Improvement in cardiac function after renal transplantation in four patients with severe left ventricular systolic dysfunction

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Introduction

Heart failure (HF) is at least 10 times more frequent in patients with chronic kidney disease (CKD) than in the general population and its prevalence increases with deteriorating renal function, reaching up to 70% in patients with end-stage renal disease (ESRD) (1, 2). The mortality rate doubles when a clinical diagnosis of HF is established (3). The prognosis is poor without transplantation, and longer waiting times result in more, and eventually irreversible, cardiac dysfunction. However, as HF is also associated with increased perioperative morbidity and mortality, the majority of the patients are reluctantly evaluated for and frequently denied of renal transplantation (4).

Here, we report four cases with severe left ventricular systolic dysfunction (LVSD) in whom systolic function dramatically recovered after renal transplantation.

Case Reports

The study was undertaken at the Yeditepe University Hospital, Istanbul. Written informed consent was obtained from the patients for sharing their relevant medical history and laboratory results.

Case 1

A 47-year-old male was referred to our cardiology outpatient clinic for evaluation for renal transplantation. He complained of peripheral edema but denied severe exertional limitation (Table 1). On his echocardiogram, his left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) were severely depressed (Fig. 1, Table 2). At another hospital, he had been evaluated for renal transplantation but found not to be suitable and recommended an implantable cardioverter-defibrillator instead. He refused in case it precludes renal transplantation and wanted to consult elsewhere. At our center, a renal transplantation from a living donor was performed. A beta-blocker and an angiotensin converting enzyme inhibitor were prescribed. After 3 months, his cardiac functions were significantly improved (Fig. 1, Video 1). The patient still enjoys a good health.

Figure 1. Pre- (upper panel) and post-transplant (lower panel) echocardiographic images from case #1 indicate a substantial improvement in left ventricular ejection fraction, left ventricular volumes, and global longitudinal strain. See Table 2 and Video 1
**Case 2**
A 57-year-old female was referred to our cardiology outpatient clinic for evaluation for renal transplantation. She complained of orthopnea, edema, and severe functional limitation (Table 1). She had no prior cardiac history, and a recent coronary angiogram was completely normal. Because of the clinical picture, she was found not to be suitable for renal transplantation at another center. Her echocardiogram revealed an LVEF of 26%, a GLS of $-7.8\%$, and severe mitral regurgitation. After an intensive dialysis program, she underwent kidney transplantation from a living donor. A beta-blocker was started. After 7 months, her LVEF normalized and mitral regurgitation significantly diminished (Table 2). She is completely asymptomatic and has an excellent functional capacity.

**Case 3**
A 49-year-old male was referred to our cardiology outpatient clinic. He had a history of hypertension and diabetes for 10 years. On his echocardiogram, LVEF was 30% with a significantly dilated left ventricle, severe diastolic dysfunction, and global hypokinesia with a GLS of $-5.4\%$. He underwent kidney transplantation from a living donor. He was prescribed an angiotensin converting enzyme inhibitor and a beta-blocker. At his 8-month follow-up, his LVEF was completely normalized, and his GLS decreased to $-11\%$. The functional capacity increased to NYHA class I.

**Case 4**
A 23-year-old male was referred to our cardiology outpatient clinic. He denied any prior cardiac disease, except hypertension diagnosed after CKD. On his echocardiogram, LVEF was 27% with a dilated left ventricle, severe diastolic dysfunction, and global hypokinesia with a GLS of $-5.4\%$. He underwent kidney transplantation from a living donor. He was prescribed an angiotensin converting enzyme inhibitor and a beta-blocker. At his 8-month follow-up, his LVEF was completely normalized, and his GLS decreased to $-11\%$. The functional capacity increased to NYHA class I.

**Discussion**
Our report supports the fact that renal transplantation can lead to substantial improvements in cardiac structure and functions in patients with CKD and HF, even in those with severe LVSD. LVEF, GLS, left ventricular diastolic function, left ventricular volumes and mass, secondary mitral regurgitation, and pulmonary artery pressure all improved along with functional capacity and symptoms.

