Kidney International, Vol. 47 (1995), pp. 884–890

Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis and risk factors

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Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis and risk factors. Cardiovascular disease is the most common cause of death in dialysis subjects. Congestive heart failure (CHF) is a common presenting symptom of cardiovascular disease in the dialysis population. Information regarding prevalence, incidence, risk factors and prognosis is crucial for planning rational interventional studies. A prospective multicenter cohort study of 432 dialysis patients followed for a mean of 41 months was carried out. Prospective information on a variety of risk factors was collected. Annual echocardiography and clinical assessment was performed. Major endpoints included death and the development of morbid cardiovascular events. One hundred and thirty-three (31%) subjects had CHF at the time of initiation of dialysis therapy. Multivariate analysis showed that the following risk factors were significantly and independently associated with CHF at baseline: systolic dysfunction, older age, diabetes mellitus and ischemic heart disease. Seventy-six of 299 subjects (25%) who did not have baseline CHF subsequently developed CHF during their course on dialysis. Compared to those subjects who never developed CHF ($N = 218$) multivariate analysis identified the following risk factors for the development of CHF: older age, anemia during dialysis therapy, hypoalbuminemia, hypertension during dialysis therapy, and systolic dysfunction. Seventy-five of the 133 (56%) subjects with CHF at baseline had recurrent CHF during follow-up. Independent and significant risk factors for CHF recurrence were ischemic heart disease and systolic dysfunction, anemia during dialysis therapy and hypoalbuminemia. The median survival of subjects with CHF at baseline was 36 months compared to 62 months in subjects without CHF. In this study the prevalence of CHF on starting ESRD therapy and the subsequent annual incidence was high. CHF was a strong, independent, adverse prognostic indicator. Risk factors for CHF include older age, pre-existing cardiac diseases (systolic dysfunction and ischemic heart disease), and potentially reversible abnormalities related to chronic uremia (anemia, hypertension and hypoalbuminemia).

Cardiac disease is the most common cause of death in dialysis patients, accounting for about 40% of deaths in this group [1, 2]. Congestive heart failure is a frequent clinical manifestation, and is associated with systolic failure, left ventricular hypertrophy and ischemic heart disease [3]. Congestive heart failure, present on the initiation of end-stage renal disease therapy, is an adverse, independent, prognostic indicator of mortality [4]. Recurrent congestive heart failure in patients established on dialysis has an adverse prognosis [5]. However, little prospective data exists concerning the risk factors for congestive heart failure, and the role of underlying cardiac disease in the etiology of congestive heart failure in dialysis patients. The best research design to identify potentially reversible risk factors, whose treatment could be tested in clinical trials, is a prospective study of a cohort of dialysis patients without congestive heart failure at baseline, some of whom subsequently develop congestive heart failure.

Therefore a prospective study of a cohort of 432 consecutive patients, who survived at least six months from the start of dialysis, was undertaken. To determine risk factors for congestive heart failure, patients with congestive heart failure on initiation of end-stage renal disease therapy were compared to those without, and patients who did not have congestive heart failure at baseline, but subsequently developed it, were compared to those who never developed heart failure. We hypothesized that patients with congestive heart failure at baseline and who had a recurrence during their life on dialysis have different risk factors from those who never had a recurrence. These two groups were also compared.

Methods

This prospective cohort study was carried out in three centers, the Royal Victoria Hospital in Montreal, Quebec starting in 1982, the General Hospital, St. John's starting in 1984 and the Grace Hospital, St. John's starting in 1985. Recruitment finished in June of 1991. Eligibility criteria for the study included survival for six months or more on dialysis, because we intended to use the data to design clinical trials of interventions in the treatment or prevention of cardiac disease in chronic uremia. Another criterion was the availability of a technically adequate echo within one year of initiating renal replacement therapy.

