SEMINARS IN
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Creatinine Clearance and Hemoglobin Concentration Before and After Heart Transplantation

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Clinical studies indicate that indices of glomerular filtration rate (GFR) as serum creatinine or creatinine clearance can predict the risk of death in congestive heart failure (CHF) and in heart transplantation. The study reports data on creatinine clearance before and after heart transplantation in 160 patients followed-up for 5 years at our Unit. Pre-transplant creatinine clearance averaged 83.5±32 mL/min × 1.73 m^2 and was not significantly associated with 5-year mortality. Creatinine clearance significantly decreased after heart transplantation with a linear trend up to 3 years for patients with complete follow-up. Data suggest that the relation between kidney function and mortality after heart transplantation is affected by several confounders with inclusion of cause of heart disease, co-morbidity, anemia, and post-transplant decrease in kidney function.

KEYWORDS **Creatinine, glomerular filtration rate, congestive heart failure, heart transplantation, mortality**

It is interesting to note that data from the community cohort at Framingham did not assign any role for cardiovascular outcomes to kidney function in 2002.[1] In the same year, data from the National Health and Nutrition Examination Survey did not identify renal function as a risk factor for cardiovascular death.[2] However, an increased number of studies were performed recently to identify independent risk factors for mortality in heart failure. Available data indicate that reduced glomerular filtration rate (GFR) and anemia have emerged as independent risk factors for cardiovascular mortality.

The Emergence of Estimated Creatinine Clearance as a Primary Risk Factor in Congestive Heart Failure

Serum creatinine level was recognized as a prognostic marker in patients with congestive heart failure (CHF) without providing evidence of an independent role.[3] When predicted creatinine clearance (CrCl) according to Cockroft and Gault[4] was used to measure GFR, as in a previous study,[3] it was shown that a GFR of less than 60 mL/min predicted pump-failure mortality and the combined end point of death or hospitalization. Therefore, the calculation of renal function started to be considered an integral part in the cure for CHF.[5]

A significant step forward was made with the study of

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Hillege et al,[6] which enrolled 1,906 patients from 13 European countries followed-up for a mean time of 277 days (range, 0-1,091). The study detected an increase in mortality risk with decreasing GFR and left ventricular ejection fraction (LVEF). In addition, LVEF showed a lower risk estimate than GFR. With decreasing GFR and increasing New York Heart Association (NYHA) class, the mortality risk also increased, however, there was a weak inverse correlation between GFR and NYHA class. The finding opened a new era in the understanding and assessing of the progression of heart failure because it showed that the relation to mortality was stronger for GFR than for indices of heart function and likely due to factors other than cardiac output. Also in the study by Mahon et al[7] in ambulatory patients with CHF the CrCl predicted all-cause mortality. Taken together, the data supported the introduction of the prognostic use of GFR, disclosing its potential in decision making, including referral for cardiac transplantation.

Creatinine and 30-Day Mortality After Cardiac Surgery

In a study of the 30-day mortality for patients undergoing cardiac surgery, Walter et al. reported a significant difference between patients with a GFR less than or greater than 55 mL/min. The CrCl was a predictor of mortality stronger than age and plasma creatinine level.[8]

An increased concentration of blood urea nitrogen, used as an index of renal hypoperfusion, was associated with an increased risk for mortality,[9] thus indicating that even the most simple and most antique and biased test of renal function may provide a better stratification of patients with severe decompensated heart failure. In the study of Aronson et al, the blood urea nitrogen/Cr ratio gave prognostic information that was no different from that provided by blood urea nitrogen alone.

In cardiac surgery the deterioration of renal function caused an associated mortality rate of 7.7% in the study by Slogoff et al[10] and 2.9% in the study by Mangano et al.[11] Abrahamov et al[12] disclosed a mortality rate of 30% during the first postoperative month in patients with renal deterioration.

Deterioration of renal function within the first postoperative weeks as ascertained by an increase of plasma creatinine concentration of at least 25%[13] was associated with an in-hospital mortality rate of 14.5% (odds ratio, 7.8; 95% confidence interval, 3.1-20.0; $P < .001$). Deterioration of renal function was associated with an increase of long-term survival (heart rate, 1.83; 95% confidence interval, 1.38-3.20; $P < .006$). On the other hand, patients requiring dialysis experience the highest mortality rate: 53.8%,[14] 63.7%,[15] and 83.3%.[13]

