

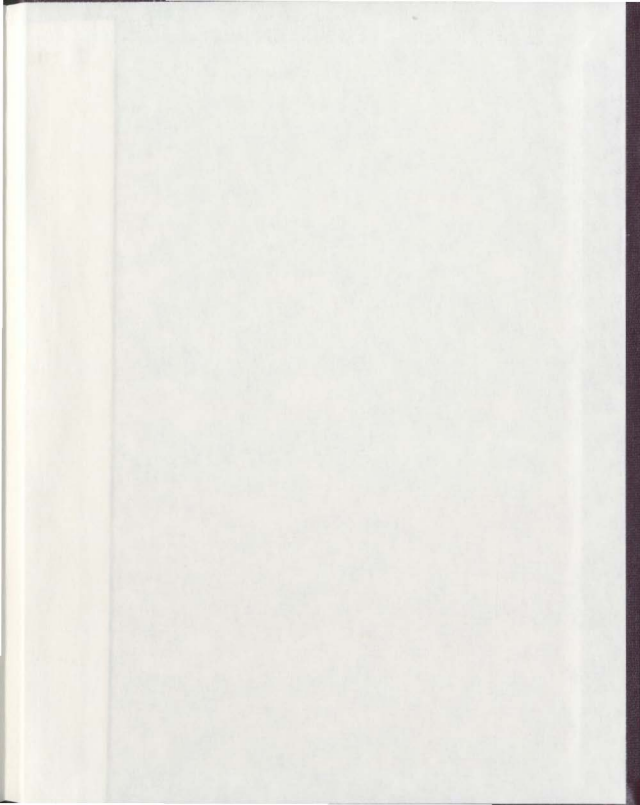
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CARDIAC DISEASE IN RENAL TRANSPLANT RECIPIENTS

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ABSTRACT

CARDIAC DISEASE IN RENAL TRANSPLANT RECIPIENTS

Cardiac disease (CVD) is a major cause of morbidity in renal transplant recipients (RTR). The relative importance of traditional vs. transplant-related risk factors, however, remains controversial, while the impact of LV disorders has not been well studied. We conducted two cohort studies to examine the incidence, determinants, and outcomes of LV disorders in RTR, and to compare the relative importance of traditional vs. transplant-related risk factors. In Study One (sequential echocardiograms in a prospective cohort of RTR), LV hypertrophy regressed over the first two post transplant years and thereafter remained stable. Older age and hypertension predicted failure to regress. In Study Two (a retrolective cohort study of 473 RTR), congestive heart failure (CHF) was as common and as adverse a morbid event as ischemic heart disease (IHD). Age, diabetes, gender, blood pressure and anemia were the dominant predictors of CHF, while age, diabetes, gender, blood pressure and cholesterol were the dominant risk factors for IHD. The determinants of de novo IHD in RTR were similar to those in general population, whereas the determinants of LV disorders are similar to those in chronic renal insufficiency. Transplant associated variables, with the exception of anemia, were not strongly associated with outcomes.

Key Words: Renal transplantation, left ventricular hypertrophy, cardiovascular disease, anemia, cohort study.

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CHAPTER 1
INTRODUCTION

In 1836, Richard Bright observed that patients with advanced uremia had high mortality rates and LV enlargement at autopsy [1]. In 1971, Clyde Shields, the first chronic hemodialysis patient, died of a myocardial infarction at age 50 [2]. While these two signal observations highlight the long and historical connection between uremia and cardiac disease, it is remarkable that during the 134 intervening years, almost no research was conducted on cardiac dysfunction in renal failure. In contrast, the subsequent three decades have added considerably to our understanding of the determinants of LV dysfunction and ischemic heart disease, albeit mostly in dialysis patients. In particular, the importance of LV dysfunction and CHF as major arbiters of prognosis and the role of uremia-specific factors, especially anemia, in the development of cardiac dysfunction in dialysis, are now well established. It is only in the past decade, however, that investigators have turned their attention to determinants of cardiac disease in non-dialysis renal populations.

Cardiovascular disease (CVD) is now recognized to be the major cause of death among renal transplant recipients (RTR). Between 17 and 50% of deaths on transplant are due to CV causes [3,4], and the incidence of CVD among RTR appears to be increased 3 to 4 fold over that observed in age-matched control populations [3]. This risk is potentially attributable to three risk factor categories: 1) Traditional cardiac risk factors (as identified by the Framingham Study) such as age, gender, diabetes, hypertension, hyperlipidemia, and smoking [5], many of which are adversely altered by renal transplantation 2) Risk factors related to the transplant state and its complications such as immunosuppression, cyclosporine vascular toxicity, graft rejection, and viral infections (e.g. cytomegalovirus), 3) Risk factors related to loss of graft function such as anemia, salt and water overload,

and hyperhomocysteinemia. Few studies have attempted to assess the impact and relative importance of these risk factors in the development of IHD using a cohort design and multivariate techniques[3,4,6-9] . Little is known about LV functional disorders in RTR, and no study has explored the outcomes of or risk factors for congestive heart failure (CHF) in RTR.

In order to address these shortcomings, we performed two studies that comprise the major components of the present thesis. The first component is an analysis of serially obtained echocardiograms in transplanted patients derived from a previous cohort. The main goals of this study were to describe the changes in LV mass occurring after the first post-transplant year and to determine risk factors predicting these changes.

The second component of this thesis is a retrospective cohort study of all RTR transplanted in Manitoba between 1969 and 1998. The primary goals of the study were to define, using multivariate techniques, the outcomes and risk factors for de novo CHF in RTR, and to explore the interrelationships between de novo CHF, de novo ischemic heart disease (IHD) and mortality in this patient population. A secondary objective was to assess the relative importance of the major risk factor categories mentioned above, and in particular to address the impact of renal function per se on the development of cardiac disease.

Finally, we explore the implications these studies have for two currently dominant paradigms of cardiac disease in renal disease: the notion of an "accelerated" atherosclerosis in uremia and the notion of a "toxic" uremic cardiomyopathy.

CHAPTER 2
REVIEW OF THE LITERATURE

2.1 Ischemic heart disease (IHD) vs. left ventricular (LV) disorders

Cardiac disease may be categorized into disorders of perfusion and disorders of cardiac geometry and function. From a theoretical perspective, they each represent adaptive (or maladaptive) responses of specific organ systems to specific physiological stressors, and can be thought of under the general rubric of "response to injury". Disorders of perfusion are primarily, but not exclusively, related to atherosclerotic disease of the coronary arteries, and thus the story of ischemic heart disease is in great part the story of atherogenesis and its determinants. Disorders of cardiac geometry (LVH, dilatation) and function, on the other hand, are aspects of a global vascular adaptation to hemodynamic stress. Although these disorders are closely interrelated, occur together frequently in the same patient and share several risk factors in common, they are nevertheless distinct pathophysiological entities.

2.2 LV disorders in RTR

2.2.1 Pathophysiology

Ventricular growth occurs in response to mechanical stresses, primarily volume or pressure overload [10] (Fig. 94-2). Volume overload results in addition of new sarcomeres in series, leading to increased cavity diameter [11]. A larger diameter results in increased wall tension, a direct consequence of Laplace's Law, which states that wall tension (T) is proportional to the product of intraventricular pressure (P) times the ventricular diameter (D): in symbols, $T=PD/4$. An increase in wall tension secondarily stimulates the addition of new sarcomeres in parallel. This remodeling thickens the ventricular wall, distributing the tension over a larger cross-sectional area of muscle and

returning the tension in each individual fiber back to normal, alleviating the stimulus to further hypertrophy. This combination of cavity enlargement and wall thickening is called eccentric hypertrophy. Pressure overload increases wall tension by increasing intraventricular pressure, resulting directly in the parallel addition of new sarcomeres and its functional consequences as described. Since sarcomeres are not added in series, isolated pressure overload does not lead to cavity enlargement, although dilatation may occur late in the evolution of the hypertensive heart. Muscular hypertrophy without cavity enlargement is called concentric hypertrophy.

Both eccentric and concentric hypertrophy are initially beneficial. Dilatation permits an increase in stroke volume without an increase in the inotropic state of the myocardium and as such is an efficient adaptation to volume overload [12]. It also permits the maintenance of a normal stroke volume and cardiac output in the presence of *decreased* contractility. Muscular hypertrophy returns the tension per muscle fiber back to normal, decreasing ventricular stress.

Ultimately, LVH becomes maladaptive. Muscular hypertrophy is associated with several progressive, deleterious changes in cell function and tissue architecture. Early in the evolution of LVH, slowed re-uptake of calcium by the sarcoplasmic reticulum (SR) leads to abnormal ventricular relaxation. Combined with decreased passive compliance of a thickened ventricular wall, these changes may precipitate diastolic dysfunction [13]. More advanced SR dysfunction is associated with calcium overload and cell death. Decreased capillary density, impaired coronary reserve and abnormal relaxation may decrease subendocardial perfusion, promoting ischemia [14]. Frequent coexistence of CAD may exacerbate ischemia and myocyte attrition [10]. Fibrosis of the cardiac

interstitium also occurs [15], and appears to be more marked in pressure than volume overload. Myocyte apoptosis, ischemia, neurohormonal activation (i.e. increased catecholamines, angiotensin II, aldosterone, among others) is thought to contribute [12,16,17]. In the late phases of chronic and sustained overload, oxidative stress is prominent and contributes to cellular dysfunction and demise [18]. Together, these various processes lead to progressive cellular attrition, fibrosis, congestive heart failure and, ultimately, death.

The renal transplant milieu may potentiate many of these processes. Hypertension is prevalent among RTR and is a major contributor to pressure overload [19-21]. Calcineurin inhibitors (Cyclosporine, FK506), allograft failure, acute rejection may all promote hypertension and thus LVH and CHF [19-22]. In failing allografts, anemia and sodium retention, may add flow (volume) overload to preexisting pressure overload. Mycophenolic acid and azathioprine are marrow suppressive, and may exacerbate anemia in the setting of progressive graft failure. Anemia promotes vascular remodeling, leading to muscular hypertrophy and dilatation of the left ventricle in chronic renal failure and dialysis patients [23]. This association may pertain in RTR as well. The primary stimuli for ventricular remodeling, pressure and flow, also promote concomitant arterial remodeling in the large and resistance arteries. This remodeling is characterized by diffuse arterial wall thickening and stiffening (arteriosclerosis), which can increase the effective pressure load on the left ventricle independently of mean arterial pressure [24,25].

The attrition of myocytes in RTR may be exacerbated by several factors. Underlying CAD promotes ischemia and infarction. The role of putative risk factors for

IHD in RTR is discussed in the next section. Immunological phenomena such as acute rejection episodes may contribute to oxidative stress, which may in turn promote cellular dysfunction and apoptosis[18]. Progressive loss of renal function from chronic allograft nephropathy may lead to malnutrition and hyperparathyroidism [10,26] . The former may contribute to cell apoptosis and the latter to myocyte dysfunction and cardiac fibrosis. Such cell death in the presence of LV hypertrophy and continuing pressure and volume overload leads ultimately to the clinical manifestations of congestive heart failure [27].

2.2.2 Epidemiology

Burden of disease

Disorders of LV geometry begin during chronic renal insufficiency, well before transplantation and indeed well before dialysis. In a cross-sectional study conducted by Greaves and coworkers, patients with chronic renal insufficiency (serum creatinine > 3.4 mg/dl) had mean LV mass index of 120 g/m², which was intermediate between that of gender and age matched controls (79g/m²) and dialysis patients (136 g/m²)[28]. An abnormal echocardiogram, primarily LVH, was observed in 63% of chronic renal insufficiency patients, versus 72% of dialysis patients, suggesting a relationship between LV morphology and worsening renal function. Levin et al have reported a prevalence of LVH of 26.7% in patients with creatinine clearance >50 ml/min, 30.8% in those with clearances of 25-49 ml/min, and 45.2% in those with clearances <25 ml/min [29]. In the prospective arm of this study, an association between rising LV mass index and falling GFR was observed. Another cross-sectional study has yielded comparable results [30].

The overall prevalence of LVH among patients beginning dialysis is 75% [31-34] . In a large prospective cohort study, only 16% had normal echocardiograms at inception. Fifteen percent (15%) had systolic dysfunction, 28% had dilatation with preserved contractility, and 41% had concentric LVH [27]. In a subset of dialysis patients who underwent yearly consecutive echocardiograms, LV mass index and LV cavity volume progressively increased, the biggest increase occurring between baseline and year [35].

By the time patients are transplanted, therefore, a significant proportion has echocardiographic abnormalities. In one longitudinal study, echocardiograms were performed just prior to transplantation and then one year post transplantation. Of the pre-transplant echocardiograms, 17% exhibited normal geometry, 41% showed concentric LVH, 32% LV dilatation, and 12% systolic dysfunction [36]. The proportion of patients with normal studies doubled (36%) and systolic function normalized in all patients with fractional shortening < 25% at one year post-transplantation [36]. Several other studies have confirmed improvement in LV function after renal transplantation. Neither the long-term evolution of LV changes, nor the development of clinical CHF, has been studied to date in RTR.

Potential risk factors for LV disorders

Age: Age is an established clinical marker of risk for LVH in the general, CRI and ESRD and RTR populations [29,37-39] .

