; NH_3-PET, 13N-ammonia positron emission tomography.

Tc-99m MIBI WR and SA improved around the LAD and LCX regions near the AMP-implanted area. The parameter details of each image modality are shown in the Supplementary material online, *Table S1*.

The patient has been outpatient for two years after the surgery without any HF readmissions.

Discussion

In this case, AMP transplantation for ICM improved CFR and mitochondrial function, reduced SA, improved cardiac function, and increased physical activity.

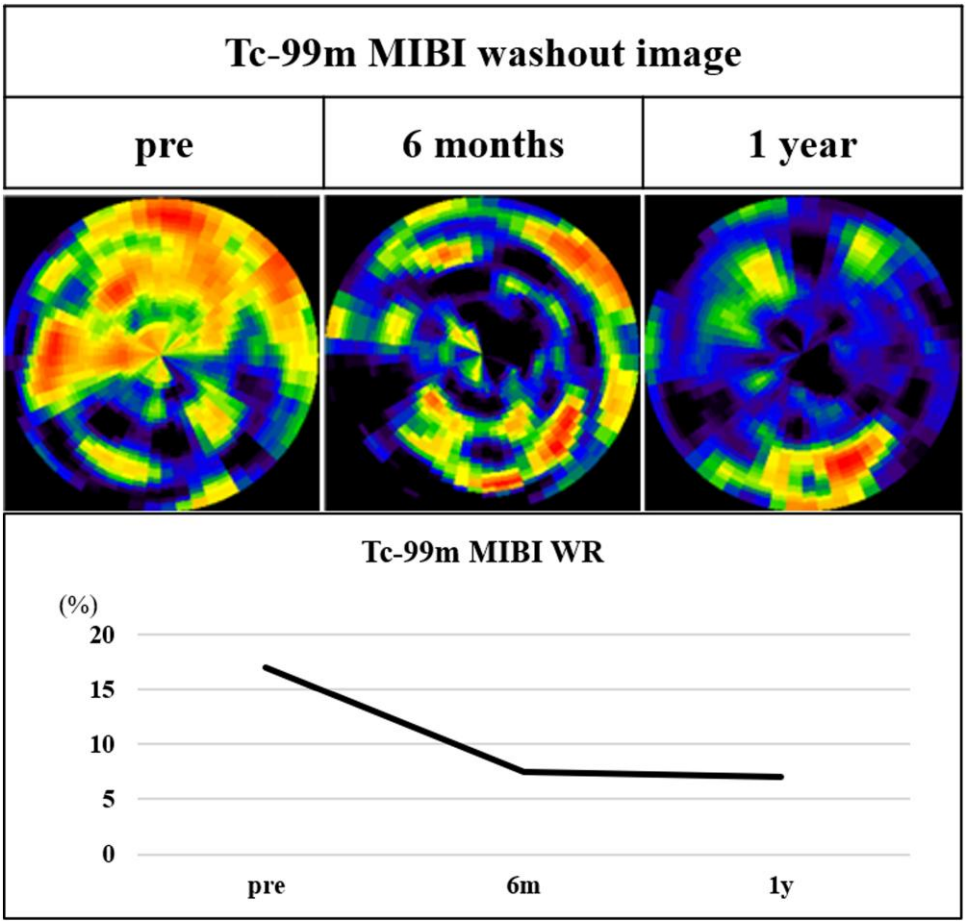

Figure 3 Changes in Tc-99m MIBI washout image and WR. In the bull's eye images, WR improved 1-year after the treatment. The chart depicts the changes in Tc-99m MIBI WR. MIBI, methoxyisbutyl isonitrile; WR, washout rate.

Mitochondrial function mainly improved around the anterior and lateral walls, suggesting significant improvement around the AMP-implanted area. Intercellular mitochondrial transfer from transplanted cells to recipient cells may have facilitated cell damage repair.[3] Hayakawa et al. reported mitochondrial migration from astrocytes to neurons after cerebral infarction, maintaining viability and protecting the brain from ischaemia,[4] while Islam et al. reported mitochondria migration from the intra-tracheally administered bone marrow-derived stromal cells to the alveolar epithelium in acute lung injury.[5] In this case, the transfer of mitochondria from the transplanted myoblasts to the damaged myocardium may have contributed to the improvement of mitochondrial function.