In building-up a clinical score to predict acute renal failure after cardiac surgery it was shown that patients with a mean preoperative plasma creatinine concentration of 1.2 ± 0.4 mg/dL had no acute renal failure whereas patients with a plasma creatinine of 1.6 ± 0.9 mg/dL required dialysis. For the clinical score (range, 0-17) a creatinine level or more than 1.20 and less than 2.1 mg/dL was evaluated as 2 points and a creatinine level of more than 2.1 mg/dL was evaluated as 5 points.[16]

Renal Function and Mortality in Heart Transplant Patients

Data from the International Society for Heart Lung Transplantation indicate that creatinine level is associated with 1-year and 5-year mortality rates. Renal dysfunction is seen in 26.2% and 35.5% of patients within 1 and 7 years, respectively. A creatinine level of less than 2.5 mg/dL is present in 16.2% and 20.2% within 1 to 7 years, a creatinine level of more than 2.5 mg/dL is seen in 8.6% of patients within 1 year and in 10.4% within 7 years posttransplant. Dialysis is needed in 1.3% of patients within 1 year and in 4.0% within 7 years, renal transplantation is needed in 0.2% of patients within 1 year and in 0.9% within 7 years. The percentage of patients with freedom from severe renal dysfunction was less than 70% with 7 years.

Creatinine Clearance in Heart Transplant Recipients at the University of Naples: A 5-Year Study

At the Second University of Naples we have followed-up 160 heart transplant recipients (Table 1). Fifteen percent of the transplant recipients had diabetes mellitus type 2. Patients were on a triple regimen: azathioprine, steroids, and cyclosporine. The posttransplant mean follow-up period averaged 4.60 ± 2.6 years (median, 4.36 y). The pretransplant creatinine and blood urea levels averaged 1.24 ± 0.58 mg/dL plasma and 55.0 ± 35 mg/dL, respectively. The creatinine clearance (Cockroft and Gault) at transplant averaged 83.6 ± 32.09 mL/min.

Figure 1 shows the time-course changes of creatinine clearance and indicates that after heart transplantation the renal function undergoes a significant decrease with a nadir at 3 years and thereafter it levels off.

Figures 2 through 5 show the subdivision by CrCl of the whole population at 6 months, 1 year, 3 years, and 5 years and the Gaussian distribution. Class 1 represents a creatinine clearance of more than 90 mL/min, class 2 represents patients with a creatine clearance between 90 and 60 mL/min, class 3 patients represents patients with a creatinine clearance between 60 and 30 mL/min, class 4 represents patients with a creatinine clearance between 30 and 15 mL/min, and class 5 represents patients with a creatinine clearance of less than 15 mL/min. Significant changes occurred in renal function. The majority of patients were initially in class 1 and 2, and after 5 years class 3 was

Table 1 Characteristics of Patients Participating in the Study

Patients, n	160
Women/men	37/123
Age (y)	47.0 ± 12.72
Body weight (kg)	72.4 ± 11.86
Body mass index (m/kg²)	26.2 ± 3.29
Diagnosis	
Idiopatic cardiomopathy	46.3%
Postischemic cardiomopathy	34.4%
Postvalvular cardiomopathy	4.4%
Other	15%
Pretransplant United Network for Organ Sharing status	
Status 1	15%
Status 2	85%
Pretransplant blood urea, mg/dL plasma	55 ± 35.2
Pretransplant creatinine, mg/dL plasma	1.24 ± 0.58
Pretransplant creatine clearance, mL/min	83.5 ± 32

represented most often. A 27.5% loss of renal function occurred in 5 years.

The data can be matched with those of Lindelow et al,[17] who provided data on 151 heart transplant recipients who were followed-up for 1 to 9 years. At the time of transplantation those patients were 44 ± 3 years and their GFR (chromium-51 edetic acid) averaged 67 ± 16 mL/min × 1.73 m^2 at baseline, 53 ± 19 mL/min × 1.73 m^2 1 year after transplantation, 46 ± 16 mL/min × 1.73 m^2 3 years after transplantation, and 45 ± 16 mL/min × 1.73 m^2 5 years after transplantation. In 5 years they lost 33% of their baseline function and had renal function lower than patients in the present study before transplantation and at any time point after transplantation. Those data were explained on the basis of the recipient's age, cyclosporine toxicity, and the effects of antithymocyte globulin.