Gender: The role of gender as a risk factor for LV disorders is less clear. In a registry based study of dialysis patients, women were found to be more likely to have radiographic cardiomegaly or a history of CHF and less likely to exhibit

electrocardiographic or echocardiographic evidence of LVH than men [40]. In contrast to this result, a large prospective cohort study of patients beginning dialysis in Canada found no relationship between gender and development of heart failure. Moreover, female gender was associated with concentric LVH, whereas male gender was predictive of LV dilatation and congestive heart failure [41]. These contrasting findings may relate to differences in sample size (5000 in the former vs. 432 in the latter), design (retrospective cohort vs. prospective cohort), and criteria for LV geometry. The role of age and gender in the evolution of LV disorders or CHF among RTR has not been examined. However, given the possible importance of gender in disease states in general, it must be considered as potential risk factor, if only for the purpose of risk adjustment.

Diabetes Mellitus: There is evidence for a specific diabetic cardiomyopathy in diabetic patients without ESRD [42, 43]. LVH is a more frequent finding in hypertensive diabetic patients than in hypertensive non-diabetic patients, as is cardiac fibrosis [43,44]. Diabetes has been identified as a predictor of hypertrophy in dialysis patients [26,28]. It is unknown whether diabetes is a risk factor for LV disorders or CHF in RTR.

Hypertension: The role of hypertension in the evolution of LVH or CHF remains controversial in all renal failure populations. Studies in dialysis patients have shown an inverse relationship between blood pressure and mortality, with hypertension predicting longer survival [45,46]. However, the high prevalence of cardiac disease at the start of ESRD therapy is a source of confounding even for well-executed prospective cohort studies. Since cardiac dysfunction can cause low blood pressure (so-called "reverse causality") and is independently associated with death, even prospective studies cannot exclude the possibility that low blood pressure is simply a surrogate marker for poor

pump function, unless patients with cardiac abnormalities at baseline are excluded from analysis. This is difficult to do in practice, since the majority (75-80%) of patients have echocardiographic abnormalities at the start of maintenance dialysis. In one prospective cohort study of 433 dialysis patients, high blood pressure was positively associated with the development of IHD and LVH but negatively associated with mortality (48% higher risk of LV hypertrophy for each 10 mmHg increment in blood pressure) [47]. In this same cohort, LVH was predictive of CHF, which in turn was associated both with mortality and with a drop in mean arterial pressure. Lower mean arterial pressure following an episode of CHF was independently associated with mortality. These observations suggest, but do not prove, the following causal sequence:

Hypertension → IHD and LVH → Pump failure → Hypotension and Death

In a large cohort of CRI patients, in whom prevalence of preexisting LVH was approximately 30%, hypertension was an independent risk factor for LV growth [23]. To date, no studies have examined the impact of hypertension on LV disorders or CHF in RTR.

Anemia: Anemia has been associated with LV dilatation and LV hypertrophy in chronic renal insufficiency and in dialysis patients (RR for LVH progression, per 10 g/L drop, is 1.74 in CRI and 1.48 in dialysis) [23,26,35,48-50]. Anemia is also a risk factor for the development of de novo cardiac failure and death in dialysis [50]. Partial correction of anemia is associated with regression of hypertrophy in cohort studies [51,52]. The impact of anemia on the heart of RTR has not to date been studied.

Ischemic Heart Disease: The risk factors and outcomes for IHD are discussed in the next section. Nevertheless, it is worth mentioning that coronary artery disease is an important

cause of systolic and diastolic dysfunction in the general population and in dialysis patients [26, 53], and likely continue to influence LV geometry and function in RTR.

Renal Function: Declining function of native kidneys has been associated with LV growth in CRI patients [23]. Once patients are on dialysis, LV growth tends to accelerate. Renal transplantation appears to favor normalization of systolic dysfunction and regression of concentric LV hypertrophy and LV dilatation, at least in individuals without clinically evident IHD [36]. Whether impaired allograft function independently affects the evolution of LV disorders or the onset of CHF is unknown.

Hypoalbuminemia: Several studies have shown that hypoalbuminemia is a predictor of CV disease in dialysis and among RTR. Hypoalbuminemia has been associated with LV dilatation and predisposes to de novo cardiac failure and ischemic heart disease among patients starting dialysis [54]. The mechanisms underlying this association are unknown. Hypoalbuminemia is associated with a hypercoagulable state and may therefore predispose to myocardial infarction and ischemic cardiomyopathy. Alternatively, it may be a marker for malnutrition, inadequate dialysis, vitamin deficiency, or a chronic inflammatory state, all of which could hypothetically accelerate myocyte death and the development of cardiomyopathy, as discussed earlier. The impact of hypoalbuminemia on CHF and LV disorders among RTR is not known.

Clinical outcome

The impact of LV disorders or CHF on morbidity and mortality has not been studied in RTR. In dialysis patients, both echocardiographic and clinical evidence of ventricular dysfunction predict adverse prognosis. The presence of concentric LVH, LV dilatation with normal contractility and systolic dysfunction at baseline has been associated with

progressively worse survival (Figure 94-4), independent of age, gender, diabetes and IHD [32]. All three abnormalities are also associated with increased risk for the development of congestive heart failure. In a Canadian cohort, the median survival of patients who had heart failure at or before initiation of ESRD therapy was 36 months, compared with 62 months in subjects without baseline CHF. The risk of developing pulmonary edema requiring hospitalization or ultrafiltration after starting maintenance hemodialysis was 10% annually [41,55]. CHF was found to be a stronger predictor of death than IHD.

Based on the data above, we expect that CHF will be a prognostically significant morbid event in RTR, although the frequency with which it occurs may be lower than in dialysis.

2.3 IHD in RTR

2.3.1 Pathophysiology

In non-renal failure populations, the initiating event of atherosclerosis appears to be endothelial injury caused by mechanical stress (e.g. hypertension) or endothelial toxins (nicotine, oxidative stress, hyperlipidemia, inflammation). This stress alters endothelial phenotype to a more permeable, activated state [56]. Endothelial denudation or, more commonly, alterations in endothelial cell surface receptor expression, permit access of lipoproteins and macrophages into the subintimal space [56,57]. Oxidative modification of lipoproteins, particularly LDL (ox-LDL), is chemotactic for macrophages and facilitates uptake of oxidized lipids by macrophage FC receptors, resulting in formation of foam cells [58]. Ox-LDL stimulates elaboration of growth factors that are mitogenic for smooth muscle and promote fibrosis [59]. These processes result in the accumulation of oxidatively modified lipids and inflammatory cells at the center of a fibrous “cap” of

variable thickness. This cap may rupture, causing thrombosis that may be minimally symptomatic or associated with acute coronary syndromes (e.g. unstable angina, myocardial infarction).

Several factors characteristic of the renal transplant state may modify the process of atherogenesis. Many traditional risk factors such as hyperlipidemia, hypertension, and diabetes are more prevalent or else are more severe in renal transplant patients [19-21]. These factors probably continue to influence atherosclerosis and vascular remodeling in RTR. Immunosuppressive agents like cyclosporine, prednisone, and tacrolimus may exacerbate hypertension, hyperlipidemia, and diabetes [22,60-63] . Cyclosporine may in addition promote oxidation of LDL and may directly activate endothelium and platelets [64-66] . Acute rejections are associated with up-regulation of inflammatory cytokines that may activate endothelium, thus directly influencing vascular disease, or may have indirect effects mediated by hypertension or resultant chronic graft failure. Chronic graft failure in turn may be associated with oxidative stress, chronic inflammation, anemia, and LVH, all of which may directly or indirectly influence atherogenesis [18,23,67,68] .

2.3.2 Epidemiology

Burden of disease

Among renal transplant recipients (RTR), the overall prevalence of CAD is approximately 15% [3] .The annual incidence of MI, revascularization, or death from MI among RTR is 1.5% [6]. These estimates are similar to those reported for chronic renal

insufficiency (CRI) (1-3% per year incidence) [69-71], and lower than in dialysis (10%/year) [55]. Cardiovascular causes account for 17-50% of deaths among RTR [3,4]

Potential risk factors

Age: Advancing age is associated with an increased risk of IHD in the general population [72,73]. Older age has been independently associated with arteriographic CAD [74], de novo occurrence of angina pectoris, myocardial infarction, or coronary revascularization in dialysis patients [45] (relative risk (RR) 1.6 per decade), and increased risk of death among dialysis patients [75]. Among RTR, age appears to be an independent risk factor for MI or coronary revascularization or death from MI (RR 1.5 per decade) [6], and for all cause death (RR 1.5 per decade) [76].

Diabetes Mellitus: Diabetes is independently associated with a relative risk of 1.5-2.2 for the development of CAD in the general population [77-81]. The link with IHD events in the CRI population has not been explicitly studied but is probably intermediate between the general population and dialysis patients. Among dialysis patients, diabetes is independently associated with the development of de novo IHD and death (adjusted RR 3.98 and 3.86, respectively) [45,76]. Among RTR, diabetes is strongly associated with multiple cardiovascular outcomes (RR of 2.09 for MI, revascularization, or death from MI; RR 2.98 for ischemic stroke, and RR of 25.7 for development of peripheral vascular disease) [6].

Hypertension: Hypertension is a long established risk factor for IHD in the general population [82,83]. Pharmacological therapy of hypertension reduces the risk of MI by 14-16% for each 6 mmHg reduction in diastolic BP [84,85].

The role of hypertension in the evolution of IHD in renal patients remains controversial. Studies in dialysis patients have shown an inverse relationship between blood pressure and mortality, likely as a result of reverse causality as previously discussed. No studies to date have assessed the role of hypertension in the evolution of IHD in CRI.

The prevalence of hypertension among transplant recipients is 70% to 80% [6]. Elevated blood pressure has been associated with shortened graft and patient survival, as well as higher rates of coronary artery disease [86,87]. However, retrospective analysis of large transplant cohorts have not found an association between hypertension and mortality after adjustment for age, diabetes, tobacco use, and time on dialysis prior to transplantation [6,88]. Further study is needed of the hypertension/IHD link in RTR populations.

Smoking: Smoking is a powerful risk factor for IHD in the general population, approximately doubling the risk of CV events in the Framingham cohort [89]. Smoking cessation can reduce the risk of IHD by 50% even in longtime heavy smokers [90].

In dialysis, approximately 30-40% of patients starting dialysis are smokers [45,55], and smoking has been associated with an excess mortality of 26% in incident hemodialysis patients, even after extensive covariate adjustment [87].

Among RTR, 25 to 40% smoke at the time of transplant assessment. Most continue to smoke after transplantation [20,91,92]. A smoking exposure of 10 to 25 pack-years has been independently associated with ischemic stroke (RR 1.2 to 1.6), peripheral vascular disease (RR 1.2-1.6), and mortality (RR 1.4-2.0) [6,92,93]. A specific association with IHD has not yet been documented.

Dyslipidemia: Elevated total cholesterol (TC), low density lipoprotein (LDL-C), lipoprotein(a) (Lp(a)), triglycerides (TG) and low high density lipoprotein (HDL-C) are associated with IHD in the general population, and the efficacy of targeted LDL-C lowering with HMG-CoA reductase inhibitors has been established in clinical trials [93-98] . An atherogenic lipid profile is highly prevalent in patients with renal disease (Table 94-1) [99], particularly in patients with nephrotic syndrome (NS).

With respect to clinical outcomes, there are yet no data linking hypercholesterolemia to cardiovascular disease in CRI.

Among dialysis patients, the data are conflicting. The highest mortality risk appears to be associated with low, not high cholesterol [100]. However, low TC is strongly correlated with poor nutritional status and low albumin levels, both of which are associated with increased mortality risk. It is therefore unclear whether low TC is causally related to death, or is a marker for malnutrition, hypoalbuminemia, or other yet unknown factors associated with death. Although definitive data are lacking, it is biologically plausible that high TC and LDL-C be risk factors in adequately nourished dialysis patients, as they are in the general population.

In RTR, hypercholesterolemia [3,101] and low HDL [6] have both been linked to ischemic events.

Other risk factors: Homocysteine is a naturally occurring byproduct of methionine metabolism, a sulfhydryl-containing essential amino acid. Several large observational studies have shown that elevation in plasma homocysteine is independently associated with cardiovascular disease in the general population [102-104] . Limited prospective data in RTR , CRI and dialysis suggest that Hcy may be an independent risk factor in

these populations as well [105-108] . Chronic endothelial activation or injury, activation of prothrombotic factors, oxidative stress, and chronic inflammation may all contribute to CV risk [18,109-113] . Viral infections, particularly CMV, have been associated with IHD in the general population and may be relevant to the renal transplant population as well [114-115].

Clinical outcome

Registry and retrospective cohort data show that presence of IHD in patients starting dialysis is associated with excess short and long-term mortality [87,116]. In a Canadian prospective cohort study, patients with clinical IHD at the start of dialysis were more likely to have an admission for CHF (RR 1.7) or to die (RR 1.5) than patients free of IHD at baseline, after adjustment for age and diabetes [45]. In these patients, most of the excess mortality associated with IHD seemed to be via the development of congestive heart failure. In diabetic RTR, presence of IHD at baseline is associated with a fourfold risk of future events and death [117]. IHD is likely to exert a powerful influence on survival in non-diabetic RTR as well.