Heart failure with recovered ejection fraction (HFrecEF) is a recently introduced term to define the patients with an LVEF of $<40\%$ at baseline, absolute improvement of $\geq10\%$ in LVEF, and a final LVEF of $>40\%$. Although these patients retain many molecular features of the failing heart and a high risk of recurrence, they have a significantly better prognosis than the patients not exhibiting such a recovery in LVEF. Female sex, younger age, non-ischemic etiology, and shorter duration of HF are associated with higher rates of LVEF recovery (5). Our cases have several of these characteristics in common: (1) the patients were young; (2) the duration of dialysis was limited; and (3) other major causes of LVSD, mainly coronary artery disease, were excluded. This is in accordance with a previous study which

| Table 1. Baseline characteristics |
|----------------------------------|
| **Case #1** | **Case #2** | **Case #3** | **Case #4** |
| Age/sex | 47/male | 57/female | 49/male | 23/male |
| HT | + | - | + | + |
| DM | - | - | + | - |
| Smoking | + | - | + | - |
| HL | - | - | - | - |
| CAD | - | - | - | - |
| CKD etiology | Hypertensive nephrosclerosis | Crescentic glomerulonephritis | Vesicoureteral reflux | Crescentic/lg A glomerulonephritis |
| Duration of dialysis | 36 months | 5 months | 18 (before the 1st Tx)+4 months | 12 months |
| Previous transplantation | - | - | Yes (2005) | - |
| Coronary angiogram | Normal (2017) | Normal (2019) | Normal (2018) | - |
| MPS (2020 – no ischemia) | - | - | - | - |
| Baseline therapy | Acetylsalicylic acid, benidipine | Prednisolone, folic acid, furosemide | Anti-phosphate, folic acid, furosemide | Amlodipine, doxazosin, ramipril |
| Potential cardiotoxic drug history | No | No | No | No |
| Pre-Tx NYHA | II | IV | II-III | II-III |

CAD - coronary artery disease; CKD - chronic kidney disease; DM - diabetes mellitus; HL - hyperlipidemia; HT - hypertension; MPS - myocardial perfusion scintigraphy; NYHA - New York Heart Association; Tx - transplantation
showed that the younger age and shorter time in dialysis were associated with a significant improvement in LVEF after renal transplantation (6). The age probably reflects the recovery potential of physiologic functions and the duration of the underlying disease as the duration of dialysis also possibly does. Although there may be a critical threshold at which the burden created by the uremic milieu causes irreversible damage, our cases indicate that it cannot be deduced from the level of the cardiac dysfunction. The absence of significant ischemia excludes the foremost competing cause for HF, namely ischemic heart disease; however, it is not known whether a similar improvement in cardiac functions could be seen in patients with significant coronary artery disease.

The clinical history of our patients partially reflects the general hesitancy for offering renal transplantation to patients with HF. Unfortunately, renal transplantation is underutilized in these patients, as evidenced by the frequency of LVSD in renal transplantation cohorts being much lower than that in patients with ESRD (1, 6). The favorable impact of kidney transplantation on cardiac function is probably far less appreciated in real clinical practice, despite being repeatedly reported previously (1, 6-10). The mechanism underlying the improvement in cardiac structure and functions after renal transplantation is not completely understood. It is possible that a combination of different factors is responsible, including the correction of volume and pressure overload (1), the restoration of normal hemoglobin levels (6), the clearance of uremic toxins (11), and being able to take heart failure medications. Although the majority of our patients were prescribed mortality-reducing heart failure medications with an expectation of benefit as shown in similar clinical scenarios (12-14), the role of these drugs in the improvement of LV functions in post-transplant patients is not yet established. The main mechanism of improvement in this subset may simply be the elimination of the offending cause, such as hypervolemia, pressure overload, uremic toxins, etc. Alternatively, these patients might have just shared the common predictors observed in HFrecEF registries (younger age, limited HF duration, etc.) and responded well to HF medications, institution and/or titration of which was facilitated by renal transplantation (15, 16). The improvement in cardiac functions is not merely a laboratory finding, (17) it has facilitated by renal transplantation (15, 16). The improvement in cardiac functions is not merely a laboratory finding, and should not recommend against operation solely because of severely depressed LVEF. On the contrary, the combination of ESRD and HF may be regarded as an earlier need for renal transplantation in selected patients.

