

Reviewers comments and responses to comments

[AO1]: *I am expecting some example*

Two algorithms are mentioned and explained in the text (section Diagnosis) that may facilitate a HFpEF diagnosis: H2FPEF (Heavy, 2 or more Hypertensive drugs, Atrial Fibrillation, Pulmonary hypertension, Elder age > 60, elevated Filling pressures) and HFA-PEFF (Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final aetiology).

The new sentence is: "Updated diagnostic algorithms for HFpEF have been recommended (H2FPEF, HFA-PEFF)."

[AO2]: *The major point of this review need to be summarized in the abstract rather than picking some of the treatment approaches*

We changed the abstract and major points of this review are now emphasized. The text of the abstract now is:

Heart failure is a major public health problem with a prevalence of 1-2% in developed countries. The underlying pathophysiology of heart failure is complex and as a clinical syndrome is characterized by various symptoms and signs. Heart failure is classified according to left ventricular ejection fraction (LVEF) and falls into three groups: LVEF \geq 50% - HFpEF (heart failure with preserved ejection fraction), LVEF <40% - HFrEF (heart failure with reduced ejection fraction), LVEF 40-49% - HFmrEF (heart failure with mid-range ejection fraction). Diagnosing heart failure is primarily a clinical approach and it is based on anamnesis, physical examination, echocardiogram, radiological findings of the heart and lungs and laboratory tests, including a specific marker of heart failure BNP (brain natriuretic peptide) or NT-proBNP (N-terminal pro-B-type natriuretic peptides) as well as other diagnostic tests in order to elucidate possible etiologies. Updated diagnostic algorithms for HFpEF have been recommended (H2FPEF, HFA-

PEFF). New therapeutic options improve clinical outcomes as well as functional status in patients with HFrEF (e.g., sodium-glucose cotransporter-2 - SGLT2 inhibitors) and such progress in treatment of HFrEF patients resulted in new working definition of the term “heart failure with recovered left ventricular ejection fraction (HFrecEF)”. In line with rapid development of heart failure treatment, cardiac rehabilitation becomes an increasingly important part of overall approach to patients with chronic heart failure for it has been proven that exercise training can relieve symptoms, improve exercise capacity and quality of life as well as reduce disability and hospitalization rates. We gave an overview of latest insights in heart failure diagnosis and treatment with special emphasize on the important role of cardiac rehabilitation in such patients.

[AO3]: *Add valvular heart diseases*

We add “valvular heart diseases” and the sentence now is:

“Most commonly, HF develops as a consequence of a myocyte injury caused by coronary artery disease, uncontrolled arterial hypertension, valvular heart diseases and diabetes mellitus, and it is important to consider pulmonary disorders such as chronic obstructive pulmonary disease or pulmonary arterial hypertension as causes that can lead to HF.”

[AO4]: *And cardiac output*

The term “and cardiac output” is inserted and the sentence now is:

“The main pathophysiological mechanisms leading to HF are increased hemodynamic overload, ischemia, myocardial dysfunction and remodeling, excessive neuro-humoral stimulation - chronic sympathetic nervous system overactivity as one of the key pathophysiological mechanisms (in the acute phase, this upregulated sympathetic activity is an essential compensatory response initiated in order to compensate for

reduced contractility, and cardiac output but in the long-term, it contributes to cardiac dysfunction as it leads to cardiac hypertrophy and cell dysfunction), activation of the RAAS (renin-angiotensin-aldosterone system), excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis, and genetic mutations.”

[AO5]: *Why repeating!*

We deleted the repeated term “heart failure with preserved/reduced/mid-range ejection fraction” and the sentence now is:

“The most common classification of HF refers to the left ventricular ejection fraction (LVEF). Accordingly, HF is classified into three groups: with preserved left ventricular ejection fraction LVEF $\geq 50\%$ - HFpEF, with reduced ejection fraction LVEF $< 40\%$ - HFrEF, and patients with a mid-range ejection fraction are between these two groups LVEF 40-49% - HFmrEF.”

