Electrocardiographic Left Ventricular Hypertrophy in Renal Transplant Recipients: Prognostic Value and Impact of Blood Pressure and Anemia

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Abstract. Left ventricular hypertrophy (LVH) is an independent risk factor for death and cardiovascular disease in the general population and dialysis patients. However, the causes and consequences of LVH have not been well described in renal transplant recipients (RTR). A retrolective cohort study was conducted in 473 RTR who were alive and free of cardiac disease at 1 yr. LVH was defined using the Cornell electrocardiographic (EKG) criteria. A total of 416 patients had an interpretable first-year EKG (88%), and 284 had an interpretable fifth-year EKG (78% of 5-yr survivors). Baseline characteristics were similar in patients with and without EKG. Of 416 patients, 57 had LVH in the first year, whereas 38 of 284 patients had LVH in the fifth year, of which 18 cases were *de novo*. Baseline LVH was a risk factor for death (RR 1.9 [1.22, 3.22]) and congestive heart failure (CHF) (RR 2.27 [1.08, 4.81]) and was independent of other major prognostic variables. Persistent or *de novo* LVH in the fifth year predicted subsequent death (RR 2.15 [1.14,4.01]) and CHF (2.71 [1.17, 6.30]). Anemia and diastolic BP were independent risk factors for increasing Cornell voltage (a marker of LV mass) between first and fifth years. Systolic BP was the only predictor of *de novo* LVH at 5 yr. It seems that EKG LVH is a significant risk factor for death and CHF in RTR and that anemia and hypertension are risk factors for LV growth. Whether aggressive treatment of hypertension and anemia can improve outcomes merits further study.

Left ventricular hypertrophy (LVH) is a well-established marker of cardiovascular risk in the general population. Both electrocardiographic (EKG) and echocardiographic (echo) LVH are strong independent predictors of outcome (1,2). EKG and echo have a similar specificity for LVH, but EKG is less sensitive for mild to moderate degrees of hypertrophy (3,4). Electrocardiography is much cheaper and more widely available than echo, however, making it a useful prognostic and epidemiologic tool.

In dialysis patients, echo LVH has been shown to predispose to death and congestive heart failure (CHF) (5). The prevalence of echo LVH increases progressively with progression of renal insufficiency (5,6,7). Hypertension and chronic anemia appear to be the dominant stimuli for left ventricular growth in renal failure patients, although age, diabetes, and metabolic factors may also play a role (5,7). In renal transplant recipients, relatively little is known about the causes and consequences of LVH. Most studies have simply documented changes in echo LVH before and after transplantation or in the first few posttransplant years (8–18). Neither the causes of LVH nor its mortal and cardiovascular consequences have been well described. Moreover, the prognostic value of electrocardiographic LVH has not been assessed in renal transplant patients.

In a recently published study of CHF in renal transplant recipients (RTR), we documented that development of CHF incurred a strong adverse risk of death (19). As in dialysis patients, hypertension and anemia were major reversible risk factors for CHF and death. We hypothesized that these hemodynamic factors stimulated LV growth, which in turn predisposed to adverse cardiovascular outcomes.

To describe the causes and prognosis of electrocardiographic LVH in RTR, we abstracted baseline and follow-up EKG in a single-center cohort of 473 RTR and applied a well-validated EKG criterion for LVH (Cornell voltage criterion) (4). The objectives of the analysis were to describe the prevalence and prognostic impact of EKG LVH at 1 and 5 yr after renal transplant and to ascertain risk factors for LV growth in the first 5 posttransplant years.

Materials and Methods

Cohort Assembly

The derivation of the study cohort is summarized in Figure 1. The present study cohort formed part of a recently published two-center study and has already been described in detail (19). We studied 473 consecutive adult RTR (age, >18 yr) followed since inception in Winnipeg, Manitoba. Only patients who were alive and free of clinical

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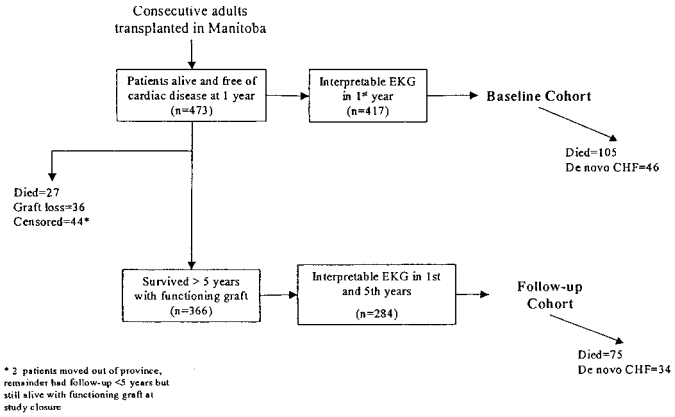

Figure 1. Derivation of the cohorts analyzed.

heart disease at 1-yr posttransplant were included to minimize confounding by pretransplant cardiovascular risk factors and disease. The cohort as defined comprised 62% of all consecutive renal transplant recipients followed in Manitoba between 1969 and 1999. Patients were followed exclusively at the Health Sciences Center, Winnipeg.

