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Is C-Reactive Protein a Useful Predictor of Outcome in Peritoneal Dialysis Patients?

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Abstract. An elevated C-reactive protein (CRP) has recently been shown to be strongly predictive of mortality in hemodialysis patients. However, its predictive value in peritoneal dialysis (PD) patients has not been assessed. A cohort of 50 PD patients was followed prospectively for a 3-yr period, after initial determination of CRP. Patients with an elevated CRP (>6 mg/L; $n = 29$) had significantly reduced plasma prealbumin (0.36 ± 0.02 *versus* 0.44 ± 0.03 g/L; $P < 0.05$), decreased total weekly creatinine clearance (C_{Cr}; 52.5 ± 2.3 *versus* 63.1 ± 3.2 L/1.73 m^2; $P < 0.01$), and increased left ventricular thickness (1.24 ± 0.05 *versus* 1.08 ± 0.06 cm; $P < 0.05$) at baseline compared with those who had a normal CRP (≤6 mg/L; $n = 21$). Baseline CRP (log-transformed) correlated weakly with baseline Kt/V, C_{Cr}, and pre-albumin. With the use of a multivariate Cox's proportional hazards model to adjust for potential confounding factors, an elevated CRP was predictive of myocardial infarction (adjusted hazard ratio, 4.8; 95% confidence interval [CI], 1.0 to 23; $P = 0.048$) and tended to be predictive of fatal myocardial infarction (adjusted hazard ratio, 6.0; 95% CI, 0.8 to 43; $P = 0.07$). However, CRP was not significantly associated with all-cause mortality (adjusted hazard ratio, 2.1; 95% CI,0.8 to 5.4; $P = 0.15$). In conclusion, CRP elevation occurs in a substantial proportion of PD patients and is independently predictive of future myocardial infarction. Such patients may warrant closer monitoring and attention to modifiable cardiovascular risk factors.

Elevated plasma concentrations of C-reactive protein (CRP), a sensitive marker of underlying systemic inflammation (1–3), have been shown strongly to predict an increased risk of future myocardial infarction and stroke in seemingly healthy men (4–6) and women (7) and a higher rate of myocardial infarction in patients with traditional cardiovascular risk factors (8–10) or established coronary artery disease (11–19). Serum CRP concentrations have also been found to be significantly elevated in hemodialysis patients (20,21), in whom the prevalence of cardiovascular disease is increased approximately 20- to 100-fold compared with the general population (22). In prospective cohort studies of hemodialysis patients, some investigators recently reported that CRP is one of the most powerful predictors of mortality (23–26), although others found that the predictive value of CRP is not independent of nutritional and traditional cardiovascular risk factors (27).

There have been no published studies of the prognostic value of CRP in peritoneal dialysis (PD) patients. However, it is conceivable that the predictive value of CRP in this setting may be different from that of hemodialysis populations because hemodialysis may itself be associated with an acute phase response (20,21,28,29). Indeed, the initiation of chronic hemodialysis therapy has been shown to be associated with a 50% increase in CRP levels (20,30), and this inflammatory response has been attributed variously to prosthetic vascular access (24), bioincompatible membranes (28,31–33), acetate dialysate buffer (34), bacterial fragments in the dialysate (35,36), and endotoxins originating from the dialysis water supply (24). In contrast, serum CRP concentrations have been reported to fall with time on PD and to be significantly lower in PD patients compared with hemodialysis patients (20). The aim of the present study was to determine the value of a single baseline CRP in predicting cardiovascular events and mortality in a prevalent cohort of PD patients.

Materials and Methods

Study Population

All patients at the Princess Alexandra Hospital who had been treated with PD from January 1, 1996, were enrolled in the study. All patients were prescribed dietary protein and energy intakes of 1.3 g and 35 kcal/kg body wt, respectively. They received four or five exchanges of 2 to 3 L during a 24-h period. Only one patient received automated PD, with a regimen of four exchanges overnight and one daytime exchange, each with a volume of 2.5 L. The dialysis prescription was modified to achieve a minimum weekly Kt/V of 2.0 and

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a normalized creatinine clearance (C_{Cr}) of at least 50 L/wk per 1.73 m^2. Dialysate glucose concentration varied depending on the individual patient's requirement for ultrafiltration.