In our patient, CFR improved post-AMP transplantation, although MBF did not. This discrepancy may be attributed to energy metabolism. ICM-induced hypoxia limits aerobic ATP production, reducing the effective energy production in mitochondria.[6] Enhanced mitochondrial function probably improved myocardial energy metabolism and decreased oxygen demand.

Microvascular dysfunction, including structural abnormalities of blood vessels, dysfunction of vascular endothelium and smooth muscle cells, and impaired blood flow regulation, has been linked to cardiovascular events.[7] While revascularization procedures like CABG can maintain macrovascular blood flow, they do not improve microvascular dysfunction. AMP transplantation has the potential to complement this. In this case, the improvement in CFR suggests amelioration of microvascular dysfunction through angiogenesis induction.

We previously reported a better long-term survival rate in AMP transplant for patients with ICM compared to epidemiological data of patients with severe HF.[8] Additionally, the relationship between CFR, mitochondrial function, LGE area on MRI, and cardiac events has been reported.[9–11] Functional improvements of each modality contribute to improved prognoses and physical activity after AMP transplantation.

On the other hand, in a randomized trial comparing autologous myoblast transplantation with a placebo for ICM, Menasché et al. observed reverse remodelling of the LV but did not find improvements in cardiac function in the myoblast transplanted group. Additionally, the myoblast transplanted group experienced frequent post-operative arrhythmic events.[12] In their study, cells were injected into the infarcted myocardium simultaneously with CABG. However, in our case, cell transplantation occurred 6 years after CABG, utilizing cultured myoblasts in a patch form and applied to the heart's surface. This suggests that the timing and method of cell transplantation may influence cardiac function improvement and the frequency of arrhythmic events after myoblast transplantation. Cultivating myoblast cells in a patch form for