2.4 Multivariate studies of cardiac disease in RTR

The retrolective or prolective cohort studies involving more than 100 patients and employing multivariate techniques in the analysis of cardiovascular risk factors are summarized in Table 2.1 [4,6-9]. Outcomes and risk factors were measured or defined differently, precluding a formal meta-analysis. Some studies have corroborated the importance of selected Framingham risk factors, others the importance of transplant risk factors. Importantly, no studies found blood pressure to be predictive of cardiovascular

events on multivariate modeling. None of the studies examined the role of anemia in CV disease. No study to date has examined the occurrence and impact of CHF in RTR. Few studies have comprehensively examined all relevant potential risk factors simultaneously. Since most risk factors are correlated to some degree with each other (e.g. age and renal function, hypertension and cyclosporine use), simultaneous modeling of all putative risk factors is crucial in assessing which risk factors dominate. Only one study has separately examined de novo cardiac events occurring after the first post transplant year [7]. Since prevalent CV disease at baseline is predictive of recurrent CV disease and since early events in the first post transplant year may relate more to pre-transplant risk exposure, analysis of events in the first year could obscure the effect of transplant related variables. An analysis of de novo cardiac events after 1 year, coupled with comprehensive risk factor assessment and simultaneous, multivariate modeling of these risk factors could shed light on the relative importance of transplant and traditional risk factors in the development of IHD in RTR.

2.5 Interrelationships between risk factors in RTR

Figure 2.1 summarizes some of the possible causal relationships between risk factors and cardiovascular outcomes in RTR. Most pathways are heavily intertwined, making it difficult to discern which pathway(s) dominate based on pathophysiological arguments alone. We have suggested in this figure that alterations in traditional Framingham risk factors are the most important but this is not clearly established. Epidemiological studies might clarify this issue by determining the strongest predictors of clinical events.

Table 2.1: Cohort studies of cardiovascular risk in RTR

Study	Reference	Design	Inception Cohort?	N	Post Tx Risk factors?	De novo events only?	Major Endpoint(s)	Incidence (/100 p-y)	Multivariate Risk Factors
Kasiske	6	Retrolective	Yes	706	Yes	No	IHD CVA PVD	1.53 1.00 1.00	Age, DM, gender, splenectomy, rejection, lipids DM, smoking, rejection, albumin DM, smoking, gender, albumin
Kasiske	7	Retrolective	Yes	1124	Yes	Yes	IHD	Not stated	Age, DM, rejection, albumin, proteinuria, lipids
Lindholm	4	Prolective	Yes	1347	Yes	Not applicable	IHD mortality	Not stated	Age, DM, gender, rejection, DGF, pre-transplant transfusion
Aker	8	Retrolective	Yes	427	No	Yes	All CV events	4.9	DM, age, BMI, Smoking, lipids, urate
Ducloux	9	Prolective	No	207	Yes	No	All CV events	8.8	Hcy, age, renal function, gender

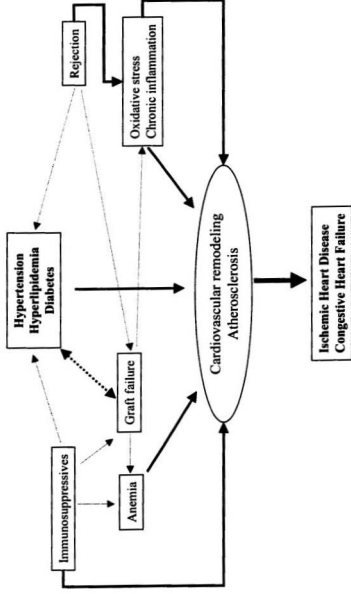


Figure 2.1 : Risk factors for cardiovascular disease in renal transplant patients: possible causal relationships

STATEMENT OF CO-AUTHORSHIP

CHAPTER 3: LONG-TERM CHANGES IN LEFT VENTRICULAR HYPERTROPHY FOLLOWING RENAL TRANSPLANTATION

Dr. Rigatto helped design the study, analyzed the data, and wrote the manuscript. Since the data were derived from a previously assembled cohort, Dr Rigatto did not participate in the assembly of the cohort or in the collection of the data.

CHAPTER 4: RISK FACTORS FOR AND OUTCOME OF DE NOVO CONGESTIVE HEART FAILURE AND ISCHEMIC HEART DISEASE IN RENAL TRANSPLANT RECIPIENTS: A RETROLECTIVE COHORT STUDY

Dr. Rigatto helped conceive the research idea and design the study. He also assembled the retrolective cohort, trained research nurses and students to collect the data, analyzed the data, and wrote the manuscript.

The generosity, advice, and intellectual guidance of Dr Rob Foley and Dr Pat Parfrey are warmly and gratefully acknowledged.

CHAPTER 3

LONG-TERM CHANGES IN LEFT VENTRICULAR HYPERTROPHY FOLLOWING RENAL TRANSPLANTATION

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3.1 Introduction

In pre-dialysis and dialysis patients, abnormalities of left ventricular geometry and function are common, progressive and closely associated with cardiac failure and death [29,32,35,118]. Partial regression of LV hypertrophy (LVH) is known to occur in the first year following transplantation [36]. The evolution of cardiac structural changes beyond the first post-transplant year, however, is unknown. The objectives of the current study were to describe the long-term evolution of LVH following renal transplantation and to determine risk factors for its progression.

3.2 Methods

Patients: A prospective inception cohort of 433 dialysis patients was assembled at three Eastern Canadian centers from 1982 to 1991. The selection criteria and definitions used for this cohort have been reported in detail elsewhere [32,118]. One hundred and forty-three (143) patients received renal allografts and comprise the study population. These patients continued to be followed according to the study protocol until study termination, death or loss to follow-up.

Data collection: Echocardiograms were scheduled at yearly intervals. Left ventricular mass was calculated according to the Penn convention [119] while left ventricular cavity volume index was calculated using the formula of Pombo et al [120]. Systolic and diastolic blood pressure, hemoglobin, serum creatinine, albumin, calcium, and phosphate were determined monthly. Serum total cholesterol was determined yearly.

Data analysis: Changes in LVMI and cavity volume index between echocardiograms performed at years 1, 2, 3 and 4 post-transplantation were compared using individual

paired T-tests, with Bonferroni correction for multiple comparisons. To explore the determinants of changes in LVMI between the first and second years, we used multiple linear regression to model the change in LVMI as a function of several predictor variables (Table 3.1) in patients who had echocardiograms done in both years. LV structure at year 1 was classified according to a previously defined classification system [32,118]. Hypertension was defined as blood pressure greater than 140/90 mmHg, as in previous publications from this cohort [32,35,118]. Longstanding hypertension was defined as blood pressure greater than 140/90 mmHg for greater than 10 years. McHenry's Selection Algorithm was used to identify the subset of variables having the strongest association with change in LVMI (NCSS software, version 2000).

3.3 Results

Baseline characteristics of the patients: Table 3.2 summarizes the baseline characteristics of the transplanted individuals. Transplanted patients were young and had little cardiovascular morbidity at the start of end-stage renal therapy. The median duration of dialysis prior to transplantation was 11 (7,21) months [median (25th, 75th percentile)] in the transplant group. Median follow-up for the transplanted cohort was 38 (17,58) months

Echocardiograms: Of the 143 transplanted patients, 113 had one interpretable post-transplant echo, 70 had a second echo, 40 patients a third, and 18 a fourth. An echo was deemed uninterpretable if essential measurements were missing, preventing calculation of LVMI or LVCVI. A patient was deemed lost to follow-up if he or she survived for at least one year after the previous echo without having a subsequent echo. Thirty-five

patients (25%) were either lost to follow-up or had uninterpretable echocardiograms. The remaining patients reached a censoring endpoint (death, graft failure, or study

Table 3.1: Variables tested in the multiple regression analysis of predictors of change in LV mass index from year 1 to year 2 in renal transplant patients.

Variable
Age at transplantation
Diabetes
Smoking
Congestive heart failure at baseline
Ischemic heart disease at baseline
Duration of hypertension > 140/90:
>10 years
≤10 years
Blood pressure
Systolic
Diastolic
Pulse pressure
Number of antihypertensives required:
< 2
≥ 2
Type of antihypertensive:
ACEI
Beta blocker
Calcium channel blocker
Other
Cyclosporine use
Hemoglobin
Creatinine
Albumin
Calcium
Phosphate
Cholesterol
Left ventricular morphology
Eccentric hypertrophy
Concentric hypertrophy
Normal ventricle

TABLE 3.2: Baseline characteristics of the transplanted patients

	Transplant Recipients (n = 143)
Age (years)	37 (35,39)
Female	31%
Diabetic	20%
Ischemic heart disease ^a	4.9%
Heart failure	15%
Hypertension > 10 years ^b	26%
Smokers	35%
Duration of dialysis prior to transplantation	11 (1,21)

Continuous variables are expressed as mean (95% CI), dichotomous variables as percentages. a. Ischemic heart disease was defined as a history of myocardial infarction, coronary revascularization, or angina. b. Hypertension was defined as blood pressure > 140/90 mm/Hg

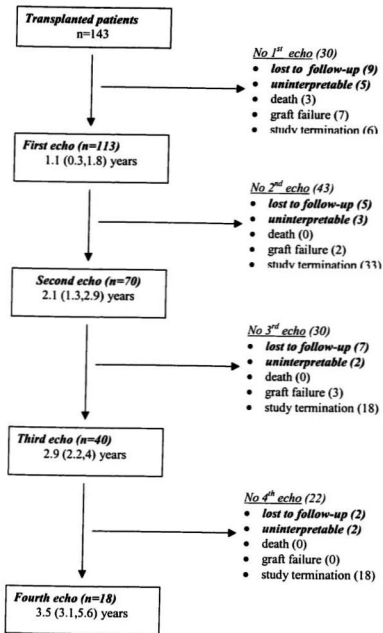


Figure 3.1: Fate of patients in the transplanted cohort

termination) before a subsequent echo was scheduled (i.e. within a year of the previous echo). The median times to echo and reasons for not having a subsequent echocardiogram are summarized in Figure 3.1.

Changes in LV mass and volume: In the 70 patients with two echocardiograms, LV mass index decreased from 161 (95% CI 145,177) g/m² at one year to 146 (134,159) g/m² at 2 years following transplantation (Bonferroni corrected $p=0.009$, Figure 3.2a). There were no further clinically important or statistically significant changes in LV mass index in years 3 ($n=40$) and 4 ($n=18$) (Figure 3.2b-c). LV cavity volume index decreased from 81 (72, 91) mL/m² at 1 year to 75 (68, 82) mL/m² at 2 years (paired t-test, $n=70$, Bonferroni corrected $p=0.05$). No further changes were seen in years 3 and 4 (Figure 3.3a-c).

Predicting changes in LV mass index: Using change in LVMI as the outcome variable, the impact of several potential predictor variables (Table 3.1) was assessed using multiple linear regression. Three of 70 patients had missing baseline data and were not included, leaving 67 patients available for analysis. The resultant model suggested that older age, duration of hypertension, number of antihypertensive medications required, low pulse pressure and LV morphology at baseline were independently and significantly associated with failure of regression of LVMI from year 1 to year 2 ($p<0.000003$, $R^2=0.44$).

Because the impact of pulse pressure seemed counterintuitive (low, as opposed to high, pulse-pressure was associated with a failure to regress), we tested for an interaction between ventricular morphology and pulse pressure. This interaction was highly significant ($p=0.007$). The model incorporating the interaction was highly successful

Figure 3.2a: Change in LV mass from 1st to 2nd echo (n=70)

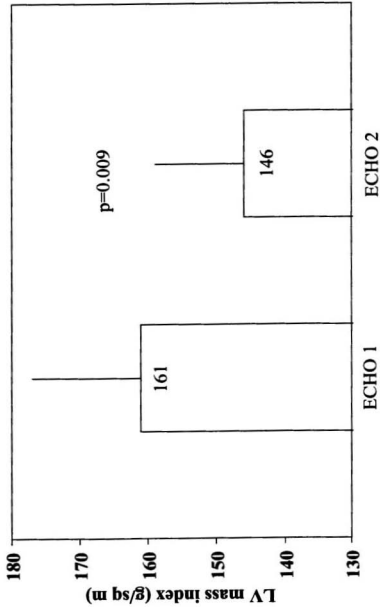


Figure 3.2b: Change in LV mass index from 2nd to 3rd echo (n=40)

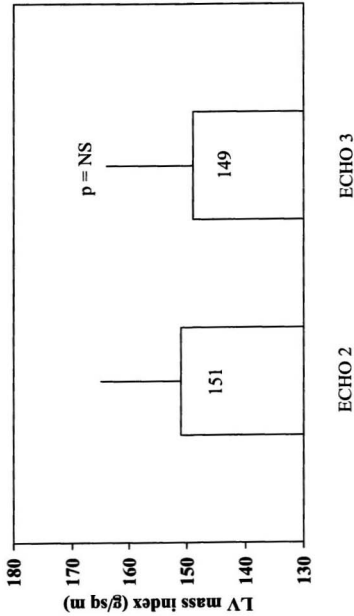


Figure 3.2c: Change in LV mass from 3rd to 4th echo (n=18)

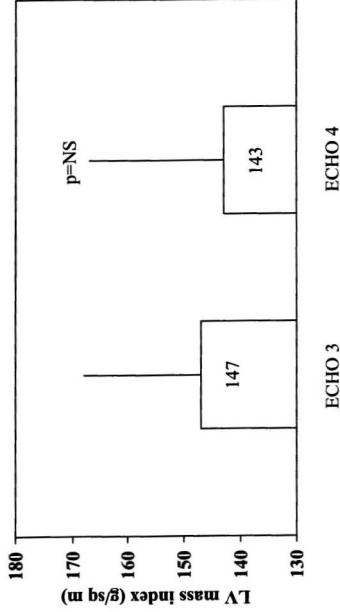


Figure 3.3a: change in LV cavity volume from 1st to 2nd echo (n=70)