At baseline, clinical and biochemical parameters of inflammation, cardiovascular risk, comorbid illness, nutrition, and dialysis adequacy were assessed. Demographic data were recorded in addition to cause of renal failure, time on dialysis, smoking history, presence of diabetes, and history of cardiovascular disease (including angina, cardiac arrhythmia, myocardial infarction, cerebrovascular disease, and symptomatic peripheral vascular disease). One dietitian, using dietary histories and food frequency questionnaires (37), obtained an estimate of dietary protein and energy intake for each patient. In estimating total energy intake, the energy provided by dialysate dextrose absorption was calculated according to the method described by Grodstein *et al.* (38). Results were normalized for dry body weight (weight empty of dialysis fluid). Other nutritional information included a subjective global assessment using the method described by Detsky *et al*. (39) and calculation of the body mass index by dividing dry weight (in kilograms) by the square of the height (in meters) (40).

Laboratory Parameters

A serum CRP level was measured at baseline by rate nephelometry (Beckman Instruments Inc., Galway, Ireland). Values less than or equal to 6 mg/L were considered normal. Urea, creatinine, and albumin levels were determined using routine methods (Hitachi 747, Boehringer Mannheim Corporation, Indianapolis, IN). Albumin concentration was determined by the bromocresol green method. Additional biochemical, inflammatory, and nutritional parameters were measured, including serum ferritin (Centaur ferritin chemiluminescence assay, Bayer Diagnostics, Sydney, Australia), pre-albumin (immunoprecipitin analysis, Incstar Corporation, Stillwater, MN), leptin (radioimmunoassay, Linco Research Inc., St. Charles, MO), and insulin-like growth factor (radioimmunoassay, Bioclone, Marrickville, New South Wales, Australia). Further determination of cardiovascular risk included measures of fasting total plasma cholesterol and triglycerides (enzymatic colorimetry, Boehringer Mannheim Corp.), high-density lipoprotein (HDL; following precipitation with $MgCl_2$) and low-density lipoprotein (LDL; calculated using the Friedwald formula). Echocardiography was performed to measure left ventricular thickness (posterior wall) and estimate ejection fraction. Estimates of PD adequacy were calculated using the PD-Adequest software program (Baxter Healthcare Corp., Deerfield, IL). Weekly C_{Cr} were normalized to 1.73 m^2 of body surface area. Peritoneal small solute transport was assessed by a standard peritoneal equilibration test (41) in which the ratio of dialysate:plasma creatinine concentration was determined at 4 h (D/P Cr). Residual renal function was calculated as the arithmetic mean of urinary urea and C_{Cr}.

Patient Follow-Up

All patients were followed until death, completion of PD therapy, or otherwise to the end of the study 3 yr later (January 31, 1999), at which point data were censored. The causes of patients' deaths were classified according to the Australian and New Zealand Dialysis and Transplant Registry codes (42). Any additional morbidity, including cardiovascular events (nonfatal myocardial infarction, cerebrovascular events, congestive cardiac failure, or symptomatic peripheral vascular disease) and infectious complications, were also recorded on the renal unit's computer database. Acute myocardial infarction was defined as the occurrence of two of three of the following: chest pain, minimum 1 mm ST segment elevation on the electrocardiogram, and elevation of the plasma troponin I concentration to a value greater than 1.2 μg/L. Congestive cardiac failure was defined as clinical left or right heart failure requiring admission to the hospital. A cerebrovascular accident was defined as the sudden onset of a transient or permanent neurologic deficit caused by either cerebral hemorrhage or ischemia. Symptomatic peripheral vascular disease was considered to have occurred when patients experienced a new onset of intermittent claudication, rest pain, or gangrene where alternative causes, *e.g.*, calciphylaxis, were reasonably excluded.