[AO6]: *Need to be specific, muscle weakness due to early fatigability*

We added this and new sentence is:

“Clinical signs and symptoms of HF include shortness of breath, dyspnoea (initially with severe physical exertion, and in the advanced stage at rest and worsening in the supine position), orthopnoea (dyspnoea in the supine position), paroxysmal nocturnal dyspnoea (sudden onset of shortness of breath at night), poor mobility, dizziness, lack of appetite, fatigue, and muscle weakness due to early fatigability.”

[AO7]: *Generalized or localized!*

We characterized the term oedema as suggested, and the sentence now is:

“In the advanced stages, physical examination and auscultation can reveal abnormal pulmonary phenomena (wheezing, crepitation), the third heart murmur (S3 gallop) that can rarely be heard, presence of an oedema (generalized or localizes), and cardiac cachexia (loss of muscle mass).”

[AO8]: *Which scale*

This is now explained in the text, the way of calculating and interpreting of HFA-PEFF score. Extended text now is:

“Other important measures include the left atrial volume index, the LV mass index, the LV relative wall thickness, tricuspid regurgitation velocity, and the LV global longitudinal systolic strain^[15]. According to the consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) and the definition of HFA-PEFF score, the major (2 points) and minor (1 point) criteria were defined from these measures^[15]. The score has functional, morphological, and biomarker domains (Figure 2). Within each domain, a major criterion scores 2 points or a minor criterion 1 point. If several major criteria within a single domain are positive, this domain still contributes 2 points. If no major but several minor criteria are positive the contribution still is 1 point. Major and minor criteria are not additive in a single domain and points are added only when they come from different domains^[15].”

[AO9]: *Please maintain consistency as in the previous statement use ACEi*

“ACE inhibitors” is replaced with “ACEi” to maintain consistency so the sentence now is:

“If the patient does not tolerate ACEi or they are contraindicated, then angiotensin receptor blockers (ARBs) are used. ACEi have been shown to reduce morbidity and

mortality in patients with HFrEF^[25-27], and data suggests that there are no differences among the available ACEi regarding their effects on symptoms or on survival^[28].”

[AO10]: *I suggest using the parasympathetic tone instead of vagus*

As suggested, we used “parasympathetic tone” instead of “vagus” and the sentence now is:

“ET reduces sympathetic tone and increases the influence of the parasympathetic tone at rest, restores baroreflex sensitivity and decreases chemoreflex sensitivity in HF..”

[AO11]: *Since Autonomic imbalance was introduced here, I suggest in the previous statement “ET reduces sympathetic tone” To highlight the effect of heart failure on the ANS balance or vice versa.*

We highlighted the pathophysiological effect of heart failure on the ANS balance and the sentence now is:

“ET reduces sympathetic tone and increases the influence of the parasympathetic tone at rest, restores baroreflex sensitivity and decreases chemoreflex sensitivity in HF which is important in term of autonomic nervous system imbalance and chronic sympathetic nervous system overactivity as one of the key pathophysiological mechanisms in HF leading to vasoconstriction, altered renal blood flow and adverse remodeling - hypertrophy and cell dysfunction.”

[AO12]: *There are many risk factors*

As indicated, the sentence is reformulated, and the new sentence is:

“A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation^[110] emphasizes that cardiac

rehabilitation program for patients with HF should include multiple components such as medical evaluation and baseline patient assessment, appropriate evaluation of many risk factors associated with such patients (e.g., concomitant diseases -anaemia, valvular heart disease, renal function, patients age), education concerning medication adherence, dietary recommendations, psychosocial support, as well as exercise training and physical activity counseling.”

[AO13]: *Frequency and type should be mentioned*

The choice on exercise modality and determining the appropriate level of ET intensity, with frequency and type is fully explained in the next section.

We changed sentence into:

“Implementation of ET requires appropriate patient selection, training protocol identification, intensity level determination, and progression monitoring.”

And this is followed by section which explains frequency and type of training with different intensity.

[AO14]: *Why specify it to small muscle group only?*

“Early mobilization of patients after an episode of acute heart failure is also recommended. At this stage, gradual mobilization, respiratory exercises, and small muscle groups exercises is needed.”