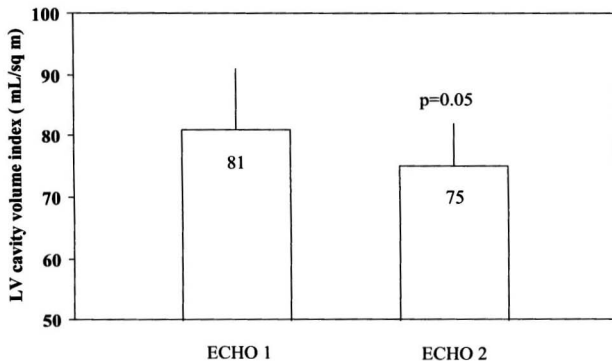


Figure 3.3b: Change in LV cavity volume from 2nd to 3rd echo (n=40)

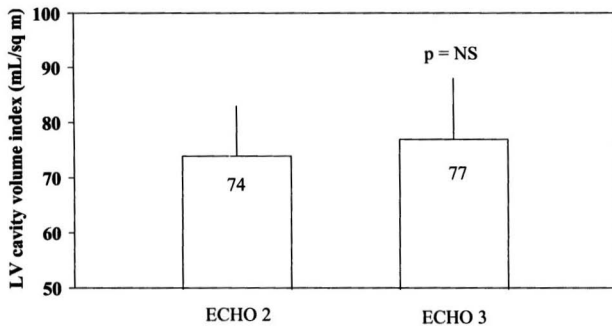
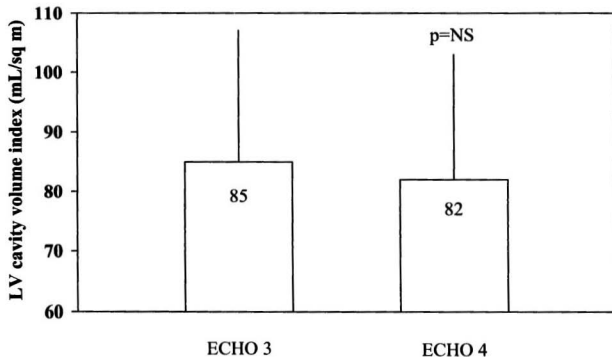


Figure 3.3c: change in LV cavity volume from 3rd to 4th echo (n=18)



($p < 0.000001$, $R^2 = 0.52$) (Table 3.3), accounting for 52% of the total variation in the change in LVMI.

Table 3.4 illustrates the interaction between ventricular morphology, duration of hypertension, and pulse pressure. In patients with normal hearts at year 1, the model predicts very little change in LVMI in those with short duration of hypertension, while patients with longstanding hypertension experience on average quite a dramatic increase in LVMI. Increasing pulse pressure is associated with increasing mass over the interval studied, and seems to identify ventricles at increased risk for progression. At the other morphological extreme, in patients with eccentric LVH, the absence of longstanding hypertension defines a subset of ventricles capable of regression. Dilated hearts in patients with longstanding hypertension do not regress, on average. The relationship between pulse pressure and change in LVMI is reversed compared with the situation in normal hearts: high pulse pressure is a marker for greater regression. Patients with concentric LVH showed behavior intermediate between these poles. A biological interpretation of these findings follows in the discussion.

Time-averaged hemoglobin and serum creatinine, albumin, calcium, and phosphate were not predictive of regression in either univariate or multivariate analyses. Similarly, duration of dialysis prior to transplantation, history of clinical congestive heart failure or ischemic heart disease, cyclosporine therapy, and class of antihypertensive agent (angiotensin converting enzyme inhibitors, calcium channel blockers, beta-blockers, diuretics and other) were not significant predictors of changes in LVMI. Because previous studies in the general population have shown that different classes of antihypertensive agent have differing effects on regression LVH, we attempted to force

Table 3.3: Predictors of change in LVMI in renal transplant recipients who had an echocardiogram in both the first and second years post transplantation (N=67), as identified by multiple linear regression analysis.

Predictor	Coefficient	P-value
Overall model	-----	< 0.000001
Age	+0.97 g/m ² per year	
Duration of hypertension	+35 g/m ² for duration >10 years	0.008
Number of medications	+24 g/m ² for > 1 antihypertensive	0.009
Pulse pressure		----- ^a
LV morphology		----- ^a
Normal ventricle		
Concentric hypertrophy	-----	
	+14 g/m ² if present	
Eccentric hypertrophy	+100 g/m ² if present	0.007
PP × LV morphology	-1.13 g/m ² per mmHg if present	
PP × concentric		
LVH	-3.2 g/m ² per mmHg if present	
PP × eccentric		
LVH		

^a Individual p-values for variables are not meaningful in the context of a significant interaction between them

Table 3.4: Predicted change in LV mass between first and second echo as a function of LV morphology, duration of hypertension, and pulse pressure.

Left Ventricular Morphology	Duration of Hypertension	Pulse Pressure*		
		39 mmHg	44 mmHg	53 mmHg
Normal (n=18)	≤10 years	+5 g/m ²	+10 g/m ²	+10 g/m ²
	>10 years	+40 g/m ²	+45 g/m ²	+54 g/m ²
Concentric hypertrophy (n=21)	≤10 years	-25 g/m ²	-25 g/m ²	-26 g/m ²
	>10 years	+9 g/m ²	+9 g/m ²	+9 g/m ²
Eccentric hypertrophy (n=28)	≤10 years	-20 g/m ²	-30 g/m ²	-48 g/m ²
	>10 years	+15 g/m ²	+4 g/m ²	-12 g/m ²

*Pulse pressure= mean systolic blood pressure-mean diastolic blood pressure in the inter-echo interval.

the inclusion of antihypertensive class in the equation. This did not improve model fit ($p>0.8$) and so was deleted from the model [121-123].

3.4 Discussion

Changes in LV structure: The primary aim of this study was to describe the long-term impact of renal transplantation on cardiac hypertrophy in a large, prospectively followed group of transplant patients. Several investigators have analyzed pre- and post-transplantation changes in echocardiographic parameters [36,124-131] but with the exception of one study [36], these reports have involved small numbers of patients, limiting the power and generalizability of the results. In a previous publication from this cohort [36], Parfrey et al. demonstrated that significant improvements in concentric LV hypertrophy and LV dilatation occur following renal transplantation, observations consistent with those made by other investigators [124-131]. The key finding in the present study is that regression of LVH continues beyond the first post-transplant year, reaches a nadir at approximately two years and appears to stabilize in the third and fourth years after transplantation. To our knowledge, this constitutes the first description to date of changes in cardiac hypertrophy occurring in the later phases of renal transplantation.

Several limitations to these observations bear discussion. Although our sample size was initially large, there were significant losses to follow-up over time, as one would expect. As a consequence, the precision of the estimates of change in LVMI is less for the later than the earlier echocardiograms. Because echocardiography was scheduled regularly in all patients, it is unlikely that the losses to follow-up resulted from ascertainment bias. However, it could be argued that since LVH is a risk factor for morbidity and death, patients with severe LVH might have been lost preferentially

because of early death or graft failure, biasing the results towards a decline in mean LV mass index. Several observations suggest that this did not happen, however. First, death caused no losses to follow-up after the year-1 echocardiogram. Graft failure resulted in the loss of only 2/113 patients (1.8%) between the first and second year, 3 / 70 (4%) patients from year 2 to 3, and no patients between year 3 and 4. These small percentages are unlikely to substantially bias the results. Most of patient losses (75/95= 80%) were due to censoring at study termination. This high rate of censoring occurred because although median follow-up for the cohort was 4 years from initiation of dialysis, transplantation occurred after a median wait of one year. Theoretically 50% of the original cohort should have been censored by 3 years from transplantation. We observed 53/113 study-end censored events between the first and last echo, or 47%, very close to the expected value. Finally, the pattern of regression over time was similar in patients with two, three and four echocardiograms, suggesting that the observed changes were independent of follow-up losses.

Identification of risk factors for progression/regression: Despite the overall tendency to regress, not all patients in this study regressed to the same degree, and some progressed. Moreover, in 39% of patients LV mass index failed to normalize even at four years [38]. Since LVH is known to confer an adverse prognosis¹²[32,47,132], we attempted to identify risk factors for progression using multiple linear regression. We developed a highly significant predictive model for changes in LVMI between the first and second post transplant year. Age, LV morphology and three independent markers of “pressure overload” (duration of prior hypertension, number of antihypertensives required, and time averaged pulse pressure) were found to be important. Moreover, the interaction between

LV morphology and pulse pressure helped unravel some of the contradictions that emerged regarding the role of blood pressure as an adverse cardiac predictor.

The direction and strength of the association between a putative risk factor and an outcome can only be properly estimated when the risk factor is measured before the occurrence of the outcome. This requirement is of even greater importance whenever the outcome can modify the risk factor, a phenomenon called “reverse causality”. Since poor ventricular function can cause low blood pressure, the inclusion of patients with significant heart disease, even in a prospective study, may confound the true relationship between blood pressure, LV morphology and mortality. In large, population based studies such as the Framingham Cohort [83,132], in which the inception cohort is mostly free of disease, confounding by reverse causality is less important. In most renal cohorts, however, heart disease is often prevalent at the time hypertensive risk is assessed. Levin et al. have shown that 27% of patients with mild renal insufficiency (CCr 50-75mL/min) already have LVH by echocardiogram, and that this proportion grows to 45% among patients with severe CRI (CCr < 25 mL/min) [23]. In the present cohort, 80% of patients had some form of LVH at the start of dialysis [32]. In this setting, confounding by reverse causality is not only possible, it is likely.

One of the strongest predictors of non-regression in the present study was the presence of longstanding hypertension. This relationship held true independent of the relatively complex interaction between pulse pressure and LV morphology. The need for multiple antihypertensive medications, a crude indication of severity of hypertension, was also independently associated with increasing LVMI. These observations are consistent

with the hypothesis that hypertension is an adverse cardiovascular risk factor in renal transplant patients.

Although the individual values of systolic and diastolic BP were not independently associated with change in LVMI, the difference between the two, the pulse pressure, was. However, the pulse pressure data must be interpreted in light of the LV morphology, since there was a highly significant interaction between the two. In patients with normal hearts, increasing pulse pressure was associated with increases in LVMI. This is compatible with the belief that pulse pressure in patients with normal hearts may be a reflection of systemic arterial compliance, which in turn may be causally related to increasing LV mass [24].

In contrast, in patients with dilated ventricles, high pulse pressure was associated with regression of hypertrophy. It is possible that in these patients, pulse pressure may be a marker for a reversible cause of eccentric hypertrophy, such as volume overload from fluid, anemia, or a patent arteriovenous fistula, abnormalities which may subsequently resolve. Data on fistula patency at time of transplantation was not available. Detailed information was available for anemia, which did not seem to predict pulse pressure very well and could not successfully be substituted for it in the model. The exact meaning of pulse pressure in this setting remains unresolved. In any case, pulse pressure seems to be a reflection of underlying hemodynamic relationships rather than a causal factor for LV mass regression. This observation reinforces the point that blood pressure measurement at or near the time of outcome assessment may lead to associations confounded by reverse causality.

The impact of ventricular morphology by itself deserves further scrutiny.

Normal-size hearts are small and compact by definition, and can only grow larger or remain the same size. They cannot grow very much smaller. It is not surprising, therefore, that normal hearts in this study were either observed to grow, or to stay the same size. In contrast, hypertrophied hearts are by definition large and heavy. Growth is possible if the hypertrophy is mild, but not if severe and at the upper limit of the physiologically possible. Regression is theoretically always possible. Thus, hypertrophied hearts were observed, on average, to regress. It is likely that the phenomenon of "regression to the mean" contributed to these observations. It would be hazardous to infer that increasing LVH "promotes" regression. However, it seems reasonable to say that hypertrophy does not appear to preclude regression. None of these considerations invalidates the primary rationale for including ventricular morphology as a covariate, which was to see whether the impact of other variables might differ according to baseline LV morphology.

No relationship between type of antihypertensive agent (particularly ACE inhibitors) and change in LVMI was seen in this study, in contrast to observations in the general population [121-123]. Although this may reflect a true difference between renal transplant patients and the general population, the possibility of a Type 2 error (failure to reject the null hypothesis) must be considered. Our results should not be interpreted as definitive evidence against the existence of class specific effects of antihypertensives on regression of LVH in renal transplant recipients. Further study is required to answer this question.

Limitations of the Analysis: Multiple linear regression is powerful and sensitive, but not infallible. Our sample size was sufficient to generate a model with up to 12 explanatory

variables. It remains possible, therefore, that a larger sample might have uncovered additional associations between the excluded variables and changes in LVMI. This possibility may be particularly relevant in the case of type of antihypertensive agent class, as discussed above.

In any multivariate analysis, the relationships uncovered are not necessarily causal. Causal inferences must be made in light of biological plausibility, which introduces a subjective component to the analysis. Furthermore, our explanatory analysis was partly data-led, and may be less reliable than a purely hypothesis led analysis. The observations made in this portion of the analysis, therefore, should be interpreted as hypotheses generated by the data rather than proven by the data. Despite these limitations, the significance and explanatory power of the model developed are considerable.