Statistical Analyses

Normality of data was evaluated by the Kolmogorov-Smirnov test with Lilliefor's correction. Log transformations were performed when necessary. Results are expressed as mean ± SEM for continuous parametric data, median (interquartile range) for continuous nonparametric data, and frequencies and percentages for categorical data. Pearson's correlation was used to assess linear associations between log-transformed CRP and other variables. The χ^2 test was used to compare differences between proportions. Comparisons between the elevated CRP and the normal CRP groups were performed using *t* test or the Mann-Whitney *U* test, depending on data distribution. Survival curves, survival probabilities, and estimated mean survival times were generated according to the Kaplan-Meier method. Differences in the survival curves between the two groups were evaluated using the log rank test. The characteristics of the normal CRP and elevated CRP patients were compared at baseline, and any variables on which differences were found (at $P < 0.2$) and thus could be considered as potential confounders (as well as albumin, which is known to be a strong predictor of survival) were adjusted for in the subsequent Cox regression analysis. A backward elimination procedure was then carried out to remove superfluous variables ($P > 0.5$) from the model until the most parsimonious model was identified. Adjusted survival curves were estimated using the Cox average covariate method, which calculates predicted survival probabilities at the mean levels of the covariates. Patients who completed PD treatment before study termination were censored at the time of their transfer to alternative renal replacement therapy. If a patient died within 2 mo of hemodialysis transfer, then he or she was not censored as the early mortality was considered to reflect health status during the period of failing PD therapy. The number of patients provided 80% power to detect a significant 50% reduction in 3-yr survival (40 *versus* 80%) between the two groups. These calculations were based on estimates derived from survival differences reported for hemodialysis patients with raised *versus* normal CRP levels (23–26). Data were analyzed using the software package SPSS for Windows release 9.0.1 (SPSS Inc., North Sydney, Australia). *P* values less than 0.05 were considered significant.

Results

Patient Characteristics

A total of 50 patients were receiving PD at the commencement of the study. No patient was lost to follow-up. The median age of patients was 63 yr (range, 25 to 78 yr), and 70% were female. The median duration of dialysis was 1.4 yr (range, 0.1 to 11.7 yr). Baseline CRP was elevated (>6 mg/L) in 29 patients (58%) and within normal range in the remaining 21 patients (42%). The two groups were well matched with respect to demographic variables, duration of dialysis, cause of renal failure, and comorbid illness (Tables 1 and 2). The only significant differences were a lower C_{Cr}, lower plasma pre-albumin, higher LDL cholesterol, higher total cholesterol, and

Table 1. Comparison of baseline characteristics of normal CRP and elevated CRP groups[a]

Characteristic	Normal CRP (n = 21)	Elevated CRP (n = 29)	P Value
Demographic			
age (yr)	56.8 ± 3.3	59.9 ± 2.4	0.43
female gender	66.7%	72.4%	0.66
Caucasian race	95.2%	96.6%	0.63
dialysis duration (yr)	2.07 ± 0.36	2.2 ± 0.44	0.85
previous transplant	9.5%	6.9%	0.40
Cardiovascular			
BMI (kg/m^2)	25.6 ± 1.4	25.2 ± 0.8	0.79
diabetes	9.5%	27.6%	0.12
lifelong nonsmokers	76.2%	58.6%	0.19
total cholesterol (mmol/L)	5.2 ± 0.2	5.9 ± 0.2	0.02
LDL cholesterol (mmol/L)	3.2 ± 0.2	3.7 ± 0.2	0.03
HDL cholesterol (mmol/L)	0.9 ± 0.06	1.0 ± 0.07	0.14
triglycerides (mmol/L)	2.93 ± 0.3	2.8 ± 0.3	0.82
previous arrhythmia	14.3%	24.1%	0.39
previous angina	38.1%	55.2%	0.23
previous myocardial infarction	19%	37.9%	0.15
cerebrovascular disease	4.8%	3.4%	0.82
peripheral vascular disease	14.3%	31%	0.17
amputation	0%	6.9%	0.22
ejection fraction	55.4 ± 3.1%	56.6 ± 1.8%	0.74
left ventricular thickness (cm)	1.09 ± 0.06	1.2 ± 0.04	0.045
Other comorbidity			
peptic ulcer disease	23.8%	37.9%	0.29
previous cancer	9.5%	13.8%	0.65
previous peritonitis	40%	51.7%	0.82
previous exit-site infection	61.9%	55.2%	0.84
previous septicemia	9.5%	3.4%	0.67
previous noncompliance	9.5%	27.6%	0.12
Dialysis parameters			
Kt/V	2.1 ± 0.09	1.9 ± 0.07	0.91
C_{Cr} (L/wk per 1.73 m^2 BSA)	63.1 ± 3.2	52.5 ± 2.3	0.008
RRF (ml/min per 1.73 m^2 BSA)	1.33 ± 0.41	0.46 ± 0.21	0.07
D/P creatinine	0.73 ± 0.03	0.7 ± 0.02	0.32
Nutritional parameters			
malnourished on SGA	14.3%	27.6%	0.18
albumin (g/L)	36 ± 1.1	34.5 ± 0.9	0.31
pre-albumin (g/L)	0.44 ± 0.03	0.36 ± 0.02	0.02
dietary protein intake (g/kg)	1.36 ± 0.11	1.27 ± 0.10	0.54
dietary energy intake (kcal/kg)	29.2 ± 2.8	29.1 ± 2.0	0.97
IGF-I (nmol/L)	19.1 ± 2.2	15.4 ± 1.5	0.15
leptin (ng/ml)	71 ± 15	63 ± 17	0.72
hemoglobin (g/L)	105.4 ± 3.1	97.4 ± 3.1	0.086
ferritin (μg/L)	379 ± 134	353 ± 53	0.84
Medications			
aspirin	100%	100%	0.32
HMG CoA reductase inhibitors	43%	59%	0.41
antihypertensives	81%	76%	0.94
β-blockers	38%	38%	0.77
ACE inhibitors	57%	52%	0.95
calcium channel blockers	48%	34%	0.48

