Kardiologia Polska 2018; 76, 6: 1015–1017; DOI: 10.5603/KP.2018.0119 ISSN 0022–9032

SHORT COMMUNICATION

Cardiac retransplantation as a promising treatment option for late graft failure — Zabrze experience

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INTRODUCTION

Heart failure (HF) emerges as a heterogenic entity with widespread distribution in the population of developed countries [1]. HF, with its typical clinical scenario, is characterised by frequent decompensations, hospital readmissions, and poor quality of life. Renal dysfunction, being common in groups of patients with HF, is associated with raised morbidity and mortality. Late graft failure (LGF), after orthotopic heart transplantation (OHT), may occur in the cardiac transplant recipient milieu, especially given that the time elapsed from the procedure is related to the raised risk of coronary artery vasculopathy (CAV). Despite the fact that many patients suffering from end-stage HF (ESHF) are eligible for mechanical circulatory support as a destination therapy, OHT is a better alternative, particularly in long-term observation [2].

METHODS

The rationale of the study was to compare the renal function before and after orthotopic cardiac retransplantation (ReOHT). We present two cases of patients referred for ReOHT due to LGF on the background of CAV.

Patient J.C., aged 65 years, underwent primary OHT in 2001. The immunosuppressive treatment with cyclosporin A (CsA) in the initial period after the first transplantation showed the features of steroid-resistant cellular rejection, which was treated with infusions of antithymocyte globulin. Fifteen years after OHT, glomerular filtration rate (GFR) values began to fall regularly below 40 mL/min/1.73 m^2. Considering the nephrotoxic influence of tacrolimus, it was decided to continue the treatment with CsA, despite the fact that the CAV had been diagnosed. In the last year before ReOHT, the patient had been hospitalised four times due to decompensation of HF. These events were accompanied by a further decline in GFR. The echocardiogram revealed impaired left ventricular (LV) systolic function with reduced LV ejection fraction.

Another patient, R.B., aged 53 years, underwent the initial OHT procedure in the year 1992. Immunosuppressive therapy in the primary phase consisted of CsA, which was replaced by tacrolimus monotherapy. From the 24th year after OHT a regular decrease in GFR below 40 mL/min/1.73 m^2 was observed. Fourteen years after OHT the patient was diagnosed with CAV with subsequent LGF. In total, the patient underwent nine percutaneous coronary interventions in all coronary arteries. Due to rapid progression of CAV, it was decided to change CsA to tacrolimus, taking into account the risk of its potential nephrotoxicity.

After ReOHT, a three-drug immunosuppressive regimen consisting of tacrolimus, mycophenolic acid, and prednisone was introduced in both patients. Remarkably, the initiation of tacrolimus administration was postponed three days after the surgery, and the drug was carefully dosed until therapeutic plasma concentrations were obtained. Therefore, induction of immunosuppression using basiliximab was carried out in both patients.

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Received: 09.04.2018 **Accepted:** 23.05.2018