3.5 Conclusion

Regression of LVH seems to continue beyond the first year after renal transplantation, reaching a nadir at two years and persisting into the third and fourth post-transplant years. Failure to regress was associated with older age, longstanding hypertension, need for more than one antihypertensive agent, high pulse pressure in patients with normal hearts and low pulse pressure in patients with dilated ventricles.

CHAPTER 4

**RISK FACTORS FOR AND OUTCOME OF DE NOVO CONGESTIVE HEART
FAILURE AND ISCHEMIC HEART DISEASE IN RENAL TRANSPLANT
RECIPIENTS: A RETROLECTIVE COHORT STUDY**

4.1 Introduction

The incidence of cardiovascular disease (CVD) among renal transplant recipients (RTR) is 3 to 4 fold greater than that observed in age-matched control populations, making it the major cause of death among RTR [3,4]. This apparent surplus risk is potentially attributable to three risk factor categories: 1) Traditional cardiac risk factors (as identified by the Framingham Study) such as age, gender, diabetes, hypertension, hyperlipidemia, and smoking [5], many of which may be adversely altered by renal transplantation 2) Risk factors related to the transplant state and its complications such as immunosuppression, cyclosporine vascular toxicity, graft rejection, and viral infections (e.g. cytomegalovirus), 3) Risk factors related to loss of graft function such as anemia, salt and water overload, and hyperhomocysteinemia. The manifestations of cardiac disease in RTR include both IHD (e.g. MI, angina pectoris) and LV functional disorders (CHF). Both CHF and IHD are important adverse prognostic markers in the general population. In dialysis patients, CHF is a more important predictor of mortality than IHD [32].

An examination of cardiac disease in RTR should ideally explore the risk factor categories listed above in relation to both CHF and IHD. Although CHF is likely a significant morbid complication in RTR as it is in dialysis, no studies to date have explored the risk factors for and outcomes of CHF in the renal transplant setting. Furthermore, while several studies have examined IHD in RTR, few studies have employed multivariate techniques to compare different risk categories, and only one study has examined exclusively de novo events in order to limit the confounding influence of pre-transplant cardiac disease [4,6-9]. No study has examined the relative

prognostic impact of CHF vs. IHD. We therefore conducted a retrolective cohort study in a single Canadian center in order to 1) describe the risk factors for and interrelationships between de novo CHF, de novo IHD, and mortality, and 2) assess the relative importance of different risk factor categories in the evolution of de novo cardiac disease in RTR.

4.2 Methods

Design

We performed a retrolective cohort study on all 775 consecutive adults receiving a renal transplant in Manitoba between 1969 and 1999. Due to the relative geographical isolation of the region, all transplanted individuals were followed exclusively at a single center in Winnipeg, Manitoba. It has been a policy of the Manitoba Transplant Program since inception to archive all clinical and hospital records, including procedure and laboratory reports. As a result, detailed clinic and hospital records were available for 98% of patients. Data on baseline demographic, clinical, and outcome variables were abstracted from a review of all inpatient and outpatient records. The detail available permitted the systematic application of a priori definitions for several outcome variables, enhancing the validity of the analysis. The completeness, detail and reliability of the data available significantly decrease the limitations inherent in retrolective (vs. prolective) data acquisition.

Study variables and definitions

Baseline Variables: All data were obtained from inpatient and outpatient records by research nurses trained and supervised by Dr. Rigatto. Age, gender, presence or absence of diabetes, living or cadaveric donor, and smoking status, were all abstracted from the

pre-transplant assessment. Ischemic heart disease (IHD), congestive heart failure (CHF), and peripheral vascular disease (PVD) were judged to be absent at baseline if the pre-transplant assessment concluded they were absent. Cardiovascular disease was a focus of the pre-transplant assessment protocol, and diagnosis was based on oral history, records review, physical examination and EKG, with further testing reserved for symptomatic individuals or diabetics older than 45 years. We did not review records prior to transplantation. The definitions of IHD and CHF as *outcome* events *after* transplantation are more precise and given below. Hypertension was defined as blood pressure >140/90 mmHg or need for antihypertensive therapy. Era of transplantation was defined as transplantation before or after 1985, the year in which cyclosporine was added to azathioprine and prednisone for routine maintenance immunosuppression. Prior to 1985, the majority of patients received azathioprine and prednisone alone. Pre-emptive transplantation was defined as transplantation at time of progression to end-stage renal disease (ESRD) without a “bridging” period on dialysis. Delayed graft function was defined as need for dialysis in the first two weeks after renal transplantation. Acute rejection was defined as an acute rise in serum creatinine of at least 10% not attributable to pre-renal causes, obstruction, or cyclosporine toxicity and treated with pulse steroids and/or anti- lymphocyte preparations. Systolic and diastolic blood pressure, hemoglobin, albumin and serum creatinine were measured at least quarterly per clinic protocol, while total cholesterol was measured yearly.

Outcome Variables: An episode of ischemic heart disease (IHD) was defined as hospitalization for acute myocardial infarction (admission with chest pain accompanied by characteristic EKG changes of infarction or a 3-fold elevation in CK) or

revascularization (coronary artery bypass grafting or percutaneous transluminal angioplasty). Chest pain was not included in the definition because it is a less specific marker of IHD. *De novo* IHD was defined as IHD occurring for the first time in a patient previously free of IHD. *Recurrent* IHD was defined as a subsequent episode of IHD in a patient having had a previous episode of IHD. Congestive heart failure (CHF) was defined as dyspnea plus two of the following: raised jugular venous pressure, bibasilar crackles, chest x-ray evidence of pulmonary venous hypertension or pulmonary edema. *De novo* and *recurrent* CHF were defined as for IHD above. Cardiovascular death was defined as death from myocardial infarction or a revascularization procedure, cardiogenic shock, primary arrhythmia, stroke, or ruptured aortic aneurysm.

Analysis

Normally distributed continuous variables are expressed as mean (SD), non-normally distributed variables are expressed as median (range). Dichotomous variables are expressed as percentages. Outcomes are described using event-free survival curves generated by the Kaplan-Meier method. Patients were censored at graft failure, latest follow-up, or death, except where death was the endpoint being analyzed. The unadjusted influence of each predictor variable was assessed using univariate Cox proportional hazards regression. Multivariate Cox modeling was used to adjust for the simultaneous influence of several variables. Backwards conditional stepping operative on the complete variable pool was used to select the “best” multivariate model. Appropriate additional terms were used to test for interactions or curvilinear relationships. The assumption of proportional hazards was checked by visual inspection of the log(-log) transformed survival curves, which proved acceptable in all cases. The variance inflation factor (VIF)

was used to screen for problems of multicollinearity among the variables: no variables required elimination from the pool for this reason. For the analysis of de novo events in patients alive and free of cardiac disease at one-year, values for SBP, DBP, hemoglobin, creatinine, Gault-Cockcroft 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.

Missing values: Missing values for continuous variables were randomly imputed assuming a normal distribution of missing values having the same mean and standard deviation as the known values. Missing values for dichotomous variables were randomly imputed assuming a binomial distribution of missing values having the same probability of being 1 or 0 as the known values [133]. The proportion of values randomly imputed were as follows: cholesterol 35.3%, smoking 20.7%, albumin 10.8%, blood pressure 9.1%, hemoglobin 8.9% and creatinine clearance 4%. All other variables were complete. The robustness of the imputation method was assessed in two ways. First, the random imputation procedure was repeated four times and the analyses repeated using each set of imputed values. The final models were very similar to each other, suggesting that random imputation had little impact on the results. As an additional check, multivariate normal imputation was used [134]. The models generated again were very similar, confirming the robustness of the results. Where relevant, the effect of the imputation method on model parameter estimates is discussed in the text.

4.3 Results

Patient Characteristics: Full cohort

There were 775 consecutive adult renal transplants performed in Manitoba between Nov 29, 1969 and Jun 1, 1999. Table 4.1 summarizes selected demographic and transplant related characteristics of this cohort. Although the transplant patients represented a select group with generally low comorbidity, three quarters were hypertensive prior to transplantation, over half were smokers and one fifth had had a prior episode of IHD or CHF. Median survival for the group, estimated using the Kaplan-Meier method was 18 (13,22) years. Median death-censored graft survival was 15 (11, 20) years. Ninety percent were first transplants.

Impact of baseline cardiovascular disease

As expected, presence of cardiovascular disease at baseline was associated with cardiovascular death (Table 4.2). When the distinct impact of IHD and CHF was examined, noteworthy trends appeared. The point estimate of the relative hazard in the multivariate models was similar for both IHD and CHF. Both appeared to confer a 60-70% increase in risk of CV death, although the confidence interval for CHF was wider, and the result not statistically significant. When both IHD and CHF were included in the model, baseline IHD was selected over CHF, suggesting that IHD is the stronger predictor of cardiovascular death. This is the reverse of the relationship in dialysis patients where CHF is the stronger predictor of death (see discussion). Cardiovascular disease was less strongly associated with all cause death, as expected. The risk associated with CHF was greater for this endpoint and the confidence interval tighter in comparison

Table 4.1: Baseline characteristics¹ of 775 renal transplant patients.

	40	(12)	years
Age	37		%
Female	18		%
Diabetic	77		%
Hypertensive	57		%
Smokers ²			
Pre-transplant cardiac disease			
IHD	10		%
CHF	11		%
IHD or CHF	19		%
Cadaveric donor	83		%
Cyclosporine regimen	63		%
Duration of dialysis	1	(0.5, 2)	years
Preemptive transplant	7		%
Previous transplant	10		%
Original disease			
Chronic GN	42		%
DM	15		%
ADPKD	8		%

1. Continuous variables expressed as mean (SD) or median (interquartile range) for the cohort as appropriate. Categorical variables are expressed as percentages. 2. Within 5 years of transplantation.

Table 4.2. Impact of baseline cardiac disease (IHD or CHF) on the risk of cardiovascular death following transplantation in a cohort of 775 consecutively transplanted adults, as determined by Cox proportional hazards regression.

All cause death	Prevalence (%)	Relative Risk	P-value
Univariate			
Baseline IHD	10	2.02 (1.41, 2.92)	0.0001
Baseline CHF	11	1.43 (0.97, 2.09)	0.07
Any CV disease ¹	23	1.99 (1.50, 2.64)	0.0005
Multivariate ²			
History of IHD	10	1.23 (0.84, 1.79)	0.2
History of CHF	11	1.45 (0.98, 2.13)	0.06
Any CV disease	23	1.37 (1.08, 2.48)	0.04
Cardiovascular death	Prevalence (%)	Relative risk	P-value
Univariate			
Baseline IHD	10	3.31 (2.06, 5.30)	0.0005
Baseline CHF	11	1.43 (0.81, 2.52)	0.2
Any CV disease ¹	23	2.84 (1.90, 4.22)	0.0005
Multivariate ²			
History of IHD	10	1.68 (1.03, 2.72)	0.04
History of CHF	11	1.57 (0.89, 2.80)	0.1
Any CV disease	23	1.64 (1.08, 2.48)	0.02

1. History of IHD, CHF, peripheral vascular disease or stroke 2. Adjusted for age, diabetes and gender

with IHD, although both intervals crossed unity. Overall, cardiovascular disease was a significant but not overwhelming predictor of early death.

Patient characteristics: de novo cohort

The derivation of the de novo cohort is illustrated in Figure 4.1. In all, 473 of the 775 patients were alive and free of cardiac disease at 1 year. Baseline characteristics and average clinical and laboratory variables in the first year are summarized in Table 4.3, and are broadly similar to those of the overall cohort.

Determinants of CHF

Over a median follow-up of 7 (4,12) years (total follow-up of 4235 patient-years), 51 patients developed de novo CHF, for an average incidence rate of 1.23 events/ 100 patient-years. The univariate predictors of novo CHF were age, diabetes, declining renal function, low albumin, higher blood pressure, and cadaveric donor (Table 4.4). The multivariate analysis reinforced the importance of age, diabetes, serum albumin and even modest elevations in diastolic blood pressure (Table 4.5). Gault-Cockcroft creatinine clearance and donor type were replaced in the multivariate model by hemoglobin, DGF, and gender. This is not surprising when one considers that hemoglobin and CCr were significantly correlated (Figure 4.2), and that DGF, hemoglobin and gender were all associated with CCr (Table 4.6) in a multiple linear regression model. The causal implications of these associations are discussed later.

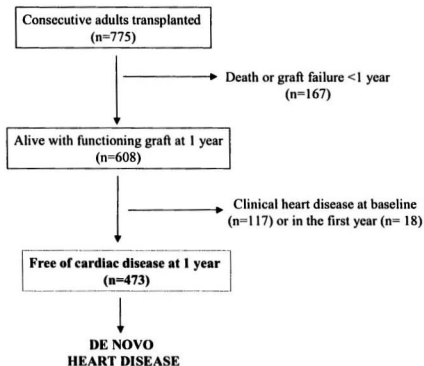


Figure 4.1: Source of the cohort analyzed for de novo heart disease

Table 4.3: Baseline characteristics¹ of 473 renal transplant patients in the de novo cohort

Age	39	(12)	years
Female	42		%
Diabetic	15		%
Smokers ²	55		%
Duration of dialysis	1	(0.5, 2)	years
Pre-emptive dialysis	8		%
Transplanted > 1985	67		%
Cadaveric donor	81		%
Delayed graft function	26		%
Cyclosporine regimen	75		%
Rejections in first year	2	(1,4)	
Systolic BP	139	(16)	mmHg
Diastolic BP	87	(8)	mmHg
Creatinine	160	(61)	μmol/L
CCr	58	(19)	mL/min
Hemoglobin	124	(19)	g/L
Total cholesterol	6.4	(1.4)	mmol/L
Albumin	38	(4)	g/L

1. Continuous variables expressed as mean (SD) or median (interquartile range) for the cohort as appropriate. Categorical variables are expressed as percentages. Time dependent variables are averaged over the first year. 2. Within 5 years of transplan.

