Enhanced Echo Intensity of Skeletal Muscle Is Associated With Exercise Intolerance in Patients With Heart Failure

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ABSTRACT

Background: Skeletal muscle is quantitatively and qualitatively impaired in patients with heart failure (HF), which is closely linked to lowered exercise capacity. Ultrasonography (US) for skeletal muscle has emerged as a useful, noninvasive tool to evaluate muscle quality and quantity. Here we investigated whether muscle quality based on US-derived echo intensity (EI) is associated with exercise capacity in patients with HF.

Methods and Results: Fifty-eight patients with HF (61 ± 12 years) and 28 control subjects (58 ± 14 years) were studied. The quadriceps femoris echo intensity (QEI) was significantly higher and the quadriceps femoris muscle thickness (QMT) was significantly lower in the patients with HF than the controls (88.3 ± 13.4 vs 81.1 ± 7.5, $P = .010$; 5.21 ± 1.10 vs 6.54 ± 1.34 cm, $P < .001$, respectively). By univariate analysis, QEI was significantly correlated with age, peak oxygen uptake (VO_2), and New York Heart Association class in the HF group. A multivariable analysis revealed that the QEI was independently associated with peak VO_2 after adjustment for age, gender, body mass index, and QMT: β-coefficient $= -11.80$, 95%CI (-20.73, -2.86), $P = .011$.

Conclusion: Enhanced EI in skeletal muscle was independently associated with lowered exercise capacity in HF. The measurement of EI is low-cost, easily accessible, and suitable for assessment of HF-related alterations in skeletal muscle quality. (*J Cardiac Fail 2020;26:685–693*)

Key Words: Heart failure, exercise intolerance, skeletal muscle, echo intensity.

Heart failure (HF) is characterized by reduced exercise capacity and aberrant skeletal muscle alterations that are involved in HF-related symptoms and the prognosis.[1,2] The muscle alterations in HF include a switch in the myofibers from slow type I to fast type II, muscle atrophy and the change in muscle composition, intermuscular fat infiltration, microvascular rarefaction, and impaired energy metabolism due to a reduction in mitochondrial density and oxidative function.[3–6] These changes have been considered as important factors in the exercise capacity of individuals with HF. Decreased percentage of oxidative fibers, oxidative enzyme activity, and microvascular dysfunction in skeletal muscle have been correlated to impaired peripheral oxygen extraction and alterations in peripheral oxygen consumption, and to related reductions in exercise capacity.[7,8] With regard to muscle energy metabolism, our prior study using magnetic resonance spectroscopy (MRS) revealed that phosphocreatine, a high-energy phosphorylated metabolite in quadriceps muscle, is prone to be depleted during maximal exercise in patients with HF.[9] Moreover, the metabolic limitation in the local limb muscle was a strong determinant of systemic exercise capacity.[10]

The deficit in muscle energy metabolism in HF has been indicated to occur as a result of impairments of oxidative phosphorylation, such as fatty acid β-oxidation through mitochondrial dysfunction.[3] Indeed, we observed an increase in intramuscular fat deposition in the tibialis anterior muscle from patients with dilated cardiomyopathy, which was negatively correlated with their exercise capacities.[11] In addition, Kitzman et al[6] showed that abnormal fat

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See page 691 for disclosure information.

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infiltration in the thigh skeletal muscle was associated with reduced exercise capacity in patients with HF with preserved ejection fraction (HFpEF), suggesting that both loss of lean body mass and quality of muscle determines peak VO_2. To detect such a deposition of intramuscular fat, however, MRI or computed tomography (CT) is essential and is not always available in general facilities.

Muscle ultrasonography (US) using a computer-aided grayscale analysis has been recognized as a useful imaging tool for the measurement of muscle quality.[12,13] In a comparison with findings obtained by MRI and a histological analysis, higher echo intensity (EI) was reported to indicate increased intramuscular fat and connective tissues.[14] It has also been shown that there is an inverse relationship between EI and the muscle strength and/or aerobic exercise workload in elderly populations, independently of the quantity of skeletal muscle.[13,15,16]

In terms of routine utility in clinical practice, US offers the substantial advantages of being safe, low-cost, and easily accessible. Elderly patients with HF in particular may benefit from these conveniences of US, because they have a high prevalence of sarcopenia and frailty. Given that the impaired energy metabolism in the skeletal muscle, specifically in the lower limb muscles, is a major contributor to lowered systemic exercise capacity,[17,18] we hypothesized that this novel approach using muscle US and a computer-aided grayscale analysis to identify muscle alterations could be useful to predict exercise intolerance associated with HF.