At the time of initiation of dialysis and at annual intervals thereafter, clinical assessment was performed to detect risk factors for the presence of cardiovascular disease. Baseline and annual echocardiography was performed using M-mode and two dimensional ultrasonography according to the criteria set forth by the American Society of Echocardiographers. Left ventricular mass index was calculated using either the regression corrected American Society of Echocardiography cubic formula or the formula of Devereux and Reichek, depending on whether the endocardium was included in the estimation of ventricular wall thickness. Both of these methods are highly correlated and have

Received for publication August 8, 1994
and in revised form October 3, 1994
Accepted for publication October 3, 1994

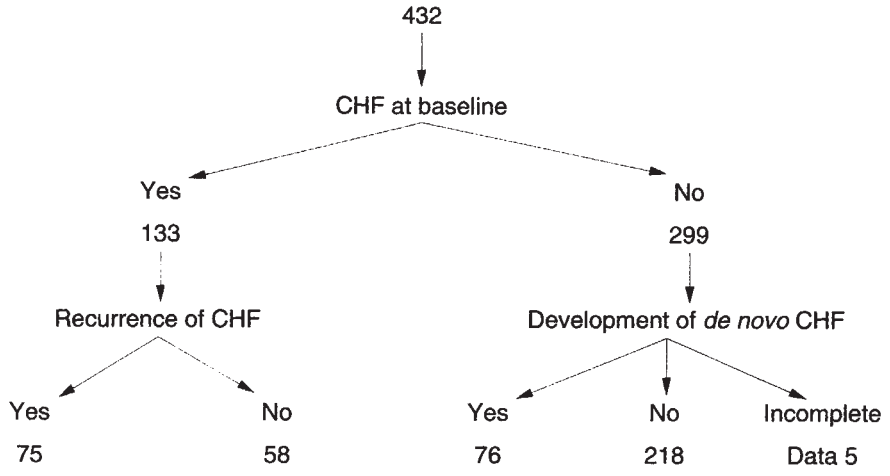

Fig. 1. *The prevalence and incidence of congestive heart failure in a cohort of 432 dialysis patients who survived at least 6 months from the start of ESRD therapy.*

strong validity when compared to autopsy data [6]. Echocardiography was performed when the patient was considered to be at or close to "dry weight." This assessment was based on clinical parameters. In addition to echocardiography 55% of patients also had radionuclide scans of the left ventricle to calculate ejection fraction. This was not however an entry requirement for the study, as it was not performed in one hospital. At monthly intervals the following data were collected: predialysis blood pressure, interdialytic weight gain, predialysis hemoglobin, serum urea, serum creatinine, electrolytes, bicarbonate, calcium, phosphorus, albumin and alkaline phosphatase. In addition to the annual clinical assessment and echocardiography the following were also undertaken: review of hospital admissions, measurement of serum cholesterol, parathyroid hormone levels, serum aluminum and ferritin levels. In addition, chest x-ray, EKG and metabolic bone surveys were also performed. Any changes in renal replacement therapy were noted. The presence and type of vascular access was noted as was the occurrence of blood transfusions, admissions to hospital, death notes and autopsy results. This study was initiated before measurement of dialysis adequacy (Kt/V) was routine. Data on dialysis prescription and dialyzer use were not studied.

Definitions

Congestive heart failure. Dyspnea plus two of the following: raised jugular venous pressure, bibasilar crackles, pulmonary venous hypertension or interstitial edema on chest x-ray [3].

Ischemic heart disease. Present or previous history of angina, myocardial infarction, coronary artery bypass surgery or percutaneous transluminal angioplasty.

Peripheral vascular disease. Symptoms of, or surgery for peripheral vascular disease.

Dysrhythmia. Atrial or ventricular rhythm disorder requiring therapy.

LV hypertrophy. Mass index >100 g/m^2 in females and mass index >131 g/m^2 in males. These values are the upper limits of normality among healthy participants in the Framingham Heart Study [7].

Systolic dysfunction. Left ventricular ejection fraction ≤40% on radionuclide scan or fractional shortening ≤25% on echocardiogram.

Analysis

The following outcome measures were used for this analysis: death, the recurrence of CHF and the occurrence of *de novo* CHF. Patients were censored at the time of renal transplantation or at the final follow-up.

Normally distributed continuous variables were compared using *t*-tests. Categorical variables were compared using Chi squared tests. Stepwise logistic regression analysis was used to identify which baseline variables were associated with the occurrence of congestive heart failure at the start of dialysis. Variables were entered using a forward stepping procedures in which the order was determined using estimates of asymptotic variance, with $P > 0.10$ to enter and $P < 0.15$ to remove at any step. Univariate survival analysis was carried out using life table analysis by the product limit method. All statistical tests are two-sided with a P value of < 0.05 taken to indicate statistical significance. The independent power of different variables to predict new CHF and mortality was assessed using Cox's Proportional Hazards Model. All statistical analysis was carried out using BMDP software [8].

