The effectiveness of renal transplantation as a treatment for recurrent uremic cardiomyopathy

Colin B Josephson MSc¹, Diego Delgado MD², J Schiff MD³, Heather Ross MD FRCPC²

CB Josephson, D Delgado, J Schiff, H Ross. The effectiveness of renal transplantation as a treatment for recurrent uremic cardiomyopathy. *Can J Cardiol* 2008;24(4):315-317.

Congestive heart failure is more prevalent in patients with end-stage renal disease than in the general population. Although optimal treatment has yet to be defined, these patients are considered to be at high risk for renal transplantation. The present report of a 27-year-old man describes a full recovery from uremic cardiomyopathy following a renal transplant. Despite the patient developing recurrent cardiac dysfunction following graft failure, a second transplant was successful, which, again, resulted in complete resolution of the cardiomyopathy. Patients with recurrent uremic cardiomyopathy following failed kidney transplantation should be considered for a second kidney transplant.

Key Words: *Cardiomyopathy; Renal failure; Transplantation*

Cardiovascular disease is the leading cause of morbidity and mortality in patients undergoing chronic maintenance dialysis. It is associated with an increased rate of hospitalization and accounts for approximately 50% of deaths in this patient population (1-3). Both systolic and diastolic dysfunction may be secondary to uremia in patients with end-stage renal disease (ESRD). Although the specific pathophysiology has yet to be fully defined, a combination of direct uremic toxicity, coronary artery disease, hypertension, and cardiovascular calcification and fibrosis are thought to cause impaired function in the setting of ESRD (4,5). This ultimately translates into a 10- to 30-fold higher prevalence of heart failure in dialysis patients than in the general population. The consequent ventricular remodelling that occurs with congestive heart failure (CHF) further predisposes patients to increased QT intervals and dispersal, arrhythmias and sudden death (6). It is not surprising that two-thirds of uremic patients who develop left ventricular (LV) hypertrophy die from either CHF or sudden cardiac death (6,7).

Despite the striking levels of morbidity and mortality, controversy exists regarding optimal treatment of systolic CHF and LV dysfunction in patients with ESRD. A lack of corroborating evidence restricts the application of consensus treatment guidelines designed for the general population to chronic dialysis patients. Although kidney transplantation has been advocated as an alternative form of treatment, these patients have historically been considered to be at high risk for surgery (8). This has led to a reluctance to perform transplant surgery that may correct the poor prognosis conveyed by compromised LV function secondary to uremia.

A beneficial response to renal transplantation has previously been identified through preliminary investigations (9,10). Transplant recipients experienced improvements in ventricular contractility, LV ejection fraction (LVEF), New York Heart Association (NYHA) functional class and regression of LV hypertrophy. However, patients

L'efficacité de la greffe rénale pour traiter la myocardiopathie urémique récurrente

L'insuffisance cardiaque congestive est plus prévalente chez les patients atteints d'une maladie rénale terminale qu'au sein de la population générale. Même si le traitement optimal n'est pas encore défini, ces patients sont considérés comme à haut risque de greffe rénale. Le présent rapport décrit la complète guérison d'un homme de 27 ans atteint de myocardiopathie urémique grâce à une greffe rénale. Le patient a présenté un dysfonctionnement cardiaque récurrent après l'échec de la greffe, mais une deuxième greffe a réussi et favorisé la résolution complète de la myocardiopathie. Après un premier échec de greffe rénale, il faut envisager une deuxième greffe rénale chez les patients atteints d'une myocardiopathie urémique récurrente.

who develop graft failure and experience a recurrence of uremic cardiomyopathy have, traditionally, not been considered to be candidates for retransplantation. In this circumstance, most centres elect to perform a combined kidney and heart transplant. Caution must be exercised, however, because experience with this procedure remains relatively limited. It constitutes less than 1% of all renal transplants, and the low operative rate results in long waiting lists, with enhanced mortality and prolonged exposure to chronic dialysis (11). An unacceptably long cold ischemic time for the cardiac graft also precludes human leukocyte antigen matching and raises concerns regarding the long-term prognosis of this patient population (11). Thus, interest exists in a second renal transplant as a means of correcting cardiac dysfunction in the presence of ESRD. In the present case report, a patient with uremic cardiomyopathy experienced complete cardiac recovery following an initial renal transplant. Subsequent graft failure resulted in recurrent uremic cardiomyopathy that was reversed with a second renal transplant.

