Acute Renal Failure after Cardiac Transplantation:
A Case Report and Review of the Literature

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Acute renal failure (ARF) is a relatively frequent complication associated with heart transplantation. It develops in the first few days postoperatively and is characterized by oliguria with laboratory and urinary indices typical of pre-renal azotemia. Cyclosporine, especially with higher doses, is one of the many factors which play an integral part in the nephrotoxicity following cardiac transplant. Poor preoperative renal function and perioperative hemodynamic compromise may also contribute to ARF. The actual incidence of ARF now encountered by transplant centers may be lower than previously reported, the result of lower cyclosporine doses. Currently, management is entirely supportive, but novel therapeutic approaches with atrial natriuretic peptide-like substances are being explored. A case illustrating the typical clinical presentation of ARF after heart transplant will be presented and the clinical features will be reviewed.

INTRODUCTION

Cardiac transplantation has been used since 1967 as a successful therapy for intractable heart failure. Subsequently, the number of heart transplants performed yearly continues to increase. As with other open-heart surgery, acute renal failure (ARF) has been a well-recognized postoperative complication of cardiac transplantation [1-5]. However, the incidence of ARF associated with cardiac transplant surgery is greater than that seen with non-transplant heart surgery. The excessive incidence of ARF in cardiac transplantation is, in part, explained by the nephrotoxic effects of cyclosporine. We here-in describe a case illustrating the typical clinical features of ARF following heart transplantation, and discuss etiology, clinical course and management. In particular, we compare cardiac-transplant associated ARF to the ARF following other open-heart surgical procedures.

CASE REPORT

A 62 year old Caucasian male with a prior history of coronary artery bypass 12 yr ago and myocardial infarction 8 yr ago, suffered a large anterolateral and inferior myocardial infarction complicated by severely impaired myocardial function with a depressed cardiac output. The patient failed tissue plasminogen activator therapy and percutaneous transluminal angioplasty, and was deemed unsuitable for surgical revascularization. An intra-aortic balloon pump (IABP) was required to maintain hemodynamic stability.

On his fourth hospital day, he was transferred to Yale-New Haven Hospital for cardiac transplantation evaluation. His BUN and creatinine were 24 mg/dl and 1.2 mg/dl, respectively, at the time of transfer. He remained on the IABP. Medications included...

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bAbbreviations: ARF, acute renal failure; IABP, intra-aortic baloon pump; ANP, atrial natriuretic peptide; OKT3, anti-thymocyte globulin; CS, cyclosporine.
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heparin, 1500 -1900 U/hr; digoxin, 0.25 mg daily; isosorbide dinitrate, 20 mg three times each day; furosemide, 80 mg every 12 hr; and captopril, 25 mg every 8 hr. An echocardiogram and multigated radionuclide ventriculography scan verified an ejection fraction of 15 percent, and the wall motion abnormalities noted previously on cardiac catheterization at the time of angioplasty.

The patient underwent cardiac transplantation 23 days after his myocardial infarction. On the day of transplantation, his BUN and creatinine were 25 mg/dl and 1.0 mg/dl, respectively. The cardiac bypass time was 2 hr 21 min, and the warm ischemia time of the allograft (period between circulatory arrest of donor and commencement of cold storage) was 1 hr 20 min. Postoperatively, he was started on methylprednisolone, 125 mg given intravenously every 8 hr, three doses; cyclosporine, 0.7 mg/kg/day administered by naso-gastric tube; azathioprine, 1 mg/kg/day by naso-gastric tube, and OKT3 (anti-thymocyte globulin) 5 mg given intravenously daily for 14 days. Subsequently, his steroid therapy was tapered to prednisone, 1 mg/kg/day and the maintenance cyclosporine dose was gradually increased according to our protocol to 4.3 mg/kg/day by the fourth postoperative day (Figure 1).

