Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Internal Medicine

Effect of Mildronate on the Existence and Severity of Fatigue in Patients with Heart Failure

Ann Rekhviashvili MD, PhD[1*], Tamar Kandashvili MD, PhD[2], Tamar Giorgobiani MD, PhD[3]

[1]Associate Professor at the P. Shotadze Tbilisi Medical Academy; Internal Medicine Department.51/2 Ketevan Dedofali Ave, Tbilisi 0144
[2]Associate Professor at the Tbilisi State Medical University, 3rd Department of Internal Medicine 33 Vazha Pshavela Ave, Tbilisi 0176
[3]Associate Professor at the Tbilisi State Medical University, Physiology Department 33 Vazha Pshavela Ave, Tbilisi 0176

DOI: 10.36347/sjams.2021.v09i05.019 | **Received:** 09.04.2021 | **Accepted:** 17.05.2021 | **Published:** 23.05.2021

***Corresponding author:** Ann Rekhviashvili MD, PhD

Abstract **Original Research Article**

Heart failure (HF) is one of the major causes of morbidity and mortality in the world. Fatigue is frequently associated with the HF and causes disability, decreased motivation and life quality etc. Aim of the study was to evaluate effect of combination therapy with recommended HF therapy and Mildronate 1000mg/day for 3 months on systolic function of the heart and fatigue level. A non-probabilistic sample of 100 adult patients with HF with reduced ejection fraction (HFrEF) being on the recommended HF treatment according to the current HF management guidelines were involved in a cross-sectional observational study. All the patients underwent to the add on therapy with Mildronate 1000mg/day for 3 months. For assessment of fatigue existence and its severity has been used the 30-item Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). Heart ultrasound and MSFI-SF was performed twice – in the beginning and after 3 months from onset of combination treatment. Combination treatment including Mildronate significantly improved EF and decreased MFSI-SF score (P<0.0001). There was observed significant improvement of fatigue, remembering things and muscle ache (P<0.0001). There was significant improvement in patients' feelings of being upset, nervous, pooped, confused, sad, depressed, tensed and/or distressed (P<0.0001). EF level was positively correlated with the severity of cheerful, relaxed, refreshed and energetic feelings assessed from 0 to 4 points. Hence, EF was negatively correlated with the severity of trouble remembering things, concentrating and paying attention, muscles ache, feel upset, nervous, pooped, confused, sad, fatigued, depressed, tensed and tired, forgetfulness, weakness in legs and hands. We recommend to use MSFI-SF scale for assessment of existence and severity of fatigue in patients with HFrEF before and after treatment to evaluate the benefit of the treatment. Mildronate as an add-on agent on the standard HF treatment showed strong ability to improve EF, clinical manifestations and fatigue.

Keywords: Heart failure, Fatigue, Systolic function, MFSI-SF scale, Ejection fraction.

INTRODUCTION

Heart failure (HF) is defined as a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [1]. According to the ejection fraction, natriuretic peptide levels and the presence of structural heart disease and diastolic dysfunction, HF has recently been classified into three subtypes, namely HF with preserved ejection fraction (HFpEF), HF with mid-range ejection fraction (HFmrEF) and HF with reduced ejection fraction (HFrEF).

According to the World Health Organization (WHO), 17.9 million people die each year from cardiovascular diseases (CVDs), which estimates a 31% of all deaths worldwide. According to the series of cross- sectional surveys using stratified, multistage probability samples designed to provide assessments on the health and nutrition status of the civilian US population in the framework of NHANES study, revealed that prevalence of HF continues to rise over time; namely, an estimated 6.2 million American adults ≥20 years of age (2.2%) had HF between 2013 and 2016 compared with an estimated 5.7 million between

2009 and 2012 [2, 3]. Heart failure prevalence is significant in other countries as well; namely, 4.2 million people have HF in China, 9 million people in Southeast Asia, etc. HF has been defined as global pandemic, since it affected nearly 40 million people worldwide in 2015. It is considered as a major clinical and public health challenge, as well as leading cause of hospitalizations, morbidity, and mortality globally. It has a considerable financial burden for healthcare system as well. Prevalence of various cardiovascular risk factors, especially arterial hypertension and diabetes mellitus, show rising tendency, which will increase the risk of HF development.

HF is non-curable "chronic" condition, which is characterized with various symptoms, namely dyspnea, nocturnal cough, fatigue, orthopnea, lower limb edema etc. These symptoms impair quality of life, increase the need for HF-related hospitalizations, and impair functional independence. From all HF symptoms, fatigue particularly has often been cited as the most common symptom that has a special importance, because it causes functional limitations that can affect patients' psychological and social conditions and impair their life quality [4, 5]. Fatigue is a subjective complaint that is considered as a multifactorial in its etiology and multidimensional, namely physical, mental, and emotional tiredness in its expression.