[a] CRP, C-reactive protein; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; C_{Cr}, creatinine clearance; BSA, body surface area; RRF, residual renal function; SGA, subjective global assessment; IGF-I, insulin-like growth factor-I; HMG CoA, hydroxymethylglutaryl coenzyme A; ACE, angiotensin-converting enzyme.

Table 2. Distribution of the causes of renal failure in the two study groups[a]

Cause	Normal CRP ($n = 21$)	Elevated CRP ($n = 29$)
Analgesic nephropathy	5 (23.8)	4 (13.8)
Tubulointerstitial disease	2 (9.5)	3 (10.3)
Renovascular nephrosclerosis	1 (4.8)	2 (6.9)
Chronic glomerulonephritis (biopsy-proven + presumed)	10 (47.6)	7 (24.1)
Diabetic glomerulosclerosis	2 (9.5)	11 (37.9)
Unknown	1 (4.8)	2 (6.9)

[a] Results are expressed as number (percentage of total). There were no statistically significant differences observed between the two groups.

greater left ventricular wall thickness in the elevated CRP group. This group also tended to have relatively reduced residual renal function and a higher prevalence of diabetes mellitus, anemia, previous cardiovascular disease, smoking, and problems with compliance than the normal CRP group. Therefore, all of these factors were included as covariates in the Cox's hazard models to adjust for potential confounding.

During the 3-yr study period, five patients (two normal CRP, three elevated CRP) transferred to hemodialysis. Nine other patients (six normal CRP, three elevated CRP) underwent renal transplantation. Data were censored at the time of transfer to these alternative renal replacement therapies. The numbers of patients who reached 0.5, 1, 1.5, 2, 2.5, and 3 yr of follow-up were 41, 27, 18, 12, 11, and 8, respectively.

C-Reactive Protein

The median (interquartile range) CRP for all patients was 8 (14) mg/L. Within each group, the median CRP was 3 (1) mg/L for the normal CRP group and 15 (23) mg/L for those with an elevated CRP. Baseline CRP for all patients correlated weakly with initial Kt/V ($r = -0.30$; $P < 0.05$), C_{Cr} ($r = -0.34$; $P < 0.05$), pre-albumin ($r = -0.36$; $P = 0.01$) (Figure 1), and previous peritonitis episodes ($r = 0.27$; $P = 0.06$). There was no significant correlation between CRP and age, dialysis duration, body mass index, leptin, albumin, insulin-like growth factor-I, nPCR, dietary protein intake, dietary energy intake, subjective global assessment, D/P Cr, ejection fraction, left ventricular wall thickness, ferritin, previous exit site infections, triglycerides, or total, LDL, or HDL cholesterol.

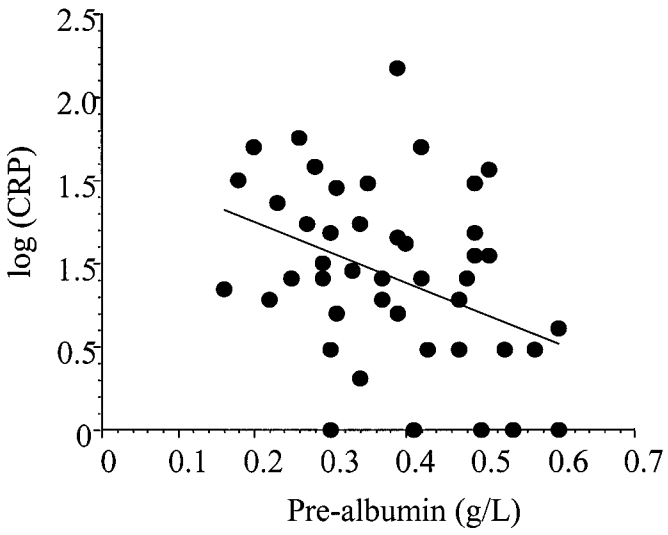

Figure 1. Relationship between log (C-reactive protein [CRP]) and pre-albumin in 50 peritoneal dialysis patients (y = 1.53 to 1.57x; $r = -0.36$; $P = 0.01$).