We conducted the present study to determine the relationship between the quadriceps muscle quality assessed by EI and the exercise capacity shown by cardiopulmonary exercise testing in patients with HF.

Methods

Patients

Fifty-eight patients with chronic HF (34 men and 24 women, 61 ± 12 years, New York Heart Association [NYHA] functional class I−III) and 28 individuals as controls (22 men and 6 women, 58 ± 14 years) were studied. HF was diagnosed based on the Framingham criteria provided in the American College of Cardiology Foundation/American Heart Association Task Force on Practice guidelines.[19] Eligible subjects were ambulatory patients at Hokkaido University Hospital who had chronic HF of NYHA class I−III, i.e., a history of 1 or more of hospitalizations due to worsening HF and ≥1 month post-discharge without worsening events. All patients were on standard medical therapies for HF, and on an optimal diuretic dose. The exclusion criteria were as follows: patients with NYHA class IV; acute decompensated patients with HF; patients with lower limb dysfunction such as orthopedic disease and intermittent claudication, as well as those with neuromuscular disease, significant pulmonary disease, or disorders other than cardiac disease that limit exercise performance; patients with infectious disease, severe liver failure, severe renal failure (on dialysis), and marked obesity (body mass index [BMI]>35). The control group consisted of subjects from the Hokkaido University Hospital who had no history of HF with a left ventricular ejection fraction (LVEF) >50%. The exclusion criteria were the same as for the patients with HF. The protocol was approved by the Medical Ethics Committee of Hokkaido University Hospital in accordance with the ethical principles described in the Declaration of Helsinki (2013 revised version), and written informed consent was obtained from all participating subjects.

Muscle Ultrasound Measurements

Ultrasound images of the quadriceps femoris muscle (QFM) in both legs, including the vastus lateralis (VL), rectus femoris (RF), vastus intermedius (VI), and vastus medialis (VM) muscles, were obtained with a HI-VISION Avius ultrasound (Hitachi, Tokyo). The ultrasound was set for 70-mm depth, 90-dB gain, and neutral time gain compensation, and was not further adjusted during the study period.

Each subject was in a supine position with the lower limbs relaxed and extended during all measurements.[20] Contact gel was applied to the skin to provide acoustic contact without compression or deformation of the muscle. Transversal images were acquired via the transverse plane view and the longitudinal plane view perpendicular to the skin using a 5−12 MHz linear-array probe. The VL muscle image was measured at 50% of the distance between the greater trochanter and the lateral superior condyle of the femur.[20] The RF and VI images were measured at 50% of the distance between the patella upper border and the anterior superior iliac spines.[21] The VM images were measured distal to 30% of the distance between the lateral knee joint cleft and the femoral greater trochanter.[22] To assess the muscle thickness, we measured the distance between the adipose tissue-muscle interface for the VL, RF, and VM, and the bone−muscle interface for the VI. The mean muscle thickness of each quadriceps portion in the right and left legs was determined, and the quadriceps muscle thickness (QMT) was calculated as the sum of the 4 individual quadriceps portions.[23]

The EI of the skeletal muscles was determined by a computer-assisted 8-bit grayscale analysis using the standard histogram function in Adobe Photoshop CC 2014 (Adobe Systems, San Jose, CA). Regions-of-interest (ROIs) were selected to include as much muscle as possible while avoiding bone and surrounding fascia. The mean EI of the ROIs was expressed as a value from 0 (black) to 255 (white). The quadriceps EI (QEI) was calculated as the mean EI of the 4 individual quadriceps muscles in both legs as described previously.[23]

Intra- and Interobserver Variability of Ultrasound Measurements

The same investigator (H.H.) took all of the measurements of QEI and QMT. To confirm the reliability of the ultrasound measurements, we assessed the intra-observer differences in repeated ultrasound measurements performed by the same examiner in 5 subjects (mean age 23 ± 2 years, all males). The intraclass correlation coefficient (ICC: 1.1) values were 0.97 for QEI and 0.99 for QMT. We also

evaluated the interobserver differences in the measurements performed by 3 independent examiners (K.Y., Y.O., N.K.) blinded to the other examiner's measurements in 5 subjects (mean age 24 ± 2 years, all males). The ICC (2.1) values were 0.89 for QEI and 0.93 for QMT.