Table 4.4: Univariate risk factors for de novo congestive heart failure (n=52) as determined by Cox regression.

Variable ¹	Relative risk ² (95% CI)	P-value
Age (years)	1.05 (1.03, 1.08)	0.00005
Female gender	1.44 (0.83, 2.48)	0.2
Diabetes	3.59 (1.97, 6.54)	0.00005
Smoker ³	0.99 (0.57, 1.71)	0.6
Creatinine Clearance (mL/min) ⁴	0.97 (0.95, 0.99)	0.001
Hemoglobin (g/L)	0.99 (0.98, 1.005)	0.2
Total cholesterol (mmol/L)	1.19 (0.98, 1.43)	0.07
Albumin (g/L)	0.91 (0.86, 0.97)	0.003
Systolic BP (mmHg)	1.04 (1.02, 1.05)	0.00005
Diastolic BP (mmHg)	1.08 (1.04, 1.11)	0.00005
Transplanted >1985	1.53 (0.85, 2.77)	0.2
Any acute rejection in first year	1.47 (0.57, 3.61)	0.4
Delayed graft function	1.54 (0.87, 2.77)	0.1
Cadaveric donor	6.90 (1.67, 28.5)	0.008
Cyclosporine use	1.27 (0.69, 2.32)	0.4
Duration of dialysis	0.87 (0.71, 1.07)	0.2
Preemptive transplant	1.20 (0.48, 3.03)	0.7

1. Continuous variables are averaged over the first year post transplantation 2. Expressed per unit change in continuous variables, e.g. for diastolic BP, RR= 1.08 for each mmHg increment. 3. Past or current smoker 4. Gault-Cockcroft estimate.

Table 4.5: Multivariate risk factors for de novo CHF as determined by Cox regression.

Variable	Relative Risk ¹	P-value
Age		
per year	1.06 (1.04, 1.09)	0.00005
>40 years	2.89	
>60 years	4.59	
Female gender	1.79 (1.01, 3.15)	0.04
Diabetes	2.57 (1.28, 5.16)	0.008
Diastolic BP		
per mmHg increase	1.07 (1.04, 1.11)	0.00005
<75 mmHg	1.00 reference	
75-90 mmHg	2.03	
>90 mmHg	6.76	
Hemoglobin		
per g/L decrease	1.02 (1.006, 1.04)	0.007
< 120 g/L	2.65 (1.44, 4.85)	
Delayed graft function		
Albumin	1.88 (1.01, 3.48)	0.047
per g/L decrease	1.09 (1.01, 1.17)	0.03

1. Expressed per unit increment in continuous variables

Figure 4.2: Correlation between Gault-Cockcroft creatinine clearance and hemoglobin in the first year

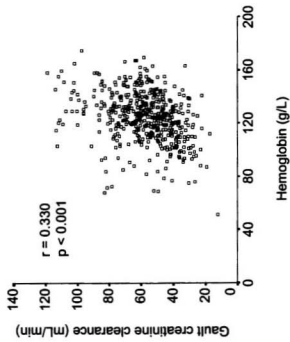


Table 4.6: Variables associated with creatinine clearance as determined by multiple linear regression in the de novo cohort.

Variable	Regression Slope ¹ (mL/min)	P-value
Age (per decade)	-3.89	<0.000001
Female gender	-4.40	0.009
Diastolic BP per 10 mmHg	-2.51	0.01
Hemoglobin per 10 g/L	-2.97	<0.000001
Delayed graft function	-4.78	0.007
Rejection in first year	-10.7	0.00001

1. Expressed per unit increment in continuous variables

Impact of de novo CHF on outcome

The crude survival of patients who developed de novo CHF versus those who did not is illustrated in Figure 4.3. Development of de novo CHF was associated with a 70% greater risk of death independent of age and diabetes (RR 1.70 (1.06, 2.71)).

Determinants of de novo IHD

Fifty-three patients developed de novo IHD over the observation period, for an average incidence rate of 1.25 events /100 patient-years. On univariate analysis (Table 4.7), age, gender diabetes and both systolic and diastolic blood pressure were significant predictors of de novo IHD and these associations persisted in the multivariate analysis. The presence of at least one rejection episode during the first year was also found to increase risk in the multivariate model (Table 4.8).

The relationship between blood pressure and de novo IHD was significantly improved by incorporating a quadratic SBP term in addition to linear diastolic and systolic terms. (Table 4.9). This quadratic term was highly significant. Figure 4.4 illustrates the curvilinear relationship between SBP and adjusted risk (relative hazard). SBP below 130 mmHg and above 160 mmHg appear to be associated with increased risk of de novo IHD (J-curve phenomenon). The power of the study was insufficient to establish both thresholds explicitly and precisely. An $SBP < 130$ appears to be associated with a relative hazard of 2.48 for IHD (Table 4.8). When the blood pressure was excluded from the model, serum cholesterol was substituted (Table 4.10).

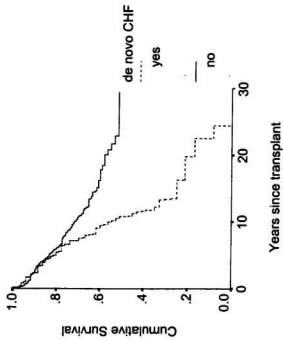


Figure 4.3: Survival in patients who developed de novo CHF versus those who did not.

Table 4.7. Univariate risk factors for de novo IHD as determined by Cox regression.

Variable ¹	Relative risk ² (95% CI)	P-value
Age (years)	1.04 (1.02, 1.06)	0.0004
Female gender	0.33 (0.16, 0.67)	0.002
Diabetes	4.53 (2.53, 8.07)	0.00005
Smoker ³	0.90 (0.52, 1.53)	0.2
Creatinine Clearance (mL/min) ⁴	0.98 (0.97, 1.0009)	0.06
Hemoglobin (g/L)	1.00 (0.99, 1.02)	0.6
Total cholesterol (mmol/L)	1.16 (0.96, 1.41)	0.1
Albumin (g/L)	0.97 (0.90, 1.03)	0.3
Systolic BP (mmHg)	1.02 (1.004, 1.04)	0.01
Diastolic BP (mmHg)	1.06 (1.02, 1.09)	0.0005
Transplanted >1985	0.95 (0.53, 1.71)	0.9
Any acute rejection in first 6 months	2.57 (0.80, 8.24)	0.1
Delayed graft function	1.03 (0.55, 1.93)	0.9
Cadaveric donor	2.19 (0.93, 5.12)	0.07
Cyclosporine use	0.99 (0.55, 1.79)	1.0
Duration of dialysis	1.00 (0.89, 1.14)	0.9
Preemptive transplantation ⁵	0.71 (0.22, 2.27)	0.6

1. Continuous variables are averaged over the first year post transplantation 2. Expressed per unit change in continuous variables, e.g. for diastolic BP, RR= 1.06 for each mmHg increment. 3. Past or current smoker 4. Gault-Cockcroft estimate. 5. Never dialyzed.

Table 4.8: Multivariate risk factors for de novo IHD as determined by Cox regression.

Variable	Relative Risk	P-value
Age (years)	1.05 (1.02, 1.07)	0.0002
>40 years	2.46 (1.26, 4.80)	
Diabetes	4.23 (2.17, 8.26)	0.00005
Male gender	2.56 (1.22, 5.28)	0.01
Diastolic blood pressure ²		0.008
per mmHg increase	1.06 (1.02, 1.11)	
DBP >80 mmHg	3.37 (1.25, 9.10)	
Systolic blood pressure		0.048
per mmHg decrease	1.02 (1.0001, 1.05)	
SBP < 130	2.48 (1.21, 5.07)	
Any rejection < 1 year	3.52 (1.08, 11.4)	0.04

1. Average diastolic blood pressure over the first year post transplantation.

Table 4. 9: Risk factors for de novo IHD¹: Incorporation of quadratic relationship with systolic blood pressure.

Variable	Relative Risk	P-value
Age (years)	1.05 (1.02, 1.08)	0.0001
Diabetes	4.01 (2.00, 8.04)	0.0001
Male gender	3.17 (1.45, 6.95)	0.004
Diastolic blood pressure ²		0.006
per mmHg increase	1.06 (1.02, 1.11)	
Systolic blood pressure ³		0.003
per mmHg increase	0.96 (0.94, 0.99)	
per (mmHg) ² increase	1.0007 (1.0002, 1.001)	
Any rejection <1 yr	3.33 (1.02, 10.8)	0.046

1. IHD=Myocardial infarction or revascularization. 2. Average diastolic blood pressure over the first year post transplantation. 3. Quadratic (curved) relationship with SBP.

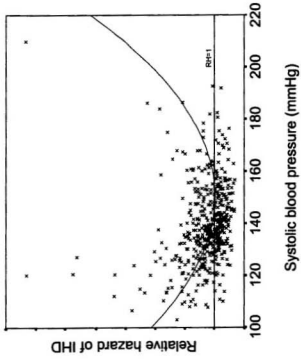


Figure 4.4: Predicted relative hazard (RH) of de novo IHD as a function of systolic blood pressure, adjusting for concurrent diastolic pressure, age, diabetes, gender and rejections in first year.

Table 4.10: Multivariate risk factors for de novo IHD: Blood pressure excluded from model.

Variable	Relative Risk	P-value
Age (years)	1.04 (1.01, 1.06)	0.001
>40 years	2.19 (1.26, 3.79)	
Diabetes	4.33 (2.39, 7.83)	0.00005
Male gender	3.06 (1.46, 6.39)	0.003
Rejections in first year	3.61 (1.11, 11.8)	0.03
Total cholesterol per mmol/L	1.24 (1.02, 1.51)	0.03

1. Average diastolic blood pressure over the first year post transplantation.

Impact of de novo IHD on outcome

The unadjusted survival curves of those who did and did not develop de novo IHD are shown in Figure 4.5. Development of de novo IHD was associated with a 74% greater risk of death independent of age, diabetes, and gender (1.74 (1.19,2.54)).

Determinants of Mortality

Cause of death and mortality rates in the de novo cohort are summarized in Table 4.11. Overall mortality was low, with approximately 3 deaths per hundred patient-years of observation. Half the deaths were from cardiovascular causes.

The univariate predictors of all-cause death after 1 year are shown in Table 4.12. The impact of age, diabetes, high blood pressure, and delayed graft function persisted after multivariate adjustment, while an independent association with anemia was uncovered (Table 4.13). Modest elevations in SBP (>130 mmHg) and modest reductions in hemoglobin (< 120 g/L) appear to be associated with increased mortality risk. Multivariate predictors of cardiovascular mortality were age, diabetes, high blood pressure, *high* cholesterol, and cadaveric donor (Table 4.14). Multivariate predictors of non-cardiovascular mortality were age, anemia, systolic blood pressure, and *low* total cholesterol (Table 4.15).

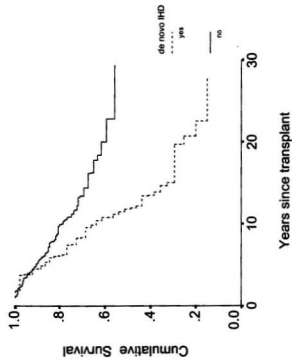


Figure 4.5: Survival in patients who developed de novo IHD versus those who did not.

Table 4.11: Causes of death in the de novo cohort.

Cause of death	N	%	Rate / 100 patient years ¹
Total	118	100	3.14
Cardiovascular	59	50	1.57
Infection	22	19	0.60
Malignancy	20	17	0.53
Other	17	14	0.44

1. Averaged over total follow-up of 4235 patient years

Table 4.12: Univariate risk factors for all-cause mortality as determined by Cox regression in the de novo cohort.

Variable	Relative Risk ¹ (95% CI)	P-value
Age (years)	1.05 (1.04, 1.07)	0.00005
Female gender	0.77 (0.52, 1.14)	0.2
Diabetes	2.92 (1.93, 4.42)	0.00005
Smoker ²	1.01 (0.70, 1.45)	0.4
Creatinine Clearance (mL/min)³	0.99 (0.98, 0.998)	0.02
Hemoglobin (g/L)	1.00 (0.99, 1.006)	0.4
Total cholesterol (mmol/L)	1.11 (0.97, 1.26)	0.1
Albumin (g/L)	0.95 (0.91, 0.99)	0.02
Systolic blood pressure (mmHg)	1.03 (1.02, 1.04)	0.00005
Diastolic blood pressure (mmHg)	1.04 (1.02, 1.06)	0.0002
Transplanted >1985	1.28 (0.86, 1.90)	0.2
Any acute rejection in first 6 months	1.45 (0.78, 2.70)	0.2
Delayed graft function	1.64 (1.12, 2.41)	0.01
Cadaveric donor	3.79 (1.84, 7.79)	0.0003
Cyclosporine use	1.40 (0.93, 2.13)	0.1
Duration of dialysis (years)	1.06 (0.99, 1.13)	0.1
Preemptive transplantation ⁴	0.86 (0.42, 1.77)	0.7

1. Expressed per unit change in continuous variables, e.g. for DBP, RR= 1.04 for each mmHg increment. 2. Past or current smoker 3. Gault-Cockcroft estimate. 4. Never dialyzed.