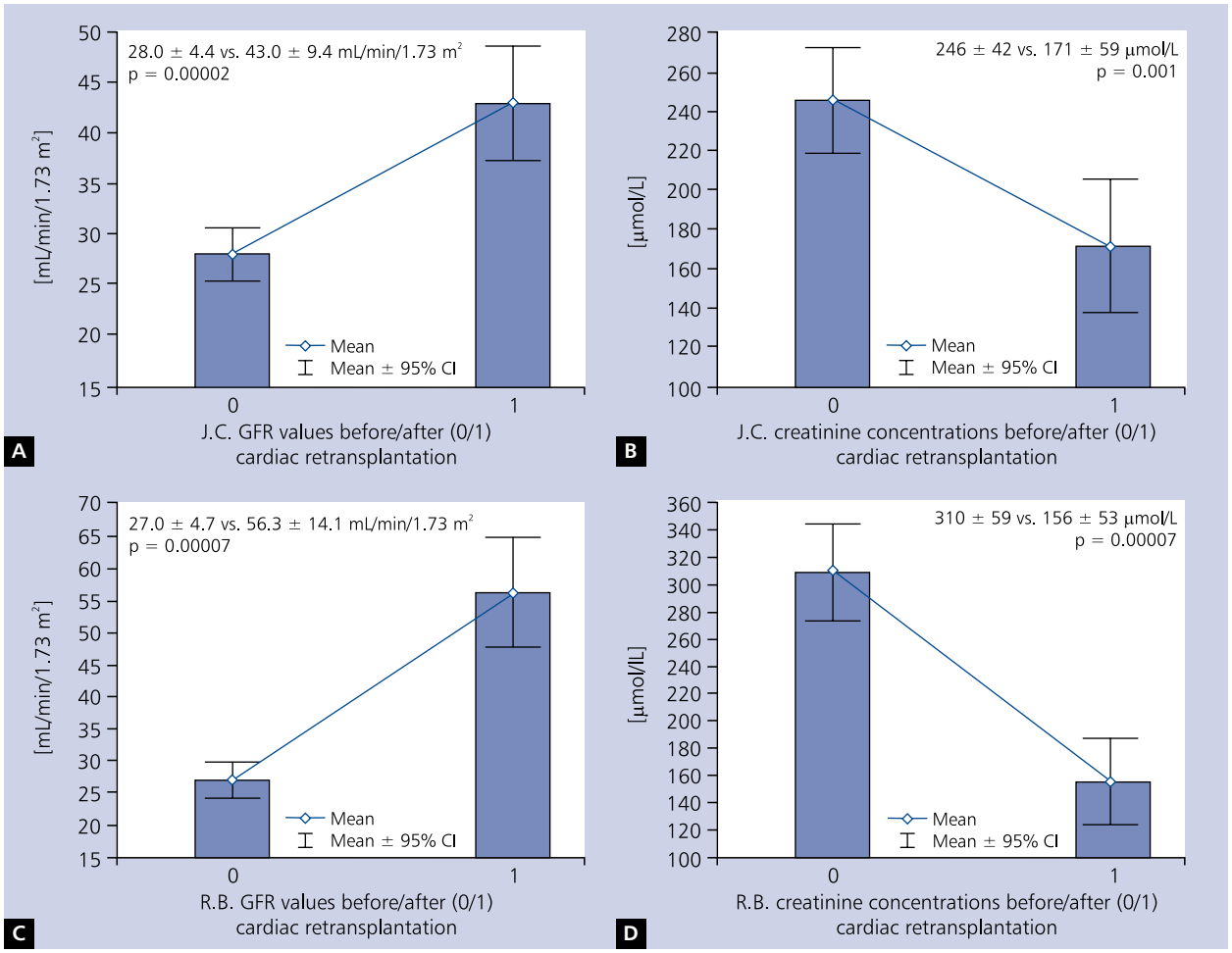

Figure 1. Glomerular filtration rate (GFR) and creatinine before and after renal function prior to and after cardiac retransplantation, assessed for each patient separately; **A.** Patient J.C. GFR values before/after (0/1) cardiac retransplantation; **B.** Patient J.C. creatinine concentrations before/after (0/1) cardiac retransplantation; **C.** Patient R.B. GFR values before/after (0/1) cardiac retransplantation; **D.** Patient R.B. creatinine concentrations before/after (0/1) cardiac retransplantation; CI — confidence interval

Patient R.B. underwent surgery in July 2017 and C.J. in January 2018. To the best of our knowledge, during the last year (until May 2018), three ReOHT operations were carried out in Poland, all in our centre. The third patient underwent surgery in April 2018, and currently the follow-up is too short to draw meaningful conclusions. The two patients we describe are still under surveillance. Noticeably, we persistently observe significantly higher GFR values than before the operation. Kidney function of the patient C.J. was not significantly deteriorated, even though he had received high doses of glucocorticosteroids due to a single episode of acute cellular rejection.

The data was statistically analysed as follows: distributions of the parameters were assessed using the Shapiro-Wilk test. Variables were expressed as the mean ± standard deviation. Variables with normal distribution were compared using Student t test. Variables with abnormal distribution were compared using the Mann-Whitney U test. Differences were considered statistically significant if $p < 0.05$. Analyses were performed using Statistica 10 with the medical package (Statsoft Inc., Tulsa, OK, USA).