The Assessment of Muscle Mass and Strength

We measured the muscle mass by conducting a bioelectrical impedance analysis (Inbody 770, Tokyo).[24] Patients with a pacemaker or implantable cardioverter defibrillator were excluded because of contraindications of this measurement. The maximal isokinetic peak torque of each right and left quadriceps femoris muscle were obtained using an isokinetic dynamometer (Biodex System 4, Biodex Medical Systems, Shirley, NY) as described previously.[25] To obtain the isokinetic peak torque, each subject performed 10 dynamic repetitions of concentric knee extensions/flexions at 180°/s. Maximal peak torque was defined as the highest value of the torque (Nm) recorded during the unilateral knee extension. Handgrip strength was measured using a grip dynamometer (Grip-D; Takei Scientific Instruments, Tokyo).

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed using an upright electromechanical bicycle ergometer (Aerobike 75XLII, Combi Wellness, Tokyo) with a ramp protocol as described previously.[26] Briefly, after 3 minutes of unloaded cycling, the exercise load was increased in 10−15 W/min increments in patients with HF and 20−25 W/min increments in the control subjects to the point of symptom-limited maximal work. The patients with HF stopped the exercise when they had severe leg fatigue and/or dyspnea. The subject's oxygen uptake (VO_2) was acquired by a breath-by-breath method at rest and throughout the exercise period by an expired gas analyzer (Aeromonitor AE-300S; Minato Medical Science, Osaka, Japan). Peak exercise HR and systolic blood pressure were obtained. Peak VO_2 was defined as the VO_2 attained at maximal exercise, and the anaerobic threshold (AT) was determined by the V-slope method.

Other Clinical Variables

Each subject's body weight and height were measured, and the BMI (body weight/[height]^2, kg/m^2) was calculated. The cause of HF and the medication(s) used by each patient were determined based on medical records. The 10-m gait speed was evaluated based on the duration of time required to walk the middle 10 m during a maximum 14-m walk.

All participants' left ventricular (LV) end-diastolic dimension (EDD), end-systolic dimension (ESD), and left atrial diameter (LAD) were measured in the parasternal long-axis view by transthoracic echocardiography. The LVEF was calculated from the apical 4- and 2-chamber views according to the modified Simpson's method. LV mass was calculated using the Devereux formula and normalized by body surface area (LV mass index [LVMI]). All patients underwent measurements of the estimated glomerular filtration rate (eGFR), hemoglobin (Hb), HbA1c, and plasma brain natriuretic peptide (BNP). The eGFR was calculated from the serum creatinine values and age using the Japanese equation.

Statistical Analyses

The required patient sample sizes were calculated based on the previous study from Fukumoto et al,[13] in which the correlation coefficient between the EI of the femora and muscle power was −0.40 in 92 healthy elderly subjects. To detect the effect compared with the threshold change of 0 under the conditions of α=0.05, β=0.2 and allocation ratio=2 (HF/controls), the sample sizes needed were calculated to be 46 for the HF group and 23 for the controls. Data are expressed as the mean ± SD for continuous variables and as numbers and percentages for categorical variables. We used the unpaired Student's t test or the Mann−Whitney U test to compare continuous variables, and the chi-square test for categorical variables. Normality was tested using the Shapiro-Wilk normality test. A univariate linear regression model was used to determine the correlations between muscle intensity and other clinical variables. We conducted a multivariable linear regression analysis, including clinical parameters or variables with a Pvalue < .2 in the univariate model, to identify the independent variables associated with muscle intensity. All analyses were performed using JMP 14.0.0 software (SAS, Cary, NC). The differences were considered significant when the P values were < .05.

Results

Patient Characteristics

The age, gender, and past history of the HF and control groups were comparable, whereas the BMI was significantly lower in the HF group (P = .037; Table 1). Regarding the NYHA functional class, 7 patients were in class I, 45 patients were in class II, and 6 patients were in class III. Twelve patients (21%) had HFpEF. The etiologies of HF were ischemic heart disease in 16 patients and non-ischemic heart disease in the other 42 patients. Angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II type I receptor antagonists (ARBs) were used in 98% of the patients with HF: β-blockers in 93%, aldosterone antagonists in 60%, and diuretics in 64%. The echocardiographic study revealed that the patients with HF had significantly greater LVEDD and lower LVEF values (both P< .001) compared with the control group. The peak VO_2 and AT values were significantly lower in the patients with HF (both P< .001). The plasma BNP values were significantly higher and the hemoglobin and eGFR values were significantly lower in the patients with HF compared with the control subjects (all P< .001).