Table 4.13. Multivariate risk factors for all-cause mortality as determined by Cox regression in the de novo cohort.

Variable	Relative Risk ^{1,2}	P-value
Age (years) >40 years	1.05 (1.03, 1.07) 2.65 (1.82, 3.87)	0.00005
Diabetes Delayed graft function	2.06 (1.26, 3.36) 1.64 (1.11, 2.44)	0.004 0.01
Systolic blood pressure per mmHg increase for SBP>130 mmHg	1.02 (1.006, 1.03) 1.82 (1.08, 3.06)	0.002
Hemoglobin per g/L decrease <120g/L	1.01 (1.002, 1.02) 1.57 (1.07, 2.30)	0.02

1. Expressed per unit change in continuous variables 2. Continuous variables averaged over first year

Table 4.14: Multivariate risk factors for cardiovascular mortality as determined by Cox regression in the de novo cohort.

Variable	Relative Risk ^{1,2}	P-value
Age (years)	1.06 (1.03, 1.08)	0.00005
>40 years	2.95 (1.68, 5.18)	
Systolic blood pressure		0.04
per mmHg increase	1.02 (1.001, 1.03)	
for SBP>145 mmHg	2.23 (1.27, 3.90)	
Diabetes	4.56 (2.47, 8.44)	0.00005
Total cholesterol		0.0008
per mmol/L increase	1.37 (1.14, 1.64)	
>5 mmol/L	2.15 (1.12, 4.10)	
Cadaveric donor	5.60 (1.23, 25.4)	0.02

1. Expressed per unit change in continuous variables 2. Continuous variables averaged over first year

Table 4.15: Multivariate risk factors for non-cardiovascular mortality as determined by Cox regression in the de novo cohort.

Variable	Relative Risk ^{1,2}	P-value
Age (years)	1.04 (1.02, 1.06)	0.0006
>40	2.07 (1.22, 3.49)	
Hemoglobin		0.03
per g/L decrease	1.02 (1.001, 1.03)	
Hgb<100g/L	2.73 (1.31, 5.70)	
Systolic blood pressure		0.03
per mmHg increase	1.02 (1.001, 1.03)	
>130 mmHg	2.23 (1.09, 4.57)	
Total cholesterol		0.03
per mmol/L increase	0.82 (0.69, 0.98)	
< 5.5 mmol/L	2.13 (1.26, 3.61)	

1. Expressed per unit change in continuous variables 2. Continuous variables averaged over first year

4.4 Discussion

A small number of retrolective cohort studies have examined risk factors for cardiac disease and death in renal transplant patients [4,6-9]. The present cohort study distinguishes itself from the preceding studies in several ways. This is the first study to examine the risk factors for and impact of CHF in RTR. Only de novo events occurring after 1 year were studied in order to lessen the confounding effect of pre-existing cardiac disease and pre-transplant risk factors on the associations between *post*-transplant variables and outcomes. Finally, a broad spectrum of putative cardiac risk factors, comprising many traditional, renal failure-related and transplant-related variables, were analyzed using multivariate techniques operating on the complete variable pool. Since several risk variables are highly correlated, discerning the independent effect of these variables requires simultaneous modeling. The outcomes and risk factors identified in this study are discussed below.

Prognostic importance of de novo CHF and IHD

Both de novo IHD and CHF were harbingers of early death and were independent of age, gender and diabetes. When both events were included in the model with age, gender and diabetes, de novo IHD remained significant whereas de novo CHF did not. De novo IHD thus appears to be the stronger predictor of all cause mortality, in contrast to studies in the dialysis population, where CHF is a stronger predictor of mortality than IHD [41,45]. The major caveat to this interpretation is that the survival analysis used graft failure as a censoring endpoint. De novo CHF was strongly and independently associated with graft loss and the combined endpoint of graft loss or death (data not shown). Moreover,

Harnett et al. [41] have shown that CHF prior to or at the initiation of dialysis is a powerful independent predictor of subsequent death on dialysis. It is likely, therefore, that the full adverse impact of CHF may only be discerned after patients with graft failure have returned to dialysis. Since events after return to dialysis were not included in this analysis, the observed impact of de novo CHF on patient survival has likely been underestimated in the present study.

Risk factors for both de novo CHF and IHD

Non-modifiable risk factors: Age and diabetes mellitus were independently associated with adverse cardiac events and death in the present study. Diabetes was not predictive of non-cardiovascular death, consistent with the notion that the mortal impact of diabetes is mediated primarily via cardiovascular complications. These results are entirely consistent with the large body of evidence in the general, dialysis and transplant populations [4-6,8,9,78,135].

Male gender has been associated with elevated risk of IHD in the general population and in the renal transplant population [4-6,9,78,135]. Our study supports this association. Interestingly, female gender was independently associated with an increased probability of de novo CHF. An association between female gender and CHF has also been found in dialysis patients [40]. It is possible that female gender is causally related to CHF because of some gender specific trait not accounted for by the other covariates in the model. On the other hand, female gender, hemoglobin, and delayed graft function, among others, were predictive of CCr under a linear regression model, so that it is possible that these three variables in combination may be surrogate markers for poor renal function, fluid

overload, and consequent CHF. Which of these possibilities is true cannot be determined by the present analysis. We did not find any independent association between gender and mortality.

Blood pressure: Hypertension has been clearly established as a risk factor for IHD, LVH and CHF in the general population [5,38,83]. It is a risk factor for both LVH and CHF in dialysis patients [47]. In the present study, DBP was a powerful predictor of de novo CHF. SBP could be substituted for DBP with no loss of predictive power in the model. High SBPs were independently associated with all-cause and cause-specific mortality. In these cases, SBP could be successfully substituted by DBP without loss in the predictive power of the model. In all cases, excess risk could be observed even with modest elevations in systolic or diastolic blood pressure.

In the case of de novo IHD, we found a curvilinear (*J* curve) association between blood pressure and outcome (Figure 4.4), showing increased relative hazard at both low and high SBP. Although this observation could be an artifact, the strength of the association argues in favor of a real effect. Moreover, both extremes of blood pressure have been linked with adverse cardiac events in other patient populations, notably dialysis [46]. Since high blood pressure is known to promote endothelial dysfunction, atherosclerosis, and LVH, a causal relationship between hypertension and de novo IHD is likely. At the other extreme, the association between low blood pressure and adverse prognosis may be non-causal. Low BP is thought to be a marker of the severity of underlying cardiac dysfunction, which in turn determines survival. Because the cohort studied was selected on the basis of being clinically free of heart disease, it is unlikely, but possible, that the presence of occult cardiac disease is responsible for the observed *J*-curve. Alternatively, a

causal relationship may exist if low BP is a result of excessive or inappropriate treatment with antihypertensive agents, leading to coronary hypoperfusion and IHD. In this regard, Kasiske et al have observed an association between dihydropyridine use and de novo IHD in RTR [7]. Other studies in the general population have suggested a similar association for short acting dihydropyridines [136,137] . We are unable to show a significant association between type or number of antihypertensives and either low blood pressure or IHD in the present data set, however.

Some authors have suggested that SBP may be a marker for pulse pressure ($PP = DBP - SBP$) [24,138]. Elevated pulse pressure is thought to reflect increased total arterial impedance, an index of diffuse arterial stiffening (arteriosclerosis), which has been linked to cardiac disease independently of mean arterial blood pressure [139]. We explicitly tested for this possibility by incorporating PP into the model, either alone or in combination with DBP or mean arterial pressure ($MAP = (2 \cdot DBP + SBP) / 3$). PP could not be successfully incorporated, however, suggesting that increased SBP is more than an indirect marker of elevated arterial impedance and target organ damage. These observations further support a causal link between elevated SBP and IHD.

Our results overall support the hypothesis that blood pressure is a causal risk factor for de novo CHF, IHD and mortality in renal transplant patients. Clinical trials in this population are needed to definitively establish causality and to determine appropriate treatment targets.

Additional risk factors for de novo IHD

Cholesterol: High total cholesterol has been shown to be an independent predictor of cardiovascular events and mortality in the general population [96]. In dialysis patients, low cholesterol is a predictor of mortality, most likely because it is a marker of malnutrition [100]. High cholesterol has been associated with cardiovascular complications in transplant patients [6].

In the present study, high cholesterol was independently associated with cardiovascular death, whereas low cholesterol was associated with non-cardiovascular death. This finding is consistent with the hypothesis that hypercholesterolemia is causally related to the development of IHD in the transplant population. Conversely, low cholesterol may be a marker of general comorbidity or malnutrition, which in turn may be associated with non-cardiovascular death. These results therefore, are biologically plausible. Since cardiovascular and non-cardiovascular deaths were equal in number in this cohort, and since the impact of cholesterol on each was opposite and of approximately equal magnitude, these effects would be expected to cancel each other out in the analysis of all cause death, as was observed.

Several important limitations to this interpretation deserve mention. First, the analysis of cause specific death is confounded by the problem of competing outcomes: if a patient is observed to die from cause A, that patient cannot also be observed to die from cause B. It is possible to argue, for example, that *low* cholesterol is causally associated with non-cardiovascular death. Patients dying of non-cardiovascular causes cannot be observed to die of cardiovascular causes. Those patients dying of cardiovascular causes will tend to

have higher cholesterol, leading to spurious, non-causal association between high total cholesterol and CV death. (The reverse argument can be made as well: a causal association between hypercholesterolemia and CV death and a spurious association between non-CV death and low cholesterol). On the basis of biological plausibility, however, we favor a real and causal association between hypercholesterolemia and cardiovascular mortality, and a real but non-causal association between low cholesterol and non-cardiovascular death.

The second limitation is that only two thirds of the patients studied had total cholesterol levels done in the first year, compared to 90-100% for most other parameters. Not surprisingly, cholesterol was found to be the parameter most sensitive to random imputation. Three of the five randomly imputed data sets gave models similar to the one discussed, whereas two of the five excluded cholesterol. However, restricting the analysis to those patients in whom cholesterol was measured, or using a multivariate normal imputation method, both led to parameter estimates for cholesterol very similar to those in the analysis presented here.

Finally, we did not show an independent contribution of high cholesterol to IHD events as one would expect. However, cholesterol *was* included in a multivariate model when blood pressure was excluded. Introduction of blood pressure terms rendered the cholesterol term non-significant and markedly diminished the hazard ratio associated with hypercholesterolemia. This model behaviour indicates the presence of confounding bias between blood pressure and cholesterol. The observation of confounding bias between traditional risk factors is not surprising; indeed, the term "Cardiovascular Dysmetabolic Syndrome (CDS)" has been used to describe the clustering of

hypertension, hyperlipidemia, obesity, and insulin resistance/diabetes [140]. Our event rate was likely too small to simultaneously resolve the independent contribution of both blood pressure and cholesterol.

We conclude that hypercholesterolemia is probably a risk factor for IHD, although the evidence is less robust and convincing than for the other risk factors.

Additional risk factors for de novo CHF

Anemia: Anemia has been associated with LVH and LV growth in chronic renal failure patients not on dialysis, and with LVH, LV dilatation, and clinical CHF in dialysis patients [23,50]. Correction of the anemia may prevent LV dilatation in dialysis patients with normal hearts at baseline [141]. In the present study, anemia was found to be an independent risk factor for de novo CHF, all-cause and non-CV mortality. Even relatively mild anemia (hgb<120) was associated with increased risk of CHF and all-cause mortality. Since the need for increased cardiac output may plausibly lead to eccentric LVH and ultimately diastolic or systolic dysfunction, the association between anemia and de novo CHF is probably causal. Alternatively, it is possible that anemia simply unmasks occult ventricular dysfunction. Although the cohort was free of clinical CHF at baseline and during the first year, echocardiography was not done and so occult LV dysfunction cannot be completely excluded. Moreover, anemia was correlated with renal impairment, and so could be a surrogate marker for a failing allograft, fluid overload, and consequent CHF. However, low hemoglobin consistently displaced creatinine clearance in the multivariate models of de novo CHF, suggesting an independent effect. On balance, our

data support but do not prove a causal role for anemia in the development of de novo CHF in RTR.

The role of anemia as a predictor of mortality is more difficult to interpret. Anemia predicted all-cause and non-CV mortality but not CV mortality, suggesting a non-CV mechanism. In this instance, anemia could be a marker for systemic disease such as neoplasia, infection, progressive allograft failure, autoimmune disease, or marrow suppression. A more discerning analysis of the determinants of anemia in this transplant cohort is planned and may shed light on this issue. Ultimately, however, the question of whether anemia is a causal risk factor amenable to intervention can only be answered by a clinical trial of anemia correction in transplant patients with chronic anemia.

