Exercise Performance Is a Prognostic Indicator in Elderly Patients With Chronic Heart Failure
– Application of Metabolic Exercise Cardiac Kidney Indexes Score –

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Background: In patients with chronic heart failure (HF) the Metabolic Exercise Cardiac Kidney Indexes (MECKI) score, is a predictor of cardiovascular death and urgent heart transplantation. We investigated the relationship between age, exercise tolerance and the prognostic value of the MECKI score.

Methods and Results: We analyzed data from 3,794 patients with chronic systolic HF. The primary endpoint was a composite of cardiovascular death and urgent heart transplantation. Older patients had higher prevalence of comorbidities and lower exercise performance compared with younger subjects (peak VO₂, 925 vs. 1,351 L/min; P<0.0001; VE/VO₂ slope, 33.2 vs. 28.3; P>0.0001). The rate of the primary endpoint was 19% in the highest age quartile and 14% in the lowest quartile. At multivariable analysis, the independent predictors of the primary endpoint were left ventricular ejection fraction (LVEF), eGFR, peak VO₂, serum Na⁺ and the use of β-blockers in patients aged ≥70 years, and LVEF, eGFR and peak VO₂ in younger subjects. The MECKI risk score increased across age subgroups, but on receiver operating characteristic curve analysis its prognostic power was similar in both patients aged ≥70 and <70 years.

Conclusions: Older patients with HF are a high-risk population with lower exercise performance. The MECKI score increased according to age and maintained its prognostic value also in older patients. (Circ J 2015; 79: 2608–2615)

Key Words: Cardiopulmonary exercise test; Elderly; Exercise performance; Heart failure; MECKI score

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Hear failure (HF) is one of the most important causes of death and the leading cause of hospitalization in patients aged >65 years.1,2 The annual incidence of HF doubles every decade in patients aged >65 years, with a prevalence reaching 10% in the patients aged >80 years.3 Age is also one of the major determinants of prognosis in patients with HF and is associated with a wider range of comorbidities that contribute to worsen outcome.4,5

MECKI Score in Elderly HF Patients

Aging is associated with several changes in the cardiovascular system and skeletal muscle that may influence the pathophysiology and clinical presentation of HF and affect exercise performance.6,7 Cardiopulmonary exercise test (CPET) is widely used to assess exercise capacity and prognosis in HF patients,1,2,8 but few data regarding its value in older patients are currently available. Recently, the metabolic exercise and cardiac and kidney indexes (MECKI) score, a prognostic score combining data from CPET with clinical, laboratory and echocardiographic measurements, was validated in patients with chronic systolic HF.9 This score includes 6 variables: hemoglobin (Hb), serum sodium, estimated glomerular filtration rate (eGFR; estimated by means of the Modification of Diet in Renal Disease equation, MDRD), left ventricular ejection fraction (LVEF), peak oxygen consumption (calculated as % of predicted value, based on age and gender) and the slope of the minute ventilation to carbon dioxide production ratio (VE/VCO2 slope). In a previous study this score had a strong association with risk of death or need for urgent heart transplantation.9 The present study is a subanalysis of the effects of age on the predictive capacity of exercise-derived HF prognostic variables.

Methods

Patients
The study cohort consisted of 3,794 patients with systolic HF recruited and prospectively followed up in 14 Italian HF centers. Patients were enrolled as part of the MECKI score research group database. Accordingly, data for some of these patients have been previously reported.9-12 At enrollment, clinical history, laboratory, electrocardiographic, echocardiographic, and CPET data were collected. Study inclusion/exclusion criteria and follow-up have been previously reported.9 Briefly, we evaluated chronic HF patients with New York Heart Association functional class I–III and present or previous history of systolic HF with former documentation of LV systolic dysfunction (LVEF <40%), on stable evidence-based pharmacological therapy since ≥3 months before enrollment. Patients with comorbidities affecting exercise capacity or with exercise-induced angina or signs of acute myocardial ischemia were excluded.

Measurements
Standard clinical, laboratory, echocardiographic and CPET measurements were collected.9 eGFR was calculated using the MDRD formula.13 LV volumes and EF were measured on echocardiography according to standard recommendations.14 MECKI score was calculated with the subsequent algorithm: exp(k)/(1+exp(k)) where k=10.3464–0.0262×MECKI score was calculated with the subsequent algorithm:

\[ \text{Na}^+ (\text{mmol/L}) - 0.0699 \times \text{exp}(k) \times \frac{1}{1+\text{exp}(k)} \]

where k=10.3464–0.0262×MECKI score. Previous studies have shown that the MECKI score has a high performance of the MECKI score in the 2 age subgroups. A second ROC analysis was carried out to directly evaluate the performance of the MECKI score to the multivariate model in patients aged <70 and ≥70 years, respectively. The variables included in the models were the following: anaerobic threshold (AT), β-blockers, body mass index (BMI), cardiac resynchronization therapy (CRT), etiology, atrial fibrillation (AF), LVEF, gender, Hb, peak heart rate, implantable cardioverter defibrillator, MDRD, sodium, pacemaker, periodic breathing, peak respiratory rate, peak ventilation, VE/VCO2 slope, VO2 at AT, ad peak VO2% of predicted.

