EXPLORING THE RELATIONSHIP BETWEEN COMPREHENSIVE RESPIRATORY ASSESSMENT AND INTRA-EXTRACARDIAC BIOMARKERS IN HEART FAILURE REHABILITATION

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eISSN: 2828-4070
Proceedings ICE on IMERI. 2024.
Received: November 28th, 2014
Accepted: December 23rd, 2024
Published online: January 17th , 2025

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Abstract

Introduction: Heart failure with reduced ejection fraction (HFrEF) is well-known as a systemic disease that involves cardiac and extracardiac issues, with respiratory function playing on of the key role in rehabilitation prognosis. Biomarkers such as soluble suppression of tumorigenicity 2 (sST2), myostatin, miRNA-133, and NT-proBNP indicate disease progression. Notably, sST2, which is also produced by the lungs, predicts heart failure outcomes. This study examines the relationship between comprehensive respiratory assessments (e.g., diaphragmatic ultrasonography, spirometry) and intra-extracardiac biomarkers to improve rehabilitation strategies. **Methods:** Sixty-nine HFrEF patients underwent respiratory evaluations, including diaphragmatic ultrasonography, spirometry, chest expansion measurements, and a six-minute walking test (6MWT). Biomarkers assessed were sST2, myostatin, miRNA-133, and NT-proBNP. Associations between respiratory parameters and biomarkers were analyzed using t-tests and correlation analyses. **Results:** The median age was 56 years, and 33 (47.82%) of the subjects had diaphragmatic dysfunction, resulting in poorer 6MWT performance (378.03±58.15 m vs 409.75±63.65 m, p=0.017) and other parameters. Superior chest expansion negatively correlated with sST2 (r=−0.387, p=0.001) and positively with miRNA-133 (r=0.442, p<0.001). Similar results were found for inferior chest expansion. No significant correlations were observed for other biomarkers. **Conclusion:** This study highlights strong associations between chest expansion and sST2/miRNA-133, suggesting that incorporating respiratory assessments and training into HFrEF rehabilitation could enhance outcomes by addressing cardiorespiratory insufficiencies. Given sST2's predictive value for heart failure prognosis,

these findings support a multi-component rehabilitation strategy incorporating respiratory training, such as aerobic and inspiratory muscle exercises, to enhance cardiopulmonary outcomes. This integrated approach offers promise for future HFrEF rehabilitation protocols.

Keywords

Heart failure reduced ejection fraction, cardiac rehabilitation, biomarkers, sST2, miRNA-133

Introduction

Heart failure (HF) is a chronic condition associated with high disability, mortality, and healthcare costs.[1] A defining characteristic of HF is exercise intolerance, arising from a complex interplay of central and peripheral pathophysiological mechanisms, ultimately impairing the cardiac capacity to meet the body's metabolic demands.[2,3] While medical therapies play a crucial role in HF management, exercise-based cardiac rehabilitation is increasingly being recognized as a cornerstone of comprehensive care.[4,5] Cardiac rehabilitation programs traditionally focus on enhancing cardiovascular function through aerobic exercise; however, emerging evidence underscores the significant impact of respiratory function on HF prognosis and the potential benefits of integrating respiratory training into rehabilitation strategies.[3,6]

The diaphragm, the primary inspiratory muscle responsible for two-thirds of the tidal volume at rest, is often compromised in HF patients.[7] Diaphragmatic dysfunction, characterized by muscle weakness and atrophy, manifests as reduced chest expansion and contributes to exercise intolerance independent of pulmonary function.[7,8] Impaired diaphragmatic function in patients with HF has been linked to a constellation of adverse outcomes, including dyspnea, sleep-disordered breathing, and an altered muscle metaboreflex, which can further exacerbate exercise limitations and contribute to a downward spiral of deconditioning.[2,7]

Assessment of diaphragmatic function, including measurement of chest expansion and diaphragm thickening using ultrasound, offers valuable insights into respiratory muscle health and can help predict exercise tolerance in patients with HF.[8,9] Furthermore, recent studies have suggested that specific biomarkers, notably soluble suppression of tumorigenicity 2 (sST2) and microRNA-133a (miRNA-133a), may reflect the degree of

diaphragmatic dysfunction and its impact on HF prognosis.[10–12] Elevated levels of sST2, a marker of cardiac stress and fibrosis in the lungs, are associated with a poorer prognosis. Conversely, reduced levels of miRNA-133a, a microRNA crucial for regulating myocardial collagen production and limiting adverse cardiac remodeling, are associated with worse HF outcomes.