Study Variables and Definitions

Baseline Variables. Age, gender, presence or absence of diabetes, living or cadaveric donor status, date of renal transplant, and smoking status were abstracted from the pretransplant assessment records. 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. Supine BP was measured at quarterly clinic visits by trained clinic nurses according to a well-established protocol. Measurements were performed after 15 min of rest in a dim room. Pressures in both arms were recorded, and the higher of the two readings was used in the analysis. Hemoglobin, albumin, and serum creatinine were measured at least quarterly, per clinic protocol. Creatinine clearance was estimated using the Gault-Cockroft method.

Outcome Variables. Congestive heart failure (CHF) was defined clinically as dyspnoea plus two of the following: raised jugular venous pressure, bibasilar crackles, chest x-ray evidence of pulmonary venous hypertension, or pulmonary edema (20). *De novo* CHF was defined as CHF occurring for the first time in a patient previously free of CHF. Cardiovascular death was defined as death from myocardial infarction or a revascularization procedure, cardiogenic shock, primary arrhythmia, stroke, or ruptured aortic aneurysm. LVH was defined using the Cornell voltage criterion, a well-validated EKG method with a reported specificity of 96% and a sensitivity of 30% (4). Cornell LVH was present if the sum of the amplitudes of the R wave in lead aVL and the S wave in lead V_3 was greater than 2.0 mV in women or 2.8 mV in men. A trained research nurse, blinded to patient outcome, examined the original 12-lead EKG and measured all QRS voltages manually.

Statistical Analyses

Normally distributed continuous variables are expressed as mean (SD). Non-normally distributed variables are expressed as median (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 endpoint being analyzed. The log-rank test was used for univariate comparisons. Cox proportional hazards regression was used for multivariate analyses. All analyses were stratified by decade of transplantation to neutralize any possible vintage effect. Forward variable selection was employed to obtain the best multivariate model. The proportional hazards assumption was checked for each model by inspection of the log (−log) transformed survival curves and was justified in all cases. Values for SBP, DBP, hemoglobin, and albumin and creatinine were averaged over the first year for each patient in the analysis of baseline LVH and over the fifth year for the analysis of the impact of persistent or *de novo* LVH at 5 yr. Extended Cox models incorporating time-dependent covariates for LVH, systolic BP, and hemoglobin were also developed to better account for the temporal variation in these measures.

Results

Baseline characteristics (Table 1) were similar in patients with and without follow-up EKG. There was a trend toward a higher prevalence of diabetes among the patients with follow-up EKG (17% *versus* 9%; $P = 0.06$), likely reflecting the usual practice of enhanced cardiac surveillance in higher risk patients. Patient survival was also not statistically different between the two groups (RR of death in patients with EKG, 1.03 [0.58, 1.85]; $P = 0.9$). These findings do not indicate

Table 1. Comparison of baseline characteristics in patients with and without EKG

Variable	Patients with EKG ($n = 284$)	Patients without EKG ($n = 82$)	*P*
Age (yr)	38 (12)	36 (12)	NS
Female gender (%)	39	35	NS
Diabetes (%)	17	9	0.06
Hemoglobin (g/L)	125 (18)	126 (19)	NS
Systolic BP (mmHg)	139 (17)	141 (16)	NS
Diastolic BP (mmHg)	86 (9)	86 (8)	NS
Gault-Cockroft clearance (ml/min)	57 (18)	57 (22)	NS
Albumin (g/L)	38 (4)	39 (4)	NS
Cadaveric donor (%)	81	77	NS
At least one rejection in first year (%)	86	82	NS
Current smokers (%)	59	50	NS

strong selection biases and suggest that the patients sampled were representative of the cohort as a whole.

