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## **Aerobic exercise capacity and kidney function decline in heart failure with preserved ejection fraction patients**

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**Objectives:** Heart failure with preserved ejection fraction (HFpEF) is a common condition, accounting for half of all heart failure patients. Chronic kidney disease (CKD) is a complication frequently found in patients with HFpEF. The development of CKD among HFpEF patients results in poor prognosis. However, factors related with increased risk of kidney function decline are not well known.

**Methods:** A total of 424 HFpEF patients with preserved kidney function (estimated glomerular filtration rate >60 mL/min/1.73 m<sup>2</sup>) were included for evaluation. Aerobic exercise function was assessed by the peak O<sub>2</sub> consumption (VO<sub>2peak</sub>) values obtained through cardiopulmonary exercise test. Primary outcome was development of incident CKD, defined as two consecutive eGFR levels <60 ml/min per 1.73 m<sup>2</sup> separated by ≥90 days, during the follow up period.

**Results:** The mean age of the patients was 64.2 ± 10.6 years and 33.5% were male. Cardiac ejection fraction and eGFR at baseline were 67.0 ± 6.8 % and 87.5 ± 12.2 mL/min/1.73 m<sup>2</sup>, respectively. During 1082.8 person-years of follow-up, overall incidence rate of CKD development was 85.0 per 1,000 person-years. When the patients were grouped in tertiles by VO<sub>2peak</sub> levels, CKD incidence rate gradually increased in groups with lower VO<sub>2peak</sub> levels. Multivariable Cox analyses with sequential adjustments revealed that 1-standard deviation increase in the VO<sub>2peak</sub> level was significantly associated with a 33% lower risk of CKD development. The adjusted hazard ratio (95% confidence interval) of the lowest VO<sub>2peak</sub> tertile was 3.07 (1.51-6.24) when compared to the highest VO<sub>2peak</sub> tertile. Linear mixed-effects models showed that annual eGFR decline was more rapid in groups with lower VO<sub>2peak</sub> levels.

**Conclusions:** Poor aerobic exercise capacity, represented by reduced VO<sub>2peak</sub> levels obtained through cardiopulmonary exercise test, is closely related with a higher risk of CKD development among patients with HFpEF.