![Figure 1: Serum creatinine, urine output and cyclosporine dose of the patient.](image-url)
He was also maintained on intravenous isoproterenol, 0.04 µg/kg/min; dopamine, 5-8 mg/kg/min; and epinephrine, 0.1 µg/kg/min for a total of 4 days. Prophylactic perioperative antibiotics included cefamandole, oxacillin and erythromycin. He was transferred to the cardiothoracic intensive care unit on ventilatory and IABP support. Systolic blood pressure remained in the range of 75-85 mm Hg for the first 12-18 hr postoperatively. On the second post-operative day, systolic blood pressure improved to 100-110 mm Hg. However, serum creatinine increased to 2.2 mg/dl on the first post-operative day followed by a rise to 3.6 mg/dl on the second post-operative day. Urinalysis revealed only rare granular casts, while urine sodium was low at 10 meq/l. Forced diuresis with intravenous bumetanide, 4 mg/hr, and chlorothiazide, 500 mg given intravenously every 8 hr, was initiated to maintain the central venous pressure below 15 cm H₂O. On the second post-operative day the patient was extubated and the IABP was removed. He was gradually weaned off the isoproterenol and epinephrine. Systolic blood pressure remained in the range of 120-140 mm Hg. The dopamine was continued at 2-3 µg/kg/min in an attempt to enhance renal perfusion. The cyclosporine levels (whole blood) ranged 156-223 ng/ml during this time. However, BUN and creatinine continued to increase despite optimal hemodynamics. In addition, urine output, which had previously been adequate, dropped precipitously to 250 ml in 24 hr. Figure 1 shows the time course of his serum creatinine and urine output in the first 17 days post-transplant. He also developed hyponatremia (131 meq/l), hyperkalemia (5.5 meq/l) and hyperphosphatemia (8.7 mg/dl). Acute hemodialysis was initiated on the 5th day after his transplant, at which time his BUN and serum creatinine were 111 mg/dl and 5.7 mg/dl, respectively. Bumetanide and chlorothiazide were subsequently discontinued. Because of the renal failure, his cyclosporine was withheld for three days. He continued to require supportive hemodialysis on a nearly alternate day basis, for a total of 5 treatments. Other post-operative problems included paralytic ileus which resolved spontaneously after 5 days. His urine output began to improve by the 9th postoperative day, and cyclosporine therapy was reinstalled. By the 13th post-operative day, his urine output was greater than 2000 ml/day and serum creatinine was decreasing. The rest of his hospital course was relatively uncomplicated. He was discharged 23 days after his transplant surgery, with a serum creatinine of 1.2 mg/dl on a stable cyclosporine dose.

DISCUSSION

Background

Acute renal failure is a common and important complication of cardiac transplantation. Various series have reported an overall incidence of ARF in the range of 0-30 percent. However, different criteria for patient inclusion in these studies may explain the wide variation in ARF incidence [1-5]. In addition, inclusion of patients with different degrees of renal failure in these series further complicates analysis of data (Table 1). Also, most series, with the exception of that by Greenberg et al. [1], do not provide data regarding the number of patients requiring dialytic intervention. Greenberg and his colleagues noted that dialysis was required in 5 percent of all post-transplant patients. However, among the post-transplant patients on cyclosporine, a higher percentage (9 percent) of patients required dialysis. Acute dialytic intervention is not entirely benign and may result in transient hemodynamic instability, transient arrhythmia due to electrolyte shifts, and, although controversial, possibly prolong time to full recovery of renal function because of hypotension-induced tubular damage. Moderate renal insufficiency occurred in 25-46 percent of patients after cardiac transplantation [1, 4]. It is important to note that the cyclosporine doses used in these series are comparatively higher than what is used in current practice.
Table 1: Incidence of ARF and renal dysfunction following cardiac transplantation