Fifty-seven (14%) of 416 patients had LVH in the first year as defined by the Cornell voltage criteria (Cornell LVH). Over a median follow-up of 7 yr (range, 1 to 29 yr), 104 deaths and 46 episodes of *de novo* CHF were observed. Of the deaths, 50% were attributable to cardiovascular disease, 19% to infection, and 17% to malignancy. Cornell LVH was associated with a significant risk of death and of CHF independently of other confounding variables (*i.e.*, age, gender, diabetes, smoking, BP, hemoglobin level, serum albumin, rejections in the first year, cadaveric donation, and creatinine clearance) (Tables 2 and 3; Figure 2A). Thirty-eight of 284 patients had Cornell LVH at 5 yr. LVH had been present since the first year in 20 of 38 patients (persistent LVH) and was a new development in 18 of 38 (*de novo* LVH). Systolic BP was the only identifiable predictor of *de novo* LVH at 5 yr (RR of *de novo* LVH per 10 mm/Hg increase in SBP: 1.39 [1.07, 1.81], $P = 0.01$). A multiple linear regression analysis identified high diastolic BP and low serum hemoglobin as independent correlates of increasing Cornell voltage, a validated surrogate of LV mass (β coefficient for DBP: 0.09 [0.03, 0.16] mV/cmHg, $P = 0.005$; β coefficient for hemoglobin: -0.03 [-0.06, -0.001] mV/g/dl, $P = 0.04$).

Persistent or *de novo* LVH in the fifth posttransplant year was significantly associated with higher risk of death independently of all other confounding variables (Table 4; Figure 2B). LVH in the fifth year was also associated with development of *de novo* CHF on univariate analysis (Table 5, Model 1). Systolic BP and hemoglobin together at 5 yr yielded the best multivariate model possible from the variables tested (*i.e.*, age, gender, diabetes, diastolic BP, serum albumin, cadaveric donor, acute rejections in the first year, smoking, and creatinine clearance; Table 5, Model 2). Addition of Cornell LVH at 5 yr to the model did not significantly improve model fit (Table 5, Model 3), suggesting that the impact of LVH at 5 yr on development of *de novo* CHF after 5 yr was not independent of the effects of anemia and hypertension, themselves predictive of LV growth (as measured by Cornell voltage) between the first and fifth years. The causal implications of these finding are explored further in the discussion.

Because BP, hemoglobin, and LVH status change over time, extended Cox models using time-dependent covariates for these risk exposures were also fitted to the data to better account for the temporal variation in these variables (Tables 6 and 7). These models were tested in the cohort of patients with follow-up EKG ($n = 284$). The results were congruent with those of the time-independent model. In the analysis of survival (Table 6), LVH, age, and diabetes persisted as independent risk factors for death, whereas gender and hemoglobin were identified as additional risk factors. In the analysis of CHF (Table 7), LVH was identified as an independent predic-

Table 2. Risk factors for mortality in 416 renal transplant recipients as determined by Cox regression. Final model included LVH, age, diabetes, hemoglobin, and systolic BP (model $P < 0.0000001$)

Variable	Relative Risk (95% CI)	*P*
LVH in first year	**1.90 (1.12, 3.22)**	**0.02**
Age (per decade)	1.74 (1.47, 2.07)	<0.001
Diabetes	2.36 (1.45, 3.83)	0.001
Hemoglobin (per 10 g/L decrease)	1.17 (1.05, 1.30)	0.005
Systolic BP (per 10 mmHg)	1.32 (1.05, 1.66)	0.02
Albumin	NS	NS
Rejection in first year	NS	NS
Cadaveric donor	NS	NS
Smoking	NS	NS

Table 3. Risk factors for *de novo* CHF in 416 renal transplant recipients as determined by Cox regression. Final model included LVH, age, diabetes, hemoglobin, and diastolic BP (model $P < 0.0000001$)

Variable	Relative Risk (95% CI)	*P*
LVH in first year	**2.27 (1.08, 4.81)**	**0.03**
Age (per decade)	1.96 (1.49, 2.57)	<0.001
Diabetes	2.94 (1.44, 6.03)	0.003
Hemoglobin (per 10 g/L decrease)	1.36 (1.18, 1.55)	<0.001
Diastolic BP (per 10 mmHg)	2.10 (1.46, 2.99)	<0.001
Albumin	NS	NS
Rejection in first year	NS	NS
Cadaveric donor	NS	NS
Smoking	NS	NS