Table 1. Characteristics of the Control Subjects and Patients With HF

	Control	HF	
	(n = 28)	(n = 58)	*P* Value
Demographic and clinical factors			
Age, y	58 ± 14	61 ± 12	.225
Male, n (%)	22 (79)	34 (59)	.069
BMI, kg/m^2	25.2 ± 3.2	23.3 ± 4.8	.037
Hypertension, n (%)	11 (39)	16 (28)	.273
Diabetes mellitus, n (%)	6 (21)	16 (28)	.540
Dyslipidemia, n (%)	15 (54)	34 (59)	.658
NYHA (I / II / III)		(8 / 41 / 6)	
HFpEF, n (%)		12 (21)	
Medication, n (%)			
ACE-Is or ARBs	7 (25)	56 (98)	<.001
Aldosterone antagonists	1 (4)	34 (60)	<.001
β-blockers	3(11)	52 (93)	<.001
diuretics	0 (0)	36 (64)	<.001
statins	12 (43)	33 (60)	.138
Etiology of HF, n (%)			
Ischemic heart disease	—	16 (28)	
Non-ischemic heart disease	—	42 (72)	
Laboratory test results			
Hb, g/dL	14.7 ± 1.2	13.5 ± 1.3	<.001
eGFR, mL/min/1.73m^2	78.4 ± 16.9	53.3 ± 19.2	<.001
HbA1c, %	5.9 ± 0.7	6.0 ± 0.7	.764
BNP, pg/mL	38.4 ± 51.6	177.2 ± 216.2	.001
Echocardiographic parameters			
LVEDD, mm	47.5 ± 3.6	60.4 ± 11.6	<.001
LVESD, mm	29.9 ± 3.3	50.0 ± 14.9	<.001
LAD, mm	37.8 ± 6.0	43.9 ± 7.6	<.001
LVEF, %	65.6 ± 4.5	38.3 ± 14.7	<.001
LVMI, g/m^2	78.7 ± 14.7	112.2 ± 33.1	<.001
Cardiopulmonary exercise test			
Peak VO_2, ml/kg/min	25.4 ± 6.1	16.2 ± 4.1	<.001
AT, ml/kg/min	13.9 ± 2.7	9.9 ± 2.1	<.001
Peak heart rate, /min	153 ± 27	113 ± 25	<.001
Peak SBP, mmHg	201 ± 22	145 ± 29	<.001
Peak respiratory exchange ratio	1.24 ± 0.08	1.19 ± 0.12	.049
Skeletal muscle findings			
QMT, cm	6.54 ± 1.34	5.21 ± 1.10	<.001
QEI	81.1 ± 7.5	88.3 ± 13.4	.010
Muscle mass, kg	48.5 ± 7.9	38.7 ± 7.4	<.001
Grip strength, kg	35.9 ± 10.6	27.9 ± 7.1	<.001
10-m gait speed, sec	5.1 ± 0.8	6.1 ± 1.5	<.001
MVC force of QFM, Nm	107.9 ± 27.5	84.2 ± 24.3	<.001

Data are mean ± SD. SBP, systolic blood pressure.

Representative images of the EI of the quadriceps muscle in a patient with HF and a control subject are displayed in Fig. 1. The QEI values were significantly higher in the HF group compared with the control group (Fig. 2A). The QMT values were also significantly lower in the HF group (Fig. 2B). The QMT and QEI of each quadriceps muscle in the patients with HF and controls are shown in Supplementary Figure S1. The values of muscle mass, grip strength, 10-m gait speed, and the maximum voluntary contraction (MVC) force of the QFM were significantly lower in the HF group.