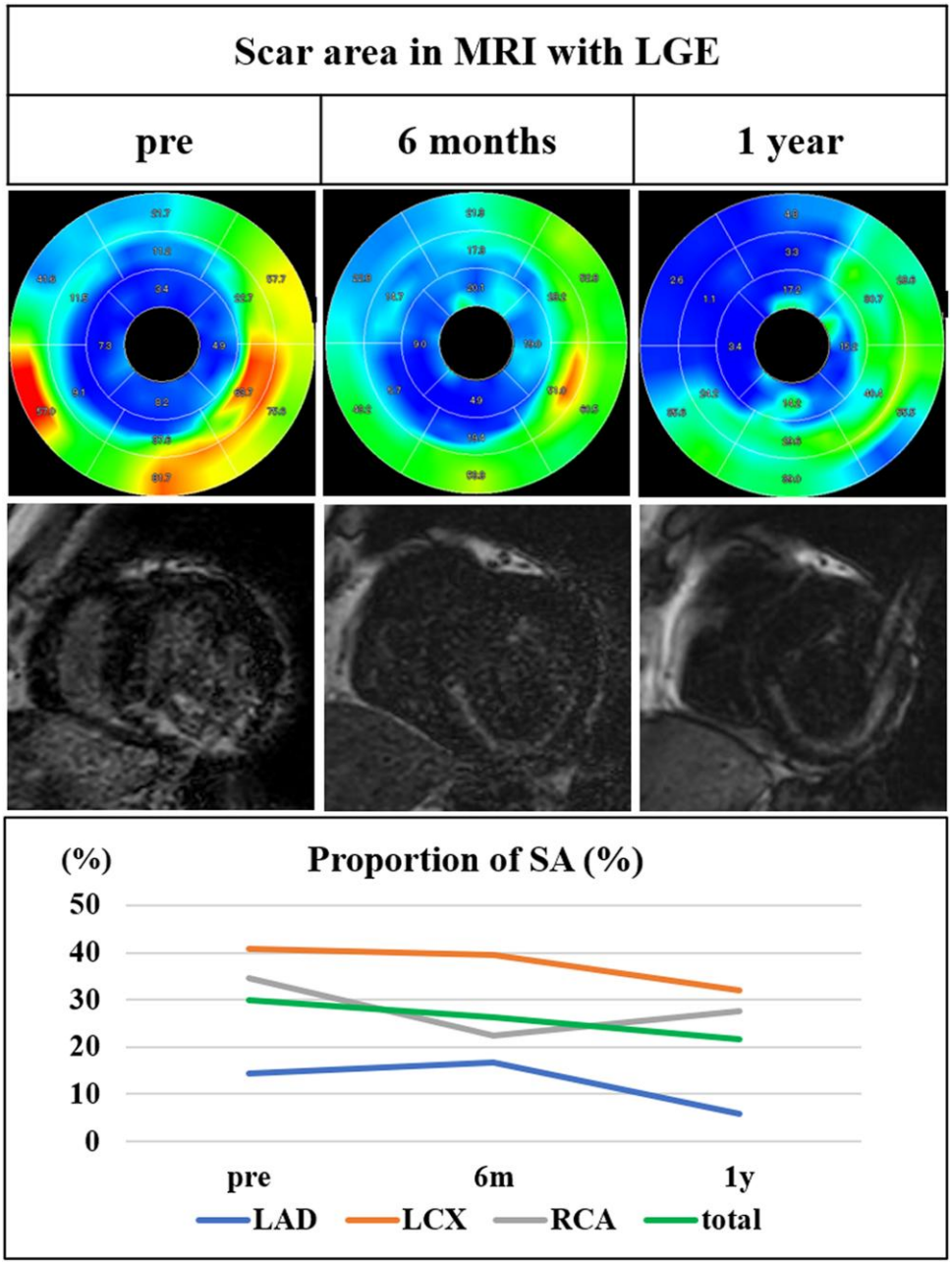

Figure 4 Serial data of SA in MRI with LGE. In the bull's eye images, SA reduced 1-year after treatment. The chart depicts changes in the SA proportions in total and in each coronary artery region. LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; SA, scar area.

transplantation may minimize inflammation and stress on the transplanted cells compared to injection, potentially favouring their survival.[13] Furthermore, Menasché et al. followed up with data for 6 months after myoblast transplantation, whereas we followed up with the case for 1 year. In this case, CFR improved 1 year post-surgery, suggesting that a longer follow-up period is necessary to assess the therapeutic effects of myoblast transplantation.

A limitation of Tc-99m MIBI scintigraphy is that nuclide distribution depends on coronary obstruction or stenosis. In this case, since complete revascularization had been achieved by CABG, the nuclides were distributed throughout the entire myocardium.

Conclusions

This case confirms that pre-clinical findings, such as recovery of mitochondrial function and CFR, can translate to patients after AMP transplantation for ICM. As currently there is no treatment for these dysfunctions, this therapeutic approach is a potential tool to cure refractory HF.

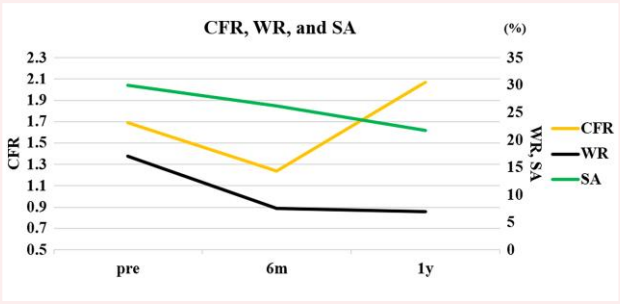

Figure 5 Relationship among changes in LVEF, CFR, Tc-99m MIBI WR, and SA. Combined data of LVEF, CFR in NH3-PET, WR in Tc-99m MIBI scintigraphy, and total SA in cardiac MRI. CFR, coronary flow reserve; SA, scar area; WR, washout rate; LVEF, left ventricular ejection fraction; MIBI, methoxyisbutyl isonitrile; MRI, magnetic resonance imaging.

Lead author biography

Yoshito Ito graduated from Osaka University in 2013, and now, he is a cardiovascular surgeon at Graduate School of Medicine, Osaka University, Japan. He is also engaged in basic research on regenerative medicine as a postgraduate student. His main interests are cardiomyopathy, coronary heart disease, and valvular heart disease.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

Acknowledgements

We thank Daisuke Yoshioka, Masashi Kawamura, Ryohei Matsuura, Ai Kawamura, and Yusuke Misumi for insightful comments and suggestions about clinical management of the patient and writing the manuscript. We thank Tomomi Shimamoto for her excellent assistance.

Consent: The authors confirm that written consent for the submission and publication of this case report, including the images and associated text, was obtained from the patient in line with the COPE guidelines.

Conflict of interest: None declared.

Funding: None.

Data availability

The data underlying this article are available in the article and in the Supplementary material online.

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