Cardiac Transplant Candidates with Renal Insufficiency or Proteinuria: the Role of Kidney Biopsy in Predicting Post Transplant ESRD

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A. Study Purpose and Rationale

Patients with advanced heart failure seeking cardiac transplant may have renal insufficiency or proteinuria. Renal insufficiency has classically been a contraindication to cardiac transplant and has been shown to be associated with decreased post transplant survival (Anguita et al). However, congestive heart failure alone can cause significant renal damage (Silverberg et al). Heart failure leads to decreased renal blood flow and decreased glomerular filtration rate (GFR); in the face of chronic ischemia, the kidney upregulates angiotensin, aldosterone, and sympathetic activity, which in turn can serve to further worsen both cardiac and renal function. It has been demonstrated that patients with such hemodynamically mediated renal failure, as opposed to primary kidney disease, can recover their native kidney function after adequate renal perfusion has been restored (Klein et al). The contribution of intrinsic renal disease versus low output state to the development of renal insufficiency or proteinuria thus may affect patient eligibility for cardiac transplant and outcome after cardiac transplant. The presence of significant intrinsic renal disease may indicate the need for concomitant renal transplant or, in patients with substantial comorbidity or advanced age, may lead to denial of cardiac transplant alone. Given that patients with heart failure often have comorbidities that may affect renal function (e.g., hypertension, diabetes mellitus, atherosclerotic disease), the predominance of primary versus secondary kidney failure can be difficult to assess in such patients by noninvasive means. In an observational study of thirteen patients with heart failure and renal insufficiency who received kidney biopsies as part of a transplant workup, neither the etiology of heart failure nor the GFR nor the degree of proteinuria reliably predicted the renal pathologic diagnosis or the degree of tubular atrophy and interstitial fibrosis seen (Arora et al). Renal biopsy was shown to provide important diagnostic information on the relative contribution of intrinsic renal disease versus low cardiac output. At Columbia University Medical Center, this information is becoming increasingly important in helping to determine the need for cardiac transplant alone versus combined cardiac/renal transplant. Patients who are found to have predominantly ischemic nephropathy on biopsy with lower indices of chronicity are often listed for cardiac transplant, with the assumption that the renal dysfunction will reverse with correction of the low output state. This study aims to test this hypothesis.

B. Study Design and Statistical Analysis

This trial will be a prospective cohort study looking at the incidence of end stage renal disease (ESRD) in heart transplant patients who had renal insufficiency at the time of transplantation and a renal biopsy consistent with a low grade ischemic nephropathy (detailed below). A sample size of 36 patients is estimated to provide 80% power to detect a 70% incidence of dialysis free survival. A Chi-squared test was used to make this calculation.

C. Study Procedure

Patients with end stage heart failure and renal insufficiency, defined as MDRD GFR < 40 and/or proteinuria > 500mg/day will be identified as potential subjects and referred for renal biopsy. Those patients shown to have predominantly ischemic nephropathy on cardiac biopsy, characterized by tubular injury, disproportionate tubular atrophy and interstitial fibrosis, and JGA hyperplasia, with less than or equal to 30 percent tubular atrophy and interstitial fibrosis will be listed for cardiac transplant (assuming

there are no other precluding factors in the transplant workup). Patients will be assessed for development of ESRD as a primary outcome at 30 days, 6 months, and 1 year from the time of cardiac transplant. Percent change in GFR will be assessed as a secondary outcome.

D. Study Drugs

Not applicable.

E. Medical Device

Not applicable.

F. Study Questionnaires

Not applicable.

G. Study Subjects

Inclusion criteria for the will be patients over the age of 21 with end stage heart failure and renal insufficiency secondary to biopsy proven ischemic nephropathy (as outlined above) with no known contraindications to cardiac transplant.

Exclusion criteria will be: patients with predominantly intrinsic renal disease on biopsy, patients who have been on dialysis for greater than 4 months at the time of cardiac transplant.

H. Recruitment of Subjects

Patients will be recruited by informed heart failure and transplant cardiologists who currently serve to identify and workup potential candidates for cardiac transplant. The patients will be made aware of the potential risks and benefits of kidney biopsy and heart transplantation, as well as the unknown outcome of long term renal function in this setting. If after that discussion the patient is agreeable, the patient will be consented for the study and enrolled.

