Predictors of Mortality in End-Stage Renal Disease Patients with Mitral Annulus Calcification

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ABSTRACT: *Objective*: Mitral annulus calcification (MAC) is an independent predictor of cardiovascular mortality in the general population. The purpose of the current historical cohort study is to assess risk factors for long-term mortality in end-stage renal disease (ESRD) patients with MAC (n = 30; age, 62 ± 2 yr), as compared to ESRD patients without MAC (n = 30; age, 63 ± 2 yr). Additional analysis compared ESRD patients with MAC to non-ESRD patients with MAC (n = 32; age, 66 ± 2 yr). *Methods:* The groups included age-matched male patients followed at a single center. Long-term survival was assessed by Kaplan-Meier analysis. Regular and stepwise Cox proportional hazards models were used to determine risk factors for mortality. *Results:* There was a similarly high prevalence of cardiovascular complications, including hypertension, coronary artery disease, left ventricular hypertrophy, atrial fibrillation, and congestive heart failure, in all three groups. Median survival time was significantly longer in non-ESRD patients (90 months), compared with the ESRD with MAC (45 months) and ESRD without MAC (45 months) patients (log-rank test; $P < 0.001$). With stepwise Cox proportional hazards model, including ESRD patients with MAC and ESRD patients without MAC, increased calcium × phosphate product, decreased serum creatinine concentration, and the presence of coronary artery disease and lower extremity amputations were independent predictors of mortality for patients with ESRD. With stepwise Cox proportional hazards model, including ESRD patients with MAC and non-ESRD patients with MAC, the presence of ESRD, atrial fibrillation, diabetes, aortic valve calcification, coronary artery disease, and tricuspid regurgitation were independent predictors of mortality. *Conclusion:* The mortality rate was high in ESRD patients, approximately 15% per year. After accounting for baseline cardiovascular disease and traditional risk factors, the presence of MAC did not confer additional risk for mortality. **KEY INDEXING TERMS:** Mitral annulus calcification; End-stage renal disease; Vascular calcification; Hemodialysis; Mortality studies. **[Am J Med Sci 2006;331(3):124–130.]**

Mitral annulus calcification (MAC) is a chronic degenerative noninflammatory process, typically affecting the base of the mitral valve.[1,2] Although MAC does not typically alter the function of the mitral valve, it has been associated with diffuse atherosclerotic vascular disease.[3] The incidence of MAC increases with advanced age and is more common in women.[1–3] An increased incidence of MAC[4–7] and vascular calcifications[7–10] has also been observed in patients with chronic kidney disease. In a cross-sectional study, mitral annulus calcification was detected in 45% of 205 chronic hemodialysis patients and 32% of 192 chronic peritoneal dialysis patients.[7,11] In hemodialysis patients, the presence of valvular calcification was correlated with coronary artery calcification, as shown by electron beam topography.[7] These data suggest that MAC may be a useful marker of atherosclerotic vascular disease in the end-stage renal disease (ESRD) patient population. Identification of cardiovascular risk factors is particularly important in the ESRD population, as cardiovascular disease continues to be the most common cause of death in this population, accounting for approximately 50% of deaths.[12]

The purpose of the current historical cohort study was to assess whether MAC serves as an independent predictor of mortality in chronic hemodialysis patients. Risk factors for long-term mortality were assessed in age- and gender-matched ESRD patients with and without MAC. For additional comparative purposes, similar analysis was performed compar-

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ing ESRD patients with MAC to age- and gender-matched non-ESRD patients with MAC.

Methods

Study Cohorts

Patients receiving nephrology care at the Veterans Affairs Medical Center, Memphis routinely receive transthoracic echocardiography as part of the evaluation for renal replacement therapy. Over an approximately 2-year period MAC was demonstrated by transthoracic echocardiogram in 30 male ESRD patients receiving renal replacement therapy. For each ESRD patient with MAC, an age- and gender-matched ESRD patient without echocardiographically detectable MAC (n = 30), who was receiving renal replacement, was selected from the database of approximately 100 patients initiating renal replacement therapy at this center during the same time interval. An additional group of non-ESRD patients with MAC detected during the same time interval was selected randomly from outpatient echocardiography records. Non-ESRD patients were referred for transthoracic echocardiography for various clinical indications by their primary care physicians. Echocardiograms were interpreted by the same cardiologist to eliminate interobserver variation. Two-dimensional echocardiograms were done using Hewlett-Packard 5500 equipment for which transducer frequencies were 2.0 to 4.0 MHz or Hewlett-Packard 2500 equipment, for which transducer frequencies were 1.7 to 2.5.