CASE PRESENTATION

A 27-year-old man was admitted to the Toronto General Hospital (Toronto, Ontario) for CHF. He had a history of biopsy-proven immunoglobulin A glomerulonephritis, which eventually required chronic hemodialysis nine months before his hospitalization. At the time of admission, he was in NYHA class III. Echocardiography (two-dimensional imaging) revealed a mildly enlarged left atrium and LV, with moderate global LV systolic dysfunction (LVEF of 20% to 39%). Moderate to severe mitral regurgitation was identified. Coronary angiography demonstrated normal coronary arteries and his ventriculogram revealed grade III LV function. A multiple-gated acquisition scan identified a resting LVEF of 18%. Viral or uremic cardiomyopathy was considered to be the most likely etiology, and medical treatment consisted of amlodipine (10 mg once daily), flosinopril (40 mg once

¹Department of Medicine, University of Toronto; ²Division of Cardiology; ³Division of Nephrology, Toronto General Hospital, Toronto, Ontario
Correspondence: Dr Heather Ross, University of Toronto, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario M5G 2C4.

Telephone 416-340-3482, fax 416-340-4134, e-mail heather.ross@uhn.on.ca

Received for publication February 14, 2006. Accepted May 11, 2006

Figure 1 Echocardiographic measurements (two-dimensional, four-chamber view) showing left ventricular (LV) parameters and function over time. **A** LV end-diastolic dimension (LVEDD). **B** LV ejection fraction (LVEF). **C** Grade of mitral regurgitation (MR). *First diagnosis of congestive heart failure; †Time of first renal transplant; ‡Cessation of immunotherapy and resection of graft; §Onset of nocturnal hemodialysis; ¶Time of second renal transplant

Figure 2 Change in right ventricular systolic pressure (RVSP) over time. *Cessation of immunotherapy and resection of graft; †Onset of nocturnal hemodialysis; ‡Time of second renal transplant

daily), metoprolol (6.25 mg twice daily), erythropoietin (6000 U three times per week), calcitriol (0.25 µg once daily) and iron (150 mg twice daily). The patient was prioritized for renal transplant in the hope that this would reverse his LV dysfunction should uremic cardiomyopathy be the diagnosis.

The patient underwent cadaveric renal transplant after one year of dialysis and was started on prednisone, cyclosporine and mycophenolate mofetil. An echocardiogram performed one month before the transplant revealed a moderately dilated LV with global hypokinesis and an LVEF of 20% to 39%. The mitral valve had an appearance consistent with low cardiac output and there was associated mild mitral regurgitation. Cardiac dimensions are displayed in Figures 1A to 1C. Right ventricular pressures are displayed in Figure 2. A preoperative electrocardiogram was normal, aside from minimal voltage criteria for hypertrophy.

All preoperative cardiac medications were discontinued and the patient was started on carvedilol 12.5 mg twice daily. Titration of the medication was difficult because the patient was admittedly noncompliant. Echocardiography performed four months postoperatively revealed improvement in mitral regurgitation and LV size (Figure 1). Electrocardiogram was normal. Within one year of transplantation, the patient was in NYHA class I. Cardiac measurements at this time revealed improvement in LVEF, reduction in LV dimensions and resolution of mitral regurgitation (Figure 1). The only medication change during this period was an increase in carvedilol to 25 mg twice daily, although patient compliance remained poor.

Four years post transplant, the patient's creatinine level rose significantly from a baseline of 200 µmol/L to 350 µmol/L. Diagnostic imaging revealed that a previously noted mass adjacent to the transplanted kidney had increased from 2.8 cm × 1.5 cm × 2.2 cm to

4.6 cm × 3.8 cm × 3.2 cm. A biopsy revealed CD20-negative post-transplant lymphoproliferative disease of the polymorphic and polyclonal type. The patient elected to avoid chemotherapy, and the decision was made to cease all immunosuppressive therapy. As a result, the graft failed, as evidenced by a corresponding one-week rise in creatinine level from 370 µmol/L to 700 µmol/L. Therefore, a decision was made to both excise the mass and perform a transplant nephrectomy, with postoperative dialysis.