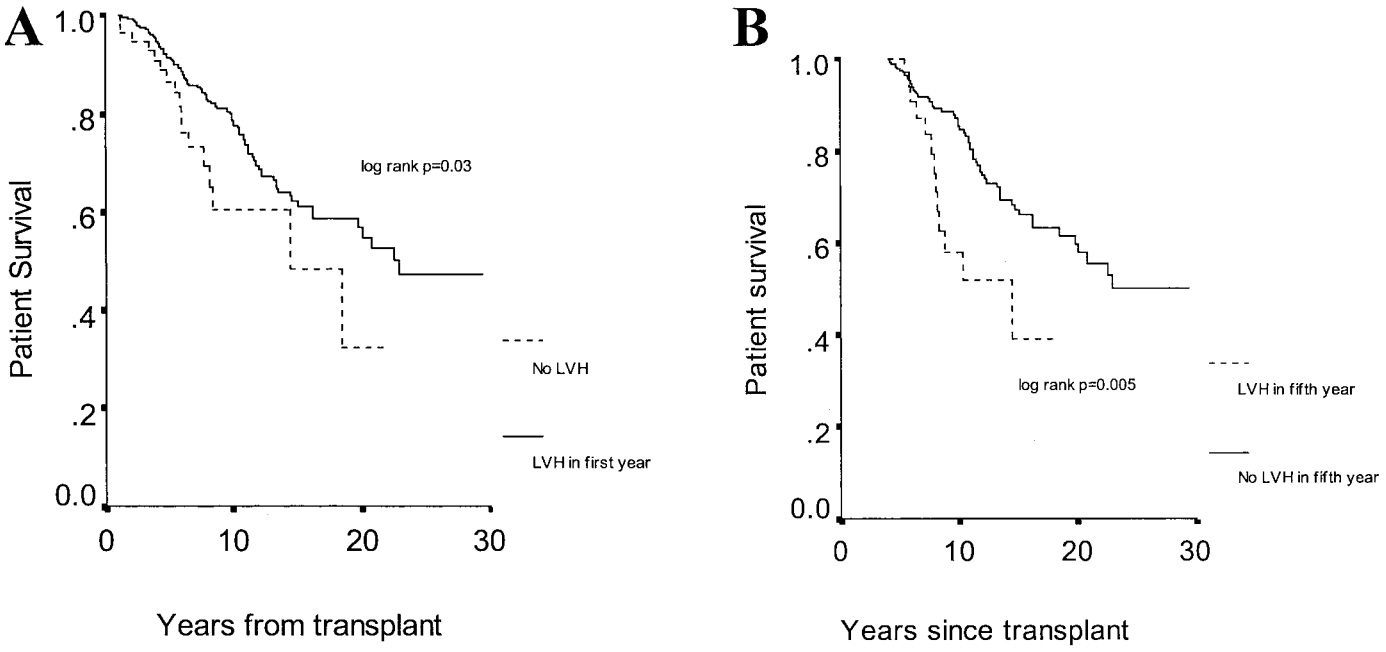

Figure 2. Patient survival as a function of (A) the presence or absence of left ventricular hypertrophy (LVH) in the first post transplant year and (B) the presence or absence of LVH in the fifth posttransplant year.

Table 4. Risk factors for death after 5 yr in 284 renal transplant recipients who survived at least 5 yr. Final Cox model included LVH, age, and diabetes (model $P < 0.0000001$)

Variable	Relative Risk (95% CI)	*P*
LVH in fifth year	**2.15 (1.14, 4.01)**	**0.02**
Age (per decade)	1.72 (1.42, 2.09)	<0.001
Diabetes	3.55 (2.11, 6.00)	<0.001
Hemoglobin (per 10 g/L decrease)	NS	NS
Diastolic BP (per 10 mmHg)	NS	NS
Albumin	NS	NS
Rejection in first year	NS	NS
Cadaveric donor	NS	NS
Smoking	NS	NS

tor of death when hemoglobin and BP were excluded from the model (Model C) but was forced out of the model when BP and anemia were added to the variable pool (Model B). This finding is consistent with the results of the time-independent analysis and is more fully discussed below.

Discussion

LVH has been shown to be a prognostically significant development in the general population and in dialysis and chronic renal failure. It is a major predictor of death and congestive heart failure in both renal and nonrenal populations. In patients with renal failure, the major reversible risk factors for left ventricular hypertrophy appear to be hypertension and anemia (1–7).