This study aimed to explore the relationship between comprehensive respiratory assessments, including chest expansion and diaphragmatic function, and biomarkers sST2 and miRNA-133a in patients undergoing HF rehabilitation. By unveiling these connections, this study seeks to strengthen the importance of tailored rehabilitation programs that integrate targeted respiratory training to improve both cardiac and pulmonary outcomes in individuals with HF.

Materials and Methods

Study Population

Initially the sample size calculation was done using one continuous sample formula with reference to previous study on biomarkers, with minimum number of sample of 60. The inclusion criteria for HFrEF diagnosis were based on established guidelines, likely encompassing clinical symptoms as classified by the Framingham criteria, echocardiographic findings (specifically, reduced left ventricular ejection fraction < 40%), and potentially elevated levels of NT-proBNP. The exclusion criteria were refusal to participate and the presence of severe valvular or congenital heart disease. Among 107 patients who were diagnosed with HFrEF in a structured cardiac rehabilitation program, this study had selected 69 patients as the final number of subjects being analyzed.

Comprehensive Respiratory Assessments

Diaphragmatic function was assessed using ultrasonography. Diaphragmatic thickness was measured using ultrasonography (USG) at both end-expiration and end-inspiration in the supine position with the head of the bed inclined to 30°, utilizing the previously published cut-off of 4 mm to denote diaphragmatic dysfunction.[8]

Standard spirometry was performed to evaluate lung function, using the forced vital capacity (FVC) maneuver and maximum voluntary ventilation (MVV) maneuver to obtain FVC, forced expiratory volume in 1 s (FEV1), and the FEV1/FVC ratio, alongside MVV. To determine chest wall mobility, chest expansion was assessed by measuring the superior (axillary level) and inferior (xiphoid level) points of the chest circumference during both maximal inspiration and expiration, as previously published.[13,14]

Finally, the six-minute walk test (6 MWT), a widely used assessment of cardiorespiratory endurance, adhered to the American Thoracic Society standard.[15,16] The distance covered by each participant during the six-minute walk was recorded.

Biomarker Analysis

Laboratory tests were conducted preemptively to eliminate any potential influence of physical activity on the assessed biomarkers, and the patients were instructed to fast for 8 hours before venous blood collection. Blood samples were obtained by a skilled laboratory analyst. Assessed biomarkers were as follows:

- NT-proBNP: A well-established marker of cardiac stress and HF severity.[10,17]
- sST2: a marker associated with cardiac fibrosis, hypertrophy, and inflammation in HF.[11,12]
- miRNA-133: A cardiomyocyte-specific microRNA implicated in regulating myocardial collagen production.[18,19]
- Myostatin inhibits muscle growth and may be associated with skeletal muscle dysfunction in HF.[10,18]

Statistical Analysis

Statistical analyses were performed using SPSS for Macintosh version 29.0 (IBM, New York, USA). Numerical data were first assessed for normality using the Kolmogorov-Smirnov test. Most variables in this study were continuous and were reported as either mean ± SD or median (range), while categorical variables were expressed as proportions (n, %). Comparisons between groups with diaphragmatic dysfunction and preserved function were performed using the independent Student's t-test and the Mann-Whitney U

test. Correlations between superior chest expansion and all variables were examined using Pearson's and Spearman's correlation analysis. Statistical significance was set at P <0.05.