I. Confidentiality of Study Data

Each study subject will be assigned a unique coding number under which all data will be recorded. These data will be stored in a secure location accessible only to the investigators.

J. Potential Conflict of Interest

None.

K. Location of the Study

This study will be conducted at Columbia University Medical Center.

L. Potential Risks

The potential risks include those normally encountered in renal biopsy, including bleeding and infection, as well as those encountered in cardiac transplantation, including bleeding, infection, stroke, and death. There is also a risk of post transplant renal failure requiring hemodialysis.

M. Potential Benefits

The subject may benefit from the prolonged survival conferred by a successful cardiac transplant. In the absence of transplant, the prognosis for survival with end stage heart failure is extremely poor. Restoration of renal perfusion may also improve the patient's renal function. If renal function is shown to improve, this study could benefit the general heart failure population by expanding the acceptable criteria for heart transplant listing.

N. Alternative Therapies

There are no alternative therapies available to these patients. Though left ventricular assist devices and ionotropic support have been used as bridges to transplant or destination therapies in cases where the patient is considered a nontransplant candidate, these are not equivalent to cardiac transplant.

O. Compensation to Subjects

There will be no compensation to subjects for participating in this study.

P. Costs to Subjects

There will be no additional costs to the subjects as a result of participating in this study.

Q. Minors as Research Subjects

There will be no minors enrolled in this study.

R. Radiation or Radioactive Substances

Not applicable.

S. References

Anguita M. Arizon JM. Valles F. Montero JA. Sancho M. Bueno G. Latre JM. Lopez-Rubio F. Concha M. Influence on survival after heart transplantation of contraindications seen in transplant recipients. Journal of Heart & Lung Transplantation. 11(4 Pt 1):708-15, 1992 Jul-Aug.

Arora N. Markowitz GS. D'Agati VD. Radhakrishnan J. Cardiac Transplant Candidates with Renal Insufficiency or Proteinuria: Role of Kidney Biopsy. ASN 38th Annual Renal Week Meeting, 2006 Nov.

Bergler-Klein J. Pirich C. Laufer G. Grimm M. Regele H. Mayer G. Oberbauer R. The long-term effect of simultaneous heart and kidney transplantation on native renal function. Transplantation. 71(11):1597-600, 2001 Jun 15.

Blanche C. Kamlot A. Blanche DA. Kearney B. Wong AV. Czer LS. Trento A. Combined heart-kidney transplantation with single-donor allografts. Journal of Thoracic & Cardiovascular Surgery. 122(3):495-500, 2001 Sep.

Col VJ. Jacquet L. Squifflet JP. Goenen M. Noirhomme P. Goffin E. Pirson Y. Combined heart-kidney transplantation: report on six cases. Nephrology Dialysis Transplantation. 13(3):723-7, 1998 Mar.

Leeser DB. Jeevanandam V. Furukawa S. Eisen H. Mather P. Silva P. Guy S. Foster CE 3rd. Simultaneous heart and kidney transplantation in patients with end-stage heart and renal failure. American Journal of Transplantation. 1(1):89-92, 2001 May.

Livi U. Milano A. Bortolotti U. Casula R. Zenati M. Casarotto D. Results of heart transplantation by extending recipient selection criteria.Journal of Cardiovascular Surgery. 35(5):377-82, 1994 Oct.

Rubel JR. Milford EL. McKay DB. Jarcho JA. Renal insufficiency and end-stage renal disease in the heart transplant population. Journal of Heart & Lung Transplantation. 23(3):289-300, 2004 Mar.

Sehgal, V. Radhakrishnan, J. Appel, G B. Valeri, A. Cohen, D J. Progressive renal insufficiency following cardiac transplantation: cyclosporine, lipids, and hypertension.
American Journal of Kidney Diseases. 26(1):193-201, 1995 Jul.

Silverberg D. Wexler D. Blum M. Schwartz D. Iaina A. The association between congestive heart failure and chronic renal disease. Current Opinion in Nephrology & Hypertension. 13(2):163-70, 2004 Mar.