The causes and consequences of LVH have not been as well studied in RTR. Most investigators have either simply described changes in LV mass before and after transplant or described changes in LVH within the first several years of transplant. By and large these studies have shown that LV mass decreases posttransplantation and that this decrease parallels posttransplant improvement in BP control (8–18). Two studies have suggested that pretransplant LVH is predictive of posttransplant mortality in the first 5 yr, but none have had sufficient power and long enough follow-up to examine whether posttransplant persistence or development of LVH are predictive of death and cardiovascular events (21,22). We have previously shown that CHF appears to be more frequent in RTR than in the general population and is independently associated with a twofold increased risk of death. Age, diabetes, hypertension, anemia, hypoalbuminemia, and cadaveric donation were the major determinants of CHF (19). We hypothesized that hypertension and anemia constituted major hemodynamic stimuli for LVH, which in turn predisposed patients to CHF and death.

Table 5. Impact of persistent or *de novo* LVH in the fifth posttransplant year on the subsequent occurrence of CHF

Model Variables	Relative Risk	*P*
Model 1		
LVH in fifth year	2.71 (1.17, 6.30)	0.02
Model 2		
systolic BP (per 10 mmHg)	1.51 (1.28, 1.79)	<0.001
hemoglobin (per 10 g/L decline)	1.24 (1.05, 1.46)	0.002
Model 3		
LVH in fifth year	2.01 (0.86, 4.72)	0.1
Systolic BP (per 10 mmHg)	1.48 (1.25, 1.77)	<0.001
Hemoglobin (per 10 g/L decline)	1.24 (1.04, 1.46)	0.013

Table 6. Time-dependent analysis[a] of risk factors for death. Final Cox model included LVH, age, gender, diabetes, and hemoglobin (model $P < 0.0000001$)

Variable	Relative Risk (95% CI)	*P*
LVH	**2.09 (1.10, 3.98)**	**0.02**
Age (per decade)	1.89 (1.55, 2.28)	<0.001
Female gender	0.38 (0.22, 0.65)	<0.001
Diabetes	3.15 (1.90, 5.23)	<0.001
Hemoglobin (per 10 g/L decrease)	1.52 (1.37, 1.71)	<0.001
Diastolic BP (per 10 mmHg)	NS	NS
Systolic BP (per 10 mmHg)	NS	NS
Albumin (per 10 g/L decrease)	NS	NS
Gault-Cockroft clearance (ml/min)	NS	NS
Rejection in first year	NS	NS
Cadaveric donor	NS	NS
Smoking	NS	NS

[a] Extended Cox model in which LVH, BP, hemoglobin, albumin, creatinine clearence are treated as time-depended variables.

The present analysis in a large subcohort of patients with serial electrocardiograms extends and refines our previous work. Using a well-validated EKG criterion for LVH, we found that electrocardiographic LVH in the first year was an independent risk factor for death and subsequent CHF. Moreover, persistent or *de novo* LVH was also a strong independent risk factor for death after 5 yr, confirming the continuing importance of LVH in the intermediate and late transplant periods. Both BP and anemia were identified as important risk factors for LV growth (as measured by Cornell voltage), a finding consistent with earlier work on RTR by our group as well as with data in dialysis and chronic renal insufficiency (CRI).

Persistent or *de novo* LVH at 5 yr was a strong univariate predictor of CHF, as expected. Interestingly, it was not independent of anemia and BP in either the time-independent or time-dependent analyses (Tables 5 and 8). LVH *was* independent of age, gender, diabetes, serum albumin, donor status, smoking, and acute rejections in bivariate, time-independent models (not shown) and in a time-dependent model in which BP and anemia were excluded (Table 7, Model C). These findings are consistent with the hypothesis that LVH is an intermediate stage in a causal progression linking hemodynamic overload from hypertension and anemia to LV growth to clinical congestive heart failure. Under this hypothesis, one would *expect* the impact of LVH to be confounded with that of its proximate causes, hypertension and anemia, limiting the power of the analysis to detect an independent effect, as proved to be the case.

Renal function was not found to be an independent predictor of LVH, *de novo* CHF, or death. This is consistent with our previous analysis of the determinants of CHF in a larger two-center cohort of RTR, which included patients from the present cohort. In that larger and more powerful analysis, we showed that the impact of renal function on CHF and death was mediated primarily by anemia and hypertension, known correlates of renal failure.

