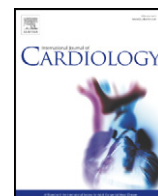




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Letter to the Editor

Stem cells transplantation combined with long-term mechanical circulatory support enhances myocardial viability in end-stage ischemic cardiomyopathy

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End-stage ischemic cardiomyopathy (ICM) with non-graftable coronary arteries is a common and debilitating problem. The ultimate therapeutic goal in such cases is cardiac transplantation which is restricted by donor availability. Alternatively, left ventricular assist devices (LVAD) are increasingly used as bridge to transplantation or more recently as destination therapy in non-transplant candidates. Although encouraging results with LVAD as a bridge to recovery have been reported from the Harefield group in patients with non-ischemic heart failure, myocardial recovery after mechanical circulatory support (MCS) rarely occurs in the severely failing ischemic heart [1].

Ischemic cardiomyopathy has the distinctiveness of irreversible myocardial damage with scar tissue formation and mainly impaired perfusion of the remaining viable myocardium. Widely used second- and third-generation continuous-flow LVAD offer symptomatic relief and prolong life. However, LV unloading rarely improves native heart function in ischemic hearts [2]. Because of this we sought after increasing myocardial viability and improving native cardiac function in a patient with end-stage ICM by injecting autologous bone marrow stem cells (BMSC) at the time of LVAD implantation.

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A 65-year-old severely symptomatic ICM patient was sustained by inotropic support (INTERMACS level 3). He was already fitted with a biventricular pacing system and an implantable defibrillator. Coronary angiography showed severe diffuse left coronary artery disease and an occluded right coronary with no conventional option for revascularization. On echocardiography LV ejection fraction (LVEF) was <15% with preserved right ventricular function. Maximum oxygen consumption was 12 ml/kg/min. Thallium scintigraphy showed extensive full thickness scar inferiorly and diffuse anterolateral scar mixed with hibernating myocardium. Overall 60% of the LV was not viable. Because of his advanced age and comorbidities including renal impairment and peripheral vascular disease, he was considered ineligible for cardiac transplantation.

The patient was recruited for MCS. Informed consent was obtained from the patient and Institutional Ethical Committee approved the study. A Jarvik 2000 LVAD was implanted via a median sternotomy using skull pedestal power delivery. Additionally, 250 ml of bone marrow were harvested from both iliac crests and the mononuclear cell fraction was isolated. Cells counts suggested that the injectate contained 2.2×10^6 endothelial progenitor cells (CD133+), 1.1×10^6 hematopoietic stem cells (CD34+) and 3.5×10^6 mesenchymal stem cells (CD105+). With the LVAD supporting the circulation, the cells were injected into ten sites within the hibernating myocardium as guided by detailed preoperative radionuclide scintigraphic mapping.

After six months on MCS the patient was restored to an active life in the community (NYHA I). Reinvestigation by thallium scintigraphy and pharmacological stress echocardiography revealed a significant improvement in both perfusion and contractility in the viable myocardium. Despite the fact that presence of the pump within the LV precludes accurate measurement of LVEF, in our case this was estimated to be around 35% with the LVAD switched off. Thallium lung uptake was significantly reduced (9.3% compared to preoperative one) indicating respective functional improvement (Fig. 1). This could be mainly attributed to the reduced LV end-diastolic pressure due to mechanical unloading. At one-year follow-up repeat thallium scintigraphy revealed an area of viable myocardium at the lateral wall, which was considered non-viable in all previous preoperative and postoperative scans (Fig. 2), leading to a net reduction in the

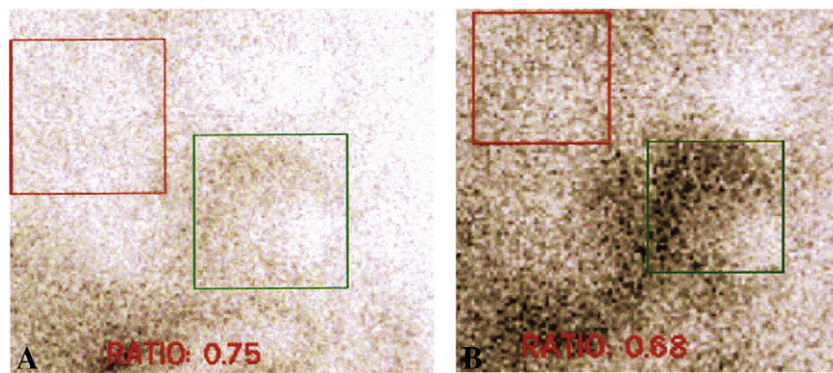


Fig. 1. ^{201}Tl lung uptake charts preoperatively (A) and six months post LVAD and autologous bone marrow stem cells transplantation (B). Note that there is a 9.3% reduction which is could be mainly attributed to ventricular unloading.

estimated infarct size. The viability of the tissue was consistent with the sites of intraoperative BMSC injection. Left ventricular EF was then increased to 45%.