In modern literature, fatigue is accepted as a subjective and multiethyological phenomenon. Its origin and expression involves physical, cognitive and emotional aspects and its identification depends on self-reporting [6]. Namely, fatigue is the early onset of tiredness, sensation of exhaustion or difficulty to carry out physical or intellectual activities after an activity has been started without recovery after a period of rest. Its impact on quality of life is huge and prevalence in different populations significant, that's why it has been included as a variable in many studies.

The term fatigue was introduced in 1988 as a nursing diagnosis and was included in the taxonomy of the North American Nursing Diagnosis Association and defined as "an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work at usual level" [7]. Fatigue can be classified as either objective or subjective; objective fatigue is defined as the observable and measurable decrement in performance occurring with the repetition of a physical or mental task, while subjective fatigue is a feeling of early exhaustion, weariness and aversion to effort [8]. According to the fatigue-lasting duration, it is classified as acute (<1 month), prolonged (>1 month, <6 months), and chronic fatigue (≥6 months), respectively.

There are several pathogenetic mechanisms suggested for fatigue development in patients with HF; namely, a) reduced cardiac output; b) inadequate rise in cardiac output while physical activity; c) reduced oxygen delivery, impaired arteriolar vasodilatation (mainly due to the excessive sympathetic activity, activation of the plasma renin-angiotensin system and increased levels of endothelin) and an early increase in plasma lactate concentration; d) abnormal capacity of skeletal muscles to utilize oxygen adequately; e) skeletal muscle atrophy and biochemical alterations, namely, abnormal fiber type distribution and water or fat infiltration of the skeletal muscles; f) dominance of catabolic processes due to the chronic, low grade haemodynamic stress existing in patients with CHF, which leads to skeletal myopathy, causing the sensation of fatigue.

Due to subjective nature, fatigue is frequently misdiagnosed and mixed up with other pathologies; first, from activity intolerance; second, asthenia, defined as the lack of strength or feeling of inability to carry out daily tasks, which is more intense at the end of the day, and usually improves after a period of sleep; and third, weakness, which is the reduction or loss of muscular strength, and the key symptom in muscular diseases.

Although fatigue is a common symptom in HF, little is known about its association with prognosis. Perez-Moreno et al. in the framework of CORONA study examined the relationship between fatigue and clinical outcome in HF patients with reduced ejection fraction (HFrEF) and revealed strong positive correlation between fatigue severity and worse clinical outcomes [9].

Severe and debilitating fatigue is a condition, which is frequently met in patients with different pathologies, namely coronary heart disease, myocardial infarction, chronic heart failure, stroke, migraine, chronic fatigue syndrome, Parkinson's disease, chronic hepatitis, multiple sclerosis, emphysema and asthma, pregnancy, arthritis, cancer etc [8, 10-17].

Fatigue is a perception, not a measurable quantity, that's why questionnaires are developed for assessment of subjective fatigue. For assessment on objective fatigue historically are used: the symptom-limited progressive exercise test, which is carried to the point of exhaustion; the test of endurance at a predetermined, usually submaximal level of exercise and the test of submaximal exercise performance, i.e. treadmill test.

Retrospective cohort study of 12,285 newly diagnosed HF patients conducted by Williams's revealed 39% prevalence of fatigue among HF patients. The study found out that fatigue mostly is part of symptom cluster and mostly, chest pain, edema, syncope, dyspnea and palpitations, as well as lower body mass index, abnormal weight loss, anemia and

volume depletion are predictors of fatigue development [5]. In other studies, notable independent predictors of fatigue were sleep apnea, female gender, vitamin D deficiency, and higher age [18, 19].

Chronic fatigue syndrome (CFS) also frequently accompanies HF. CFS is characterized by a permanent strong fatigue sensation of unknown origin associated with joint and muscle pain, anxiety, depression, headaches, intolerance to physical exertion, cognitive and sleep disorders, orthostatic intolerance, which limit functional capacity of the person and produce varying degrees of disability [20]. There are known variety of names of CFS, namely allergic encephalomyelitis, immune dysfunction syndrome, neuroendocrine immune dysfunction syndrome, post viral syndrome, Iceland disease, neurasthenia, and Royal Free disease.