Five hundred and eighteen patients were identified who had survived at least six months from the start of endstage renal disease therapy and 432 of these 518 (84%) had an adequate echocardiogram within one year of starting dialysis therapy. Echocardiography was performed at a mean (standard deviation) interval of 3.3 (3.9) months from the time of first dialysis. Mean duration of follow-up was 41.1 (25.7) months. Hemodialysis, peritoneal dialysis and renal transplantation accounted on average for 18.8, 12.8 and 9.5 months, respectively, of total follow-up. The mean age of the patients was 51 years. Sixty-four percent of the patients were males and 27% were diabetics. The vast majority of patients were Caucasian. An initial report on the adverse impact of clinical and echocardiographic variables on patient survival has been recently published [9].

Results

Figure 1 demonstrates that, on initiation of ESRD therapy, 31% of patients had congestive heart failure or a history of this condition, 56% of whom had a recurrence of heart failure during dialysis therapy. Twenty-five percent of patients without heart

Table 1. Demographic and clinical data on starting ESRD therapy in those with and without congestive heart failure on the initiation of dialysis therapy

	CHF (N = 133)		No CHF (N = 299)		
	N	%	N	%	P
Male	80	60	198	66	NS
Cigarette smoking	53	40	98	33	NS
Diabetes mellitus	56	42	60	20	<0.0001
Myocardial infarction	34	26	18	6	<0.0001
Angina	46	35	37	10	<0.0001
Coronary artery bypass graft	8	6	6	2	0.03
Peripheral vascular disease	23	17	13	4	<0.0001
Arrhythmias	20	15	11	4	<0.0001
	Mean	SD	Mean	SD	
Age *years*	59	14	48	17	<0.0001
Serum cholesterol *mmol/liter*	5.4	1.8	5.2	1.5	NS
Serum creatinine *μmol/liter*	801	348	930	426	0.001
Systolic BP *mm Hg*	152	26	151	24	NS
Diastolic BP *mm Hg*	82	15	84	13	NS
Serum albumin *g/liter*	34	5.5	35	6	NS
Hemoglobin *g/liter*	85	18	83	16	NS

Table 2. Echocardiographic data on starting ESRD therapy in those with and without congestive heart failure on the initiation of dialysis therapy

	CHF (N = 133) Mean ± SD		No CHF (N = 299) Mean ± SD		P
LV mass index g/m^2	172 ± 47		152 ± 48		<0.0001
LV end diastolic diameter *mm*	53 ± 8		51 ± 7		0.009
LV end systolic diameter *mm*	37 ± 9		33 ± 7		<0.0001
Post LV wall thickness in diastole *mm*	12 ± 2		12 ± 2.5		NS
Fractional shortening *%*	30.5 ± 9		35.4 ± 7		<0.0001
	N	%	N	%	
Systolic dysfunction	44	33	20		<0.0001
LV dyskinesia	47	36	33	11	<0.0001
Normal echocardiogram	15	11	78	26	0.0009

Table 3. Multiple logistic regression showing factors independently associated with congestive heart failure present at the initiation of dialysis therapy

	Odds ratio	P
Age (per 10 years)	1.44	<0.001
Diabetes mellitus	2.64	<0.001
Ischemic heart disease	1.98	0.021
Systolic dysfunction	5.34	<0.001
LV mass index	NA	NA
Hemoglobin at start	NA	NA
Serum albumin at start	NA	NA
Diastolic blood pressure at start	NA	NA

NA is not associated.

failure at baseline developed *de novo* heart failure during dialysis therapy.