Role of renal function:

Renal insufficiency per se has been associated with adverse risk of death in several cross-sectional surveys. This effect has been found to be statistically independent of age, gender, hypertension and CAD. Such observations have suggested that uremia per se, independent of effects on hypertension, anemia, lipids and so forth, may exert an accelerative affect on cardiac disease. Prevalence studies, however, cannot discern whether renal insufficiency is a cause of CVD or a marker for other causal factors. In the prospective Framingham Heart Study cohort, the CVD event rate in men with mild RI was 21.3/1000 person years and 25.6 in women vs. 18.5 in men and 11.0 in women with normal serum creatinine. However, RI was not an independent risk factor for CVD in men or women, after adjustment for age, body mass index, diabetes, systolic blood

pressure, antihypertensive agents, total cholesterol, HDL cholesterol, smoking, prevalent CVD, use of cardiac medications, and left ventricular hypertrophy [142].

In the present study, we did not find renal function, as estimated by the Gault-Cockcroft creatinine clearance (CCr), to be an independent predictor of CHF or IHD. With respect to de novo CHF, CCr was replaced by anemia in the multivariate model, suggesting that its univariate impact was mediated primarily by anemia and blood pressure. CCr was not a significant predictor of de novo IHD in either the univariate or multivariate models.

In the present study, it would seem that the impact of renal insufficiency on cardiac disease is 1) apparent only with respect to disorders of cardiac function (CHF) and not perfusion (IHD) and 2) is largely accounted for by blood pressure and anemia, known correlates of renal failure.

Role of transplant related variables

Donor type, acute rejections in the first year, and delayed graft function have all been associated with poorer graft and patient survival [4,6,9]. In addition, it has been suggested that cyclosporine is a risk factor for cardiovascular disease [21,60]. However, with the exception of anemia, which is discussed separately, transplant-related risk factors were not strongly associated with outcome in the present study. Only DGF in the case of de novo CHF and acute rejection in the case of de novo IHD were significant in the multivariate models. This occurred despite the fact that we analyzed de novo events in patients free of cardiac disease in their first transplant year, a strategy designed to enhance the sensitivity to transplant related variables.

The link between transplant variables and cardiovascular risk found in previous studies may reflect direct or indirect causality, or result from a non-causal association. For example, DGF and rejections may be associated with a systemic inflammatory response, endothelial activation, and cardiovascular disease [67]. Cyclosporine is an endothelial toxin, enhances platelet activation, enhances oxidation of LDL and may thus also directly promote atherosclerosis [64-66]. On the other hand, the latter variables are associated with graft failure and hypertension, while cyclosporine is linked to hypertension and hypercholesterolemia [22,60]. Under this latter scheme, an indirect link between transplant associated variables and outcome would be mediated via “traditional” risk factors such as blood pressure and high cholesterol. Our study results are more consistent with the latter hypothesis, since the impact of transplant-associated variables is weaker than age, diabetes, blood pressure and cholesterol when the effect of these variables is adequately taken into account. Our results support the hypothesis that traditional cardiovascular risk factors plus anemia are the major causal determinants of cardiovascular outcomes in transplant patients.

Limitations of the analysis

The cohort design used is considered more reliable than case-control or cross-sectional designs. The major disadvantages of retrospective vs. prospective cohort designs are that in the former, data may at times be missing, the assessment of risk factors and outcomes may be subject to bias because they may not have been defined a priori as is the case with a prospective design, and certain risk factors and outcomes of interest may not have been assessed in the past. In the case of the present database, two of these methodological pitfalls are minimized. The exclusive follow-up of patients by a single renal transplant

program operating in relative geographic isolation in a province with a stable population has permitted excellent data capture over a long follow-up period (up to 29 years). Most of the risk factors of interest were obtained as part of the clinic protocol. The availability of complete outpatient and hospital records has allowed the application of a priori study definitions to outcome events. The reliability of the data may thus approach that of a prospective cohort study.

With respect to the third limitation, there are several risk factors that we could not analyze. Lipoprotein fractions (LDL, HDL) were available in only half the patients in whom cholesterol was measured. Lp(a) and homocysteine were not routinely measured until recently. Cytomegalovirus (CMV), which has been associated with endothelial dysfunction, was measured at baseline in patients only after 1990, representing less than 50% of the present cohort. Prospective cohort studies will be necessary to analyze these factors.

Finally, the present study looked at determinants of de novo cardiac events after the first year. This was done in order to lessen the confounding impact of pre-existing renal disease in this population. Since we did not analyze outcome events occurring in the early post-transplant period, we cannot comment on risk factors for CVD in the first year after transplantation. Many of these risk factors will pertain to exposures during chronic renal insufficiency and dialysis, and may well be different from those identified in this study.

4.5 Conclusions

De novo CHF occurs as commonly as de novo IHD, and appears to carry a similar adverse prognosis. The incidence of CHF was considerably higher than observed in the

Framingham cohort, whereas the incidence of IHD was remarkably low, of the same order as observed in the Framingham study cohort. Age, diabetes, gender, blood pressure and anemia, appear to be the dominant factors in the development of de novo CHF, while age, diabetes, gender, blood pressure and cholesterol appear to be the dominant risk factors for de novo IHD in renal transplant recipients. Once these strong risk factors are taken into account, the incremental impact of renal function, delayed graft function and graft rejection on all outcomes is small, and cyclosporine use does not appear to be a risk factor at all. Optimal strategies for treatment of blood pressure, anemia and cholesterol will need to be determined by randomized clinical trials.

CHAPTER 5:

GLOBAL SUMMARY: ARE THE PARADIGMS OF CARDIAC DISEASE STILL VALID?

5.1 Paradigms of cardiac disease in RTR

Historically, cardiac complications in patients with renal disease have been thought parenthetical to the process of uremia. From the 1970's onwards, the observation of an elevated prevalence of both LV functional disorders and IHD in dialysis led to concepts of "accelerated atherosclerosis" and "uremic cardiomyopathy". These terms reflected the belief that the rate of development cardiac disease was accelerated by loss of renal function and that uremia intrinsically modified these processes independently of known risk factors. These arguments were supported by registry data and prevalence studies showing an excess burden of cardiovascular mortality after adjustment for known risk factors [143,144]. More recent studies of incident events in prospective cohorts have questioned this view. Renal dysfunction may not be an independent predictor of incident IHD, once traditional risk factors have been taken into account, and the association of renal failure with LV disorders may be largely explained by the excess prevalence of hypertension and anemia [69,142].

Although the prevalence of cardiac disease is much lower in RTR, the paradigm of "accelerated atherosclerosis" has been extended to this population [3]. Emphasis has been placed on the immunological milieu, in accordance with the traditional view of renal transplantation as an immunological disorder. In contrast, the notion of a transplant specific "cardiomyopathy" has not developed, in large part because relatively few studies have looked at the question of LV functional disorders in the renal transplant setting. Since our own data appear to contradict the prevailing view of cardiac disease in uremia, it seems appropriate to revisit these concepts as they pertain to RTR.

5.2 Cardiomyopathy

In ESRD patients, the notion of a toxic “uremic cardiomyopathy” derives from the experience, now rare, of a severely uremic patient with a dilated, poorly contractile heart that becomes normally functional after institution of dialysis. Patients with persistently poor systolic function (fractional shortening <25%) prior to renal transplantation seem to show normalization of systolic function after transplantation [36]. These observations have suggested the presence of an unmeasured uremic factor (or combination of factors), which is removed upon partial or complete restoration of renal function (dialysis or renal transplantation).

In contrast to the indirect evidence cited above, a careful analysis of a prospectively followed CRI cohort showed that the impact of declining renal function on progression of LVH was largely accounted for by anemia and hypertension [23]; that is, the LVH of CRI seemed to be the consequence not of retained uremic toxins, but of chronic flow (anemia) and pressure (hypertension) overload. Our own data in RTR are strikingly similar. In the present analysis, age and blood pressure were the key determinants of persistent cardiac hypertrophy during transplantation, while age, gender, diabetes, blood pressure, and anemia, were the key predictors of de novo CHF. The fate of the heart in RTR appears dominated by the same hemodynamic factors operative in CRI.

The similarity between RTR and CRI patients is worth exploring further. Halloran et al., among others, have documented the importance of non-immune mechanisms such as age, nephron dosing, and blood pressure, in the progressive loss of graft function. These non-immune factors appear to dominate after the first post-transplant year [145]. They have

promoted a new terminology, chronic allograft nephropathy (CAN) as opposed to “chronic rejection”, in order to more accurately describe a process of renal attrition that is only partly immune mediated [146]. In this light, CAN is analogous to loss of renal function in native kidneys with chronic autoimmune nephropathies, in which both immune activity and non-immune factors (particularly blood pressure) contribute to renal decline. The National Kidney Foundation Task Force on Cardiovascular Disease seems to sanction this view and considers RTR a special case of CRI [147].

Our own data are congruent with the wider literature on the pre-eminence of non-immune factors in graft and patient outcomes in renal transplantation. LV functional disorders in RTR appear to result primarily from pressure and flow overload (anemia), observations analogous to those in CRI. We find little evidence of a “toxic”, “uremic” or “transplant” cardiomyopathy. The implication of such a shift in paradigm is that greater emphasis could be placed on potentially treatable complications of renal transplantation such as hypertension and anemia.

5.3 Accelerated atherosclerosis

The term “accelerated atherosclerosis” implies a higher rate of development (i.e. a higher *incidence*) of IHD in RTR. A direct comparison of incident IHD in RTR and the GP, controlling for differences in risk-factor profile, has not been done, however. The incidence is generally assumed to be higher, based on the known higher *prevalence* of IHD in RTR compared with the general population. This inference is not necessarily valid and requires objective confirmation in prospective studies directly measuring the incidence of new IHD in both the RTR and GP.

We observed a rate of de novo IHD of 1.25% per year in the present cohort. It is interesting to note that the crude incidence of CVD in the Framingham study was 1.8% per year for males and 1.1% per year for females [142]. These rates are not strictly comparable because the endpoints differ, recurrent disease was included in the Framingham study, and adjustment for differences in population characteristics such as diabetes, age, gender and hypertension have not been made. Nevertheless the event rates for de novo IHD in RTR and the GP may be similar, rather than several-fold higher as currently believed. We observed further that the dominant factors for de novo IHD were concordant with the traditional, Framingham type risk factors: age, diabetes, and blood pressure. The contribution of transplant variables was less important. The portrait of IHD in RTR that emerges from our study is one that is broadly similar in frequency and risk factor profile to that in the general population. This is not to say transplant and renal failure related variables are irrelevant; rather, the contribution of these variables is probably exerted *indirectly*, mediated via changes to traditional risk factors such as diabetes and blood pressure. What residual *direct* influence they exert on the atherosclerotic process is likely of a minor and modulatory nature. As was the case with LV functional disorders, our analysis shifts emphasis away from the immunological paradigm. Our work supports the idea that the development of IHD in RTR is fundamentally similar to that in the GP, while the evolution of clinical disorders of LV function and geometry is similar to that in CRI.

5.4 Future directions

We have suggested in this paper that existing paradigms of heart disease in renal failure, based as they are on analyses of prevalent disease or of incident disease in populations

with a high baseline prevalence of heart disease, may be inaccurate. From a methodological viewpoint, it is imperative that *incident* CVD in renal populations with a *low baseline prevalence* of heart disease (i.e. CRI and RTR cohorts) be intensively studied, since only in such populations can one adequately eliminate the confounding by reverse causality inherent in populations with a high baseline prevalence of heart disease. Examination of comorbidity-adjusted incident event rates for CHF and IHD in GP, CRI, and RTR cohorts, using similar definitions and statistical procedures, are needed to more rigorously compare these patient populations, and to help shed light on differences in causation, if any exist. Such analyses are being planned. Our observations further suggest that patients may benefit from more aggressive treatment of reversible risk factors such as hypertension, anemia, and hypercholesterolemia than is currently practiced. Clinical trials will be necessary to confirm the value of aggressive interventions on these risk factors and to determine optimal treatment thresholds.

The importance of anemia as a risk factor for LV dysfunction in RTR is a new observation, and merits further exploration. A causal relationship between anemia and CHF would be further supported by evidence that the impact of anemia on CHF is mediated by the development of LVH. Such an analysis, using EKG criteria for LVH, will be performed on this cohort in the near future. Ultimately, intervention trials of aggressive anemia management in RTR must be done in order to validate the causal inferences drawn from observational studies.

The risk factors for cardiac disease in any population have not been completely defined. Even in the GP, risk models predict only half of all events. In RTR,

hyperhomocysteinemia and CMV infections are potential but unproven causal agents for IHD. Further insights will undoubtedly accrue on these risk factors.

The notion that genetic variation may explain much of the residual risk for cardiac disease in many populations is a new and promising one. Nascent gene chip technology may facilitate exploration of the cardiac impact of genes coding for peptides and proteins involved in vascular/endothelial regulation, apoptosis, acute and chronic inflammation, mutagenesis, and repair. Our immunology laboratory in Winnipeg, under the direction of Dr. Peter Nickerson, is presently able to identify allelic variation in the genes coding for six cytokines involved in inflammation and repair (IL-10, TNF- α , IL-6, TGF- β , IFN- γ). We have begun to enroll an inception cohort of dialysis patients in order to explore the impact of allelic variations in these genes on cardiovascular outcomes in dialysis. As discussed at the beginning of this section, this study must expand to CRI and RTR cohorts in order to reduce survivorship bias and confounding by reverse causality. We hope this novel direction of inquiry may help explain the remaining 50% of cardiovascular events that current models cannot predict.

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