Wyller et al. revealed abnormal sympathetic predominance in the autonomic cardiovascular response to gravitational stimuli in patients with CFS and orthostatic intolerance [21]. Moreover, Miwa K. revealed that CFS patients with coexisting orthostatic intolerance have had a small left ventricular size with a low cardiac output [22]. In 2015, US Institute of Medicine (IOM) reported diagnostic criteria for CFS as follows; three mandatory symptoms, a substantial impairment in activities accompanied by fatigue persisting for more than 6 months, post-exertional malaise (PEM) and unrefreshing sleep, and one optional symptom among cognitive impairment or orthostatic intolerance [11].

Ekmann et al.. Studied 1,696 participants and followed up for 2-10 years for investigation of predictive value of fatigue for IHD in older than 70 years nondisabled individuals free of cardiovascular disease. They concluded that fatigue in nondisabled older adults free of cardiovascular disease is an early predictor for development of subsequent poor general health and IHD [23].

Through decades physician's attention was directed to the therapeutic strategies for reducing the fatigue in patients with HF. It was revealed that physical training has a positive influence on an improvement of fatigue by improving metabolism, skeletal muscle function and endothelial function. Similarly, ACEIs showed their positive effects on fatigue. However, topic is still open for debates and future studies are still needed to solve the problem.

Lately, more attention is paid on usage of metabolic therapy in management of heart failure and patients with fatigue and asthenia. Dzerve et al. studied effect of Mildronate on peripheral circulation of patients with chronic heart failure. This study revealed the advantage of the combined treatment with lisinopril and mildronate over the treatment with lisinopril alone on the leading symptoms of CHF, exercise capacity, life quality, peripheral circulation and vasodilation capacity of the marginal and resistance vessels at rest and during exercise [24, 25]. Earlier, Chumburidze et al. showed that mildronate is an effective drug in complex treatment of chronic heart failure [26]. Similar to studies discussed above, Statsenko et al. revealed that mildronate, as a part of complex CHF therapy, improved quality of life, carbohydrate and lipid metabolism, cardiac autonomous function, anti-ischemic effect, and significantly reduced CHF clinical manifestations [27].

Aim of the study was to study existence and level of fatigue among patients with HFrEF and effect of 3 months therapy with 1000mg/day dosage Mildronate (Meldonium) along with the prescribed recommended therapy on heart systolic function, existence and severity of fatigue.

MATERIAL AND METHODS

A non-probabilistic sample of 100 adult patients with chronic heart failure from outpatient's department of Al. Aladashvili hospital were involved in a cross-sectional observational study. Researchers previously checked the medical records of potentially eligible patients for their recruitment. Those who met the inclusion criteria were invited to participate in the study. Written Informed Consent was obtained from all the study participants after detailed introduction of study purpose and used methods.

The inclusion criteria were: both sex patients from 45 to 65 years old age, confirmed medical diagnosis for HF with reduced ejection fraction (EF<40%). Patients with acute myocardial infarction, acute kidney injury, chronic kidney disease more than 3b stage, electrolyte imbalance (hyper- or hypokalemia), oncological diseases, COPD, bronchial asthma, chronic fatigue syndrome, anemia, severe dysrhythmias and endocrine-metabolic diseases without treatment (for example, diabetes mellitus or thyroid diseases) were excluded from the study.

Heart ultrasound and ECG were performed in all the patients. For assessment of fatigue existence and its severity we used the 30-item Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), which was validated before [28-32]. MFSI-SF was given to all the patients for self-feeling. Each question was assessed with maximum 4 points. Hence, maximal total score of the questionnaire was 120 points. According to the American Academy of Family Physicians' recommendations, all the study participants underwent to physical examination, detailed history taking and initial laboratory testing (complete blood count; urinalysis; comprehensive metabolic panel; measurement of thyroid-stimulating hormone and free

T4, C-reactive protein, and phosphorus levels) to rule out other possible causes of the fatigue.

To distinguish fatigue from chronic fatigue syndrome we used "Diagnostic Criteria for Chronic Fatigue Syndrome" recommended by the Centers for Disease Control and Prevention. If the patient had at least 4 positive criteria, diagnosis of CFS was stated and patient was rejected from the study. Diagnostic criteria for CFS are: 1) Headache of new type, pattern, or severity; 2) Polyarthralgia without swelling or erythema; 3) Muscle pain; 4) Post-exertional malaise for longer than 24 hours; 5) Significant impairment in short-term memory or concentration; 6) Sore throat; 7) Tender lymph nodes; 8) Unrefreshing sleep [33].

At the moment of inclusion in a study, all the patients were on the recommended heart failure treatment according to the current heart failure management guidelines. All the patients underwent to the therapy with Mildronate 1000mg/day for 3 months. Heart ultrasound and MSFI-SF was performed twice – in the beginning and after 3 months from onset of combination treatment.

