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Congestive Heart Failure in Renal Transplant Recipients: Risk Factors, Outcomes, and Relationship with Ischemic Heart Disease

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Abstract. Cardiovascular disease (CVD) is the major cause of death in renal transplant recipients (RTR). Several cohort studies have examined CVD in RTR, but none have addressed the development of congestive heart failure (CHF). CHF would hypothetically be a frequent and prognostically important event in RTR. A retrolective cohort study was, therefore, conducted in two Canadian centers to describe the incidence, risk factors for, and interrelationships between *de novo* CHF, *de novo* ischemic heart disease (IHD), and mortality in 638 consecutive adult RTR who were free of cardiac disease at 1 yr posttransplant. Detailed clinic and hospital records were available for 99% of patients. Median follow-up was 7 yr (range, 1 to 28 yr). *De novo* CHF occurred as frequently as *de novo* IHD (1.26 *versus* 1.22 events/100 patient-years, respectively) and appeared to carry a similar prognosis (relative risk for death, 1.78 [confidence interval, 1.21 to 2.61] for CHF *versus* 1.50 [1.05 to 2.13] for IHD). The incidence of CHF was considerably higher than that in the Framingham cohort, whereas the incidence of IHD was not, suggesting that renal transplantation might correspond more to a state of "accelerated heart failure" than to "accelerated atherosclerosis." Age, diabetes, gender, BP, and anemia were identified as independent risk factors for *de novo* CHF, whereas age, diabetes, gender, BP, and rejection were independent risk factors for *de novo* IHD. Optimal strategies for treatment of BP and anemia in RTR will need to be determined in randomized controlled trials.

Cardiovascular disease (CVD) is the major cause of death among renal transplant recipients (RTR) (1,2). The manifestations of cardiac disease comprise both disorders of perfusion, presenting primarily as ischemic heart disease (IHD; *e.g.*, myocardial infarction [MI], angina pectoris) and disorders of left ventricular function, presenting primarily as congestive heart failure (CHF). Both CHF and IHD are important adverse prognostic markers in the general population. In dialysis patients, CHF occurs frequently and is a stronger predictor of mortality than IHD (3).

Although several high-quality cohort studies have addressed the subject of cardiovascular disease in RTR, none have examined the incidence, determinants, and prognosis of CHF in renal transplants (1,2,4–7). As renal transplantation is often a state of chronic renal insufficiency, we hypothesized that CHF would occur frequently, would be associated with potentially reversible risk factors, and would be a prognostically important event among RTR. We therefore conducted a retrolective cohort study in two Canadian centers to describe the risk factors for and interrelationships between *de novo* CHF, *de novo* IHD, and mortality in a cohort of patients who were alive with a functioning graft and free of clinical cardiac disease at 1 yr after transplantation.

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Materials and Methods

Design

Cohort Definition. We assembled a retrolective cohort of 638 consecutive adult RTR (age, >18 yr) who were followed since inception in Winnipeg, Manitoba ($n = 473$) and St. John's, Newfoundland ($n = 165$). Patients were included in the cohort if they were alive with functioning graft and free of clinical heart disease at 1 yr after transplantation. Patients with known pretransplant cardiac disease were excluded, because cardiac disease at the time of transplantation is due to risk exposures before transplantation and might confound the relationship between posttransplant risk factors and subsequent outcomes. Patients having events in the first year were excluded because events in the first year could not be reasonably attributed to posttransplant variables measured during the same interval. The cohort as defined comprised 62% of all consecutive RTR followed in Manitoba and Newfoundland between 1969 and 1999.

The Manitoba patients received transplants between 1969 and 1999, and the Newfoundland patients received transplants between 1975 and 1999. All patients were followed exclusively at the Health Sciences Center, Winnipeg, and the Health Sciences Center, St. John's. Detailed clinic and hospital records were available for 99% of patients. Trained research nurses reviewed all inpatient and outpatient records, abstracting data on baseline demographic, clinical, and outcome variables. The detail available permitted systematic application of a priori definitions for most outcomes.