The patient redeveloped heart failure following nephrectomy. Echocardiography revealed dilated cardiomyopathy, with an estimated LVEF of 20% to 25% and moderate to severe global LV dysfunction. Functional class deteriorated as the patient developed NYHA class II to III symptoms. Ramipril was added, although compliance was inconsistent. Echocardiographic parameters continued to decline, despite enhanced medical treatment. One year following nephrectomy, the patient's LVEF was measured at 27%. The right ventricle was mildly enlarged with global hypokinesis. Mild to moderate mitral regurgitation and restrictive diastolic filling were noted (Figures 1 and 2). By the time the patient initiated nocturnal hemodialysis, his LVEF had fallen below 20%, with concomitant moderate to severe mitral regurgitation and severe tricuspid regurgitation. Aberrant right-sided hemodynamics were evidenced by right ventricular end-systolic pressure of 75 mmHg, and the patient's daily functioning was restricted to that recommended for patients in NYHA class III.

After extensive discussion regarding operative and postoperative risk, the decision was made to proceed with a second transplant to improve cardiac function. Pretransplant echocardiographic parameters included an LV end-diastolic diameter of 71 mm, LV end-systolic diameter of 64 mm, LVEF of 20% and right ventricular systolic pressure of 76 mmHg (Figures 1 and 2). An electrocardiogram demonstrated minimal voltage criteria for LV hypertrophy. An uncomplicated cadaveric renal transplant was performed. Given his high immunological risk (peak panel reactive antibody 40% with class II immunoglobulin G antibodies), he received a course of intravenous immunoglobulin (total dose 2 g/kg) in conjunction with intraoperative and postoperative thymoglobulin (total dose 6 mg/kg). Maintenance immunosuppression consisted of steroids and mycophenolate mofetil, followed by tacrolimus. Despite this intense immunosuppression regimen, the patient developed an episode of acute cellular rejection two weeks post transplant, which responded to treatment with steroids, thymoglobulin and intravenous immunoglobulin. Eight months post transplant, his renal function was excellent, as evidenced by a serum creatinine level of 125 µmol/L.

A cardiac assessment two months postoperatively revealed improvement in all cardiac indexes. The electrocardiogram had normalized and echocardiography demonstrated reduction in ventricular size, improved LVEF and normalizing pressure (Figures 1 and 2). This trend continued six months after the operation (Figures 1 and 2) and was reflected in the patient's improvement in functional status to an NYHA class I.

DISCUSSION

Uremic cardiomyopathy has traditionally been managed conservatively through pharmacological treatment. This approach has primarily focused on hyperparathyroidism, aberrant changes in pressure and volume load and anemia as potential therapeutic targets (12-15). Volume and electrolyte control is generally achieved using either long-duration hemodialysis or conventional dialysis schedules. Beta-blockers and angiotensin-converting enzyme inhibitors have been used to correct abnormal hemodynamic parameters. Carvedilol, in particular, has been demonstrated to reduce mortality, hospital admissions and cardiovascular death in patients with dilated cardiomyopathy (16). As such, the Kidney Disease Outcomes Quality Initiative (K/DOQI) (17) guidelines have recommended carvedilol and angiotensin-converting enzyme inhibitors as primary and secondary pharmacological therapy in the treatment of uremic cardiomyopathy.

Patients with intractable systolic heart failure are usually not referred for kidney transplantation because of the perception of poor outcomes (18). However, a recent study of more than 100 dialysis patients with decreased systolic function (LVEF 40% or lower) and heart failure demonstrated improved outcome with a renal transplant. There were no perioperative deaths, the mean LVEF increased from 32% to 52% and more than two-thirds of patients achieved an LVEF of greater than 50%. Improvements were also noted in functional

class, rates of hospitalization and overall mortality (9). However, patients undergoing kidney retransplantation were excluded from this analysis, limiting the application of these results to patients undergoing a second graft.