Influence of CRP on Cardiovascular Events

Twenty patients experienced a myocardial infarct during the 3-yr period of the study; 5 patients (24%) in the normal CRP group and 15 patients (52%) in the abnormal group were affected. In a univariate analysis, an elevated CRP was predictive of future myocardial infarction (log rank, 3.8; $P < 0.05$; Figure 2) but not of death as a result of myocardial infarction ($P = 0.15$). In a multivariate Cox's proportional hazards model, the effect of CRP as a predictor of myocardial infarction was still significant (adjusted hazard ratio, 4.8; 95% confidence interval [CI], 1.0 to 23; $P = 0.048$) after adjustments were made for diabetes mellitus, previous cardiovascular disease (myocardial infarction, angina, and peripheral vascular disease), previous smoking, C_{Cr}, pre-albumin, and albumin (Figure 3). The only other variables, besides CRP, that remained significant independent predictors of myocardial infarction–free survival were albumin ($P < 0.05$), pre-albumin ($P = 0.05$), smoking status ($P < 0.05$), and C_{Cr} ($P < 0.01$). CRP elevation tended to be associated with an increased risk of death as a result of myocardial infarction (adjusted hazard ratio, 6.0; 95% CI, 0.8 to 43; $P = 0.07$; Figure 4). The median duration of follow-up for cardiovascular mortality was 1.43 yr (range, 0.17 to 3.0 yr).

Patients with an abnormal CRP also tended to experience more combined adverse cardiovascular events ($P = 0.07$), but this was mainly influenced by myocardial infarction risk. An elevated CRP was not a significant predictor of congestive cardiac failure ($P = 0.7$), cerebrovascular accidents ($P = 0.67$), or peripheral vascular disease ($P = 0.26$).

Influence of CRP on Survival

Overall, 19 patients (65.5%) in the elevated CRP group and 9 patients (42.9%) in the normal CRP group died ($P = 0.10$).

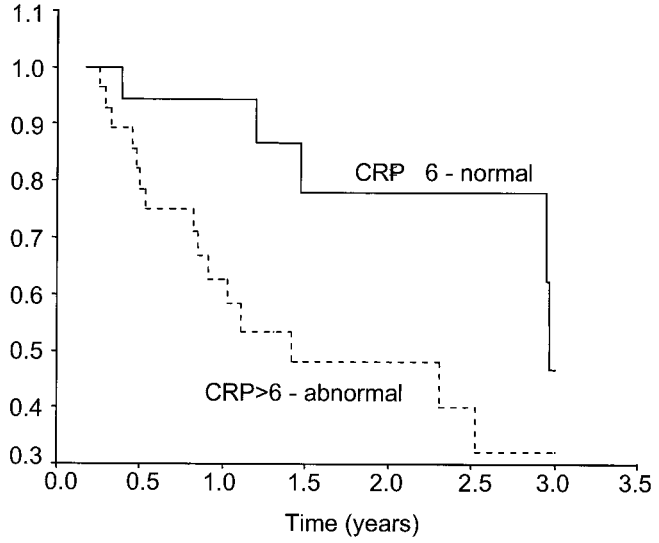

Figure 2. Kaplan-Meier estimate of time to myocardial infarction for normal *versus* elevated CRP (log-rank, 3.8; $P < 0.05$).

