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RESEARCH LETTER

Edema Index Predicts Cardiorespiratory Fitness in Patients With Heart Failure With Reduced Ejection Fraction and Type 2 Diabetes Mellitus

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Fluid overload, a cardinal feature of heart failure (HF), is difficult to accurately assess noninvasively. Bioelectrical impedance analysis, an objective, noninvasive, reproducible, and relatively inexpensive method to estimate fluid status,[1] allows the measurement of the edema index (EI), a surrogate for extracellular volume status.[2] In this cross-sectional analysis, we investigated whether EI predicts cardiorespiratory fitness (CRF) in patients with HF with reduced ejection fraction (EF) and type 2 diabetes mellitus, and hypothesized that greater EI would predict reduced CRF.

The data that support the findings of this study are available from the corresponding author on reasonable request. We prospectively collected data on stable patients with symptomatic HF with reduced EF (New York Heart Association class II–III; left ventricular EF <50%) and type 2 diabetes mellitus. We measured peak oxygen consumption (VO_2), a measure of CRF, and exercise time, a measure of functional capacity, during maximal cardiopulmonary exercise testing.[3] EI was measured with single-frequency bioelectrical impedance analysis (RJL System, Inc, Clinton Township, MI) by dividing the percentage of extracellular water by total body water. Subjects underwent venipuncture to measure serum creatinine, CRP (C-reactive protein), hemoglobin, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and sodium. Health-related quality of life was assessed using the Minnesota Living With HF Questionnaire.

Data are reported as median and interquartile range (IQR). Spearman rank correlation coefficients were estimated to measure the association. Nonparametric Wilcoxon rank-sum test was used for group comparison. To investigate independent predictors for the response variable, peak VO_2, we used penalized quantile regression models with and without adjustments for age, sex, race, body mass index (BMI), biomarkers, and major comorbidities, to model the median peak VO_2. Analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC). The Virginia Commonwealth University Institutional Review Board approved the study, and all patients provided written informed consent.

Seventy-two patients (median age, 58 [IQR, 52–62] years; women, n=50 [69%]; Black race, n=34 [47%]; hypertension, n=63 [88%]; hyperlipidemia, n=56 [77%]; median BMI, 33.9 [IQR, 31.2–37.6] kg/m^2) were evaluated. Peak VO_2 and EI were 15.7 (IQR, 12.8–18.4) mL·kg^{-1}·min^{-1} (62% [IQR, 55%–69%] predicted) and 46% (44%–48%), respectively. Median respiratory exchange ratio was 1.06 (IQR, 1.03–1.11), 344 (IQR, 113–709) pg/mL for NT-proBNP, 34% (IQR, 26%–41%) for left ventricular EF, 7.8% (7.2%–8.7%) for glycosylated hemoglobin, 13.3 (IQR, 12.5–14.4) g/dL for hemoglobin, 1.1 (IQR, 0.89–1.3) mg/dL for creatinine, 2.45

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(IQR, 1.0–4.7) mg/dL for CRP, and 140 (IQR, 138–142) mEq/L for sodium. Men presented a higher median EI than women (48.2% [IQR, 43.7%–50.4%] versus 44.9% [IQR, 44.1%–46.8%]; P=0.013), and Black people had a significantly greater EI than White people (median, 46.2 [IQR, 44.8–49.7] versus 44.6 [IQR, 43.5–47.0]; P=0.020).

EI was positively associated with BMI (ρ=0.388; P=0.001) and negatively associated with age, serum creatinine, and hemoglobin (ρ=−0.239, P=0.040; ρ=−0.296, P=0.011; and ρ=−0.329, P=0.004, respectively). EI was inversely associated with peak VO_2 and exercise time (Figure). EI was also inversely associated with the ventilatory anaerobic threshold (ρ=−0.309; P=0.008) and O_2 pulse (ρ=−0.308; P=0.008), but not significantly with minute ventilation/carbon dioxide production slope (ρ=−0.091; P=0.440) nor respiratory exchange ratio (ρ=−0.009; P=0.941). Increased BMI, NT-proBNP, and Minnesota Living With HF Questionnaire score, and lower hemoglobin levels, were also associated with lower peak VO_2 (ρ=−0.353, P=0.002; ρ=−0.318, P=0.006; ρ=−0.248, P=0.035; and ρ=0.288, P=0.014, respectively).

From univariate quantile regression, each 1% absolute increase in EI was associated with a significant decrease in median peak VO_2 (β=−0.613; 95% CI, −0.885 to −0.340; P<0.001), and a significant decrease in median exercise time in seconds (β=−24.0; 95% CI, −35.3 to −12.7; P<0.001). In addition, each 1% absolute increase in EI was associated with significant decreases in 25th percentile peak VO_2 (β=−0.455; 95% CI, −0.826 to −0.085; P=0.017) and 25th percentile exercise time (β=−15.4; 95% CI, −26.9 to −3.9; P=0.009). Furthermore, each 1% absolute increase in EI was associated with a significant decrease in 75th percentile peak VO_2 (β=−0.506; 95% CI, −0.781 to −0.231; P<0.001) and a significant decrease in 75th percentile exercise time (β=−11.9; 95% CI, −23.7 to −0.2; P=0.046).