| Ref | No. of patients (Subgroups) | Immunosuppression | ARF/Severe Renal Dysfunction (% of patients) | Moderate Renal Dysfunction (% of patients) | Definition of ARF/renal dysfunction |
|-----|-----------------------------|-------------------|---------------------------------------------|-------------------------------------------|-----------------------------------|
| 1   | 43 (Group 1)                | Cs/Pred           | 12                                          | 58                                        | ARF: Cr > 8 mg/dl, need for dialysis moderate azotemia: Cr 2-8 mg/dl, BUN 40-140 mg/dl |
|     | 41 (Group 2)                | Aza/Pred          | 0                                           | 34                                        |                                   |
|     | 84 (total)                  |                   | 6                                           | 46                                        |                                   |
| 2   | 17 (Group 1)                | Aza/ATG/Pred      | 0                                           | NS                                        | ARF: Cr > 3 mg/dl + uremia, BUN > 150, need for dialysis |
|     | 23 (Group 2)                | Cs/Pred           | 22                                          | NS                                        |                                   |
|     | 7 (Group 3)                 | Cs*/ATG/Pred      | 0                                           | 11                                        |                                   |
|     | 47 (total)                  |                   | 11                                          |                                           |                                   |
| 3   | 21                          | Cs*/ATG/Pred      | 0                                           | NS                                        | ARF output < 1000 cc/day |
| 4   | 61                          | Cs/Aza/ATG/Pred   | 21                                          | 25                                        | severe renal dysfunction: Cr > 3 mg/dl moderate renal dysfunction: Cr 2-3 mg/dl |
| 5   | 23                          | Cs/Pred +/- Aza   | 30                                          | NS                                        | severe renal dysfunction: Cr >3 mg/dl BUN > 100 mg/dl, inability to maintain urine output of 1 ml/kg/hr |

**“Low-dose” cyclosporine**

Abbreviations: Cr - serum creatinine; Cs - cyclosporine; Pred - prednisone/steroids; Aza - azathioprine; ATG - antithymocyte globulin; NS - not stated

In contrast to heart transplantation, the reported incidence of ARF complicating open heart surgery has varied from 1.5 percent to 7 percent [6-8]. In a recent report of 5,181 patients, the incidence of ARF (defined as oligoanuria, BUN greater than 84 mg/dl, and need for dialysis) was only 1.5 percent [6]. Prolonged aortic cross-clamp time and cardiopulmonary bypass time were risk factors for ARF in open heart surgery. To evaluate the incidence of ARF in both types of procedures, Greenberg directly compared heart transplantation to other open heart surgery requiring cardiopulmonary bypass [1]. ARF occurred in 6 percent of all transplant patients, regardless of immunosuppression protocol. Remarkably, no episodes of ARF developed in the group of patients who underwent open heart surgery. The overall incidence of moderate azotemia was 46 percent in the transplant group, compared to 4 percent in the non-transplant group. All patients who required dialysis eventually recovered renal function after an unspecified period of time. One death occurred; however, this was unrelated to renal causes.

Predisposition to renal failure in the transplant patients included the following factors (Table 2): a serum creatinine greater than 2 mg/dl or a creatinine clearance less than 55 ml/min the year before transplant, any hospitalization before transplantation, and perioperative cardiovascular compromise [2, 5]. Our patient was hospitalized prior to transplantation, and developed transient post-operative hypotension which required vasopressor support (dopamine 5-8 μg/kg/min). These factors likely predisposed him to the development of acute renal failure following transplantation.
It is interesting to note that despite the higher incidence of ARF in heart transplants, the mortality rates (20-29 percent) in the groups studied were very similar to each other [1, 2, 5]. Deaths were unrelated to renal causes. This rate of mortality is significantly lower than the mortality rates (50-89 percent) reported for patients with ARF following non-transplant open heart surgery [6-8]. Although the exact cause of the disparity in mortality rates is unclear, one possibility is better heart function postoperatively compared to preoperatively, leading to a generalized improvement in organ perfusion. Also, heart-transplant candidates usually have only single organ failure prior to surgery, are generally younger with mean ages ranging from 41 to 52 yr [1, 3, 5] and are healthier than the elderly diabetics with peripheral vascular disease who require cardiac surgery. Finally, ARF in open-heart surgery patients usually accompanies other organ failure, a reflection of the poor over-all status of the patient. In heart-transplant patients, ARF appears to be more related to cyclosporine therapy than to the underlying condition of the patient.

**Role of cyclosporine**

Cyclosporine is a well-known nephrotoxin used to modify immune tolerance in the setting of organ transplantation. The proposed mechanisms for cyclosporine nephrotoxicity include alteration in efferent sympathetic signals to the kidney, altered levels of circulating catecholamines, loss of vasodilatory effects of prostanoids, and induction of renal cortical vasoconstriction [9]. In addition, recent data suggest that the alteration in renal function induced by cyclosporine may be related to endothelin-1, a potent endothelium-derived vasoconstrictor and mitogenic peptide [10].