Receiver operating characteristic (ROC) curves were used to compare the performance of the MECKI score to the multivariate model in patients aged <70 and ≥70 years. Moreover, a second ROC analysis was carried out to directly evaluate the performance of the MECKI score in the 2 age subgroups. P<0.05 was considered statistically significant. Statistical analysis was performed using SAS (version 9.2 SAS Institute, Cary, NC, USA).
was 62 years (IQR, 53–70 years). Median peak VO$_2$ was according to age quartile are listed in Table 1. The median age and angiotensin-converting enzyme inhibitors (70% vs. 84%; P<0.0001), and have a higher proportion of subjects on diuretics, amiodarone and statins (Table 2).

### Results

**Follow-up**

The median follow-up was 1,117 days (IQR, 574–1,792) for the whole group. During follow-up 654 patients (17%) died of cardiovascular causes or underwent urgent heart transplantation. The number of events rose across subgroups from 14% in younger patients (<50 years) to 19% in the ≥70-year quartile. Specifically, cardiovascular death occurred in 373 (37.5/ year) and 184 (51.9/year) younger and elderly patients, respectively. Urgent cardiac transplant occurred in 94 cases in the whole group. During follow-up 654 patients (17%) died of cardiovascular causes or underwent urgent heart transplantation.

**Baseline Characteristics**

We analyzed 3,794 patients enrolled in the MECKI HF Italian registry. The clinical characteristics of the whole group and according to age quartile are listed in Table 1. The median age was 62 years (IQR, 53–70 years). Median peak VO$_2$ was 14.2 ml·kg$^{-1}$·min$^{-1}$ (IQR, 11.5–17.3) with a percent of predicted value of 53.3% (IQR, 42.8–64.9).

Compared to patients in the lowest quartile of age (<50 years), patients in the highest quartile (≥70 years) were more likely to have an ischemic etiology of HF and had a higher prevalence of comorbidities such as atrial fibrillation AF (24% vs. 8%; P<0.0001), lower Hb (13.0 vs. 14.0 g/dl; P<0.0001), and lower eGFR (58.1 vs. 83.8 ml/min/1.73 m$^2$; P<0.0001). The proportion of patients with a pacemaker or CRT was higher in older patients. Elderly patients also had lower lymphocyte count (expressed as percent of whole white cell count) and increased uric acid.

At echocardiography, patients in the highest age quartile had higher LVEF (34% vs. 30%; P<0.0001), smaller LV volumes and increased systolic pulmonary artery pressure (36 mmHg vs. 32 mmHg; P<0.0001). With regards to HF treatment, older patients were less likely to receive evidence-based medications for HF, namely, β-blockers (76% vs. 88%; P<0.0001) and angiotensin-converting enzyme inhibitors (70% vs. 84%; P<0.0001), and have a higher proportion of subjects on diuretics, amiodarone and statins (Table 2).

Peak exercise performance decreased steadily across the age...
MECKI Score in Elderly HF Patients

Prognostic Assessment
MECKI score increased with age from 0.04 (IQR, 0.02–0.09) to 0.07 (IQR, 0.03–0.14; P<0.0001) in the first and the last quartile, respectively (Table 4). In the Cox models for age quartiles, MECKI score had similar HR, showing that its prognostic power was similar across the age classes (P for interaction=0.734; Table 5).

In a multivariate model we analyzed the predictors of cardiovascular death or urgent heart transplantation in patients <70 years and ≥70 years, excluding MECKI score (Table 6).
In patients aged <70 years, the independent predictors of death or urgent heart transplantation were LVEF, eGFR and peak VO2 (expressed as percentage of the predicted value). In the older group (age ≥70 years), the independent predictors of the primary endpoint were LVEF, eGFR, peak VO2 (expressed as percentage of the predicted value), serum Na++ and the use of β-blockers.

On ROC curves analysis the present multivariate risk model was compared with the MECKI score model. In patients aged <70 years the two models did not differ significantly (multivariate model: AUC: 0.734 (95% confidence interval CI, 0.704–0.764) vs. MECKI model: AUC: 0.735 (95% CI, 0.706–0.765), respectively, which was not significantly different (P=0.857, χ² test; Figure 1A). Similarly, in patients aged ≥70 years the two models did not differ significantly (multivariate model: AUC, 0.712; 95% CI, 0.668–0.757 vs. MECKI model: AUC, 0.693; 95% CI, 0.646–0.740; P=0.172, χ² test; Figure 1B). In the direct comparison of the MECKI score model in patients aged <70 or ≥70 years, no significant difference was found (Figure 2), confirming that MECKI score can be applied in both age subgroups. Also, using only cardiovascular death as the endpoint, AUC did not differ in the younger group, being 0.724 for cardiovascular death and 0.735 for the composite endpoint of cardiovascular death and urgent cardiac transplant.