Study Variables and Definitions. *Baseline Variables.* Age, gender, presence or absence of diabetes, living or cadaveric donor status, and smoking status were abstracted from the pretransplant assessment records. IHD and CHF were judged to be absent at baseline if the pretransplant assessment concluded that they were absent. Cardiovascular disease was a focus of the pretransplant assessment protocol, and diagnosis was based on oral history, records review, physical examination, and electrocardiogram, with further testing reserved for symptomatic individuals or diabetics. Hypertension before transplantation was defined as BP >140/90 mmHg or need for antihypertensive therapy. Use of angiotensin-converting enzyme inhibitors was recorded. Era of transplantation was defined as transplantation before or after 1985, the year in which cyclosporine became part of the routine maintenance immunosuppression protocol at both centers. Before 1985, the majority of patients received azathioprine and prednisone alone. Delayed graft function was defined as need for dialysis in the first 2 wk after renal transplantation. Acute rejection was defined as an acute rise in serum creatinine of at least 10% that was not attributable to prerenal causes, obstruction, or cyclosporine toxicity and that was treated with pulse steroids and/or antilymphocyte preparations. Delayed graft function (DGF) was defined as need for dialysis in the first 2 wk after transplantation. Systolic and diastolic BP, hemoglobin, albumin, and serum creatinine were measured at least quarterly per clinic protocol, and total cholesterol was measured yearly.

Outcome Variables. CHF was defined clinically as dyspnea plus two of the following: raised jugular venous pressure, bibasilar crackles, chest x-ray evidence of pulmonary venous hypertension, or pulmonary edema (8). *De novo* CHF was defined as CHF occurring for the first time in a patient previously free of CHF. An episode of IHD was defined as hospitalization for acute MI or revascularization (coronary artery bypass grafting or percutaneous transluminal angioplasty). MI was defined as the presence of chest pain accompanied by characteristic electrocardiogram changes of infarction or a threefold elevation in creatine kinase levels. Cardiovascular death was defined as death from myocardial infarction or a revascularization procedure, cardiogenic shock, primary arrhythmia, stroke, or ruptured aortic aneurysm.

Statistical Analyses

Normally distributed continuous variables are expressed as mean (SD); non-normally distributed variables are expressed as median (interquartile range). Categorical variables are expressed as percentages. Outcomes are described using event-free Kaplan-Meier survival curves. Patients were censored at graft failure, latest follow-up, or death, except where death was the end point being analyzed. Cox proportional hazards regression was used for both univariate and multivariate analyses. Backwards conditional stepping operative on the complete variable pool was used to select the best multivariate model. The proportional hazards assumption was checked by inspection of the log (−log)–transformed survival curves. Values for systolic BP, diastolic BP, hemoglobin, creatinine, Gault-Cockroft creatinine clearance, and albumin were averaged over the first year for each patient. If more than one total cholesterol level was available in the first year, these were also averaged.

Time-Dependent Analyses. To estimate the impact of intermediate events (*i.e., de novo* CHF and IHD) occurring at variable follow-up times on subsequent mortality, time-dependent variables were created and included in a time-dependent proportional hazards analysis (9). For the case of CHF, the time-dependent variable created was assigned a value of 0 for follow-up times before the first *de novo* CHF episode and a value of 1 for follow-up times after the first episode. For patients who did not develop *de novo* CHF, the time-dependent variable was always 0. The time-dependence of *de novo* IHD was handled in the same way. The independent effect of *de novo* IHD and CHF on mortality was estimated by including both time-dependent covariates in the same model. CHF and IHD were assessed independently, and the observations were not mutually exclusive; therefore, the model correctly handled the occurrence of both events in the same patient. The impact of *de novo* IHD on subsequent CHF was handled analogously by including the time-dependent IHD variable as a covariate in a proportional hazards model of predictors of *de novo* CHF. Only IHD events preceding or coincident with CHF were analyzed this way, because events occurring after the development of CHF cannot be causally associated with that end point.