In this sentence we referred to small muscle group only because the discussion is about early mobilization after an episode of acute heart failure where respiratory training, and small muscle strength exercise is used as first line of mobilization of such patients with achieving clinical stability prior to regular ET.

The sentence now is: "At this stage, gradual mobilization, respiratory exercises, and small muscle groups exercises is needed to establish clinical stability and help patients to achieve a sufficient level of functional capacity and trust prior to conducting a symptom-limited exercise test and initiating regular ET."

[AO15]: *This statement is vague, Exercise modality are known to be safe for HF patient when given at the right intensity and duration. The overall concept in ET is to be done gradually and individualized.*

As suggested, we reformulated insufficiently clear sentence ("Each exercise modality should be tested on an individual patient to confirm clinical and hemodynamic tolerance, determine acceptability, and prove safety") and the new sentence is:

"Exercise modalities are known to be safe for HF patients when given at the right intensity and duration. The overall concept in ET is to be done gradually and individualized."

[AO16]: *This need to be introduced as Volume of oxygen*

We introduced volume of oxygen for VO₂ and the sentence is:

"The volume of oxygen (VO₂) measured in patients with chronic heart failure at the end of the exercise test is not the maximum VO₂ value because such patients cannot reach it."

[AO17]: *Identify which one do you mean (0-10) or scale from (6-20)*

As suggested, we clarified which scale is mentioned and recommended intensity of training according to Borg RPE scale.

“In practice, heart rate (HR) reserve (HRR) - the difference between the basal and peak HR (the training in the range of 40 - 70% HRR is recommended), and rating of perceived exertion (RPE) (training of 10/20-14/20 of the Borg RPE is recommended) are used.”

[AO18]: *Keep it consistent VO₂peak*

As suggested, peak VO₂ in the sentence is changed into VO₂ peak in order to be consistent and the sentence is:

“HIIT is not superior to MCT in changing left ventricular remodeling or aerobic capacity[115] but the recent meta-analysis showed that improves VO₂ peak and should be considered as a component of care of HF_rEF patients^[116].

[AO19]: *More elaboration is needed in this paragraph. The intensity of exercise in HF patients need to be considered before administration of exercise. So please elaborate on this. As this is a critical point for HF patients since they suffer from easy fatiguability*

As suggested, we elaborated how should me RST administered in HF patients.

The text that is added: “As HF patients suffer from easy fatiguability, the initiation of an RST programm must be individually adjusted to the patient under medical supervision and each patient must be individually introduced into the training regimen. The amount of cardiovascular stress expected during RST depends on the magnitude of the resistance [% of one repetition maximum (% 1-RM)], the size of the working muscle mass and the relation between the duration of the muscle contraction and rest period between repetitions^[110]. The minimum recommendations for implementation of an RTS in three progressive steps are: 1. “ Instruction phase” - pre-training to learn and practice slow conduction, without or at very low resistance (RPE <12, <30% 1-RM). 2. “Resistance/endurance phase” - start of training with a high number of repetitions and a low intensity (RPE 12-13, 30-40% 1-RM). 3. “Strength phase” - higher intensity (RPE

<15, 40-60% 1-RM), increasing muscle mass^[110]. Surveillance over each step is necessary because of the possibility of abdominal straining and consequent blood pressure elevations so prescribing the appropriate level of training according to the patient's clinical stability, motivation, and experience with RST is of great importance."

[AO20]: *Please add a conclusion to summarize the key points and what is mentioned in this review*

As suggested, we added a conclusion with key points and messages of these review.

New paragraph is:

"Conclusion

New diagnostic methods and treatment options of HF are evolving rapidly. Accordingly, the number of patients with recovered LVEF (HFrecEF) and improved functional status is increasing. Beside medicament options to maintain future stable state of the patients with HF, cardiac rehabilitation is an important part of care, ET is proved to be safe in HF patients and should be implemented as a part of overall approach. Nowadays it is important to emphasize the role of cardiac rehabilitation in patients with chronic HF, raise consciousness that HF is not yet an indication for rehabilitation in many countries, at least not as a first diagnosis, and nurture a holistic approach to patients with HF."

Figures and tables

All figures and tables are made by the authors and not copied. The source of data used in figures and tables are referenced in the caption.