Congestive heart failure on initiation of ESRD therapy

Table 1 demonstrates that patients with congestive heart failure at baseline were significantly older, with a higher prevalence of diabetes mellitus, ischemic heart disease, and lower baseline serum creatinine values. There were no differences in serum cholesterol or albumin, systolic and diastolic blood pressure, or hemoglobin levels on initiation of ESRD therapy. Table 2 presents data on echocardiographic characteristics at baseline. Subjects with CHF had significantly higher left ventricular mass index, increased left ventricular end diastolic and end systolic diameters, and lower fractional shortening, when compared to those without congestive heart failure at baseline. There was also a higher prevalence of systolic dysfunction, and left ventricular dyskinesia (which included global and segmental dyskinesia). Multiple logistic regression (Table 3) indicates that systolic dysfunction, older age, diabetes mellitus and ischemic heart disease were independently associated with the occurrence of congestive heart failure at baseline, whereas LV mass index (LVMI) was not.

The median survival of subjects with congestive heart failure was 36 months, compared to 62 months in subjects without congestive heart failure ($P < 0.0001$) (Fig. 2). This adverse prognosis was independent of age, diabetes, ischemic heart disease, hemoglobin level during dialysis therapy, serum albumin, diastolic blood pressure during dialysis therapy, and LVMI (Table 4). There was no difference in survival among patients with CHF comparing those with and without systolic dysfunction controlling for age and diabetes.

De novo development of congestive heart failure during dialysis therapy

These analyses studied 299 patients who were free of congestive heart failure at the start of dialysis. Seventy-six of these developed CHF after a median time of 15 months, 218 did not develop CHF up to the time of last follow-up or censoring, and in 5 patients we had incomplete data. Subjects who developed *de novo* congestive heart failure during the course of dialysis were significantly older, with a higher prevalence of myocardial infarction at baseline, lower mean of serial serum albumin levels, and lower mean hemoglobin levels during follow-up, compared to patients who never developed heart failure (Table 5). The overall prevalence of cardiovascular disease in those who developed *de novo* CHF was much lower than in the group who had congestive heart failure at baseline (Tables 1 and 5). Subjects who developed *de novo* congestive heart failure had increased left ventricular mass index, elevated left ventricular end diastolic diameter, and a higher prevalence of systolic dysfunction at baseline, when compared to those patients who remained free of congestive heart failure (Table 6). Multivariate analysis, using Cox's Proportional Hazards Model, identified the following independent risk factors for the

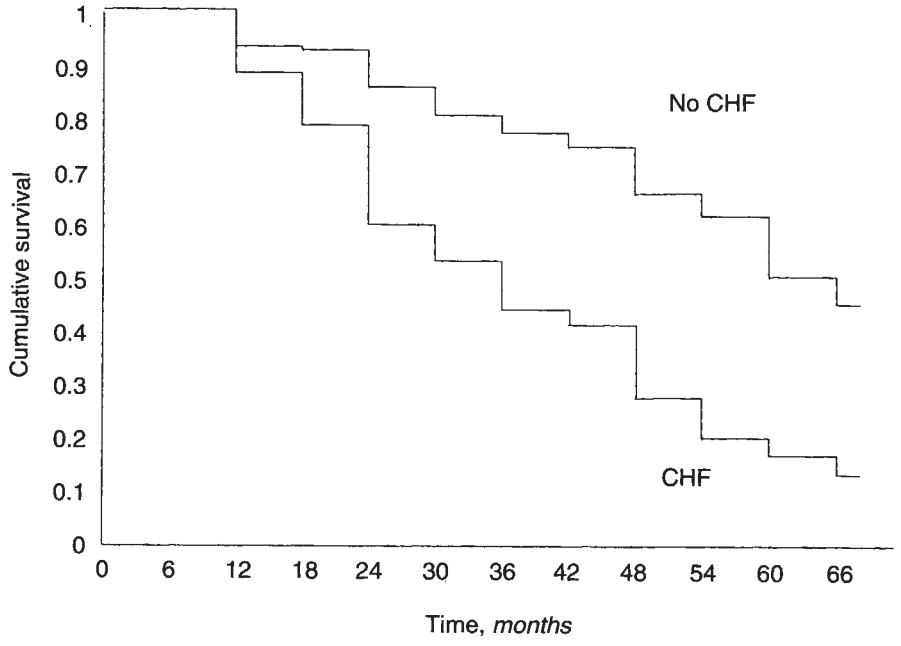

Fig. 2. *Unadjusted survival curves comparing those with congestive heart failure on initiation of ESRD therapy to those without.* $P < 0.001$.