The Relationships Between the EI of Quadriceps Muscle and Other Clinical Variables

There was a significant negative correlation between QEI and peak VO_2 ($r = -0.38$, $P = .006$) among the patients with HF as well as among all participants ($r = -0.34$, $P = .002$; Fig. 3A, B). Similarly, QMT was positively correlated with peak VO_2 among the patients with HF ($r = 0.29$, $P = .038$) as well as among all participants ($r = 0.53$, $P < .001$; Fig. 3C, D). The QEI and QMT did not differ between HFpEF and HF with reduced EF (HFrEF) patients (Supplemental Table S2). In the univariate analysis, QEI was significantly correlated with age ($r = 0.266$, $P = .046$), NYHA class ($r = 0.353$, $P = .007$), AT ($r = -0.326$, $P = .018$), and peak VO_2 ($r = -0.378$, $P = .006$), but not with BMI, LVEDD, LVEF, eGFR, HbA1c, or the plasma log BNP level (Table 2). There was also no significant correlation between QEI and QMT, muscle mass, grip strength, 10-m gait speed, or MVC force of QFM. In the multivariable analysis, peak VO_2 (β-coefficient= −11.80, 95%CI [−20.73, −2.86], $P = .011$) and BMI (β-coefficient= −11.67, 95%CI [−22.2, −1.12], $P = .031$) were identified as independent determinants of the QEI conditional on the other predictors (Table 3).

Discussion

The major findings of this study are that 1) the EI of the quadriceps is increased in patients with HF compared with control subjects; and 2) the muscle EI rather than the muscle thickness is more closely associated with peak VO_2, even after adjustment for age, gender, BMI, and muscle thickness. The EI of lower limb muscle may be a surrogate marker reflecting the muscle quality that determines systemic exercise capacity in HF. Several studies have reported that skeletal muscle changes by HF are associated with peak VO2 by using dual-energy X-ray absorptiometry (DEXA) and MRI[27,28]; US is simple, easily interpreted, noninvasive, and cost effective, and can be used within both community and hospital settings; it is especially useful for assessment in frail elderly patients with HF. To the best of our knowledge, this is the first study that focused on the clinical application of US for the assessment of HF-associated alterations in muscle quality.

Skeletal muscle EI has been shown to rise under several pathological conditions; i.e., sarcopenia,[23,29,30] chronic obstructive lung disease,[31] and myopathic disorders[32] and it is linked to muscle strength and exercise capacity.[15,23,33] The intramuscular fat deposition observed in MRI was reported to correspond to lesions of thigh muscle EI.[14] Moreover, Reimers et al[34] reported a positive correlation between muscle EI and the fat infiltration rate in muscle biopsies. As such, enhanced EI is thought to reflect the accumulation of intramuscular fat. This intermuscular fat is reported to produce proinflammatory cytokines, and these cytokines have direct catabolic effects on skeletal muscle. In addition, it promotes insulin resistance leading to muscle catabolism, promotes mitochondrial dysfunction, and impairs protein synthesis in skeletal muscle.[35] Increased thigh intermuscular fat may "steal" blood that would normally be delivered to the active muscles during exercise, thereby reducing perfusive oxygen delivery to the thigh muscle.[36] Indeed, in the present study the muscle QEI was