Table 1

**Table 1.** Baseline characteristics among tertile groups stratified by the level of VO<sub>2peak</sub>.

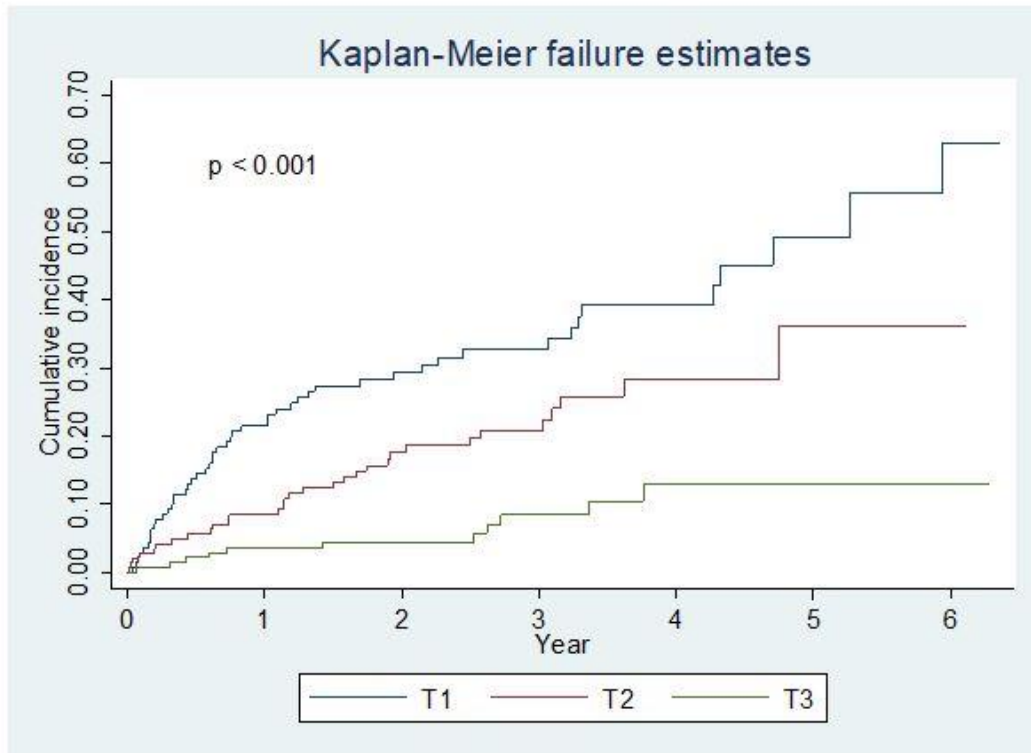
	Tertile groups stratified by the level of VO <sub>2peak</sub>				P
	Total (N=424)	T1 (N=140)	T2 (N=142)	T3 (N=142)	
<b>Demographic data</b>					
Age (year)	64.2 ± 10.6	68.8 ± 10.1	64.1 ± 10.0	59.6 ± 9.9	<0.001
Male	142 (33.5)	44 (31.4)	36 (25.4)	62 (43.7)	0.004
BMI (kg/m <sup>2</sup> )	24.8 ± 3.5	25.3 ± 3.5	24.5 ± 3.6	24.5 ± 3.2	0.09
<b>Comorbidities</b>					
Hypertension	366 (86.3)	128 (91.4)	121 (85.2)	117 (82.4)	0.08
Diabetes	100 (23.6)	42 (30.0)	38 (26.8)	20 (14.1)	0.004
Dyslipidemia	263 (62.0)	87 (62.1)	91 (64.1)	85 (59.9)	0.76
Atrial fibrillation	42 (9.9)	18 (12.9)	14 (9.9)	10 (7.0)	0.26
Stroke	46 (10.8)	22 (15.7)	15 (10.6)	9 (6.3)	0.04
<b>Laboratory parameters</b>					
eGFR (mL/min/1.73m <sup>2</sup> )	87.5 ± 12.2	84.2 ± 11.7	87.4 ± 11.7	90.8 ± 12.3	<0.001
Proteinuria	56 (16.7)	20 (16.7)	24 (21.4)	12 (11.5)	0.15
Hemoglobin (g/dL)	13.4 ± 1.4	13.1 ± 1.3	13.3 ± 1.3	13.9 ± 1.4	<0.001
NT-proBNP (pg/mL)	87.0 [44.0-196.5]	138.0 [67.5-345.5]	93.0 [45.0-220.0]	52.5 [30.0-107.0]	<0.001
<b>Medications</b>					
RAS inhibitors	210 (49.5)	70 (50.0)	79 (55.6)	61 (43.0)	0.10
Diuretics	197 (46.5)	86 (61.4)	67 (47.2)	44 (31.0)	<0.001
Beta blockers	140 (33.0)	58 (41.4)	47 (33.1)	35 (24.6)	0.01
Other anti-hypertensives	140 (33.0)	48 (34.3)	47 (33.1)	45 (31.7)	0.90
Statins	166 (39.2)	60 (42.9)	51 (35.9)	55 (38.7)	0.49
<b>Echocardiography</b>					
Ejection fraction (%)	67.0 ± 6.8	66.5 ± 7.1	67.1 ± 6.9	67.2 ± 6.4	0.64
LVMi (g/m <sup>2</sup> )	94.7 ± 21.2	96.4 ± 24.0	94.5 ± 20.5	93.4 ± 19.0	0.48
LAVI (ml/m <sup>2</sup> )	32.6 ± 10.9	34.5 ± 12.6	32.1 ± 9.6	31.2 ± 10.2	0.03
E/E' ratio	11.8 ± 3.5	13.0 ± 3.7	11.9 ± 3.8	10.6 ± 2.5	<0.001
<b>CPET parameters</b>					
VO <sub>2peak</sub> (mL/kg/min)	23.9 ± 5.6	18.1 ± 2.5	23.4 ± 1.4	30.1 ± 3.7	<0.001
Baseline SBP (mmHg)	123.0 ± 16.2	121.2 ± 17.7	124.5 ± 15.5	123.2 ± 15.1	0.21
Peak SBP (mmHg)	187.9 ± 30.7	176.4 ± 30.5	190.2 ± 31.6	196.7 ± 26.4	<0.001
Base HR (bpm)	72.1 ± 12.8	73.2 ± 14.5	72.7 ± 12.0	70.4 ± 11.7	0.15
Peak HR (bpm)	147.8 ± 22.7	131.9 ± 22.3	149.2 ± 19.7	162.0 ± 14.5	<0.001
RER	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	<0.001
VE/VCO <sub>2</sub> slope	31.0 ± 6.0	33.5 ± 6.8	30.4 ± 5.5	29.1 ± 4.8	<0.001
LT time (sec)	485.4 ± 262.8	323.8 ± 242.3	520.0 ± 233.8	610.3 ± 227.4	<0.001
VD/VT	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.48
PetCO <sub>2</sub> (mmHg)	36.9 ± 5.1	35.5 ± 5.6	37.4 ± 4.7	37.6 ± 4.8	<0.001
Chronotropic incompetence	95 (22.4)	66 (47.1)	24 (16.9)	5 (3.5)	<0.001
Abnormal HRR	58 (13.7)	40 (28.6)	13 (9.2)	5 (3.5)	<0.001
<b>HFA-PEFF scores</b>					
Intermediate	315 (74.3)	85 (60.7)	103 (72.5)	127 (89.4)	
High	109 (25.7)	55 (39.3)	39 (27.5)	15 (10.6)	

**Note:** Data are presented as mean ± SD, median [interquartile range], or n (%).

**Abbreviations:** BMI, body mass index; CPET, cardiopulmonary exercise testing; E, early diastolic mitral inflow velocity; E', early diastolic septal tissue doppler velocity; eGFR, estimated glomerular filtration ratio; HR, heart rate; HRR, heart rate recovery; LAVI, left atrial volume index; LT, lactate threshold; LVMi, left ventricular volume index; NT-proBNP, N-terminal pro B-type natriuretic peptide; PetCO<sub>2</sub>, end tidal carbon dioxide; RAS, renin-angiotensin system; RER, respiratory exchange ratio; SBP, systolic blood pressure; VD/VT, dead space/tidal volume ratio; VE/VCO<sub>2</sub> slope, minute ventilation-carbon dioxide output relationship; VO<sub>2peak</sub>, peak oxygen consumption.

Figure 1

**Figure 1.** Kaplan-Meier curves for the cumulative incidence of incident chronic kidney disease based on the  $VO_{2peak}$  categories.



**Notes:** Statistical analysis was performed using the log-rank test.

**Abbreviations:**  $VO_{2peak}$ , peak oxygen consumption.