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REVIEW

Current concept in the diagnosis, treatment and rehabilitation of patients with congestive heart failure

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Abstract

Heart failure (HF) is a major public health problem with a prevalence of 1%-2% in developed countries. The underlying pathophysiology of HF is complex and as a clinical syndrome is characterized by various symptoms and signs. HF is classified according to left ventricular ejection fraction (LVEF) and falls into three groups: LVEF ≥ 50% - HF with preserved ejection fraction (HFpEF), LVEF < 40% - HF with reduced ejection fraction (HFrEF), LVEF 40%-49% - HF with mid-range ejection fraction. Diagnosing HF 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 markers of HF - brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide 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 "HF with recovered left ventricular ejection fraction". In line with rapid development of HF treatment, cardiac rehabilitation becomes an increasingly important part of overall approach to patients with chronic HF 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 HF diagnosis and treatment with special emphasize on the important role of cardiac rehabilitation in such patients.

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Core Tip: Diagnostic methods and treatment of heart failure (HF) are evolving rapidly. Making a firm diagnosis of HF with preserved ejection fraction is a challenge, and although diagnostic algorithms have been recommended further research is needed for better classification. Therapeutic options improve morbidity, mortality, as well as functional status of patients with HF with reduced ejection fraction and the new term - HF with recovered left ventricular ejection fraction is a result of successful therapy. Only a small part of patients with chronic HF participates in cardiac rehabilitation programs. Cardiac rehabilitation in patients with HF is an important part of care and should be implemented as a part of holistic approach because it improves exercise capacity and quality of life, reduces disability and hospitalization rates.

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INTRODUCTION

Heart failure (HF) is one of the major public health problems with a prevalence of 1-2% in developed countries (varies by definition and region), and it increases with age (rising to over 10% in people over 70 years of age)[1]. Approximately 33% of men and 28% of women at the age of 55 have a lifetime risk of developing HF[1].

The pathophysiology of HF is complex and it is therefore a clinical syndrome characterized by various symptoms and signs, which is caused by structural and/or functional abnormalities of the heart. HF can be a terminal stage of many cardiovascular diseases, including myocardial infarction, heart valve disease, tachyarrhythmias, congenital heart defects, and cardiomyopathies[1]. 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[1-3].

The main pathophysiological mechanisms leading to HF are increased hemodynamic overload, ischemia, myocardial dysfunction and remodelling, excessive neurohumoral 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 renin-angiotensin-aldosterone system (RAAS), excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis, and genetic mutations[3-6] (Figure 1). HF is associated with a variety of complications, such as frequent hospitalizations, fatal arrhythmias, and death in the advanced stage of the disease.

CLASSIFICATION

As mentioned, HF is caused by a number of conditions, causing left and right ventricular dysfunction[6-8]. 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 ≥ 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% - HF with mid-range ejection fraction

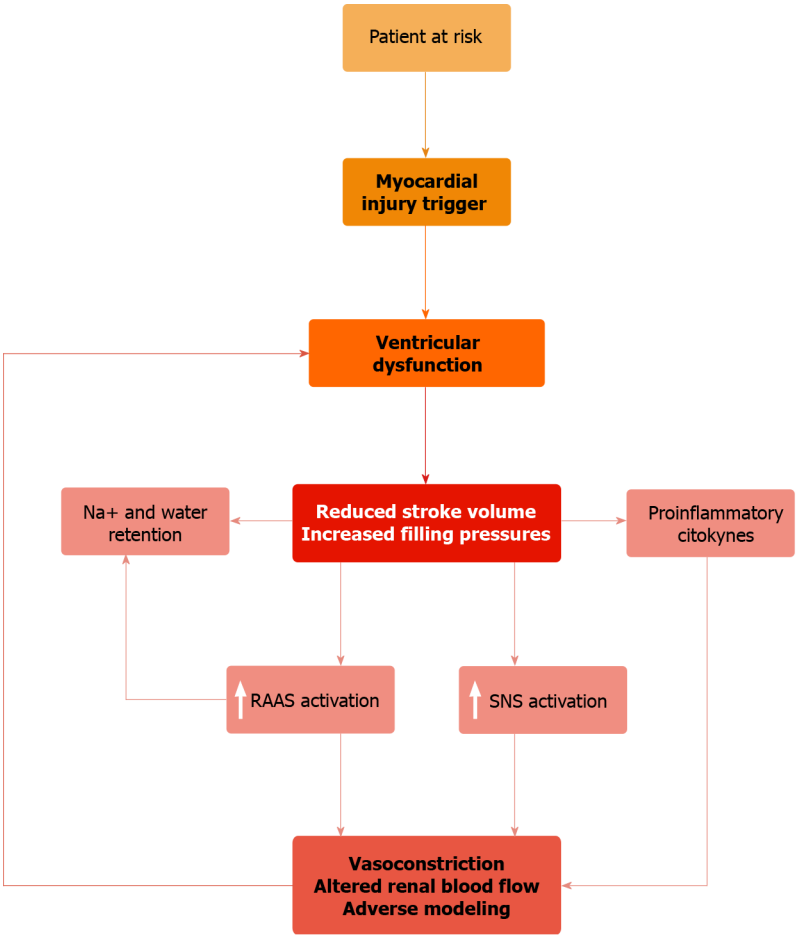

Figure 1 Pathophysiological mechanisms in chronic heart failure (data from[3]). RAAS: Renin-Angiotensin-Aldosterone System; SNS: Sympathetic nervous systems.

(HFmrEF)[1,2].