Results

Table 1 shows the differences between patients with diaphragmatic dysfunction and those with preserved diaphragmatic function. This table shows that out of 69 patients with HFrEF, 33 (47.82%) had diaphragmatic dysfunction, defined as a diaphragmatic ultrasound thickness of < 4 mm. This dysfunction was significantly associated with poorer performance in the 6-minute walking test (6 MWT), with an average distance of 378.03±58.15 meters compared to 409.75±63.65 meters in patients with preserved function (p=0.035). Additionally, inferior chest expansion was significantly lower in patients with diaphragmatic dysfunction (2.39±.94 cm vs 3.04±1.71 cm, p=0.027). As expected, patients with diaphragmatic dysfunction had significantly thinner diaphragms during both inspiration and expiration, confirming an ultrasound-based diagnosis. The two groups had no statistically significant differences in other parameters, such as age, ejection fraction, and various biomarkers, such as NT-proBNP, sST2, myostatin, and miRNA-133.

Table 1. Comparison between diaphragmatic dysfunction (defined as Diaphragmatic USG thickness of inspiration lower than 4 mm) and preserved function

	Diaphragmatic Dysfunction (n=33)	**Preserved Diaphragm Function (n=36)**	**p**
Age (years)	55.52±6.47	53.64±9.33	0.339
Female (n, %)	5 (15.2%)	2 (5.6%)	0.247[b]
EF (%)	27.23±6.82	30.40±8.02	0.111
TAPSE	17.59±4.54	18.52±5.19	0.429
BMI (kg/m^2)	25.87±4.50	26.58±4.98	0.540
6MWT Distance (m)	378.03±58.15	409.75±63.65	0.035
Superior Chest Expansion (cm)	1.96±.79	2.09±1.07	0.565
Inferior Chest Expansion (cm)	2.39±.94	3.04±1.71	0.027
Diaphragmatic Inspiratory Thickness by USG (cm)	0.27±.05	0.50±.10	<0.001

Diaphragmatic Expiratory Thickness by USG (cm)	0.18±.06	0.24±.08	<0.001
NT pro BNP (pg/mL)	943 (112-8563)	649.00 (125-6208)	0.118[a]
sST2	3203.49 (1491.71-3528.06)	3129.58 (1318.26-3610.01)	0.962[a]
Myostatin	775.30 (274.60-1306.05)	786.55 (341.06-1416.59)	0.848[a]
MiRNA-133	30.75 (23.95-36.66)	31.06 (26.02-35.47)	0.371[a]
Forced Vital Capacity (% Pred)	46.08±10.40	50.39±13.91	0.076
Forced Expiratory Volume in 1 second (% Pred)	55.70±13.39	59.58±15.32	0.134
FEV1/FVC	97.16±0.06	96.28±0.08	0.610
Peak Expiratory Flow (% Pred)	78.82±29.59	79.39±26.86	0.467
Maximal Voluntary Ventilation (% Pred)	49.01±17.56	54.42±17.58	0.103

*****All the tests were performed with an independent t-test except for [a]Mann-Whitney U Test and [b]Fisher's Exact Test

The correlations between superior chest expansion and the other variables are presented in Table 2. There was a strong positive correlation between superior and inferior chest expansion (r=0.800, p<0.001). It was also positively correlated with the 6 MWT distance (r=0.332, p<0.001), forced vital capacity (r=0.226, p=0.019), forced expiratory volume in 1 s (r=0.309, p=0.001), peak expiratory flow (r=0.187, p=0.054), and maximal voluntary ventilation (r=0.307, p=0.001). Importantly, the analysis showed a significant negative correlation between superior chest expansion and sST2 levels (r=−0.387, p=0.001) and a positive correlation with miRNA-133 (r=0.442, p<0.001). These correlations suggest that superior chest expansion may be a valuable indicator of overall respiratory health and its potential impact on HFrEF progression.