Missing Values. Missing values were replaced by random imputation (10). The proportion of values randomly imputed were as follows: creatinine clearance, 4%; hemoglobin, 7.7%; BP, 7.8%; albumin, 12.5%; cholesterol, 41%; smoking, 15.7%; and DGF, 26%. All other variables were complete. The random imputation procedure was repeated four times, and the data were reanalyzed using each set of imputed values to test the robustness of the results. As an additional check, multivariate normal imputation was used (11). The resultant models were nearly identical; therefore, the imputation method had negligible impact on the results.

Results

Patient Characteristics

Of the 1021 adult patients followed since inception at both centers from 1969 to 1999, 638 (62%) were alive with functioning graft and free of cardiac disease at 1 yr (Figure 1). Selected baseline characteristics and averaged clinical and laboratory variables in the first year are summarized in Table 1.

Incidence and Determinants of De Novo CHF

Over a median follow-up of 7.2 yr (range, 1 to 28 yr) (total follow-up of 5654 patient-years), 63 patients developed *de novo* CHF after the first posttransplant year. The average incidence rate of CHF was 1.26 events/100 patient-years. The cumulative incidence of *de novo* CHF, estimated using the

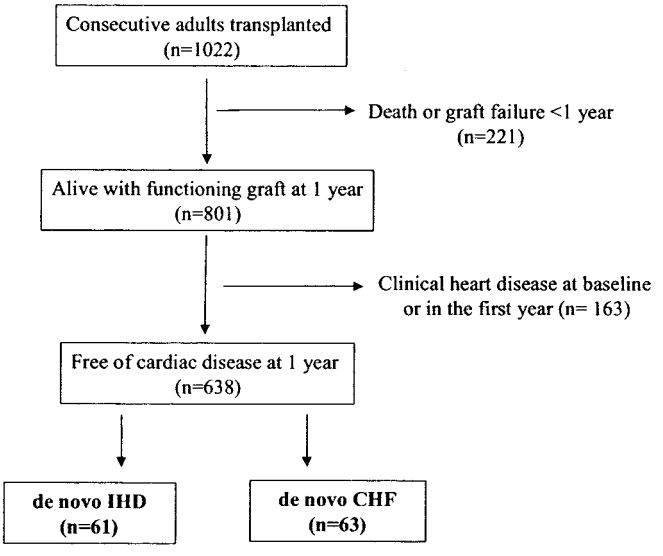

Figure 1. Source of the cohort analyzed for *de novo* heart disease.

Table 1. Selected baseline characteristics of 638 consecutive renal transplant patients free of cardiac disease at 1 yr posttransplant[a]

Age (yr)	38 (12)
Female	38%
Diabetic	17%
Smokers[b]	55%
Duration of dialysis (yr)	1 (0.5 to 2)
Transplanted > 1985	69%
Cadaveric donor	74%
Delayed graft function	26%
Cyclosporine regimen	76%
ACE inhibitors[c]	9%
Rejections in first year (*n*)	2 (1 to 4)
Systolic BP (mmHg)	138 (16)
Diastolic BP (mmHg)	85 (8)
Creatinine (μmol/L)	160 (61)
Estimated creatinine clearance[d] (ml/min)	55 (19)
Hemoglobin (g/L)	126 (19)
Total cholesterol (mmol/L)	6.4 (1.3)
Albumin (g/L)	39 (4)

[a] Continuous variables expressed as mean (SD) or median (interquartile range) as appropriate. Time-dependent variables are averaged over the first year.
[b] Within 5 yr of transplant.
[c] Angiotensin converting enzyme; % patients taking drug in first year.
[d] Gault-Cockroft estimate.

Kaplan-Meier method, was 3.6% (range, 2.0 to 5.2%) at 5 yr, 12.1% (8.6 to 15.5%) at 10 yr, and 21.6% (15.0 to 28.2%) at 20 yr (Figure 2A). The univariate predictors of *de novo* CHF were age, diabetes, declining renal function, low hemoglobin, low albumin, higher BP, cadaveric donor, and allograft rejection (Table 2). The multivariate analysis identified age, diabetes, low hemoglobin, elevated systolic BP, low serum albumin, and cadaveric donation as significant independent risk factors for *de novo* CHF (Table 2). Diastolic BP could be substituted for systolic without diminishing model significance. Gault-Cockroft estimated creatinine clearance (ECC) and rejection were NS after multivariate adjustment.