RESULTS AND DISCUSSION

In patient J.C. GFR and creatinine values before vs. after cardiac retransplantation were 28.0 ± 4.4 mL/min/1.73 m² vs. 43.0 ± 9.4 mL/min/1.73 m² ($p = 0.002$) and 246 ± 42 µmol/L vs. 171 ± 59 µmol/L ($p = 0.001$), respectively. In patient R.B. GFR and creatinine values before vs. after cardiac retransplantation were 27.0 ± 4.7 mL/min/1.73 m² vs. 56.3 ± 14.1 mL/min/1.73 m² ($p = 0.007$) and 310 ± 59 µmol/L vs. 156 ± 53 µmol/L ($p = 0.007$), respectively. The data are depicted in Figure 1.

Nearly 100 (n = 98) patients were referred for OHT in the year 2017 in Poland, which, considering the permanently growing population of HF patients from the epidemiological point of view, is highly insufficient. Notably, organ availability

plays a key role in limiting the number of surgical procedures, therefore the idea of ReOHT grew in the controversial environment of previously reported unequivocal results [3]. The frequency of ReOHT as a method of choice in the management of acute rejection and chronic graft failure varies in the literature between 2% and 5% and is engaged more often in American institutions as compared to others. Because ReOHT was reported to be associated with increased mortality compared to primary OHT at one (19% vs. 16%), five (37% vs. 28%), and 10 years (54% vs. 40%), it is crucial to discriminate the potential risk factors for poor outcomes [4]. Interestingly, both OHT and ReOHT groups of patients were characterised by similar short- and mid-term, and different long-term survival results. The significance of differences in survival rates emerges with the time elapsed from the initial surgical procedure [5]. Patients suffering from late graft failure due to CAV have better outcomes, so the role of careful patient selection deserves emphasising. Lietz and Miller [6] assessed survival rates of patients with ESHF on the basis of the United States United Network of Organ Sharing (UNOS) database and reported that they significantly improved over time from 49.5% in 1990 to 69.0% in 2005. Multivariable analysis revealed that serum creatinine level > 1.5 mg/dL was associated with an increased risk ratio (RR) of death (RR 1.77; 95% confidence interval 1.47–2.12; $p < 0.001$). Strikingly, progressive deterioration of renal function expressed as a gradual decrease of GFR in post-transplant patients was simultaneously observed by many researchers. Al Aly et al. [7] found a significant difference between GFR prior to transplantation (63.8 ± 18.4 mL/min/1.73 m^2) and at five years (54.4 ± 15.5 mL/min/1.73 m^2) and 10 years (52.7 ± ± 23.6 mL/min/1.73 m^2) post-transplantation ($p \leq 0.006$ for both). A significant linear correlation between GFR and time after OHT was reported by Przybyłowski et al. [8] ($r = –0.59$, $p < 0.001$). Ostermann et al. [9] compared the GFR values at registration and transplantation in nearly 900 patients submitted to OHT. In 214 (24.9%) patients renal function deteriorated to the extent that they entered a lower GFR group. A total of 67 (8.8%) patients moved from a standard risk group with GFR > 50 mL/min/1.73 m^2 and 30-day mortality of 9.5% to a group with increased 30-day mortality rate of 16.7% ($p = 0.06$). ESHF and graft failure are two different clinical scenarios with a similar physiological background. The impairment of the LV systolic function results in organ hypoperfusion; therefore, a significant GFR decrease is reported to be an eligible marker associated with poor outcomes.

In conclusion, whether the positive fluctuation of GFR and creatinine values observed in the laboratory findings will have a positive impact on prognosis in our group of patients requires further observation. It is important to keep in mind that ReOHT is a feasible option of treatment for patients with LGF, especially on the background of CAV, offering good short- and mid-term results basically undifferentiated from the initial OHT procedure.

Acknowledgements

We would like to thank the anonymous reviewer who significantly contributed to the final version of the manuscript.

Conflict of interest: *none declared*

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Cite this article as: Kubiak GM, Kwieciński R, Zakliczyński M, et al. Cardiac retransplantation as a promising treatment option for late graft failure — Zabrze experience. Kardiol Pol. 2018; 76(6): 1015–1017, doi: 10.5603/KP.2018.0119.