STATISTICAL ANALYSIS

Data were analyzed using Statistical Package SPSS version 16.0 software. Data were summarized using mean and standard deviation values, as well as percentage for qualitative variables. Comparison between groups was done using chi-square test for qualitative variables and Mann-Whitney test for scores. Correlations were performed by using Spearman's rank correlation method. A 2-tailed probability value of <0.05 was considered statistically significant.

RESULTS

Mean EF of patients involved in a study was 35.88±2.75. Initial assessment of patients with MFSI-SF scale revealed mean score of 97.93±6.61. Majority of patients had trouble in remembering things with the mean score of 1.25±0.91. Muscle ache and weakness of legs were present in absolute majority of patients with mean scores of 2.37±0.99 and 2.65±0.93, consequently. Initial assessment revealed existence of "feeling upset" in 100% of cases (mean score 2.15±0.96), being nervous in 94% (mean score 2.4±0.99), feeling pooped in 91% (2.13±1.12), confused in 58% (1.15±1.16), sad in 90% (2.31±1.23), depressed in 97% (2.23±0.91), tense in 100% (2.81±0.84) and distressed in 100% (2.49±1.05). 65% of patients feel themselves cheerful (namely, 1.01±0.95), 68% lively (1.08±0.85), 49% relaxed (0.71±0.85), 68% refreshed (0.84±0.69), 53% energetic (0.7±0.74) and 48% calm (0.72±0.69). Feeling fatigued was reported by 100% of patients with mean score 2.63±1.0.

All the study participants underwent to the second time assessment of EF and MFSI-SF scale to evaluate effect of 3 months therapy with 1000mg/day dosage of Mildronate on heart failure and fatigue. In comparison with the initial data, EF was improved after treatment (35.88±2.75 vs 38.03±3.35; respectively. P<0.0001). Mean score of MFSI-SF scale significantly decreased after 3 months from onset of therapy (97.93±6.61 vs 41.37±5.44; P< 0.0001). Treatment with Mildronate was associated with the significant improvement of feeling fatigued (2.63±1.02 vs 1.32±1.02; respectively; P<0.0001), remembering things (1.25±0.91 vs 2.97±0.83; P<0.0001), relieve of muscle ache (2.37±0.99 vs 0.87±0.81; respectively; P<0.0001) and weakness of legs (2.65±0.93 vs 1.3±0.91; respectively; P<0.0001). Number of patients as well as scores of MFSI-SF scale were increased after Mildronate treatment who felt themselves calm (0.72±0.69 vs 2.13±0.70, respectively; P<0.0001), refreshed (0.84±0.69 vs 2.12±0.72, respectively; P<0.0001), cheerful (1.01±0.95 vs 2.56 0.75, respectively; P<0.0001), energetic (0.7±0.vs 2.26±0.71, respectively; P<0.0001) or lively (1.08±0.85 vs 2.02±0.68, respectively; P<0.0001). Treatment with Mildronate along with the standard recommended therapy significantly improved patients' feelings of being upset (2.15±0.96 vs 0.88±0.86, respectively; P<0.0001), nervous (2.4±0.99 vs 1,31±1.01, respectively; P<0.0001), pooped (2.13±1.12 vs 1.19±0.99), confused (1.15±1.16 vs 0.46±0.69, respectively; P<0.0001), sad (2.31±1.23 vs 1.45±1.09, respectively; P<0.0001), depressed (2.23±0.91 vs 1.01± 0.94, respectively; P<0.0001), tensed (2.81±0.84 vs 1.25±1.06, respectively; P<0.0001) and/or distressed (2.49±1.05 vs 1.4±0.94, respectively; P<0.0001).

Difference was found between the positive cases of MSFI-SF scale parameters between initial and after treatment assessment. Namely, "feeling upset" – 100% vs 61% of cases, being nervous - 94% vs 73% of cases, feeling pooped - 91% vs 69% of cases, confused - 58% vs 34% of cases, sad - 90% vs 73% of cases, depressed - 97% vs 61% of cases. Muscle ache and weakness in legs also decreased after treatment (97% vs 63% and 96% vs 77%, respectively). Fatigue was reported in 95% cases initially and in 74% cases after treatment.

Severity of presentation of some MSFI-SF scale parameters are given below graphically.