To explore the relationship between hemoglobin and *de novo* CHF, we modeled the relative hazard associated with each hemoglobin quartile adjusted for the influence of the other

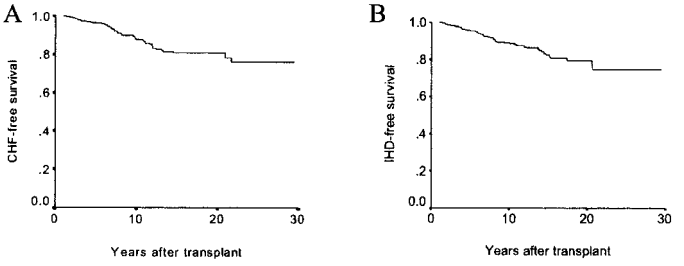

Figure 2. Kaplan-Meier event-free survival curves for *de novo* congestive heart failure (CHF) (A) and *de novo* ischemic heart disease (IHD) (B).

Table 2. Risk factors for *de novo* CHF as determined by Cox regression in 638 adult patients who were alive with functioning graft and free of clinical heart disease (CAD or CHF) at 1 yr[a]

Variable	Univariate		Multivariate	
	Relative Risk (95% CI)	*P*	Relative Risk (95% CI)	*P*
Age (decade)	1.63 (1.34 to 1.99)	<0.001	1.43 (1.16 to 1.77)	0.001
Female gender	1.49 (0.91 to 2.45)	0.1		
Diabetes	3.14 (2.01 to 4.90)	<0.001	2.30 (1.43 to 3.69)	0.001
Smoker[b]	1.59 (0.94 to 2.67)	0.08		
Creatinine clearance (per 10 ml/min)[c]	0.72 (0.61 to 0.86)	<0.001		
Hemoglobin (per 10 g/L decrease)	1.20 (1.06 to 1.36)	0.004	1.24 (1.10 to 1.39)	0.001
Serum total cholesterol (per 10 mmol/L)	1.06 (0.88 to 1.28)	0.6		
Serum albumin (per 10 g/L decrease)	2.77 (1.56 to 4.90)	<0.001	2.10 (1.08 to 4.07)	0.03
Systolic BP (per 10 mmHg)	1.47 (1.28 to 1.66)	<0.001	1.29 (1.10 to 1.50)	0.001
Diastolic BP (per 10 mmHg)	1.80 (1.35 to 1.41)	<0.001		
Transplanted > 1985	1.37 (0.80 to 2.34)	0.2		
Acute allograft rejection	1.97 (1.07 to 3.63)	0.03		
Delayed graft function	1.36 (0.80 to 2.32)	0.2		
Cadaveric donor	5.18 (2.07 to 12.9)	<0.001	3.18 (1.24 to 8.18)	0.02
Cyclosporine use	1.42 (0.81 to 2.48)	0.2		
Duration of dialysis (per mo)	0.95 (0.84 to 1.08)	0.4		
Center	0.6 (0.32 to 1.19)	0.2		

[a] CHF, congestive heart failure; CAD, coronary artery disease.
[b] Past or current smoker.
[c] Gault-Cockroft estimate.

variables in the model (Figure 3). We found a progressive increase in relative hazard with a decline in hemoglobin <138 most pronounced and significant for patients in the lower two quartiles (hemoglobin <126). This suggests that even modest reductions in hemoglobin may be associated with cardiac morbidity. Similar trends were observed in a quartile analysis of BP (Figure 4). As with hemoglobin, a threshold effect was not apparent.

Renal function (ECC) was not independently associated with CHF in the present cohort, although it was a strong univariate predictor. We searched for confounding bias between ECC and other variables to identify which variables replaced it in the multivariate analysis. BP was the most powerful confounder, followed by hemoglobin, age, and diabetes. With these four variables added to the model, the relative risk reduction associated with a 10 ml/min increment in ECC became negligible, suggesting that the impact of ECC on CHF is mediated primarily by hemodynamic factors, age, and diabetes.

