SUPPLEMENTARY MATERIALS AND METHODS

Patient Population

The CPET was carried out on the first non-dialysis day on patients who were hemodialysis (HD) dependent, at least 12 hours after the last dialysis session in order to avoid the effects of interdialytic weight gains and hemodialysis-induced myocardial stunning[1, 2] on cardiovascular reserve assessment.

Delivered dose of HD was determined by the monthly measure of urea reduction ratio (URR). Calculation of URR used the formula URR = (pre-BUN – post-BUN)/pre-BUN, whereby BUN = blood urea nitrogen. The dose of peritoneal dialysis (PD) was quantitated by 24-hr collection of effluent dialysate and urine, with representative aliquots of these assayed for urea nitrogen to determine the total delivered Kt/V_{urea}. A total of three measurements of URR and two measurements of Kt/V_{urea} were collected within 6 months of CPET and their means were used for analysis.

Clinical Risk Factors

CKD-related comorbidities and clinico-pathological factors were grouped as follows: *(1)* history of cardiovascular disease (CVD) (that included nonfatal heart failure, myocardial infarction, acute coronary syndrome, percutaneous coronary intervention or coronary artery bypass graft, cerebrovascular disease or peripheral vascular disease), *(2)* diabetes, *(3)* dyslipidemia, *(4)* hypertension, *(5)* CKD duration, *(6)* dialysis vintage >1 year, (*7)* albumin *(8)* C-reactive protein, *(9)* left ventricular mass index (LVMI) and *(10)* left ventricular ejection fraction (LVEF).

Outcome

For the purpose of this study, deaths classified as cardiovascular was derived from primary causes of death listed as any of the following: cardiac arrhythmia, cardiac arrest, heart failure, cardiomyopathy, myocardial infarction and atherosclerotic heart disease.

Statistical Methods

For a further analysis, patients were grouped according to the tertiles of AT. Cox proportional hazards regression models were again used to estimate the independent prognostic effect of AT on survival time. The Cox proportional hazards model also assessed established CKD related factors for mortality such as hypertension, diabetes, dyslipidemia, prior CVD, dialysis vintage >1 year, CKD duration, LVMI LVEF, serum albumin and CRP. Hazards ratios (HRs) and 95% confidence intervals (CIs) were constructed to provide an estimate of the overall mortality risk posed by each of these variables. Variables with p-value <0.05 in a univariate Cox regression analysis plus known confounders were collectively modeled for the identification of the best fitting survival model. P-values <0.05 were used for the exclusion and inclusion of variables in this selection process. To evaluate the consistency of results, three different variable selection methods (forward selection, backwards elimination and stepwise selection) were used to identify the most accurate model (denoted *final model*). Furthermore, the effect of kidney transplantation in a subset of patients with AT <40 % predicted peak VO_2 was analyzed separately.

REFERENCES

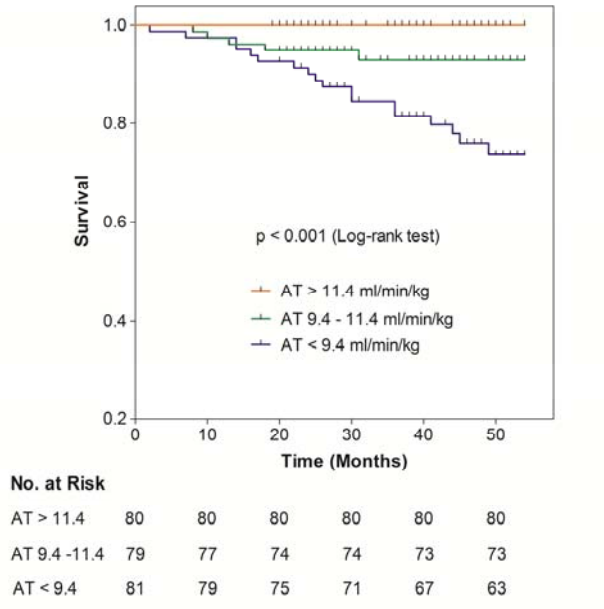
1. Burton, JO, Jefferies, HJ, Selby, NM, McIntyre, CW: Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol,* 4**:** 1925-1931, 2009.
2. Burton, JO, Jefferies, HJ, Selby, NM, McIntyre, CW: Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol,* 4**:** 914-920, 2009.

Table 1.SDC. Comorbid Factors between Patients with AT <40% and AT ≥40% of predicted peak VO_2 (n=240).

Comorbid Factors	**AT < 40% pred peak VO_2 (n = 135)**	**AT ≥ 40% pred peak VO_2 (n = 105)**	**p-value**
Age, y	47.9 ± 11.6	54.6 ± 12.3	< 0.001*
Smoking, n (%)	73 (54.1)	55 (52.4)	0.87
Dialysis modality			0.57
Pre-dialysis, n (%)	37 (27.4)	35 (33.3)	
Hemodialysis, n (%)	76 (56.3)	56 (53.3)	
Peritoneal dialysis, n (%)	22 (16.3)	14 (13.3)	
URR – hemodialysis (%)	68.5 ± 7.5	70.8 ± 6.8	0.06
Kt/V_{urea} – peritoneal dialysis (%)	2.5 ± 0.4	2.3 ± 0.3	0.28
CKD duration, months	132 (48, 203)	120 (60, 224)	0.97
>1 year dialysis, n (%)	78 (57.8)	47 (44.8)	0.05
Hypertension, n (%)	127 (94.1)	99 (94.2)	0.95
Dyslipidemia, n (%)	59 (43.7)	51 (48.6)	0.56
Diabetes, n (%)	16 (11.9)	20 (19)	0.12
Prior CVD, n (%)	24 (17.8)	14 (13.3)	0.35
Laboratory			
Albumin, g/L	42 (39, 44)	43 (40, 45)	0.11
C-reactive protein, mg/L	4 (0, 9)	4 (0, 9)	0.85
Echocardiographic			
LA diameter, cm	3.9 ± 0.8	3.8 ± 0.7	0.66
LVMI, g/m^2	131.8 ± 39.6	118.9 ± 36.3	0.02*
LVEF, %	59.8 ± 11.1	62.7 ± 9.5	0.04*
LVIDd, cm	4.9 ± 0.7	4.8 ± 0.6	0.41