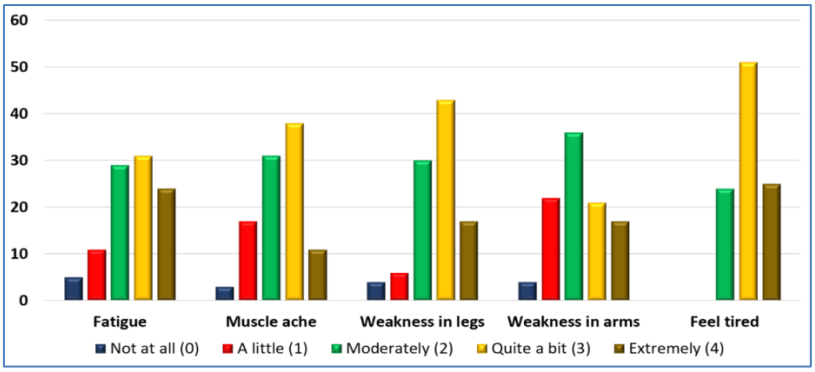

Fig-1a: Initial data of MFSI-SF scale

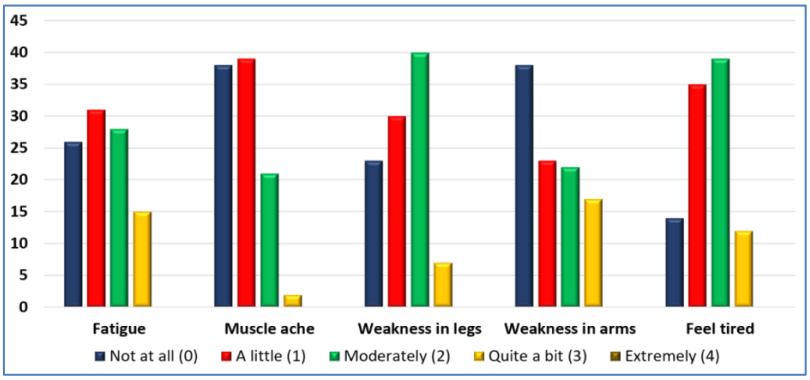

Fig-1b: MFSI-SF scale parameters after 3 months therapy with Mildronate and standard therapy

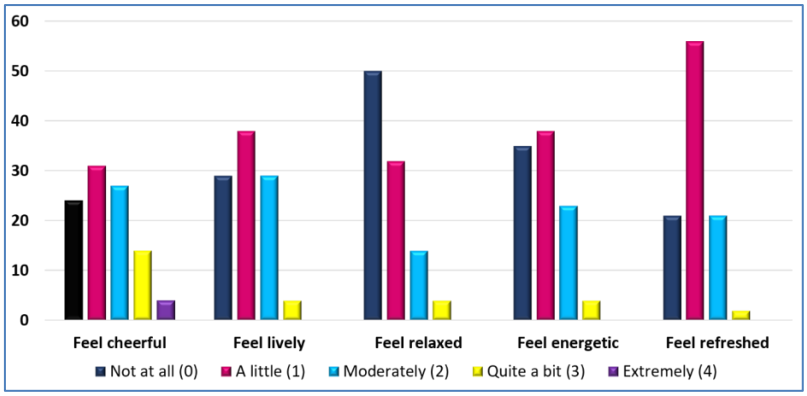

Fig-2a: Initial data of MFSI-SF scale parameters with positive feelings

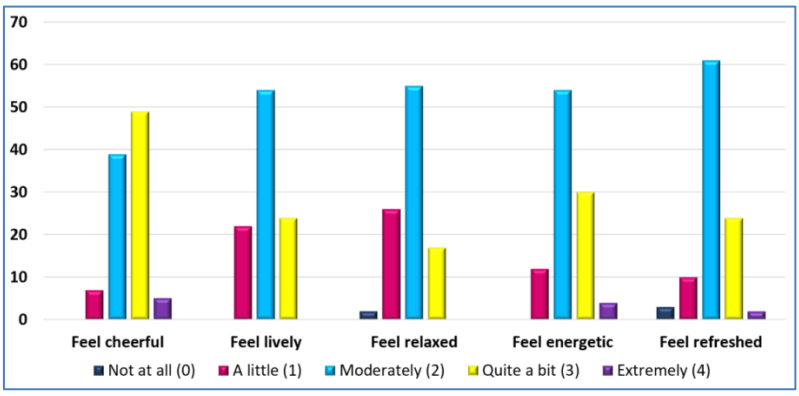

Fig-2b: MFSI-SF scale parameters with positive feelings after 3 months of treatment

Presented figures point out on improvement of self-feeling and regression of fatigue and tiredness symptoms of heart failure patients after 3 months therapy with combination of standard heart failure therapy and Mildronate.