Incidence and Determinants of De Novo IHD

Sixty-one patients developed *de novo* IHD over the observation period. The average incidence was 1.22 events/100 patient-years, the same as that of *de novo* CHF. The cumulative incidence of *de novo* IHD, estimated using the Kaplan-Meier method, was 4.5% (2.7 to 6.3%) at 5 yr, 11.5% (8.1 to 14.9%) at 10 yr, and 22.9% (15.5 to 30.3%) at 20 yr (Figure 2B). On univariate analysis (Table 3), age, gender, diabetes, BP, and allograft rejection were significant predictors of *de novo* IHD, and these associations persisted in the multivariate analysis (Table 3). A center effect was observed in the univariate analysis but disappeared in the multivariate model, suggesting the effect was due to case-mix differences between centers.

Prognostic Impact of De Novo CHF and De Novo IHD

The crude survival of patients who developed *de novo* CHF and *de novo* IHD *versus* those who did not is illustrated in Figure 5, A and B. Using a proportional hazards model incorporating time-dependent covariates for the occurrence of CHF and IHD, we found that the relative hazard of death associated with *de novo* CHF was very similar to that associated with *de novo* IHD (Table 4). These effects were independent of age, diabetes, and gender.

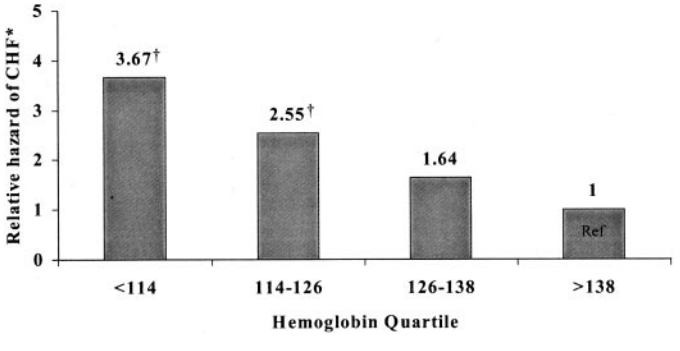

Figure 3. Relative hazard (risk) of *de novo* CHF as a function of hemoglobin quartile in a cohort of 638 renal transplant recipients (RTR) alive with functioning graft and free of clinical heart disease at 1 yr posttransplant. **Adjusted for age, diabetes, systolic BP, donor status, and serum albumin; †$P < 0.03$ with respect to reference quartile.

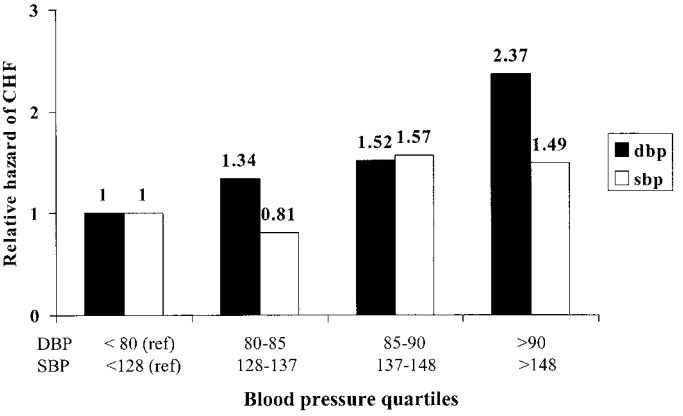

Figure 4. Relative hazard (risk) of *de novo* CHF as a function of systolic and diastolic BP quartiles in a cohort of 638 RTR alive with functioning graft and free of clinical heart disease at 1 yr posttransplant.

Role of IHD in the Genesis of CHF

Of the 63 patients who developed *de novo* CHF, 19 patients (30%) also developed IHD. IHD preceded CHF in 13 cases, coincided with it in 5, and followed it in only one case. Using a proportional hazards model incorporating a time-dependent covariate for the occurrence of IHD, development of *de novo* IHD was associated with a twofold risk for *de novo* CHF, independent of all the previously identified risk factors for *de novo* CHF summarized in Table 2. These other risk factors, particularly low hemoglobin and high BP, remained significant independently of IHD.