Table 2. Correlation with superior chest expansion

	Correlation Coefficient	**p**
Superior Chest Expansion	Ref	
Inferior Chest Expansion	0.800	**<0.001[a]**
Age	0.031	0.802[a]

EF	0.118	0.335[a]
TAPSE	-0.232	0.055[a]
BMI	-0.224	0.064[a]
6MWT	0.332	**<0.001[a]**
Diaphragmatic Inspiratory Thickness	0.143	0.142[a]
Diaphragmatic Expiratory Thickness	0.014	0.884[a]
NT pro BNP (pg/mL)	-0.051	0.604
sST2	-0.387	**0.001[b]**
Myostatin	0.035	0.778[b]
MiRNA-133	0.442	**0.001[b]**
Forced Vital Capacity	0.226	**0.019[a]**
Forced Expiratory Volume in 1 sec	0.309	**0.001[a]**
Peak Expiratory Flow	0.187	0.054[a]
Maximal Voluntary Ventilation	0.307	**0.001[a]**

[a] Pearson Correlation; [b] Spearman Correlation

Discussion

This study identified diaphragmatic dysfunction in a significant proportion (47.8%) of patients with HFrEF. This finding aligns with the existing literature that highlights the prevalence of respiratory muscle weakness in this patient population, particularly affecting the diaphragm, which is the primary muscle responsible for inspiration.[8] The results of this study reinforce the understanding that diaphragmatic dysfunction is not merely a consequence of heart failure but also a contributing factor to its overall severity and potentially poorer prognosis.[7,8]

Several factors contribute to diaphragmatic dysfunction in heart failure. These include muscle atrophy and weakness, reduced muscle fiber thickness, and alterations in muscle metabolism.[7] Importantly, this dysfunction can exacerbate exercise intolerance in HFrEF independent of any coexisting lung problems.[8,20] The crucial role of the diaphragm in respiration and circulation means that its impairment can lead to a cascade of negative effects, including reduced exercise capacity, increased breathlessness, and ultimately, diminished quality of life.[3,7]

This study underscores the significance of chest expansion as a noninvasive indicator of diaphragmatic function and its relationship with heart failure prognosis.[7] Patients with diaphragmatic dysfunction exhibited significantly reduced inferior chest expansion, enhancing the results of previous studies demonstrating that compromised chest wall mobility often reflects underlying respiratory muscle weakness.

The strong correlation observed between superior and inferior chest expansions suggests that chest wall mobility is a coordinated process.[13] This finding implies that assessments of chest expansion, particularly superior chest expansion owing to its ease of measurement, can offer valuable insights into the overall chest wall and diaphragmatic function, particularly in daily rehabilitation settings.

A central novelty of this study was the correlation between chest expansion and the levels of two key biomarkers, sST2 and miRNA-133, as shown in Figure 1. The negative correlation between superior chest expansion and sST2 levels was particularly noteworthy. sST2, a marker of myocardial fibrosis, inflammation, and adverse cardiac remodeling, is increasingly being recognized as a powerful predictor of poor outcomes in heart failure.[21] Elevated sST2 is associated with a higher risk of hospitalization and death in patients with heart failure, and its prognostic value extends across various heart failure phenotypes, including both reduced and preserved ejection fractions.[12]

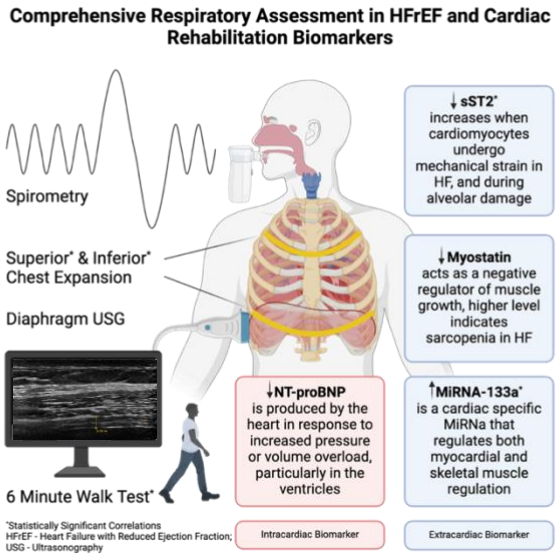

Figure 1. Respiratory assessment and cardiac rehabilitation biomarkers

The inverse relationship between chest expansion and sST2 suggests that limited chest wall mobility, potentially indicative of diaphragmatic dysfunction, may contribute to a pro-inflammatory state and exacerbate cardiac remodeling processes. These findings have important implications for rehabilitation. This underscores the need to address not only cardiac function but also respiratory muscle strength and chest wall mobility to potentially mitigate the adverse effects reflected by elevated sST2, as suggested by the significant impacts of the extracardiac system on ergoreflex, such as the musculoskeletal system.[2,17]