EF level was positively correlated with the severity of cheerful, lively, relaxed, refreshed and energetic feelings assessed from 0 to 4 points. Hence, EF was negatively correlated with the severity of trouble remembering things, concentrating and paying attention, muscles ache, feel upset, nervous, pooped, confused, sad, fatigued, depressed, tensed and tired, forgetfulness, weakness in legs and hands.

DISCUSSION

Studies which were addressed to the fatigue assessment in HF population, mainly studied relationships between fatigue and heart rate and/or blood pressure. There are only few reports published, where relationships of cardiac function parameters, namely cardiac output and stroke volume and fatigue severity are assessed. Nelesen et al. examined the relationship between self-reported fatigue and hemodynamic functioning at rest and in response to a public speaking stressor in healthy 142 individuals. They found out that fatigue was not associated with blood pressure or heart rate at rest, but was significantly associated with decreased cardiac index (P<.001; 95% confidence interval, −0.046 to −0.014) and stroke index (P=.002; 95% confidence interval −0.664 to −0.151). Hence, they concluded that fatigue complaints may have hemodynamic correlates even in practically healthy individuals [34].

In contrast with our study, where fatigue was reported by 100% of patients, previous studies have reported that the prevalence of fatigue in patients with HF is around 44% (from 28 to 59%). This discrepancy may have several explanations. First, the authors have used different methods for fatigue assessment and involved patients had different severity of fatigue [5, 9]. Second, in our study were only involved patients with decreased EF, while in other studies all the patients with HF despite EF level. Fatigue at rest or on mild physical activity was revealed from 27 to 43% of patients with HF diagnosis [9, 35, 36].

In the secondary analysis of the CORONA trial, Perez-Moreno et al. did not reveal positive significant association between level of fatigue and risk of all-cause mortality (p = 0.26) in patients with systolic HF of ischemic origin [9]. Similarly, Ekman et al. reported no independent prognostic effect of fatigue among systolic HF patients enrolled in COMET (Carvedilol or Metoprolol European Trial) [37]. Therefore, both studies did show significant association of fatigue with an increased risk of HF hospitalization and worsening HF [9, 37].

Our study showed positive and negative correlations of EF with the severity level of MFSI-SF parameters. Hence, similar to Donovan et al. who conducted a systematic review of 70 publications and evaluated the use of the 30-item Multidimensional Fatigue Symptom Inventory-Short Form, we strongly recommend to use this high reliable MFSI-SF scale in future studies [30].

Our study revealed a positive effect of 1000mg/day dosage of mildronate on an EF and MFSI-SF scale parameters of patients with HFrEF. Solomenchuk et al. showed that the use of antihypertensive therapy with the addition of meldonium results in significant reduction in fatigue assessed by MFSI-SF scale and improves quality of life in patients with arterial hypertension [38]. Statsenko et al. used meldonium as part of combination therapy in the early post-infarction period in patients with CHF and observed significant clinical improvement, reduction in the rate of angina attacks and in the need for nitrates, and favorable changes in cardiac structural and functional parameters [39]. Later on, the same group of authors demonstrated the ability of meldonium to significantly improve endothelial function and the state of microcirculatory vascular bed in patients with Chronic Heart Failure of Ischemic Etiology and Type 2 Diabetes Mellitus [40]. Voronkov et al. performed a double-blind crossover study, where they revealed a positive influence of mildronate on endothelial function in patients with CHF [41]. Mildronate showed antiasthenic efficacy in elderly hypertensive patients [42].

In conclusion, according to its reliability we recommend to use MSFI-SF scale for assessment of existence and severity of fatigue in patients with HFrEF before and after treatment to evaluate the progress and benefit of the treatment. Standard HF treatment with addition of mildronate showed strong ability for improvement of clinical manifestations, life quality, fatigue expression and general asthenia.

REFERENCES

1. Authors/Task Force Members, McMurray, J. J., Adamopoulos, S., Anker, S. D., Auricchio, A., Böhm, M., ... & Ponikowski, P. (2012). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European heart journal, 33(14), 1787-1847.
2. Moonesinghe, R., Yang, Q., Zhang, Z., & Khoury, M. J. (2019). Prevalence and Cardiovascular Health Impact of Family History of Premature Heart Disease in the United States: Analysis of the National Health and Nutrition Examination Survey,