Determinants of Mortality

Overall mortality in this healthy cohort was low (2.5 deaths/100 patient-years). Nearly half the deaths were from cardiovascular causes (Table 5). As expected, factors predicting *de novo* CHF or IHD (*i.e.*, age, diabetes, anemia, hypertension, cadaveric donation, and smoking) also predicted all-cause and cardiovascular death (Table 6).

Discussion

A small number of high-quality cohort studies have examined risk factors for cardiovascular disease and death in renal transplant patients (1,2,4–7). Our study is the first to examine the incidence, determinants, and prognosis of CHF in RTR. We found that *de novo* CHF occurred as frequently as *de novo* IHD and was associated with a similar adverse risk of death. This observation is consistent with data in dialysis patients and (8,12), but it contrasts with data in the general population, where CHF occurs much less frequently than IHD. Whereas the incidence of *de novo* CHF in our cohort was approximately two to five times higher than observed in population-based

Table 3. Risk factors for *de novo* IHD as determined by Cox regression in 638 adult patients who were alive with functioning graft and free of clinical heart disease at 1 yr[a]

Variable	Univariate		Multivariate	
	Relative Risk (95% CI)	*P*	Relative Risk (95% CI)	*P*
Age (per decade)	1.50 (1.23 to 1.84)	<0.001	1.45 (1.18 to 1.78)	<0.001
Female gender	0.28 (0.14 to 0.58)	<0.001	0.32 (0.16 to 0.65)	0.002
Diabetes	3.11 (2.01 to 4.82)	<0.001	2.40 (1.49 to 3.87)	<0.001
Smoker[b]	0.99 (0.60 to 1.64)	1.0		
Creatinine clearance (per 10 ml/min)[c]	0.93 (0.79 to 1.08)	0.3		
Hemoglobin (per 10 g/L)	1.03 (0.88 to 1.18)	0.7		
Serum total cholesterol (per mmol/L)	1.05 (0.87 to 1.28)	0.6		
Serum albumin (per 10 g/L)	1.52 (0.80 to 2.89)	0.2		
Systolic BP (per 10 mmHg)	1.25 (1.08 to 1.44)	0.002		
Diastolic BP (per 10 mmHg)	1.72 (1.28 to 2.30)	<0.001	1.41 (1.03 to 1.94)	0.03
Transplanted > 1985	1.00 (0.58 to 1.74)	1.0		
Acute allograft rejection	3.01 (1.48 to 6.11)	0.002	2.68 (1.32 to 5.47)	0.007
Delayed graft function	1.01 (0.51 to 2.00)	1.0		
Cadaveric donor	2.19 (0.93 to 5.12)	0.07		
Cyclosporine use	1.11 (0.63 to 1.96)	0.7		
Duration of dialysis	1.01 (0.92 to 1.13)	0.7		
Center	0.43 (0.21 to 0.92)	0.03		

[a] IHD, ischemic heart disease.
[b] Past of current smoker.
[c] Gault-Cockroft estimate.

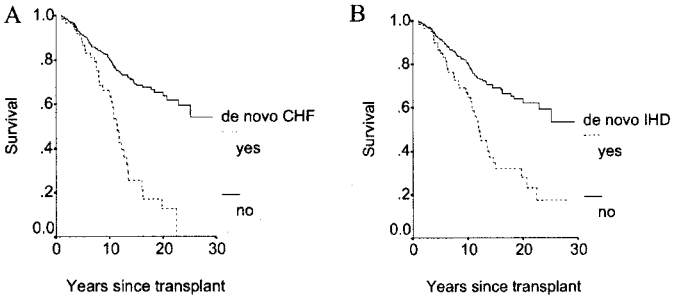

Figure 5. Survival in patients who did and did not develop *de novo* CHF (A) and *de novo* IHD (B).