At the Second University of Naples, where the present

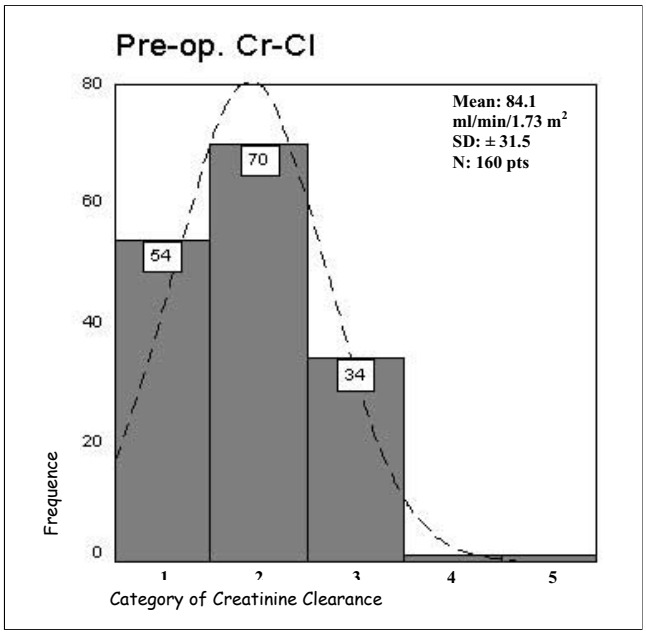

Figure 1 Distribution of predicted creatinine clearance before heart transplantation. Category 1: CCr more than 90 mL/min; category 2: CCr = 89-60 mL/min; category 3: CCr = 59-30 mL/min; category 4: CCr = 29-15 mL/min; category 5: CCr less than 15 mL/min.

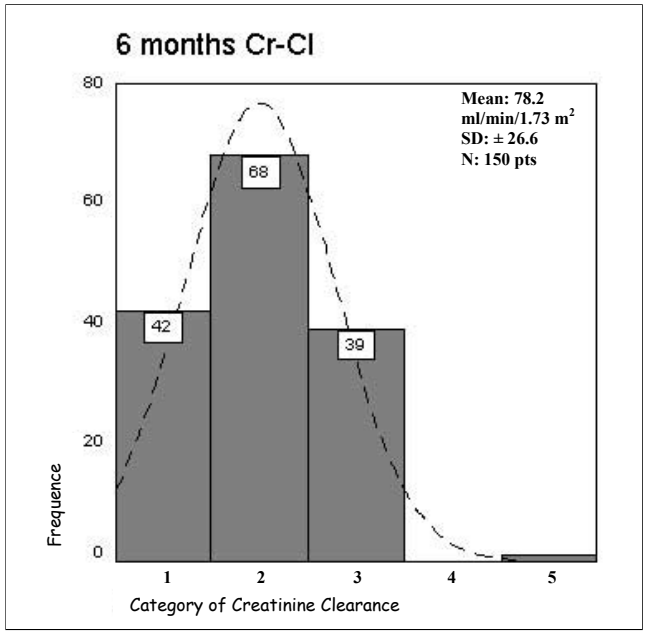

Figure 2 Distribution of predicted creatinine clearance 6 months after heart transplantation. Category 1: CCr more than 90 mL/min; category 2: CCr = 89-60 mL/min; category 3: CCr = 59-30 mL/min; category 4: CCr = 29-15 mL/min; category 5: CCr less than 15 mL/min.

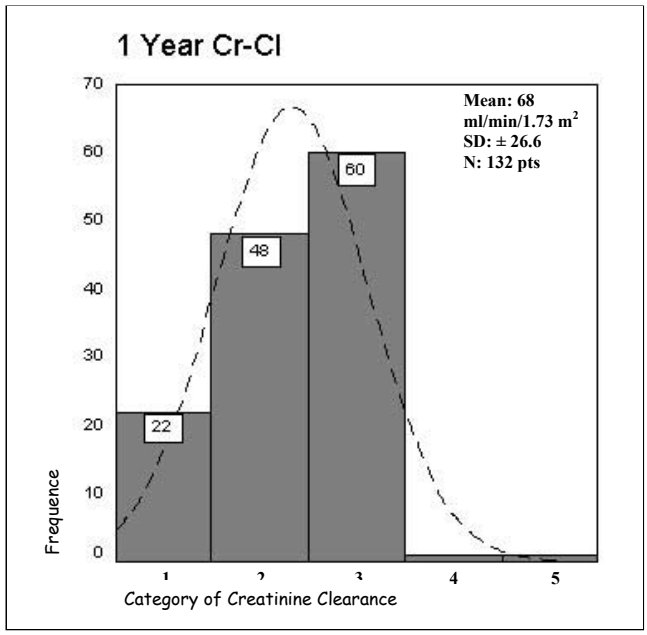

Figure 3 Distribution of predicted creatinine clearance 1 year after heart transplantation. Category 1: CCr more than 90 mL/min; category 2: CCr = 89-60 mL/min; category 3: CCr = 59-30 mL/min; category 4: CCr = 29-15 mL/min; category 5: CCr less than 15 mL/min.