Data are mean ± SD, median (IQR) or frequencies (%). Analyzed using independent samples t-test, Mann-Whitney U test or χ^2. URR and Kt/V_{urea} are measures of hemodialysis and peritoneal dialysis adequacy respectively for dialysis dependent patients; CKD, chronic kidney disease; CVD, cardiovascular disease; LA, left atrium; LVMI, left ventricular mass index corrected to body surface area; LVEF, left ventricular ejection fraction; LVIDd, left ventricular end-diastolic internal dimension. * $p < 0.05$.

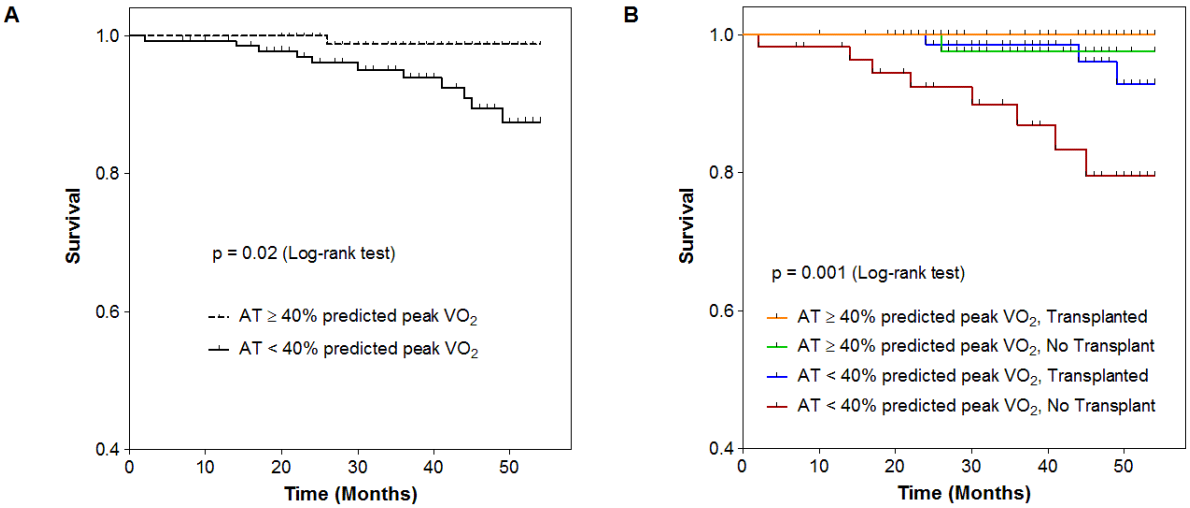
Figure 1.SDC. Kaplan-Meier survival curves for each tertile of AT for all-cause mortality.



No. at Risk

AT > 11.4	80	80	80	80	80	80
AT 9.4 -11.4	79	77	74	74	73	73
AT < 9.4	81	79	75	71	67	63

Figure 2.SDC. Kaplan-Meier survival curves using AT <40% predicted peak VO_2 as cut-off point for cardiovascular death (Panel A). Panel B shows Kaplan-Meier survival curves for cardiovascular mortality of 4 groups of patients (AT ≥40%: transplanted and those without a transplant; AT <40%: transplanted and those without a transplant).



No. at Risk

AT ≥ 40%	105	105	105	104	104	104
AT < 40%	135	128	123	119	116	112

No. at Risk

AT ≥ 40%, Transplanted	46	46	46	46	46	46
AT ≥ 40%, No Transplant	59	59	59	58	58	58
AT < 40%, Transplanted	78	78	78	77	77	75
AT < 40%, No Transplant	57	55	53	52	50	48

Appendix

Calculation of the predicted risk using patient's data and Cox proportional hazards regression *Model 1*:

The risk of all-cause mortality at up to 5 years follow-up is calculated as *hazard* = exp[0.05*Age + (-0.21*Sex) + (-0.22*AT) + 0.02*LVMI + (-0.02*LVEF) + (-1.09*Dialysis >1 year) + 0.44*Hypertension + 0.85*Dyslipidemia + (-1.88*Diabetes) + 1.59*Kidney transplant status + 0.12*Prior CVD + (-0.04*Albumin) + 0.01*C-reactive protein].
The measured values are entered for the variables Age, AT, LVMI, LVEF, Albumin and C-reactive protein, whilst Sex is coded as either 1 (female) or 0 (male), Dialysis > 1 year as either 1 (yes) or 0 (no), Hypertension as 1 (yes) or 0 (no), Dyslipidemia as either 1 (yes) or 0 (no), Diabetes as either 1 (yes) or 0 (no), Kidney transplant status as either 1 (no) or 0 (yes), prior CVD as either 1 (yes) or 0 (no).

Calculation of the predicted risk using patient's data and multiple Cox proportional hazards regression *Model 2*:

The risk of all-cause mortality at up to 5 years follow-up is calculated as *hazard* = exp[0.02*Age + 0.29*Sex + (-0.15*AT) + 1.58*Kidney transplant status.
The measured values are entered for the variables Age and AT, whilst whilst Sex is coded as either 1 (female) or 0 (male) and Kidney transplant status as either 1 (no) or 0 (yes).