Table 4. Impact of *de novo* CHF and IHD on survival in 638 adult patients who were alive with functioning graft and free of clinical heart disease (CAD or CHF) at 1 yr

Variable	Relative Hazard	*P*
Age	1.04 (1.03 to 1.06)	<0.001
Diabetes	2.23 (1.65 to 3.00)	<0.001
De novo CHF	1.78 (1.21 to 2.61)	0.003
De novo IHD	1.50 (1.05 to 2.13)	0.02

cohorts from Framingham and Minnesota (13,14), the incidence of *de novo* IHD was similar to that observed in Framingham (15). Relative to the general population, the renal transplant state may be characterized more by a tendency toward CHF than toward IHD, in contrast to the prevailing paradigm (1). A more formal comparison, adjusting for case-mix differences between renal transplant and general population cohorts, would have to be performed to further explore this hypothesis.

Our multivariate analysis showed that age, diabetes, development of IHD, BP, anemia, serum albumin, and cadaveric donation were independently associated with *de novo* CHF. Although IHD appears to be an important element in the causation of CHF, *de novo* IHD preceded *de novo* CHF in only 18 (29%) of 63 patients, suggesting other factors are responsible in many cases. Hypertension and anemia are recognized hemodynamic stressors and imparted substantial risk of CHF even after adjustment for *de novo* IHD. Several direct and indirect observations support a causal association between these hemodynamic factors and CHF. First, both anemia and hypertension were documented to exist well before the development of CHF. Second, a monotonic increasing risk of CHF was observed with worsening hypertension and anemia (Figures 3 and 4), consistent with a causal association. Third, studies in renal transplantation, chronic renal insufficiency, and dialysis have consistently documented the association between hypertension/anemia and left ventricular growth (15–17). It is therefore plausible that anemia and hypertension promoted ventricular growth and remodeling in our cohort, leading to congestive heart failure.

The role of hypoalbuminemia in the development of CHF is less clear. Hypoalbuminemia has also been associated with

congestive heart failure and progressive left ventricular cavity enlargement in dialysis patients (18). It is thought to be a marker of malnutrition and/or chronic inflammation, either of which could promote cardiomyocyte attrition, cardiomyopathy, and CHF (19). The role of cadaveric donation in the genesis of CHF is probably noncausal, reflecting unmeasured patient selection biases, with cadaveric kidneys being preferred in cases of marginal recipients.

Although acute rejection was not directly associated with *de novo* CHF, it was predictive of *de novo* IHD, which in turn predicted *de novo* CHF. Acute rejection was not a marker for the adverse risk associated with steroid or OKT3 treatment, because neither factor was linked to cardiac outcomes (data not shown). Repeated episodes of acute rejection may cause upregulation of acute phase reactants, such as CRP. These factors have been independently associated with adverse cardiac events in the general population (20). A similar association may pertain in RTR.

Renal function was not an independent predictor of incident IHD or CHF. Multivariate modeling suggested that the impact of renal function on CHF is largely the result of hypertension and anemia, known correlates of renal failure. Similarly, immunosuppressive regimen was not associated with cardiovascular outcomes after multivariate adjustment.

These observations may be integrated into the pathophysiologic schema proposed in Figure 6. In this hypothesis, age, diabetes, and markers of unmeasured patient factors (*e.g.*, cadaveric donation) determine the baseline cardiac geometry. Chronic hemodynamic stresses from anemia and hypertension promote wall hypertrophy and cavity enlargement. Tissue ischemia (*i.e.*, IHD), malnutrition, and inflammation contribute to cardiomyocyte death and left ventricular dilation. The resultant cardiomyopathy is clinically expressed as CHF. Although omitted for clarity, factors such as renal function, rejection, and immunosuppressive medications can still influence development of CHF indirectly via effects on BP, anemia, nutrition, and IHD. Further testing of this framework will require clinical trials of risk factor interventions, especially for hypertension and anemia, here identified as major reversible risk factors.