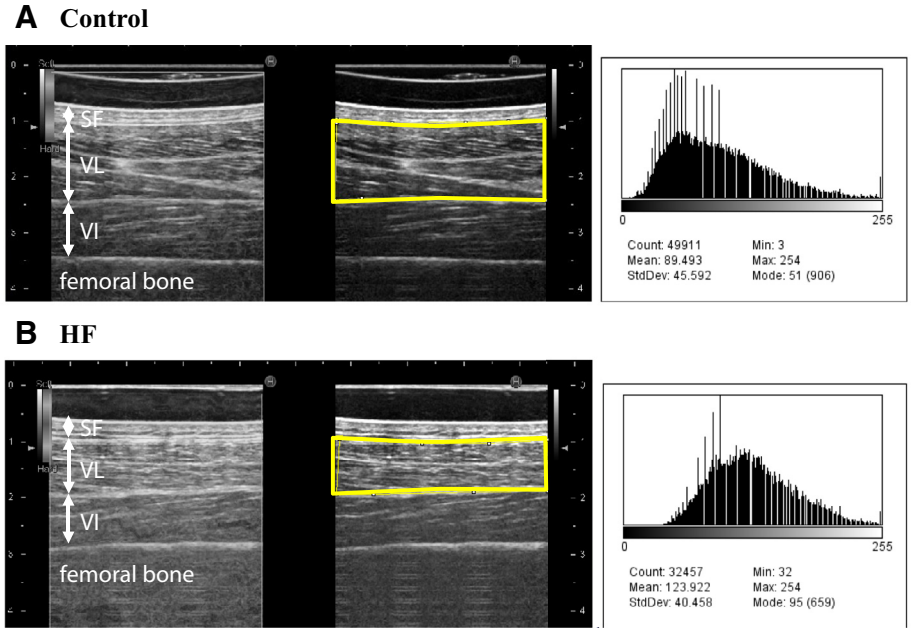

Fig. 1. Representative images of muscle EI. Images show the 8-bit grayscale analysis of the ultrasound image of VL muscle from (**A**) a control subject and (**B**) a patient with HF. The EI within the ROI is represented by the mean value of the histogram shown on the right. SF, subcutaneous fat.

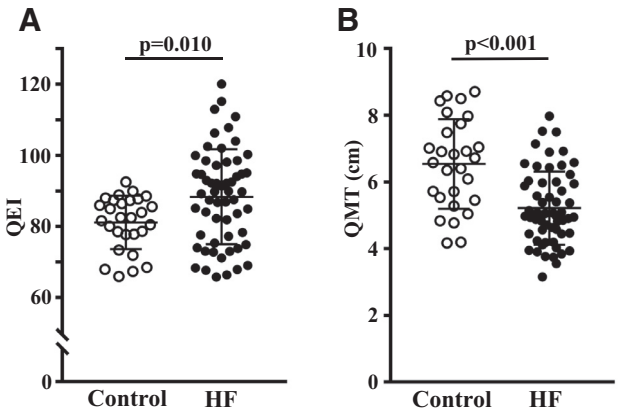

Fig. 2. QEI (**A**) and QMT (**B**) in the control subjects (open circles; n=28) and patients with HF (closed circles; n=58).

higher in the HF group than the controls, which is consistent with our previous observation of high intramuscular lipid content detected by MRS in patients with HF.[11] Moreover, the QEI values were more broadly distributed in the HF group than in controls, suggesting the presence of a wider range of muscle qualitative impairments related to HF.

We speculate that the increased muscular fat accumulation may be attributable to impaired fatty acid β-oxidation in the skeletal muscle, because low activity of β-hydroxyacyl coenzyme A dehydrogenase (an enzyme of fatty acid β-oxidation) was previously documented in biopsied muscle from patients with HF.[3] As more direct evidence, we recently demonstrated that mitochondrial oxidative phosphorylation was impaired in the skeletal muscle of a murine model of HF,[37] accompanied by alterations in the post-translational control of fatty acid β-oxidation enzymes.[38] In line with our findings, van der Zwaard et al[39] revealed that peak VO_2 is closely associated with mitochondrial oxidative capacity, as indicated by the succinate dehydrogenase activity in the quadriceps muscle of patients with HF.

In addition, Pillen et al[40] reported that increased muscle EI indicated fibrotic tissues in the skeletal muscle in a canine model of muscular dystrophy. Intramuscular fibrosis is also known to occur in the skeletal muscle in patients with HF, concomitantly with cardiac fibrosis.[41] However, little is known about the skeletal muscle fibrosis in patients with HF, and further investigations will be needed on this topic. As such, the enhanced EI reflecting the intramuscular fat accumulation may represent impaired metabolic capacity specifically in muscle mitochondria; it remains to be determined whether increased EI reflects adipose and/or fibrotic lesions.

Our present findings demonstrated a negative association between limb muscle EI and peak VO_2, a systemic exercise tolerance parameter. We and other groups using MRS-based metabolic measurements have demonstrated that the metabolic derangements in lower limb muscles contribute to the limitations of systemic exercise capacity in patients with HF.[9,10] Alternatively, a local quadriceps muscle training (e.g., knee-extensor exercise) successfully improved peak VO_2 in an HF population.[18] Although the QEI indicates a regional metabolic change in the skeletal muscle, the QEI has the potential to provide critical clues regarding the qualitative muscle alterations involved in systemic exercise performance.