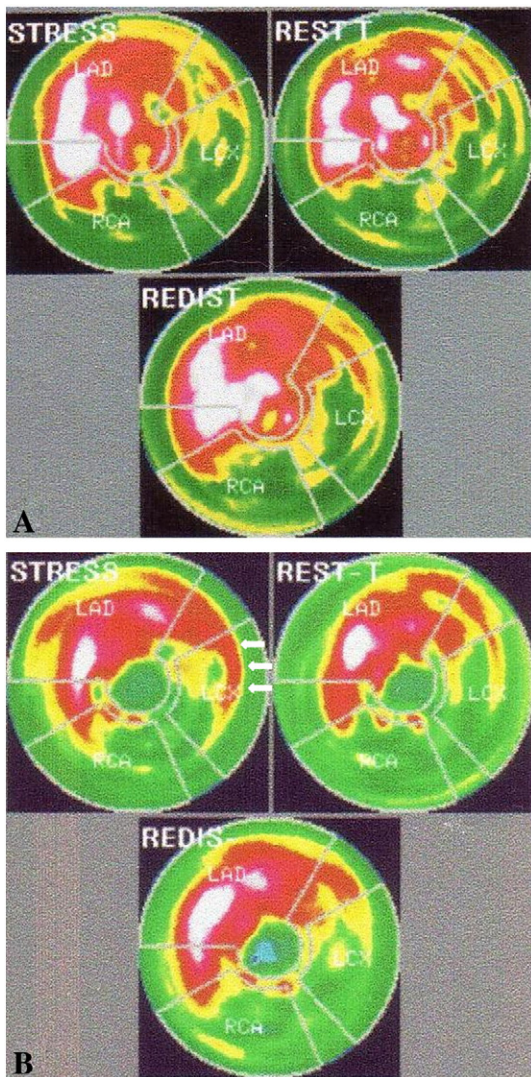


Fig. 2. ^{201}Tl single photon emission computed tomography preoperatively (A) and at twelve-month follow-up (B). White arrows indicate area of viable myocardium at the lateral wall previously characterized as scarred tissue which corresponds to the stem cell injection territory.

Maybaum et al. showed that although cellular recovery and improvement in ventricular function are evident during LVAD support, degree of clinical recovery is insufficient for device explantation in patients with ICM [2]. Therefore, novel strategies should be sought in order to enhance myocardial recovery during LVAD support. Replacement of scarred tissue and regeneration of viable myocardium remains a challenging target of cell transplantation. Even though initial studies reported that injected BMSCs could differentiate in an experimental myocardial infarction model into cardiomyocytes that reduce infarct size and improve myocardial function, Murry et al. showed that the injected BMSCs very rarely, if ever, do they differentiate into cardiomyocytes [3].

The most intriguing finding of our case is the detection of viable tissue at the site of stem cells injection which enhanced myocardial perfusion during MCS in end-stage ICM. Letsou et al. assessed myocardial perfusion by positron emission tomography during long-term MCS and concluded that no significant change in relative perfusion should be expected with increasing LVAD support, mainly attributed to a cardiac autoregulatory mechanism [4]. Research focused on the mechanism of action of stem cells in the ischemic myocardial environment revealed that cardiac repair is promoted through paracrine activity, cell fusion, passive mechanical effects and stimulation of endogenous repair by resident cardiac stem cells [5]. Traditional theory that transplanted stem cells transform into new, functioning cardiomyocytes improving cardiac performance is inferential. Implanted cells respond to their environment by secreting cytokines and growth factors which act both in an autocrine fashion on the donor cells and exert paracrine effects on the host cells. This process stimulates vasculogenesis and angiogenesis and could explain the net reduction in scarred tissue and enhanced myocardial viability in myocardial areas previously characterized as non-viable.

In the clinical setting of stem cells transplantation combined with long-term MCS in end-stage ICM the blood pump provides early symptomatic improvement, whilst stem cells may eventually provide the synergistic benefit of improving native ventricular function. Gojo et al. described cardiac recovery allowing for LVAD explantation in a patient with ICM, after staged LVAD and stem cells implantation delivered intracoronary through previously constructed vein grafts [6]. We advocate concomitant intramyocardial administration of BMSC at the time of LVAD implantation so as to enhance engraftment into the host environment. This hybrid approach in the setting of end-stage ICM may eventually provide a realistic alternative to cardiac transplantation allowing scarce donor hearts to be used for more complex cardiac defects. This concept has to be tested through further well-designed randomized controlled studies.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010;144:1–2).

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