Questions still exist regarding the optimal management of cardiac function following graft failure. The present case suggests that selected patients who develop recurrent uremic cardiomyopathy following renal graft failure are able to safely undergo renal retransplantation with resolution of cardiac dysfunction. This can be achieved without concurrent cardiac transplantation. The capacity to undergo single-organ replacement may also decrease the wait times associated with combined heart-kidney transplants. This is crucial, because increased duration of preoperative dialysis is inversely correlated with post-transplant improvement in LVEF (9,19).

CONCLUSIONS

Effective treatment can be offered to selected patients with normal coronary arteries if expeditious renal retransplantation is considered. The present report also suggests that the operation can be performed safely in patients with an LVEF of lower than 20%. Early kidney retransplantation in patients who develop uremic cardiomyopathy following renal graft failure will limit azotemic exposure, thereby improving the likelihood of alleviating reversible myocardial dysfunction.

REFERENCES

- Venkatesan J, Henrich WL. Anemia, hypertension, and myocardial dysfunction in end-stage renal disease. *Semin Nephrol* 1997;17:257-69.
- Churchill DN, Taylor DW, Cook RJ, et al. Canadian Hemodialysis Morbidity Study. *Am J Kidney Dis* 1992;19:214-34.
- Trespalacios FC, Taylor AJ, Agodoa LY, Bakris GL, Abbott KC. Heart failure as a cause for hospitalization in chronic dialysis patients. *Am J Kidney Dis* 2003;41:1267-77.
- London GM. Cardiovascular calcifications in uremic patients: Clinical impact on cardiovascular function. *J Am Soc Nephrol* 2003;14(Suppl 4):S305-9.
- Mall G, Rambauck M, Neumeister A, Kollmar S, Vetterlein F, Ritz E. Myocardial interstitial fibrosis in experimental uremia – implications for cardiac compliance. *Kidney Int* 1988;33:804-11.
- Stewart GA, Gansevoort RT, Mark PB, et al. Electrocardiographic abnormalities and uremic cardiomyopathy. *Kidney Int* 2005;67:217-26.
- Paoletti E, Specchia C, Di Maio G, et al. The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: A 10 year survey. *Nephrol Dial Transplant* 2004;19:1829-34.
- Hunt SA, Baker DW, Chin MH, et al; American College of Cardiology/American Heart Association. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2001;38:2101-13.
- Wali RK, Wang GS, Gottlieb SS, et al. Effect of kidney transplantation on left ventricular systolic dysfunction and congestive heart failure in patients with end-stage renal disease. *J Am Coll Cardiol* 2005;45:1051-60.
- Parfrey PS, Harnett JD, Foley RN, et al. Impact of renal transplantation on uremic cardiomyopathy. *Transplantation* 1995;60:908-14.
- Castillo-Lugo JA, Brinker KR. An overview of combined heart and kidney transplantation. *Curr Opin Cardiol* 1999;14:121-5.
- Lai KN, Ng J, Whitford J, Buttfield I, Fassett RG, Mathew TH. Left ventricular function in uremia: Echocardiographic and radionuclide assessment in patients on maintenance hemodialysis. *Clin Nephrol* 1985;23:125-33.
- London GM, Fabiani F, Marchais SJ, et al. Uremic cardiomyopathy: An inadequate left ventricular hypertrophy. *Kidney Int* 1987;31:973-80.
- Ikram H, Lynn KL, Bailey RR, Little PJ. Cardiovascular changes in chronic hemodialysis patients. *Kidney Int* 1983;24:371-6.
- Hung J, Harris PJ, Uren RF, Tiller DJ, Kelly DT. Uremic cardiomyopathy – effect of hemodialysis on left ventricular function in end-stage renal failure. *New Engl J Med* 1980;302:547-51.
- Cice G, Ferrara L, D'Andrea A, et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: A prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003;41:1438-44.
- K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005;45:S1-153.
- Ventura HO, Mehra MR. Improvement of heart failure after renal transplantation: The complex maze of cardio-renal interaction. *J Am Coll Cardiol* 2005;45:1061-3.
- Vanholder R, Glorieux G, De Smet R, Lameire N; European Uremic Toxin Work Group. New insights in uremic toxins. *Kidney Int Suppl* 2003;63:S6-10.