Most authors have noted a much higher incidence of ARF in patients treated with cyclosporine as part of their immunosuppression regimen. ARF (Table 1) occurred in 12-22 percent of cyclosporine-treated patients, but was absent in the azathioprine-treated patients [1, 2]. Moderate renal dysfunction (Table 1) was seen in 58 percent of cyclosporine-treated patients, as compared with 34 percent of azathioprine-treated patients [1]. Moreover, acute nephrotoxicity is clearly dose-related. The high incidence of ARF reported in these studies occurred with the use of cyclosporine doses as high as 17.5 mg/kg/day for induction, and experience with renal transplantation highlight the dose-toxicity relationship [11]. Macris suggested that high risk patients, as defined by a pre-transplant creatinine clearance below 55 ml/min, any hospitalization before transplant and perioperative cardiovascular compromise, should not be treated with intravenous cyclosporine as part of induction [5]. Other authors have used antithymocyte globulin and steroids with very low doses of cyclosporine for induction. The course of these patients was not complicated by significant infection, rejection, or ARF [2, 3]. As a result of increased recognition for potential serious nephrotoxicity associated with cyclosporine in cardiac transplantation, the currently recommended dosing regimens are associated with a lower incidence of ARF. However, the aggressive use of diuretics postoperatively has enhanced the renal toxicity associated with cyclosporine, in one surgeon’s experience [see discussion in ref. 5]. Despite receiving a low dose of cyclosporine initially for induction, our patient still

**Table 2: Factors predisposing to ARF after cardiac transplantation**

| Factor | Description |
|--------|-------------|
| Serum creatinine > 2 mg/dl at time of transplant | |
| Creatinine clearance < 55 ml/min at time of transplant | |
| Any hospitalization prior to transplantation | |
| Perioperative cardiovascular compromise | |
| Higher cyclosporine dose (?) | |

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developed ARF. As noted, other factors such as aggressive diuresis and hemodynamic compromise, and use of vasopressor medications in the early postoperative period increased the nephrotoxic actions of cyclosporine.

**Clinical features**

The ARF typically develops within the first few days after transplantation (Table 3). In Greenberg's series, a decrease in urine output heralded the occurrence of renal failure [1, 11]. Oliguria persisted throughout the period of renal impairment. BUN and creatinine peaked at 4-5 days post-operatively while recovery at 7-10 days was most often spontaneous after a reduction in cyclosporine dose. A markedly elevated BUN to creatinine ratio, low urine sodium (less than 10 meq/l), and inactive urine sediment suggest severe renal hypoperfusion with intact tubular function. Hyperkalemia disproportionate to the degree of renal impairment also occurs. Our patient demonstrated most of these abnormalities, although the presence of a few granular casts in the urine suggest an additional component of mild acute tubular necrosis. His renal function began to improve after the cyclosporine doses were temporarily withheld.

**Table 3: Clinical features of ARF after cardiac transplantation**

| Occurs within first 4 days following transplant |
| BUN, creatinine peaks at 4-5 days following transplant |
| Recovery after reduction in cyclosporine dose (usually) |
| Oliguria |
| Elevated BUN/creatinine ratio |
| Hyperkalemia disproportionate to azotemia |
| Low UNa (<10 meq/l) and FENa (<1%) |
| Inactive urine sediment |
| Lower mortality compared to ARF following other open heart surgery |

These data suggest that a state of pre-renal azotemia, as seen in true volume depletion or heart failure (effective volume depletion) develops in these patients. However, relative volume expansion, as indicated by higher body weights immediately after surgery, and improved postoperative cardiac pump function make these causes of pre-renal azotemia unlikely. It is more likely that inadequate levels of vasodilator substances to maintain renal cortical blood flow, or potent vasoconstrictor effects of cyclosporine explain this clinical picture. This short-lived nephrotoxicity occurs reproducibly, is dose-related, and responds to discontinuation of cyclosporine [11]. However, other factors undoubtedly contribute to and exacerbate the nephrotoxicity associated with cyclosporine therapy in the cardiac transplant patient.

A protracted form of renal failure beyond 7-10 days occurs less frequently than the early transient renal injury. Prolongation of ARF in bone-marrow and heart-transplant patients whose course has been complicated by septicemia or surgery has been observed. In addition, this phenomenon is also well-recognized in renal transplant patients. Failure to withdraw cyclosporine under these circumstances has been associated with irreversible renal failure [9].