From the cardiology perspective, these findings have two important implications:

- Cardiologists should be aware that renal transplantation constitutes an exceptional HF treatment that results in unparalleled improvement in cardiac functions, at least in a subgroup of patients with HF.
- They should assume a more active role during perioperative evaluation to encourage the transplantation team and should not recommend against operation solely because of severely depressed LVEF. On the contrary, the combination of ESRD and HF may be regarded as an earlier need for renal transplantation in selected patients.

Considering the long waiting times in cadaveric transplantation lists, the possibility of transplantation from a living donor should be actively searched and considered in the patients with

| Table 2. Echocardiographic findings     | Case #1 Preoperative | Postoperative | Case #2 Preoperative | Postoperative | Case #3 Preoperative | Postoperative | Case #4 Preoperative | Postoperative |
|-----------------------------------------|----------------------|---------------|----------------------|---------------|----------------------|---------------|----------------------|---------------|
| LVEF                                    | 15%                  | 69%           | 26%                  | 61%           | 30%                  | 65%           | 28%                  | 67%           |
| GLS                                     | −1%                  | −13.7%        | −7.8%                | −19.4%        | −11.5%               | −16.6%        | −5.4%                | −11%          |
| LV diastolic dysfunction                |                      |               |                      |               |                      |               |                      |               |
| IVS, mm                                 | 17                   | 16            | 13                   | 11            | 16                   | 14            | 15                   | 14            |
| PW, mm                                  | 16                   | 16            | 12                   | 11            | 15                   | 13            | 16                   | 15            |
| LVEDd mm                                | 54                   | 51            | 57                   | 45            | 71                   | 55            | 60                   | 42            |
| LVEsd mm                                | 51                   | 35            | 48                   | 30            | 62                   | 37            | 50                   | 28            |
| LAD mm                                  | 48                   | 44            | 46                   | 37            | 41                   | 40            | 42                   | 27            |
| LVEDV mL                                | 194                  | 116           | 148                  | 65            | 265                  | 86            | 228                  | 162           |
| LVESV mL                                | 169                  | 36            | 109                  | 25            | 185                  | 48            | 162                  | 52            |
| LV mass, g                              | 435                  | 338           | 236                  | 124           | 474                  | 261           | 348                  | 196           |
| LV mass index, g.m⁻²                    | 212                  | 165           | 191                  | 83            | 270                  | 142           | 228                  | 162           |
| Mitral regurgitation                     | Mild                  | Mild          | Severe               | Mild          | Mild                  | Trivial       | Mild                  | Trivial       |
| sPAP, mm Hg                             | 50                   | 30            | 45                   | 25            | 30                   | 20            | 35                   | 20            |

IVS - interventricular septum; GLS - global longitudinal strain; LAD - left atrial anteroposterior diameter; LV - left ventricle; LVEDd - left ventricular end-diastolic diameter; LVEsd - left ventricular end-systolic diameter; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESd - left ventricular end-systolic diameter; LVESV - left ventricular end-systolic volume; sPAP - systolic pulmonary artery pressure; PW - posterior wall.
HF and ESRD to limit the waiting time for transplantation and to preclude further cardiac deterioration.

**Conclusion**

Our report supports the notion that renal transplantation can lead to substantial improvements in cardiac structure and functions, even in patients with severe LVSD at baseline. Patients with ESRD and accompanying HF should be encouraged to undergo renal transplantation, preferably from a living donor, to limit the waiting time for transplantation.

**Informed consent:** Written informed consent was obtained from the patients for sharing their relevant medical history and laboratory results.

**Video 1.** Pre- (a and b) and post-transplant (c and d) echocardiographic images from case #1 indicate a substantial improvement in left ventricular systolic performance and left ventricular mass and volumes.

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