Electronic medical records were reviewed retrospectively for demographic data and evidence of cardiovascular problems, including, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, cardiac valve replacement, and peripheral vascular disease requiring surgical amputation. Laboratory data collected included hematocrit and serum calcium, phosphate, and creatinine concentrations. Calcium × phosphate products were calculated for each individual. Diagnostic criteria for coronary artery disease included previous coronary artery bypass grafting, documentation of myocardial infarction, and evidence of coronary ischemia by noninvasive stress testing or by cardiac catheterization. The diagnosis of congestive heart failure was based on typical clinical features, radiographic findings, and echocardiographic evidence of decreased systolic function (ejection fraction $< 40\%$). Plain radiographs of the chest, abdomen, and extremities were reviewed for evidence of radiographically detectable vascular calcifications. The study was approved by the Institutional Review Board, Veterans Affairs Medical Center.

Statistical Analysis

Data were analyzed using SAS Release 8.02 statistical program for Windows (SAS Institute, Cary, NC, USA). The long-term survival of three groups of patients (ESRD with MAC, ESRD without MAC, non-ESRD with MAC) was assessed using Kaplan-Meier estimates and the log-rank test for equality of survival curves. Cox proportional hazards and stepwise Cox proportional hazards (forward, Wald) models were used to determine risk factors of mortality. Significance levels for entry and stay in the stepwise Cox regression model were 25% and 10%, respectively. Two separate models were used: 1) comparing ESRD patients with MAC to ESRD patients without MAC, and 2) comparing ESRD patients with MAC to non-ESRD patients with MAC. In each model, the dependent variable was months of survival. Duration of survival (months) was calculated from the time of onset of dialysis in ESRD patients. For non-ESRD patients, the time of onset of dialysis for a unique age- and gender-matched ESRD patient was used for calculating duration of survival. Independent variables for both models included demographic data (age and ethnicity), clinical data (diabetes mellitus, hypertension, congestive heart failure, atrial fibrillation, coronary artery disease, amputation, presence of vascular calcification), echocardiographic data (left ventricular hypertrophy, decreased systolic function, diastolic dysfunction, aortic valve calcification), and laboratory data (hematocrit, concentrations of albumin, creatinine, calcium, phosphorus, and calcium phosphorus products). ESRD was included as an independent variable in the model comparing ESRD patients with MAC to non-ESRD patients with MAC. MAC was included as an independent variable in the model comparing ESRD patients with MAC to ESRD patients without MAC. Group comparisons were performed using unpaired *t*-tests for continuous variables and χ^2 analyses for discontinuous variables. Significance was determined at a *P*-value less than 0.05.

Results

There were no differences in age, ethnicity, or body surface area between ESRD patients with and without MAC. Non-ESRD patients with MAC were older than ESRD patients with MAC and ESRD patients without MAC. There were significantly more African-Americans in both ESRD groups, compared to non-ESRD patients. Body surface area was significantly greater in the non-ESRD group, compared to the ESRD groups (Table 1).

There were no differences in laboratory parameters between ESRD patients with and without MAC, other than small but statistically significant differences in serum calcium and creatinine concentrations; both were lower in the ESRD without MAC group (Table 2). Serum phosphate concentration, calcium phosphorous product, and serum creatinine concentrations were significantly lower, whereas hematocrit and serum albumin concentration were significantly higher in the non-ESRD group, as compared with the ESRD groups. Serum calcium concentrations did not differ between ESRD and non-ESRD groups with MAC.

There was a high prevalence of hypertension, coronary artery disease, and atrial fibrillation in all three groups. There was no significant difference in the frequency of these complications among the three groups. Radiographically detectable vascular calcifications were highly prevalent in both ESRD groups. There were insufficient numbers of radiographs available for comparison in the non-ESRD group. Amputations were more frequent in the ESRD groups than in non-ESRD patients.

Left ventricular hypertrophy was similarly highly prevalent in all three groups. Aortic valvular calcifications, hemodynamically significant aortic stenosis, and echocardiographically detectable aortic insufficiency were more common in both ESRD and non-ESRD patients with MAC, as compared to ESRD patients without MAC. There was no difference in the frequency of either systolic or diastolic dysfunction among the three groups. Aortic valve replacement was required in two patients in both ESRD and non-ESRD patients with MAC. No patients required replacement of the mitral valve.

Survival Comparison of End-Stage Renal Disease with Mitral Annulus Calcification versus End-Stage Renal Disease without Mitral Annulus Calcification

Kaplan Meier analysis (Figure 1) revealed that survival of ESRD patients with and without MAC