**Pathology**

Although most of the literature on the pathology of cyclosporine nephrotoxicity comes from renal transplant studies, the histologic appearance is apparently very similar.
There is vacuolization of the proximal tubular cells with destruction of apical microvilli. Giant mitochondria, dilatation of the ergastoplasmic cisternae, and numerous lysosomes are seen on electron microscopy. The arterioles exhibit small foci of fibrinoid parietal necrosis, endothelial cell swelling and occasionally microthrombi. In later stages, this may progress to a fibrous endarteritis. These vascular changes may result in ischemic retraction of the glomerulus. Otherwise, glomerular findings are typically minimal. The pathologic features of cyclosporine nephrotoxicity are reviewed elsewhere [9, 12].

Management

At this time, the treatment of ARF in the heart-transplant patient is mainly supportive. Reduction of cyclosporine dose when possible, maintenance of euvoelma, and dialytic intervention (intermittent or continuous) are the mainstays of therapy. The potential role of atrial natriuretic peptide (ANP)-like substances has also been studied [13-15]. Urodilatin is a polypeptide extracted from human urine and belongs to a family of natriuretic-vasorelaxant peptides found in the cardiac atria, one of which is called CDD/ANP-99-126. It is thought to have vasorelaxant effects on renal, pulmonary and coronary vascular smooth muscle, and its effects are thought to be mediated by the natriuretic peptide receptor with cGMP as its second messenger [16]. Like atrial natriuretic factor, it causes preglomerular vasodilation and efferent vasoconstriction, raising glomerular hydrostatic pressure and increasing glomerular filtration rate. Its effects are more prominent in the cortical glomerular arterioles. A continuous infusion of urodilatin for 96 hr postoperatively has resulted in maintenance of nonoliguria, a lower peak BUN and creatinine compared to historical controls (BUN 109 vs 155 mg/dl and creatinine 1.5 vs 2.9 mg/dl, respectively), and decreased requirement for dialysis (6 percent vs 10 percent in controls) [13, 14]. Moreover, treatment with urodilatin in established renal failure in heart and liver transplants has resulted in diuresis within a few hours of infusion [15].

Chronic cyclosporine nephrotoxicity

Late onset renal failure is not simply a continuation of early azotemia or incomplete recovery of renal function. No correlation has been seen between peak creatinine in the perioperative period and creatinine at 6, 12, or 24 months. This suggests that the early form of renal dysfunction does not predispose to chronic nephrotoxicity. [17] Furthermore, 3-7 percent of heart-transplant patients surviving more than two years have been noted to progress to end-stage renal disease [17, 18]. This is likely the result of cyclosporine associated chronic nephropathy. An extensive body of literature on chronic cyclosporine effects on renal function in heart-transplant patients is available elsewhere for review [17-19].

SUMMARY

ARF is a relatively frequent complication associated with heart transplantation. Patients usually develop oliguria, laboratory features typical of pre-renal azotemia, and a bland urine sediment. Cyclosporine plays a major etiologic role, and the ARF is often dose-related. Poor preoperative renal function and perioperative hemodynamic compromise also predispose patients to the development of ARF. Current management is entirely supportive; a minority of patients require dialysis. The use of ANP-like substances in the prevention and treatment of ARF after heart and liver transplantation has been studied, and appears to show promise. Interestingly, the mortality of these patients is lower than that of patients who develop ARF after other cardiac surgery.
REFERENCES

1. Greenberg, A., Egel, J.W., Thompson, M.E., Hardesty, R.L., Griffith, B.P., Bahnhon, H.T., Bernstein, R.L., Hastillo, A., Hess, M.L., and Puschett, J.B. Early and late forms of cyclosporine nephrotoxicity: studies in cardiac transplant patients. Am. J. Kidney Dis. 9:12-22, 1987.

2. McGiffin, D.C., Kirklin, J.K., and Naftel, D.C. Acute renal failure after heart transplantation and cyclosporine therapy. J. Heart Transplant. 4:396-399, 1985.

3. Deeb, G.M., Kolff, J., McClurken, J.B., Dunn, J., Balsara, R., Ochs, R., Badellino, M., Holland, T., Eldridge, C., Clancy, M., Brownstein, L., and Coakley, J. Antithymocyte gamma globulin, low dosage cyclosporine, and tapering steroids as an immunosuppressive regimen to avoid early kidney failure in heart transplantation. J. Heart Transplant. 6:79-83, 1987.