Table 4. The effect of clinical and echocardiographic variables on starting ESRD therapy, and of mean hemoglobin, albumin and diastolic blood pressure levels measured during dialysis therapy, on survival using Cox's Proportional Hazards Model

	Odds ratio	*P*
Age (per 10 years)	1.25	0.0036
Diabetes mellitus	1.99	0.0003
Ischemic heart disease	1.38	0.1087
Congestive heart failure	1.89	0.0013
Systolic dysfunction	1.53	0.059
Hemoglobin per 10 g fall	1.14	0.048
Serum albumin per 5 g fall	1.61	<0.0001
Diastolic blood pressure per 5 mm fall	1.13	0.0267
LVMI per 20 g/m^2	1.04	0.352

development of congestive heart failure: older age, anemia, hypoalbuminemia, high diastolic blood pressure, and perhaps systolic dysfunction (Table 7). The median survival following the development of new congestive heart failure during the course of dialysis was 18 months.

In the subset of hemodialysis patients who developed *de novo* CHF there was no difference in weight gains between dialyses, compared to those who never developed CHF (2.14 ± 1.16 kg vs. 2.05 ± 0.91 kg, P = NS). There was no difference in the proportions who had average inter-dialytic weight gains > 4 kg (0% vs. 2.7%).

Recurrent heart failure

Of the 133 patients who had congestive heart failure at baseline, 75 developed recurrent heart failure and 58 remained free of congestive heart failure recurrence during the time of follow-up. The median survival for those with recurrent heart failure was 29

Table 5. Demographic and clinical data on starting ESRD therapy, together with serial blood pressure and laboratory values, in those who developed *de novo* congestive heart failure following the initiation of dialysis therapy, compared to those who did not develop heart failure

	New onset CHF (N = 76)		No CHF (N = 218)		
	N	%	*N*	%	*P*
Male	46	61	149	68	NS
Cigarette smoking	28	37	68	31	NS
Diabetes mellitus	18	26	38	17	NS
Myocardial infarction	8	10.5	10	4.6	<0.0001
Angina	10	13	20	9	NS
Coronary artery bypass graft	2	2.6	4	1.8	NS
Peripheral vascular disease	3	4	10	5	NS
Arrhythmia	5	7	6	3	NS
rHuEPO therapy	28	37	50	23	0.02
	Mean ± SD		Mean ± SD		*P*
Age *years*	54 ± 16		46 ± 17		<0.0001
Mean serum cholesterol *mmol/liter*	5.1 ± 1.5		5.25 ± 1.5		NS
Mean serum creatinine *μmol/liter*	961 ± 239		965 ± 303		NS
Mean systolic BP *mm Hg*	150 ± 25		151 ± 24		NS
Mean diastolic BP *mm Hg*	83 ± 13		84 ± 14		NS
Mean serum albumin *g/liter*	35 ± 6		37 ± 4		0.02
Mean hemoglobin *g/liter*	83 ± 17		88 ± 16		0.05

Serial values were obtained from the start of dialysis to development of *de novo* congestive heart failure or to last follow-up on dialysis.

Table 6. Echocardiographic data on starting ESRD therapy in those who subsequently developed *de novo* congestive heart failure compared to those who did not

	New onset CHF (N = 76) Mean ± SD		No CHF (N = 218) Mean ± SD		P
LV mass index g/m^2	164 ± 40		148 ± 50		0.007
LV end diastolic diameter *mm*	53 ± 7		50 ± 6		0.03
LV end systolic diameter *mm*	34 ± 8		32 ± 6		0.16
Posterior LV wall thickness in diastole *mm*	12 ± 1.5		12 ± 2.8		NS
Fractional shortening %	36 ± 9		35 ± 6		NS
	N	%	N	%	P
Systolic dysfunction	10	13	9	4	0.006
LV dyskinesia	10	13	18	8.4	NS

Table 7. Independent risk factors for the development of *de novo* congestive heart failure in dialysis subjects

Risk factor	Relative risk	P
Age *decade*	1.32	0.0045
Diabetes mellitus	1.63	0.0969
Ischemic heart disease	1.00	0.9949
Systolic dysfunction	2.05	0.0814
Hemoglobin per 10 g fall	1.49	<0.0001
Serum albumin per 5 g fall	1.34	0.0073
Diastolic blood pressure per 5 mm increase	1.32	0.0005
LV mass index per 20 g/m^2	1.04	0.494

The data are a multivariate analysis using Cox's Proportional Hazards Model, of the impact of clinical and demographic factors present at the initiation of ESRD therapy, and of mean serial hemoglobin, albumin, and blood pressure levels measured during dialysis therapy.