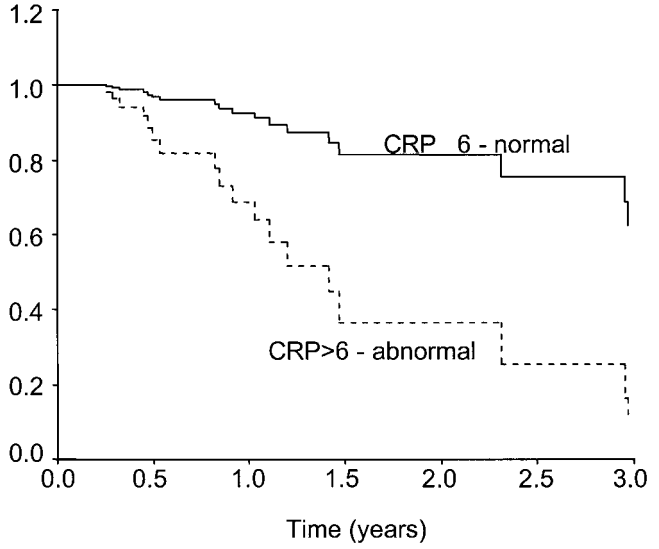

Figure 3. Adjusted myocardial infarction–free survival estimates for the normal and elevated CRP groups, using a Cox's proportional hazards model. Myocardial infarction–free survival was adjusted for diabetes mellitus, previous cardiovascular disease (myocardial infarction, angina, and peripheral vascular disease), creatinine clearance (C_{Cr}), previous smoking, pre-albumin, and albumin. The difference between the two groups was statistically significant ($P < 0.05$).

The causes of death in the elevated CRP group included cardiovascular disease (57.9%), infection (15.8%), dialysis withdrawal (15.8%), abdominal viscus perforation (5.2%), and accidental death (5.2%). Corresponding causes of death in the normal CRP group were cardiovascular disease (44.4%), infection (33.3%), dialysis withdrawal (11.1%), and abdominal viscus perforation (11.1%). There were no significant differences in the causes of death between the two groups. The mortality rate ratio associated with an elevated CRP compared with a normal CRP was 1.69 (95% CI, 0.8 to 3.7), and the odds

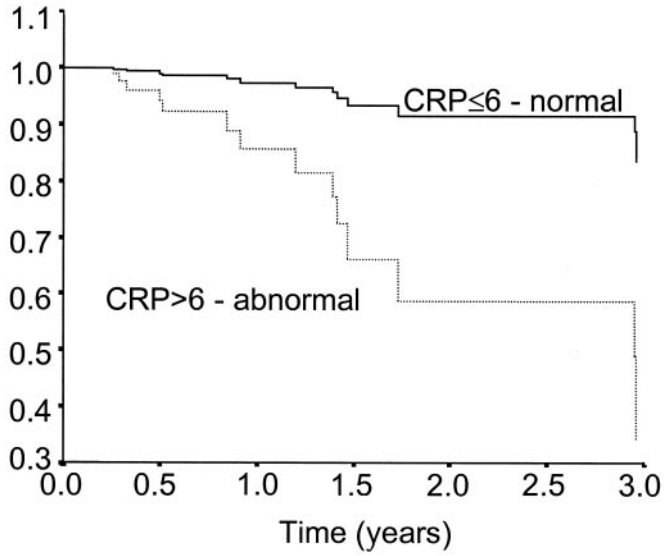

Figure 4. Adjusted time to fatal myocardial infarction estimates for the normal and elevated CRP groups, using a Cox's proportional hazards model. Time to fatal myocardial infarction was adjusted for diabetes mellitus, previous cardiovascular disease (myocardial infarction, angina, and peripheral vascular disease), C_{Cr}, previous smoking, pre-albumin, and albumin. The difference between the two groups failed to reach statistical significance (adjusted hazard ratio [HR], 6.0; 95% confidence interval [CI], 0.8 to 43; $P = 0.07$).

ratio was 2.5 (95% CI, 0.8 to 8.0). The median duration of follow-up for death was 1.47 yr (range, 0.17 to 3.0 yr).

A Cox's proportional hazards model was used to examine overall patient survival in the normal and elevated CRP groups (Figure 5) and included terms for diabetes mellitus, previous cardiovascular disease (myocardial infarction, angina, and peripheral vascular disease), history of smoking, pre-albumin, albumin, Kt/V, residual renal function, and C_{Cr} as covariates. In this model, the adjusted hazard ratio for an elevated CRP was 2.1 (95% CI, 0.7 to 5.9), but this failed to reach statistical significance ($P = 0.18$). The independent predictors of survival were pre-albumin ($P < 0.05$), albumin ($P = 0.003$), Kt/V ($P < 0.05$), nonsmoking status ($P = 0.02$), and absence of peripheral vascular disease ($P < 0.004$).