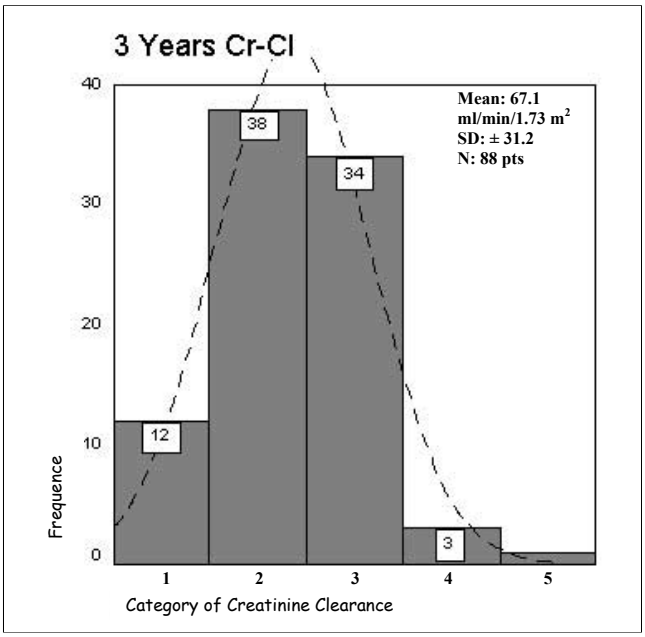

Figure 4 Distribution of predicted creatinine clearance 3 years after heart transplantation. Category 1: CCr more than 90 mL/min; category 2: CCr = 89-60 mL/min; category 3: CCr = 59-30 mL/min; category 4: CCr = 29-15 mL/min; category 5: CCr less than 15 mL/min.

findings were obtained, determinants of hospital mortality were cause ($P < .027$), United Network for Organ Sharing status 1 ($P < .001$), donor age more than 45 years ($P < .007$), and cardioplegia ($P < .009$). However a significant correlation was disclosed between worse preoperative renal function and hemoglobin concentration with higher pretransplantation status ($P = .002$ and $P < .0001$, respectively).

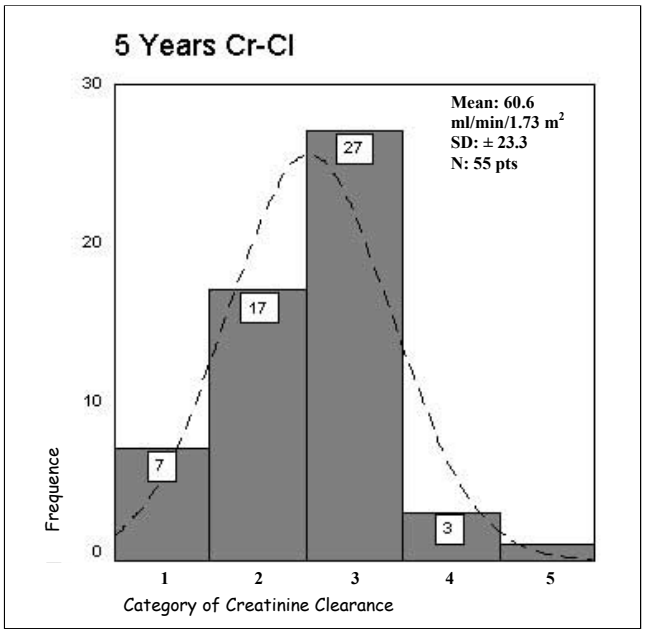

Figure 5 Distribution of predicted creatinine clearance 5 years after heart transplantation. Category 1: CCr more than 90 mL/min; category 2: CCr = 89-60 mL/min; category 3: CCr = 59-30 mL/min; category 4: CCr = 29-15 mL/min; category 5: CCr less than 15 mL/min.