Table 8. Demographic and clinical factors present at the initiation of ESRD therapy, together with serial blood pressure and laboratory data in those who had congestive heart failure on initiation of ESRD therapy, who did and who did not develop a recurrence of congestive heart failure, during their life on dialysis

	Recurrent CHF (N = 75)		No recurrence (N = 58)		
	N	%	N	%	P
Male	41	55	39	67	NS
Cigarette smoking	32	43	21	37	NS
Diabetes mellitus	30	45	26	40	NS
Myocardial infarct	27	36	7	12	0.001
Angina	33	44	13	22	0.009
Coronary artery bypass graft	3	4	5	9	NS
Peripheral vascular disease	16	21	7	12	NS
Arrhythmia	12	16	8	14	NS
rHuEPO therapy	19	26	17	30	NS
	Mean ± SD		Mean ± SD		
Age	61 ± 12		55 ± 16		0.02
Serum cholesterol *mmol/liter*	5.4 ± 1.8		5.3 ± 1.6		NS
Serum creatinine *μmol/liter*	796 ± 359		808 ± 337		NS
Systolic BP *mm Hg*	150 ± 24		154 ± 23		NS
Diastolic BP *mm Hg*	82 ± 16		82 ± 13		NS
Serum albumin *g/liter*	33 ± 5.7		34 ± 5.3		NS
Hemoglobin *g/liter*	83 ± 20		87 ± 17		NS

Serial values were obtained from the initiation of ESRD therapy to the development of first recurrence of heart failure or to last follow-up on dialysis.

Table 9. Echocardiographic data on starting ESRD therapy in patients who had congestive heart failure on initiation of ESRD therapy, comparing those who had and who did not have a recurrence of CHF

	Recurrent CHF (N = 75) Mean ± SD		No recurrence of CHF (N = 58) Mean ± SD		P
LV mass index g/m^2	159 ± 37		161 ± 36		NS
LV end diastolic diameter *mm*	53 ± 8		53 ± 8		NS
LV end systolic diameter *mm*	38 ± 9		36.5 ± 9		NS
Posterior LV wall thickness in diastole *mm*	12 ± 1.8		12 ± 2.4		NS
Fractional shortening %	30 ± 9		31.5 ± 9		NS
	N	%	N	%	P
Systolic dysfunction	30	40	14	25	0.06
LV dyskinesia	31	42	16	28	NS
Normal echocardiogram	11	15	9	15	NS

months and for those without it was 45 months (P = 0.006). Table 8 reveals that patients with recurrent heart failure were significantly older, with a higher prevalence of ischemic heart disease. Table 9 shows no significant differences in echocardiographic measurements. However multivariate analysis, using the Cox's Proportional Hazards Model, shows that the risk factors for recurrent congestive heart failure are the presence of ischemic heart disease at baseline, anemia and hypoalbuminemia during dialysis therapy and the presence of baseline systolic dysfunction on echocardiogram (Table 10).

Discussion

The prevalence of congestive heart failure on the initiation of end-stage renal disease was high (31% of patients in a selected population of those who survived at least 6 months) as was its incidence after the initiation of dialysis: 25% of patients without heart failure at baseline subsequently developed heart failure, at a rate of 7% per year. These rates are similar to those observed in the Canadian hemodialysis morbidity study [10]. The prognosis of congestive heart failure was poor; in those with heart failure at baseline the median survival was 36 months. This adverse prognosis was independent of age, diabetes and ischemic heart disease, confirming a long recognized observation [4]. Patients who never had a recurrence of congestive heart failure had a better prognosis

Table 10. Independent risk factors for congestive heart failure recurrence

Risk factors	Relative risk	*P*
Age (per 10 years)	1.09	0.4532
Diabetes mellitus	1.34	0.315
Ischemic heart disease	3.10	0.0019
Systolic dysfunction	1.92	0.0170
Hemoglobin per 10 g fall	1.25	0.020
Serum albumin per 5 g fall	1.37	0.048
Diastolic blood pressure per 5 mm increase	1.02	0.318
LV index per 20 g/m^2	1.00	0.994

Multivariate analysis using Cox's Proportional Hazards Model was used, of demographic and clinical factors present on starting ESRD therapy and of mean hemoglobin, albumin and blood pressure levels measured during dialysis therapy.