Discussion

The results of the present study indicate that an elevated CRP in PD patients is associated with an increased risk of myocardial infarction and a trend toward an increased risk of both cardiovascular death and all-cause mortality. Even when adjustment is made for the other adverse associations of an elevated CRP, including depressed nutritional indices, poor small solute clearances, atherogenic lipid profiles, left ventricular hypertrophy, and antecedent vascular disease, the predictive value of CRP for myocardial infarction remains significant.

The finding of the ability of CRP to predict future myocardial infarction in the setting of end-stage renal failure has not been previously published but is in agreement with earlier studies of vascular risk in seemingly healthy men and women

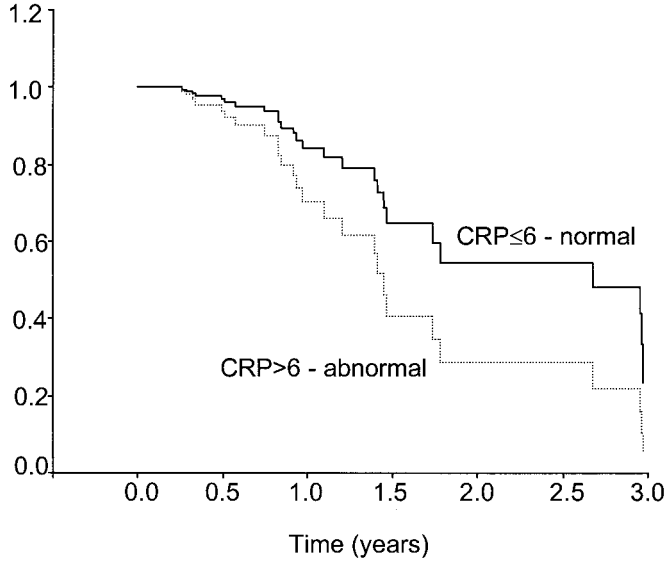

Figure 5. Adjusted overall survival estimates for the normal and elevated CRP groups, using a Cox's proportional hazards model. Overall survival was adjusted for diabetes mellitus, previous cardiovascular disease (myocardial infarction, angina, and peripheral vascular disease), C_{Cr}, previous smoking, residual renal function, Kt/V, pre-albumin, and albumin. The difference between the two groups failed to reach statistical significance (adjusted HR, 2.1; 95% CI, 0.7 to 5.9; $P = 0.18$).

(4–7). The mechanism of this association is uncertain but may reflect persistent, low-grade inflammatory activity in patients with preclinical atherosclerosis, whereby CRP elevations occur in response to ongoing vascular injury and the release of proinflammatory cytokines (including interleukin-1 and interleukin-6) by monocytes and macrophages recruited into early atherosclerotic plaques (1). CRP may also be detecting chronic inflammation generated by past infections with agents that have been linked with coronary artery disease, including *Helicobacter pylori*, *Chlamydia pneumoniae*, cytomegalovirus, herpes simplex virus, and several bacterial agents associated with periodontal disease (43). Alternatively, it has been suggested that the observed association between CRP and cardiovascular risk represents bronchial inflammation induced by smoking (9). However, this hypothesis was refuted by the finding of the present study that the predictive value of CRP for myocardial infarction was independent of smoking status. Moreover, there is now experimental and clinical evidence to suggest that CRP may itself directly promote cardiovascular injury via activation of complement (44) and induction of monocyte expression of tissue factor (a membrane glycoprotein important in initiating coagulation) (45). Thus, there are multiple, biologically plausible mechanisms that could explain the strong association observed between elevated CRP and risk of myocardial infarction in both uremic and nonuremic populations.

It is interesting that in the present study, a significant association was observed between CRP and risk of myocardial infarction despite the liberal prescription of anti-inflammatory therapies, such as aspirin and hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors. This finding contrasted with data from the Physicians Health Study (5), which demonstrated that low-dose aspirin therapy substantially attenuated the association between baseline CRP level and risk of myocardial infarction in individuals with normal renal function. Moreover, a nested case-control analysis of post–myocardial infarction patients in the Cholesterol and Recurrent Events trial (11,46) revealed that the association between CRP and risk of recurrent coronary events was significant among those randomized to placebo (relative risk, 2.1; $P < 0.05$), but was reduced and no longer significant among those assigned to pravastatin (relative risk, 1.29; $P =$ NS). Although 52% of PD patients in the current study were receiving HMG CoA reductase inhibitors (primarily simvastatin), it is possible that the abrogation of the predictive value of CRP in the Cholesterol and Recurrent Events trial was due to a specific effect of pravastatin *per se*, rather than to a class effect of HMG CoA reductase inhibitors. Alternatively, it is possible that the accelerated atherogenesis observed in patients with end-stage renal failure is less amenable to therapy with aspirin and HMG CoA reductase inhibitors, thereby resulting in a preserved strong relationship between CRP and risk of coronary events.