2007–2014. Journal of the American Heart Association, 8(14), e012364.
3. Rajadurai, J., Tse, H. F., Wang, C. H., Yang, N. I., Zhou, J., & Sim, D. (2017). Understanding the epidemiology of heart failure to improve management practices: an Asia-Pacific perspective. Journal of cardiac failure, 23(4), 327-339.
4. Sears, S. F., Woodrow, L., Cutitta, K., Ford, J., Shea, J. B., & Cahill, J. (2013). A patient's guide to living confidently with chronic heart failure. Circulation, 127(13), e525-e528.
5. Williams, B. A. (2017). The clinical epidemiology of fatigue in newly diagnosed heart failure. BMC cardiovascular disorders, 17(1), 1-10.
6. Fini, A., & Cruz, D. D. A. L. M. D. (2009). Characteristics of fatigue in heart failure patients: a literature review. Revista latino-americana de enfermagem, 17(4), 557-565.
7. Fini, A., de, Almeida, L., Monteiro, da, Cruz, D. (2009). Characteristics of fatigue in heart failure patients: a literature review. Rev. Latino-Am. Enfermagem, 17(4):18-22.
8. Acciarresi, M., Bogousslavsky, J., & Paciaroni, M. (2014). Post-stroke fatigue: epidemiology, clinical characteristics and treatment. European neurology, 72(5-6), 255-261.
9. Perez-Moreno, A.C., Jhund, P.S., Macdonald, M.R. (2014). Fatigue as a Predictor of Outcome in Patients With Heart Failure Analysis of CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). J Am Coll Cardiol HF, 2:187–197.
10. Alsén, P., Thörn, S., Nordqvist, L., & Berndtsson, I. (2016). Men's Experience of Difficulties during First Year Following Myocardial Infarction—Not Only Fatigue. Health, 8(15), 1654-1667.
11. Son, C. G. (2019). Differential diagnosis between "chronic fatigue" and "chronic fatigue syndrome". Integrative medicine research, 8(2), 89.
12. Crane, P.B., Efird, J.T., Abel, W.M. (2016). Fatigue in Older adults Postmyocardial infarction. Frontiers in Public Health, 4:55-57.
13. Eckhardt, A.L., DeVon, H.A., Piano, M.R. (2014). Fatigue in the Presence of Coronary Heart Disease. Nursing research, 63(2):83-93.
14. Kostić, V. S., Tomić, A., & Ječmenica- Lukić, M. (2016). The pathophysiology of fatigue in Parkinson's disease and its pragmatic management. Movement disorders clinical practice, 3(4), 323-330.
15. Mortazavi, F., & Borzoee, F. (2019). Fatigue in Pregnancy: The validity and reliability of the Farsi Multidimensional Assessment of Fatigue scale. Sultan Qaboos University Medical Journal, 19(1), e44.
16. Seo, J. G., & Park, S. P. (2018). Significance of fatigue in patients with migraine. Journal of Clinical Neuroscience, 50, 69-73.
17. Van Herck, M., Spruit, M. A., Burtin, C., Djamin, R., Antons, J., Goërtz, Y. M., & Van't Hul, A. J. (2018). Fatigue is highly prevalent in patients with asthma and contributes to the burden of disease. Journal of clinical medicine, 7(12), 471.
18. Doehner, W., Von Haehling, S., & Anker, S. D. (2013). Anaemia predicts health related quality of life in heart failure patients. International journal of cardiology, 162(2), 67-68.
19. Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey Jr, D. E., Drazner, M. H., & Wilkoff, B. L. (2013). 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation, 128(16), 1810-1852.
20. Bozzini, S., Albergati, A., Capelli, E., Lorusso, L., Gazzaruso, C., Pelissero, G., & Falcone, C. (2018). Cardiovascular characteristics of chronic fatigue syndrome. Biomedical reports, 8(1), 26-30.
21. Wyller, V. B., Saul, J. P., Walløe, L., & Thaulow, E. (2008). Sympathetic cardiovascular control during orthostatic stress and isometric exercise in adolescent chronic fatigue syndrome. European journal of applied physiology, 102(6), 623-632.
22. Miwa, K. (2015). Cardiac dysfunction and orthostatic intolerance in patients with myalgic encephalomyelitis and a small left ventricle. Heart and vessels, 30(4), 484-489.
23. Ekmann, A., Petersen, I., Mänty, M., Christensen, K., & Avlund, K. (2013). Fatigue, general health, and ischemic heart disease in older adults. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 68(3), 279-285.
24. Dzerve, V., Matisone, D., Kukulis, I., Romanova, J., Putane, L., & Grabauskienė, V. (2005). Mildronate improves peripheral circulation in patients with chronic heart failure: results of clinical trial (the first report). Sem Cardiol, 11(2), 56-64.
25. Dzerve, V., Matisone, D., Kukulis, I., Romanova, J., Putane, L., & Grabauskienė, V. (2005). Mildronate improves peripheral circulation in patients with chronic heart failure: results of clinical trial (the first report). Sem Cardiol, 11(2), 56-64.
26. Chumburidze, V., Kikalishvili, T., & Sulashvili, T. (2005). Definition of therapeutic effect of mildronate in patients with chronic heart failure. Georgian medical news, (122), 25-29.
27. Statsenko, M. E., Turkina, S. V., & Belenkova, S. V. (2009). Mildronate therapy in patients with chronic heart failure, type 2 diabetes mellitus and autonomous cardiac neuropathy. Russian Journal of Cardiology, (3), 69-75.
28. Chan, A., Lew, C., Wang, X. J., Ng, T., Chae, J. W., Yeo, H. L., ... & Gan, Y. X. (2018). Psychometric properties and measurement equivalence of the Multidimensional Fatigue Syndrome Inventory-Short Form (MFSI-SF) amongst breast cancer and lymphoma patients in