As for the association between muscle EI and muscle performance, our present findings contradict those of prior

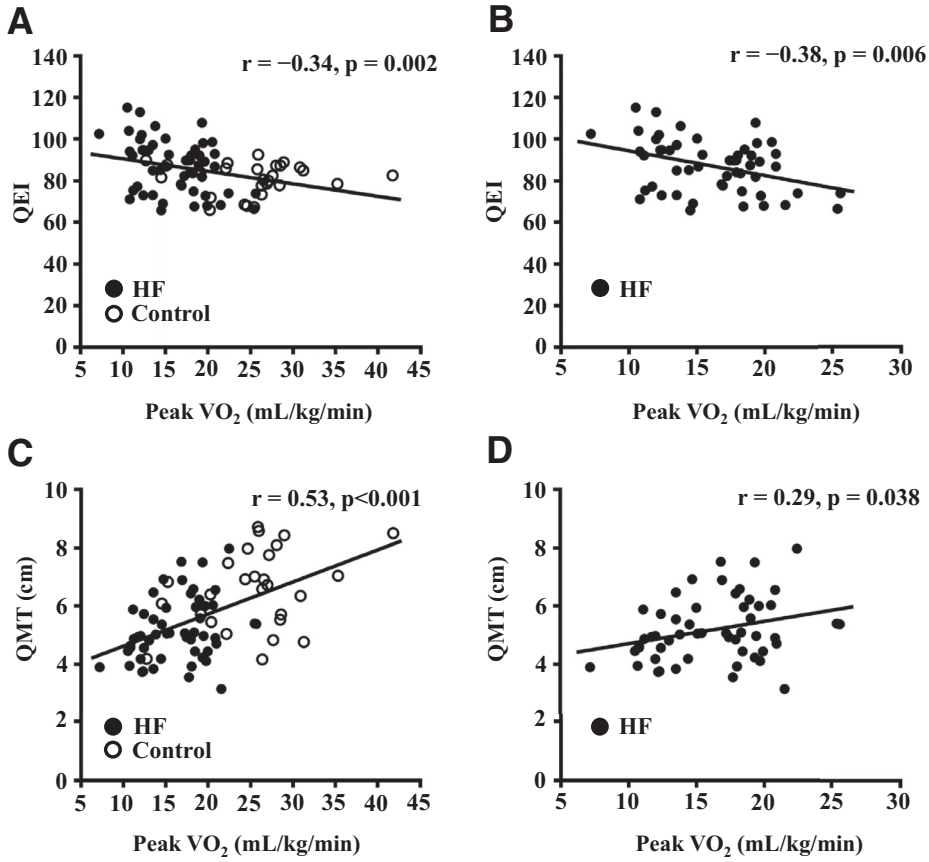

Fig. 3. Correlation between QEI and peak VO_2 in the (**A**) control subjects (open circles; n=28) and patients with HF (closed circles; n=58), and in (**B**) the patients with HF only. Correlation between QMT and peak VO_2 in (**C**) the control subjects (open circles; n=28) and patients with HF (closed circles; n=58), and in (**D**) patients with HF only.

studies of elderly individuals, in which a positive correlation was observed between the QEI and the contracting performance of the quadriceps.[15,33] Because both age and BMI are known to influence the EI,[23,42] this discrepancy in results may be explained by the relatively young age of our subjects compared with the subjects of previous studies. The discrepant results may also suggest that the qualitative muscle change in patients with HF is distinguished from that in aging populations. Nevertheless, our finding of a significant correlation between EI and peak VO_2 even after adjusting for age and BMI as well as muscle mass underscores the important role of muscle quality in the exercise intolerance of patients with HF.

Low BMI was also independently associated with high QEI. Low BMI is known as a risk factor for both current and future sarcopenia. Because so-called sarcopenic obesity worsens exercise intolerance, our present results may highlight the importance of low BMI in reduced muscle quality and exercise intolerance. However, high BMI in obese

Table 2. Univariate Linear Model of Quadriceps Echo Intensity in the HF Group

	Univariate	
Variable	Correlation Coefficient	*P* Value
Age, y	0.266	.046
BMI, kg/m^2	−0.144	.285
NYHA class	0.353	.007
LVEDD, mm	−0.120	.374
LVEF, %	0.021	.880
Peak VO_2, mL/kg/min	−0.378	.006
AT, mL/kg/min	−0.326	.018
eGFR, mL/min/1.73m^2	0.054	.693
Log BNP, pg/mL	0.191	.156
HbA1c, %	−0.034	.807
QMT, cm	−0.238	.075
Muscle mass, kg	−0.281	.194
Grip strength, kg	−0.177	.189
10 m gait speed, sec	−0.105	.440
MVC force of QFM, Nm	−0.200	.136