### Discussion

In the present study, in patients with chronic HF, exercise tolerance decreased according to age. Peak VO2, however (expressed as percentage of the predicted value), retained its prognostic value in the elderly population. When we applied the MECKI risk score, we observed a similar trend. Indeed, the MECKI score increased across age subgroups, but its predictive power was constant for both younger and older patients.

Aging is characterized by a progressive worsening of exercise capacity and cardiac dysfunction further impairs this physiological impairment. Elderly patients with HF have a blunted hemodynamic response to exercise due to both reduced stroke volume and chronotropic incompetence that leads to suboptimal exercise performance. In addition, older patients frequently have a sedentary lifestyle, which favors muscle bulk loss, and a higher prevalence of comorbidities, namely AF, renal dysfunction, chronic obstructive pulmonary disease, peripheral vascular disease, and orthopedic disorders.
MECKI Score in Elderly HF Patients

There is limited experience of CPET in elderly patients with HF in clinical practice. Although the strong prognostic value of CPET parameters in large HF series is well known, few clinical studies have evaluated its prognostic role in older patients. Scardovi et al showed that CPET was safe and feasible in HF patients aged ≥70 years, reporting also a high proportion of subjects who reached a significant respiratory exchange ratio and a detectable AT. In the present study AT was detectable in 74% of patients aged ≥70 years, with a reduction of VO₂ at AT in comparison with other subgroups, showing that submaximum exercise parameters are reduced in older patients and may be a marker of worse prognosis, as confirmed by a recent study.

In a subanalysis of the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION), the authors observed a decrease in peak VO₂ and a concomitant increase in VE/VO₂ in patients aged ≥70 years, compared with younger patients. The multivariable model of this study showed that age was the strongest independent predictor of peak VO₂ even after adjustment for concomitant diseases. Our data are consistent with these results. Interestingly, we observed that peak VO₂, despite its reduction in the elderly population, remained a strong predictor of cardiovascular events. Furthermore, we showed that the MECKI score increased significantly across age subgroup, resulting in worse outcome.

Similar risk models, which also included CPET variables, have been published previously, but the specific characteristics of the cohorts used to develop these scoring systems limit their validation in a broad range of HF patients. HF survival score was designed at an early phase of the β-blocker era, using a relatively young population (mean age, 50 years), which differs significantly from the current population of patients with HF. The risk score model of the HF-ACTION trial included CPET data, namely exercise duration, serum urea nitrogen, female sex, and BMI, but it was developed using a selected population of HF patients who met the eligibility criteria of the trial. Conversely, the MECKI score is based on a multicenter registry and the patients’ characteristics are closer to the current clinical practice. In addition, this model

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**Figure 1.** Area under the curve for the metabolic exercise and cardiac kidney indexes (MECKI) model and the present multivariate model based on (A) left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), and peak oxygen output (VO₂) in patients aged <70 years; and (B) left ventricular ejection fraction, eGFR, Na⁺, β-blocker and peak VO₂ in patients aged ≥70 years. ROC, receiver operating characteristic.

**Figure 2.** Area under the curve for the metabolic exercise and cardiac kidney indexes (MECKI) model in patients aged <70 years and ≥70 years. ROC, receiver operating characteristic.
includes data regarding renal function and hemoglobin, both known as important prognostic factors in patients with HF.

Although the original MECKI score model was developed in patients of all ages, in the present study the comparison of MECKI score with the multivariate models and the performance of MECKI score to predict cardiovascular events were similar in both younger and older patients, showing that MECKI score can be applied independently of age in a broad population of patients with HF. However, group analyses according to age may affect predictive models and several variables may gain or lose their prognostic role. Notably, in our multivariate models the main difference between younger and older patients was the strong prognostic role of β-blocker treatment in the elderly population. This is likely related to the lower percentage of elderly patients receiving β-blockers, leading to a significant difference between β-blocker treated and untreated patients. In future, a MECKI score algorithm selected for specific populations may need to be implemented.

Finally, it is recognized that elderly patients rarely undergo cardiac transplant. Accordingly, in our study, only younger patients underwent cardiac transplant, and this may have affected the primary endpoint. The composite endpoint, however, which has been used in several previous MECKI score studies, was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified, and the exclusion of urgent heart transplantations was pre-specified. According, in our study, only younger patients underwent cardiac transplant, and in future, a MECKI score algorithm selected for specific populations may need to be implemented.

Conclusions

Elderly patients with chronic systolic HF are a high-risk population with several comorbidities and lower exercise performance compared with younger patients. Exercise tolerance is a strong predictor of cardiovascular events in all age subgroups. MECKI risk score was increased in older patients, but its prognostic value was maintained independently of patient age, with a similar predictive power across age groups. Our study confirmed that MECKI score can be applied to a broad range of patients with chronic HF.

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