We have generated a hypothetical causal framework integrating the observations of the present study with those of our previous analysis on determinants of CHF in RTR (19) (Figure 3). Under this schema, cardiac geometry at time of transplantation is the product of factors such as age and diabetes and presumably also prior exposure to risk factors on dialysis such as hypertension and anemia. During the transplant period, persistence or evolution of hypertension and anemia promote LVH, predisposing to CHF and death. Hypertension and ane-

Table 7. Time-dependent analysis[a] of the impact of persistent or *de novo* LVH on the subsequent occurrence of CHF

Model Variables	Relative Risk	*P*
Model A		
LVH	2.48 (1.18, 5.25)	0.02
Model B		
age	1.54 (1.18, 2.02)	0.001
DM	3.59 (1.74, 7.40)	0.001
systolic BP (per 10 mmHg)	1.21 (1.04, 1.41)	0.01
hemoglobin (per 10 g/L)	1.62 (1.38, 1.88)	<0.001
albumin (per 10 g/L)	3.23 (1.40, 7.83)	0.01
Model C (BP and HGB excluded)		
LVH	2.56 (1.20, 5.47)	0.015
age	1.52 (1.16, 1.95)	0.002
diabetes	2.90 (1.47, 5.72)	0.001
albumin (per 10 g/L decrease)	2.46 (1.09, 5.51)	0.03

[a] Extended Cox model in which LVH, BP, hemoglobin, serum albumin, and creatinine clearance are treated as time-dependent variables.

mia may also precipitate CHF independently of their effects on LVH, as depicted. Hypoalbuminemia (which may be a marker of poor nutrition or chronic inflammation) and IHD have been shown to predict CHF and death (19) and likely contribute to attrition of cardiomyocytes, ventricular remodeling, CHF, and death.

The major strengths of the present work are its relatively large size (the largest study published on LVH in RTR), its long follow-up, and its comprehensive assessment of clinical outcomes. Several limitations deserve mention, however. Although most patients had an EKG in the first year, only 78% of survivors had follow-up EKG. Patients with and without follow-up EKG had similar baseline characteristics and overall survival; it is therefore unlikely that our results were strongly biased by the missing tracings. The Cornell EKG criterion for LVH has been well validated in the general population and has a test specificity similar to that of echocardiography. It has approximately one third the sensitivity of echo, however (30% *versus* 90%). Consequently, the prevalence of LVH in our study was approximately one third that reported in studies using echo definitions of LVH (8–18). The lower sensitivity of the Cornell EKG criteria for LVH is largely due to the poor sensitivity of EKG for mild hypertrophy; therefore, our findings pertain to individuals who would most likely have moderate to severe hypertrophy by echocardiography, and they may not apply to individuals with milder increases in LV mass. The Cornell voltage criterion was derived in nonrenal transplant patients; therefore, it may not represent the ideal threshold for diagnosis of LVH in RTR. None of these limitations, however, invalidate our finding that Cornell LVH, when present as defined in the study, was associated with a significant risk of death and CHF in RTR. We are unable to comment on the impact of angiotensin-converting enzyme inhibitors on cardiovascular outcomes because so few patients were on these agents in the cohort studied. Finally, as is true of any observational design, the causal inferences drawn from the data should be considered hypotheses and ideally should be proven in interventional (*i.e.*, experimental) studies.

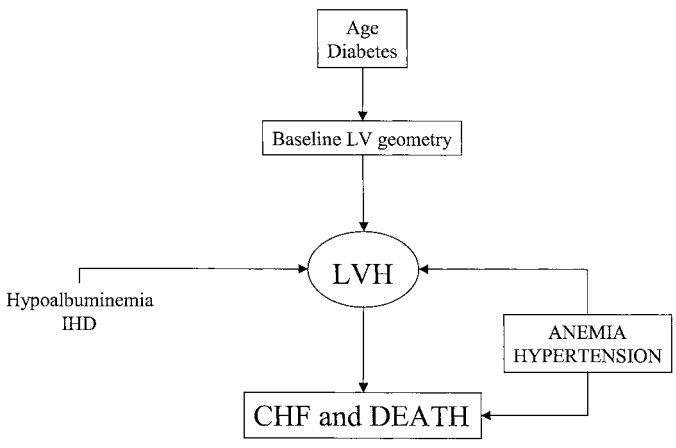

Figure 3. Pathogenesis of congestive heart failure (CHF) in renal transplant recipients (RTR): A causal hypothesis.

In conclusion, electrocardiographic LVH appears to be a predictor of death and CHF in RTR. Hypertension and anemia appear to be the major predictors of LV growth (as estimated by changes in Cornell voltage over time), a result consistent with the hypothesis that anemia and hypertension in RTR are causally linked to death and CHF in part via the development of LVH. Whether treatment of hypertension and anemia in RTR can abrogate LV growth, reduce morbidity from CHF, and increase survival merits further study in clinical trials.

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