Using multivariable quantile regression with adaptive least absolute shrinkage and selection operator, EI together with all other collected variables was initially included for modeling the association with peak VO_2 and exercise time, separately. The most parsimonious quantile regression models were obtained on the basis of the selected nonzero regression coefficients, for 25th, 50th, and 75th percentiles of the response variables. EI remained negatively associated with 25th percentile peak VO_2 (β=−0.431; 95% CI, −0.790 to −0.072; P=0.019), with median peak VO_2 (β=−0.364; 95% CI, −0.589 to −0.138; P=0.002), and with 75the percentile peak VO_2 (β=−0.430; 95% CI, −0.810 to −0.052; P=0.027). Age was significantly associated with median peak VO_2 (β=−0.161; 95% CI, −0.260 to −0.062; P=0.002), as well as BMI with median peak VO_2 (β=−0.231; 95% CI, −0.369 to −0.093; P=0.001) and Minnesota Living With HF Questionnaire with median peak VO_2 (β=−0.032; 95% CI, −0.058 to −0.006; P=0.018).

Similarly, EI remained negatively associated with 25th percentile exercise time (β=−20.7; 95% CI, −29.3 to −12.2; P<0.001), median exercise time (β=−14.1; 95% CI, −22.5 to −5.5; P=0.002), and 75th percentile exercise time (β=−13.9; 95% CI, −29.9 to 1.9; P=0.083). Also, age was significantly associated with median exercise time (β=−4.6; 95% CI, −7.9 to −1.2; P=0.009), NT-proBNP was associated with median exercise time (β=−0.063; 95% CI, −0.101 to −0.025; P=0.003), and Minnesota Living With HF Questionnaire was associated with median exercise time (β=−0.998; 95% CI, −1.869 to −0.128; P=0.025).

In this study, we showed for the first time that bioelectrical impedance analysis–measured EI, which reflects increased extracellular volume, serves as an independent

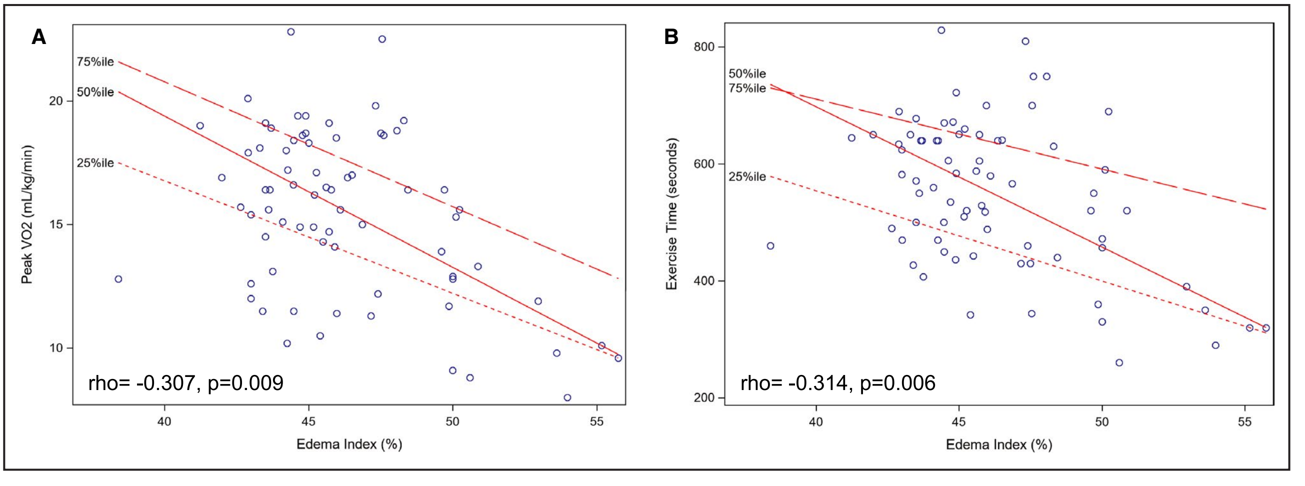

Figure. Edema index, cardiorespiratory fitness, and functional capacity.
Edema index was inversely associated with peak oxygen consumption (VO_2) (**A**) and exercise time (**B**), measured during maximal cardiopulmonary exercise testing in patients with type 2 diabetes mellitus and heart failure with reduced ejection fraction.

predictor of CRF in patients with HF with reduced EF and type 2 diabetes mellitus. Greater EI was also associated with worse functional capacity (ie, exercise time).

In patients with acute decompensated HF, EI was previously found to be a predictor of HF readmissions and all-cause mortality.[4] Our study, however, included long-term stable patients, therefore complementing the prior study on the potential utility of EI. Measuring EI in this population could therefore provide an early opportunity for optimization of medical therapy, perhaps resulting in increased CRF.

In conclusion, although limited by the cross-sectional nature of the study and relatively small sample size, we have shown that an increased EI was associated with worse CRF and functional capacity in patients with HF with reduced EF and type 2 diabetes mellitus.

ARTICLE INFORMATION

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