In contrast to sST2, superior chest expansion positively correlated with miRNA-133 levels. Although the exact role of miRNA-133 in heart failure is still under investigation, evidence suggests that it may play a protective role in the heart.[18,22] miRNA-133 is involved in regulating cardiac muscle cell growth and differentiation and has been shown to be downregulated in failing hearts.[18,19]

The positive association between chest expansion and miRNA-133 might indicate that better respiratory function and diaphragm health contribute to maintaining physiological levels of this potentially beneficial miRNA. However, further investigation is required to establish a causal link and elucidate the underlying mechanisms.

The findings of this study strongly advocate for a more holistic approach to heart failure rehabilitation that integrates respiratory muscle training alongside traditional cardiac-focused aerobic exercise interventions. Given the negative impact of diaphragmatic dysfunction on both exercise capacity and levels of prognostic biomarkers such as sST2, incorporating interventions to improve respiratory muscle strength and chest wall mobility may be critical to enhancing rehabilitation outcomes.

Several studies have shown that inspiratory muscle training that targets the diaphragm and other inspiratory muscles can lead to promising improvements in inspiratory muscle strength, exercise capacity, and quality of life in patients with HFrEF.[3,6] By strengthening the diaphragm, IMT may help enhance ventilation, reduce dyspnea, improve gas exchange during exercise in an attempt to restore the metaboreflex, and potentially attenuate the adverse cardiac remodeling processes reflected by elevated sST2 levels.

Although this study provides valuable insights, further research is required to confirm these findings and explore their clinical implications. The sample size of this study

was modest; thus, future studies should include larger and more diverse populations of HFrEF patients as well as explore the impact on heart failure with preserved ejection fraction (HFpEF) subjects.[9,12] Longitudinal studies should also be conducted to examine the impact of incorporating targeted respiratory muscle training into rehabilitation programs on long-term outcomes, including sST2 and miRNA-133 levels.[21]

The results of this study, coupled with the existing literature, highlight the interconnectedness of respiratory and cardiac functions in heart failure. They advocate moving beyond a solely cardiac-centric view of HFrEF to embrace a more comprehensive approach to rehabilitation management, incorporating strategies to address respiratory muscle weakness and improving chest wall mobility. This multidisciplinary strategy holds promise for enhancing the effectiveness of heart failure rehabilitation and ultimately improving patient outcomes.

Conclusions

Diaphragmatic dysfunction, a prevalent issue in patients with HFrEF, further underscores the importance of respiratory assessment in rehabilitation. The diaphragm, the primary muscle for inspiration, plays a critical role in ventilation and circulation. This dysfunction can exacerbate exercise intolerance and contribute to poor outcomes. Incorporating respiratory assessments and training into HFrEF rehabilitation protocols can address these cardiorespiratory insufficiencies, potentially leading to better management and improved prognosis of patients with HFrEF.

The negative correlation between superior chest expansion and sST2 levels suggests that compromised respiratory function may exacerbate heart failure progression. This study also found that superior chest expansion was positively correlated with miRNA-133, which potentially plays a protective role in the heart. This finding indicates that enhancing respiratory function through targeted interventions may improve cardiopulmonary health. Further studies should expand these results and determine whether longitudinal correlations occur after rehabilitation.

Competing Interests

Hajime Katsukawa received a salary from the Japanese Society for Early Mobilization (a nonprofit society) as a chair (full-time). The authors have no conflicts of interest to declare.

Acknowledgments

The authors thank all contributors to this study, especially the Secondary Prevention and Cardiac Rehabilitation team and the Research and Development team at Harapan Kita Hospital, Jakarta, Indonesia.

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