Singapore. Health and quality of life outcomes, 16(1), 1-14.
29. ANTONIO, D. A. D. F., Muller, A. G., & BUTCHER, R. D. C. G. (2019). Reliability and viability of using the Multidimensional Fatigue Inventory-20 in patients with chronic coronary artery disease. Revista da Escola de Enfermagem da USP.
30. Donovan, K. A., Stein, K. D., Lee, M., Leach, C. R., Ilozumba, O., & Jacobsen, P. B. (2015). Systematic review of the multidimensional fatigue symptom inventory-short form. Supportive Care in Cancer, 23(1), 191-212.
31. Stein, K. D., Jacobsen, P. B., Blanchard, C. M., & Thors, C. (2004). Further validation of the multidimensional fatigue symptom inventory-short form. Journal of pain and symptom management, 27(1), 14-23.
32. Treanor, C., & Donnelly, M. (2015). A methodological review of the Short Form Health Survey 36 (SF-36) and its derivatives among breast cancer survivors. Quality of life research, 24(2), 339-362.
33. Yancey, J. R., & Thomas, S. M. (2012). Chronic fatigue syndrome: diagnosis and treatment. American family physician, 86(8), 741-746.
34. Nelesen, R., Dar, Y., Thomas, K., & Dimsdale, J. E. (2008). The relationship between fatigue and cardiac functioning. Archives of internal medicine, 168(9), 943-949.
35. Edelmann, F., Wachter, R., Schmidt, A. G., Kraigher-Krainer, E., Colantonio, C., Kamke, W., ... & Aldo-DHF Investigators. (2013). Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. Jama, 309(8), 781-791.
36. Ingle, L., Rigby, A. S., Carroll, S., Butterly, R., King, R. F., Cooke, C. B., ... & Clark, A. L. (2007). Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. European heart journal, 28(5), 560-568.
37. Ekman, I., Cleland, J. G., Swedberg, K., Charlesworth, A., Metra, M., & Poole-Wilson, P. A. (2005). Symptoms in patients with heart failure are prognostic predictors: insights from COMET. Journal of cardiac failure, 11(4), 288-292.
38. Solomenchuk, T. M., Kopchak, L. M., & Tshngryan, G. V. (2018). Астенія і якість життя хворих з артеріальною гіпертензією: ефективність мельдонію. Likarsʹka sprava, (3-4), 105-114.
39. Statsenko, M. E., Shilina, N. N., & Turkina, S. V. (2014). Use of meldonium in the combination treatment of patients with heart failure in the early post-infarction period. Therapeutic archive, 86(4), 30-35.
40. Statsenko, S., Turkin, S. V., Fabritskaya, S. V., & Shilina, N. N. (2017). Efficacy of short-term therapy with meldonium in patients with chronic heart failure of ischemic etiology and type 2 diabetes mellitus. Kardiologiia, 57(4), 58-63.
41. Voronkov, L.G., Shkurat, A.A., Lutsak, E.A. (2008). Mildronate effect on endothelium-dependent vasodilation in patients with chronic heart failure: double blind crossover study. Rational Pharmacotherapy in Cardiology, 4(2):38-40.
42. Statsenko, M.E., Nedogoda, S.V., Turkina, S.V., Tyshchenko, I.A., Poletaeva, L.V., Tsoma, V.V., Ledyaeva A.A., Chumachok, E.V. (2013). Asthenic disorders in elderly patient s with arterial hypertension: management potential of meldonium. Rational Pharmacotherapy in Cardiology, 9(1):25-30.