Several limitations of this analysis deserve mention. First, in retrolective cohort designs, relevant data may at times be missing. This problem was minimized in this study by the exclusive follow-up of patients at two centers, each operating in relative geographic isolation. This resulted in excellent data capture over a long follow-up period. Most of the risk factors of interest were obtained as part of the clinic protocols. The availability of complete outpatient and hospital records allowed the application of a priori study definitions to outcome events. The quality of the data may approach that obtainable in a prolective cohort study. Second, in observational studies,

Table 5. Causes of death in 638 renal transplant patients who were alive with a functioning graft and free of cardiac disease at 1 yr posttransplantation

Cause of Death	*n*	%	Rate/100 patient-years
Total	145	100	2.56
Cardiovascular	67	46	1.18
Infection	28	19	0.50
Malignancy	25	17	0.44
Other	25	17	0.44

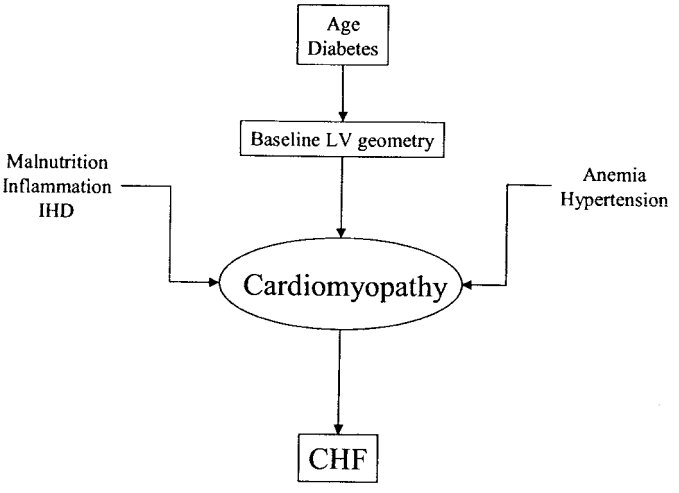

Figure 6. Pathogenesis of CHF in RTR: A hypothesis.

Table 6. Multivariate risk factors for all-cause and cardiovascular death as determined by Cox regression in a cohort of 638 adult patients who were alive with a functioning graft and free of clinical heart disease at 1 yr

Variable	All-Cause Death		Cardiovascular Death	
	Relative Risk (95% CI)	*P*	Relative Risk (95% CI)	*P*
Age (per decade)	1.51 (1.31 to 1.73)	<0.001	1.67 (1.35 to 2.06)	<0.001
Diabetes	2.10 (1.52 to 2.92)	<0.001	3.11 (1.97 to 4.91)	<0.001
Hemoglobin (per 10 g/L decrease)	1.16 (1.07 to 1.26)	0.001	1.15 (1.01 to 1.30)	0.03
Systolic BP (per 10 mmHg)	1.14 (1.03 to 1.27)	0.009	1.20 (1.02 to 1.39)	0.02
Cadaveric donor	2.04 (1.19 to 3.51)	0.01	4.74 (1.45 to 15.5)	0.01
Allograft rejection	1.69 (1.10 to 2.59)	0.02	3.13 (1.45 to 6.76)	0.004
Smoking	1.47 (1.04 to 2.06)	0.03	NS	NS

causal inferences are weaker than in experimental designs addressing the same hypothesis. Our findings regarding hypertension and anemia should ideally be confirmed in clinical trials. Finally, because most of the cohort was derived from the 1970s and 1980s, use of angiotensin-converting enzyme inhibitors was limited, and the impact of this variable on outcome could not be addressed.

In conclusion, *de novo* CHF occurs as commonly as *de novo* IHD in RTR, and it carries a similar adverse prognosis. The incidence of CHF appears to be considerably higher than that in the general population, whereas the incidence of IHD was not, suggesting that renal transplantation may correspond better to a state of "accelerated heart failure" than to one of "accelerated atherosclerosis." Age, diabetes, gender, BP, and anemia appear to be dominant risk factors in the development of *de novo* CHF, whereas age, diabetes, gender, BP, and rejection appear to be dominant risk factors for *de novo* IHD in renal transplant recipients. Effective strategies for treatment of reversible risk factors, in particular BP and anemia, will need to be determined in randomized controlled trials.

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