Although CRP predicted future myocardial infarction in PD patients, no independent association could be demonstrated between CRP and survival after adjustment for confounding variables. A type 2 statistical error as a result of insufficient sample size conceivably could have accounted for the negative finding, but it is important to note that traditional mortality risk factors, such as pre-albumin, Kt/V, smoking status, and previous vascular disease, remained significant independent predictors of patient survival in the multivariate Cox's proportional hazards model analysis. Therefore, if CRP is associated with mortal risk in PD patients, then its predictive value is substantially less than the accepted measures of nutrition, dialysis adequacy, and cardiovascular risk.

The findings of the present analysis are also supported by the largest study to date of CRP as a prognostic marker for survival in hemodialysis patients (27). Owen and Lowrie (27) reported that an elevated baseline CRP in a prevalent cohort of 1054 hemodialysis patients was associated with impaired biochemical nutritional markers (including pre-albumin) and an increased mortality at 6 mo. However, multivariate analysis failed to find a significant, independent relationship between CRP and the odds risk of death. On this basis, the authors argued that nutritional depletion of body proteins rather than inflammation was a major contributor to all-cause mortality in end-stage renal disease.

In contrast, other investigators using multivariate Cox regression analysis have reported that CRP remains a strong predictor of death in hemodialysis patients (23,24,26,47). Some of the disparity between these findings and those of Owen and Lowrie and the present study may relate to the extent of adjustment for potential confounding variables. For example, the former studies did not make statistical adjustment for hemoglobin concentration, cholesterol level (in one study), smoking status, left ventricular hypertrophy, or dialysis small

solute clearance. The inclusion of these covariates in the proportional hazards models in the hemodialysis studies may have removed the predictive value of CRP, particularly in view of the strong network of associations observed among these factors, CRP, and survival in the present study.

An alternative explanation for the difference in the prognostic value of CRP between hemodialysis and PD populations may be the activation of an acute phase response by the hemodialysis process itself. Docci *et al.* (21) found that CRP levels were comparable between healthy subjects and predialysis end-stage renal failure patients but were significantly higher in individuals who were receiving hemodialysis. Furthermore, the degree of elevation of CRP was correlated directly with the duration of hemodialysis. Haubitz *et al.* (20,30) similarly demonstrated that serum CRP concentrations rose by approximately 50% after initiation of hemodialysis with cuprophan membranes. CRP values in hemodialysis patients were approximately threefold higher than their PD counterparts from the same center. Biocompatible dialysis membranes seem to have less of an effect on CRP levels (28,32), but an appreciable acute phase response still may be generated in hemodialysis patients by prosthetic vascular grafts (24) and endotoxin contamination of dialysate (24,36). Thus, differential activation of inflammatory pathways by the two dialysis modalities may influence differentially the relative value of CRP as a prognostic marker in uremic individuals.

Volatility of the CRP measurement is unlikely to have influenced significantly the findings of this study because there was a high concordance between CRP measurements performed at baseline and those repeated 6 mo later ($r = 0.78$; $P < 0.05$). Although it is impossible to exclude occult infection in those who had an initially elevated CRP, the relative stability of the CRP elevation reported in our study and in other studies (20,48) argues against this. Moreover, a history of bacteremia and PD-related infections (peritonitis and exit-site infections) were included as covariates in the Cox regression analysis and did not independently influence survival.

In conclusion, this prospective observational study demonstrated that an abnormally elevated CRP level occurred in 58% of our PD population and was associated with an increased risk of future myocardial infarction for at least 3 yr. The predictive value of CRP was independent of nutritional indices, small solute clearance, smoking status, and other possible confounders and was clearly evident despite the liberal prescription of aspirin and HMG CoA reductase inhibitors. These data suggest that PD patients with high plasma CRP concentrations may warrant closer monitoring and extra attention to modifiable cardiovascular risk factors.

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