Table 3. Multiple Regression Analysis of Quadriceps Echo Intensity and Other Clinical Variables in the HF Group

Variable	Correlation Coefficient	95% CI	*P* Value
Age, y	4.85	−2.37 – 12.1	.183
Male (0)	−0.96	−4.54 – 2.61	.589
BMI, kg/m^2	−11.67	−22.2 to −1.12	.031
QMT, cm	2.69	−6.80 – 12.17	.572
Peak VO_2, mL/kg/min	−11.80	−20.73 to −2.86	.011

Male and female were assigned values of 0 and 1, respectively.

patients with HF is also known to contribute to worse symptoms of HF.[43] Further results must be accumulated before we can adequately discuss the relationship between QEI and BMI.

In this study, the QMT was reduced in the patients with HF compared with the controls, and it was positively correlated with peak VO_2. The QMT has been shown to reflect the whole muscle mass,[44] which is also supported by the present positive association between QMT and muscle mass assessed by BIA ($r = 0.741$ in all of the participants; $r = 0.598$ in patients with HF). Because the muscle atrophy coexisting in HF is reported to have a negative impact on exercise capacity,[4,45] a reduced QMT, indicating muscle atrophy, is likely to be associated with the lowered exercise capacity in HF. Of note, the relationship between the QMT and peak VO_2 was significant but weak in the present HF group compared with the entire study population. One potential reason for this is that all of the patients with HF were ambulatory patients who had relatively mild atrophy of skeletal muscle. Nevertheless, the EI-derived muscle quality remains a major determinant of exercise capacity even in such patients with HF with a mild phenotype of muscle atrophy.

There are several limitations of this study that should be acknowledged. First, our cross-sectional observation of a relatively small number of patients was not able to clarify any causal relationship between exercise capacity and EI-based quadriceps quality. Further large-population longitudinal studies are needed to identify whether EI-assessed muscle quality contributes to future changes in peak VO_2 in HF. Second, there is currently a lack of standardized protocol for the US assessment of skeletal muscle, and there is no definitive agreement as to which muscle group should be measured or what probe site should be used. Moreover, the muscle EI is a relative value, and thus the value standardization is difficult. In addition, US measurements generally depend on the proficiency of the examiner, and though the measurements of skeletal muscle are reported to have high reliability and reproducibility,[44,46,47] and the present study showed high ICCs, we still cannot definitively ensure the accuracy of these measurements. In-depth comparisons with other gold-standard data will be needed to establish their validity and reliability. Third, our patients with HF consisted of both HFpEF and HFrEF, and though the QEI and QMT did not differ between the groups, we did not further compare the results between the 2 groups because of the limited sample size. Fourth, we cannot exclude the possibility that the EI values were affected by subcutaneous fat thickness even after the adjustment for BMI. Finally, as we mentioned earlier, it remains to be determined whether increased EI of skeletal muscle reflects adipose and/or fibrotic lesions in patients with HF, reflecting HF-related changes in muscle quality. Further evaluation and validation with other modalities and histological analysis are essential before our results can be broadly applied.

Clinical Implications

Although exercise training is the gold standard for the treatment of muscle impairments in patients with HF, evaluating skeletal muscle is not always easy in current clinical practice, especially for frail elderly patients who lack access to adequate equipment. Moreover, although several studies have suggested that exercise training reverses HF-associated myopathy, as evidenced by increases in the percentage of aerobic fibers, oxidative metabolism, capillarity, and mitochondrial size, these results have not been reproduced in all studies. This discrepancy may suggest that the effects of exercise training differ according to the quality of skeletal muscle. From the results of our present study, evaluating muscle quality by US may be a useful, convenient, and valuable method for classifying subjects that shows most effects of exercise training, and may contribute to more widespread use of individualized HF exercise programs.

Conclusion

Our findings suggest that the muscle echo intensity in the lower limbs could be a simple and clinically useful marker to identify metabolic derangements in the skeletal muscle that could determine the exercise capacity in HF. Pharmacotherapy and exercise training targeted at EI-based muscle quality could be a novel approach to improve exercise intolerance in patients with HF.

Disclosures

There is no conflict of interest that should be declared.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.09.001.

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