(median survival = 45 months) than those who had a recurrence (29 months), but this survival was lower than those without congestive heart failure at baseline (62 months).

In this prospective study independent predictors for the presence of congestive heart failure on initiation of end-stage renal therapy were systolic dysfunction, older age, diabetes mellitus, and ischemic heart disease. Independent predictors for the recurrence of heart failure following the initiation of dialysis therapy were ischemic heart disease, anemia, hypoalbuminemia, and systolic dysfunction at baseline. However the best design to identify risk factors for the development of new congestive heart failure is the nested case control study, in which patients without congestive heart failure at baseline are followed prospectively. Patients who develop congestive heart failure *de novo* while on dialysis can then be compared to those who do not. The independent risk factors identified in this group were older age, low mean of serial hemoglobin levels, hypoalbuminemia, diastolic hypertension, and perhaps systolic dysfunction at baseline. Thus it appears that the most important underlying cardiac diseases predisposing to congestive heart failure include systolic dysfunction and ischemic heart disease, and the most important uremia related risk factors, independent of underlying cardiac disease and present during dialysis therapy, include anemia, hypoalbuminemia and hypertension. This study does not rule out excess salt and water retention as a cause of CHF, but we found no evidence that chronic excessive weight gains between dialyses predisposed to the development of CHF. Furthermore when mean inter-dialytic weight gain was included in the multivariate models it did not predict CHF.

We have already reported that anemia is an independent predictor of mortality in chronic uremia [11]. The current analysis suggests that anemia predisposes to cardiac morbidity. Consequently, amelioration of anemia with erythropoietin may improve both cardiac morbidity and mortality. Several reports [12, 13] have identified hypoalbuminemia as an adverse prognostic factor. This study is the first to suggest that its adverse effect may be exerted through the heart, as it is associated with both the recurrence of congestive heart failure and with the *de novo* development of heart failure during end-stage renal disease therapy. The mechanisms whereby hypoalbuminemia leads to cardiac dysfunction is unclear. Hypertension is an accepted risk factor for congestive heart failure in the general population [14]. In our patients with chronic uremia blood pressure control has been reasonable during dialysis therapy: mean blood pressure was 143 ± 17/80 ± 10 mm Hg, but high mean diastolic values are associated with the development of congestive heart failure. We have previously shown that a low diastolic blood pressure independently predicts overall mortality in dialysis subjects.

Much research remains to be undertaken. Cohort studies of subjects with chronic uremia (before and after initiation of dialysis) to identify the most important potentially reversible risk factors for systolic dysfunction, LV hypertrophy and ischemic heart disease should be carried out. Intervention studies to test the effect of normalization of hemoglobin using erythropoietin and to identify the best target hemoglobin are needed. Correction of hypoalbuminemia by nutritional intervention or by increased amount of dialysis, and trials of antihypertensive agents to identify the optimal target blood pressure in these subjects are also necessary. This study did not investigate the effect of dialysis prescription on the natural history of congestive heart failure, an important area for future endeavors.

We conclude that the prevalence and incidence of congestive heart failure is high, that its prognosis is adverse, that predisposing cardiac diseases include systolic dysfunction and ischemic heart disease, and that potentially reversible risk factors present during dialysis therapy include anemia, hypoalbuminemia and hypertension.

Acknowledgments

This study was supported by grants from the Kidney Foundation of Canada, the General Hospital and Amgen Inc., California. During the preparation of this research Dr. Harnett was a Scholar of the Kidney Foundation of Canada and Dr. Foley was a Baxter/Canadian Society of Nephrology/Kidney Foundation of Canada Fellow.

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