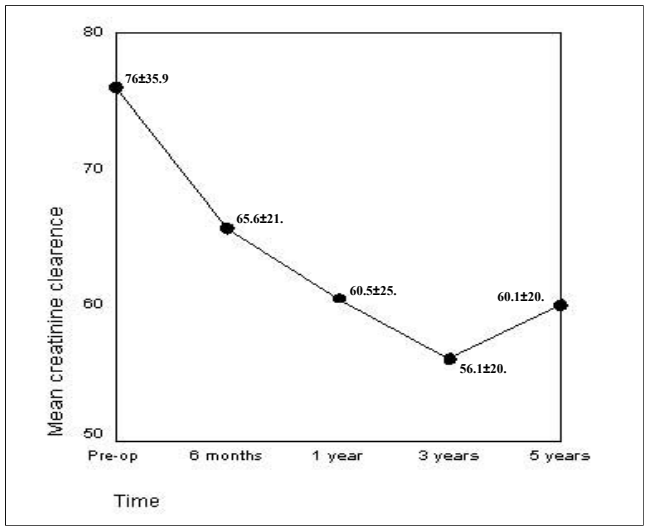

Figure 6 Mean creatinine clearance in 55 patients followed-up for 5 years after transplantation. Multivariate analysis for repeated measurements. $P < .001$ for comparisons among all time-points with exception of comparison betwen 1 year and 5 years. .

Is Preoperative Plasma Creatinine Level of 1.5 mg/dL an Inevitable Risk Factor?

In a study at the Second University in Naples, which comprised a group of 160 patients 55 with complete follow-up of at least 5 years, the mean pretransplant plasma creatinine level averaged 1.24 ± 0.58 mg/dL as reported previously. Survival versus preoperative creatinine level did not disclose any significant difference between those with a preoperative creatinine level of less than 1.5 mg/dL and those with a plasma creatinine level of more than 1.5 mg/dL (Fig 6). A statistically non-significant trend was detected.

Anemia as a Risk Factor

In 1987, the Framingham study identified anemia as an independent predictor for the appearance of CHF.[18] However, only in 1999 did CHF anemia start to attract the interest of cardiologists.[19] Therefore, it was possible to show that anemia is a predictor of CHF severity, hospitalization, and death.[20-23] In 2004, a review showed that the prevalence rates of anemia were in the range of 9.9% to 55.6% of CHF patients.[24]

Silverberg et al[20,21] and Wexler et al[24] have contributed greatly to our understanding of anemia in CHF and the readers are referred to their report in the present issue and to their previous reports. They have provided evidence that erythropoietin administration along with intravenous iron improves

shortness of breath, fatigue, and LVEF. They also showed that the rate of hospitalization and the use of diuretics were reduced significantly by correcting anemia, whereas renal function was stabilized.

According to a study by Wexler et al,[24] anemia was present in 51.0% of 202 consecutive male patients and in 54.4% of 136 female patients admitted to hospitals for CHF. Anemia was correlated negatively with plasma creatinine level, but not with NYHA class. The study was discussed in light of all available literature that has reported that anemia is more prevalent in CHF patients either admitted to hospitals, or in the elderly, or in those with higher NYHA class, or with higher serum creatinine level, or in diabetic patients, hypertensive patients, dyslipidemic patients, or ischemic heart disease patients.[24] Chronic kidney disease has a role in the genesis of anemia in CHF, however, in more than one third of patients with a normal GFR, anemia is present.[25] Other candidates are cytokines secreted by the failing heart, tumor necrosis factor α in particular, the use of angiotensin-converting enzyme inhibitors, blood loss, urinary iron loss, transferrin and erythropoietin, and hemodilution.[26-29]

The Emergence of Anemia as a Risk Factor for Life Expectancy After Heart Transplantation

Studies from the erythropoietin era obtained data from patients undergoing heart and heart-lung transplantation and did not disclose cases of unexplained anemia. Anemia was linked either to immunosuppression, or to a disturbed iron metabolism.[30] The clinical relevance of anemia in those patients was not shown.

A total of 17 deaths were observed in a group of 60 patients with mild chronic anemia who were followed-up for up to 5 years after heart transplantation. The deaths were associated with a statistically significant shorter survival period. Anemia did not depend on immunosuppression, iron, or vitamin B_{12} deficiency.[31]

The effect of hemoglobin level measured 7 to 12 months after heart transplantation was investigated in a retrospective analysis of 156 heart transplant recipients. Anemia (hemoglobin level $<$ 12.07 g/dL in men and $<$ 11.69 g/dL in women) was found in 91.6% of patients. Anemia was associated significantly with a higher serum creatinine level and a lower creatinine clearance. In the multivariate analysis only a low creatinine clearance emerged as a risk factor for survival. Therefore, anemia is a nondemographic surrogate marker for reduced survival mainly integrating GFR loss.[32]

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