4. Merli, M., Milazzo, F., Visigalli, M.M., and Civati, G. Renal function early post operatively in patients undergoing heart transplantation: experience with 61 patients. J. Cardiothor. Anesth. 3(5 Suppl 1):62, 1989.

5. Macris, M.P., Ford, E.G., Van Buren, C.T., and Frazier, O.H. Predictors of severe renal dysfunction after heart transplantation and intravenous cyclosporine therapy. J. Heart Transplant. 8:444-449, 1989.

6. Joachimsson, PO., Stahle, E., Nystrom, S.O., and Tyden, H. Incidence of acute renal failure in open heart surgery. J. Cardiothor. Anesth. 3(5 Suppl 1):58, 1989.

7. Abel, R.M., Buckley, M.J., Austen, W.G., Barnett, G.O., Beck, C.H., and Fischer, J.E. Etiology, incidence and prognosis of renal failure following cardiac operations. J. Thor. Cardiovasc. Surg. 71:323-333, 1976.

8. Hilberman, M., Myers, B.D., Carrie, B.J., Derby, G., Jamison, R.L., and Stinson, E.B. Acute renal failure following cardiac surgery. J. Thor. Cardiovasc. Surg. 77:880-8, 1979.

9. Myers, B.D. Cyclosporine nephrotoxicity. Kidney Int. 30:964-974, 1986.

10. Grief, M., Loertscher, R., Shobaib, S.A., and Stewart, D.J. Cyclosporine-induced elevation in circulating endothelin-1 in patients with solid organ transplants. Transplantation 56:880-884, 1993.

11. Greenberg, A. Renal failure in cardiac transplantation. Cardiol. Clinics. 20:189-98, 1990.

12. Chomette, G., Auriol, M., Beaufils, H., Rottenburg, J., and Cabrol, C. Morphology of cyclosporine nephrotoxicity in human heart transplant recipients. J. Heart Transplant. 5:273-278, 1986.

13. Hummel, M., Kuhn, M., Bub, A., Bittner, H., Kleefeld, D., Marxen, P., Schneider, B., Hetzer, R., and Forssmann, W.G. Urodilatin: a new peptide with beneficial effects in the postoperative therapy of cardiac transplant recipients. Clin. Invest. 70:674-682, 1992.

14. Hummel, M., Kuhn, M., Bub, A., Mann, B., Schneider, B., von Eckstedt, K.W., Forssmann, W.G., and Hetzer, R. Urodilatin, a new therapy to prevent renal failure after heart transplantation. J. Heart Transplant. 12:209-218, 1993.

15. Cedidi C, Kuse ER, Meyer M, Oldhafer K, Ringe B, Wahlers T, Cremer J, Frei U, Pichlmayr R, and Forssmann WG. Treatment of acute post-operative renal failure after liver and heart transplantation by urodilatin. Clin Invest 71:135-136, 1993.

16. Endlich, K., Forssmann, W.G., Steinhausen, M., and Dussel, R. Effects of urodilatin in the rat kidney: comparison with ANF and interaction with vasoactive substances. Kidney Int. 47:1558-1568, 1996.

17. Greenberg, A., Thompson, M.E., Griffith, B.J., Hardesty, R.L., Kormos, R.L., El-shawhawy, M.A., Janosky, J.E., and Puschett, J.B. Cyclosporine nephrotoxicity in cardiac allograft patients - a seven year follow-up. Transplantation 50:589-593, 1990.

18. Myers, B.D., Sibley, R., Newton, L., Tomlanovich, S.J., Boshkos, C., Stinson, E., Leutscher, J.A., Whitney, D.J., Krasney, D., Coplon, N.S., and Perlroth, M.G. The long-term course of cyclosporine-associated chronic nephropathy. Kidney Int. 33:590-600, 1988.

19. Ruggenenti, P., Perico, N., Amuchastegui, S., Ferrazzi, P., Mamprin, F., and Remuzzi, G. Following an initial decline, glomerular filtration rate stabilizes in heart transplant patients on chronic cyclosporine. Am. J. Kidney Dis. 24:549-553, 1994.