HF is often considered as a left-sided failure when caused primarily by left heart pathologies (*e.g.*, left ventricular, mitral valve, or aortic valve dysfunction). The ventricle fails in its ability to eject blood, or can do so only at the cost of high filling pressures[6,7]. Right-sided or right ventricular HF also has a complex pathophysiology and it is influenced by multiple factors (such as volume status, pulmonary vascular resistance, right ventricular, pulmonic valve, or tricuspid valve dysfunction, left ventricular function) and usually occurs as a result of left ventricular HF[8,9]. Left and right ventricular HF may overlap or occur separately and most patients with right HF have some elements of left HF.

Considering the clinical presentation, HF is divided into acute and chronic[1,2]. Patients with a low LVEF and no symptoms or signs of HF are characterized as asymptomatic patients with a reduced left ventricular systolic function. Those who have signs and symptoms of HF belong to the group of patients with chronic HF, and those who do not experience worsening of symptoms within at least a month are considered stable patients with chronic HF[6]. Acute HF includes the worsening of chronic HF, pulmonary oedema, and cardiogenic shock. There are a number of factors that can trigger acute HF, *e.g.*, myocardial disfunction, pericardial tamponade, and acute valve insufficiency, which are among the most frequent primary cardiac causes of acute HF[1,2]. Decompensation of chronic HF can occur without known precipitant factors, but infection, uncontrolled hypertension, rhythm disturbances, exacerbation of chronic obstructive pulmonary disease, or non-adherence to medicaments can be the cause of decompensation[1,2].

Chronic HF is a complex of multiorgan dysfunction, characterized by the impaired function of the heart, kidney, and skeletal muscles, with increased stimulation of the sympathetic nervous system and numerous humoral and neuroendocrine disorders. The severity of symptoms in chronic HF is classified according to the New York Heart Association (NYHA)[10] and American College of Cardiology/American Heart Association (ACC/AHA)[11] in four stages[2] (Table 1). The NYHA functional classi-

Table 1 Comparison of American College of Cardiology/American Heart Association Stages of HF and New York Heart Association Functional Classifications (data from[2])

ACC/AHA Stages of HF		NYHA Functional Classification	Restriction of physical activity
A At high risk for HF but without structural heart disease or symptoms of HF (*e.g.*, diabetes, arterial hypertension)		/	/
B Structural heart disease but without symptoms of HF	I	Regular physical activity does not cause dyspnea and fatigue – asymptomatic	No limitation of physical activity
C Structural heart disease with prior or current symptoms of HF	I	Regular physical activity does not cause dyspnea and fatigue – asymptomatic	No limitation of physical activity
	II	Moderate physical activity results in milder dyspnea and fatigue	Slight limitation of physical activity
	III	No difficulty at rest; minimal physical activity leads to exhaustion, dyspnea, and fatigue	Marked limitation of physical activity
	IV	Symptomatic at rest	Unable to carry on any physical activity without symptoms of HF
D Refractory HF requiring specialized interventions	IV	Symptomatic at rest	Unable to carry on any physical activity without symptoms of HF

ACC/AHA: American College of Cardiology/American Heart Association; HF: Heart failure; NYHA: New York Heart Association.

fication is an independent predictor of mortality and it is widely used in clinical practice[12].

CLINICAL PRESENTATION

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. Due to compensatory mechanisms, in the early phase of HF patients do not have to present with all the specific symptoms and physical signs, such as those related to fluid retention. 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 localized), and cardiac cachexia (loss of muscle mass). The signs of predominantly right-sided HF are distended jugular veins, ascites, hepatojugular reflux (pressing the hands on the abdomen leads to a more pronounced filling of the jugular veins), and oedema of the legs[1-4].

DIAGNOSIS

The cornerstone in the diagnosis of HF is primarily established by a clinician's assessment and it is based upon a careful medical history (coronary heart disease, arterial hypertension, diabetes, valve disease, cardiotoxic drugs, irradiation, *etc.*), a physical examination, an electrocardiogram (ECG), an ultrasound of the heart (echocardiography), radiological findings of the heart and lungs, laboratory tests, including a specific markers of HF - brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), as well as other diagnostic tests, in order to elucidate possible aetiologies [*e.g.*, invasive coronary angiography, magnetic resonance (MR), or computed tomography (CT)][1,6-8].

Even though a decreased left ventricular ejection fraction identifies patients with HFrEF, the echocardiogram alone does not establish or exclude the diagnosis of HF, since approximately half of the patients with HF have a preserved left ventricular ejection fraction. The most common patients with HFpEF are elderly women with hypertension, ischemic heart disease, atrial fibrillation, obesity, diabetes mellitus, renal disease, or obstructive lung disease[13]. Echocardiography is important in revealing findings that go along with HF and in verifying possible causes of HF (*e.g.*, left

ventricular diastolic dysfunction, left ventricular systolic dysfunction, valve dysfunction, regional wall motion abnormalities, left ventricular hypertrophy, left atrial enlargement).

Two algorithms, Heavy, 2 or more Hypertensive drugs, Atrial Fibrillation, Pulmonary hypertension, Elder age > 60, elevated Filling pressures (H2FPEF)[14] and HF Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology (HFA-PEFF)[15] may facilitate a HFpEF diagnosis[13]. The H2FPEF score, which relies on simple clinical characteristics and echocardiography, enables the discrimination of HFpEF from noncardiac causes of dyspnoea and assists in the determination of the need for further diagnostic testing[14]. Elevated natriuretic peptides support a diagnosis of HFpEF[16] but normal levels do not exclude it. Echocardiography has a relevant role in HFpEF and is used for the non-invasive hemodynamic assessment of high LV filling pressures (indirectly pulmonary capillary wedge pressure, PCWP). Early (E) transmitral filling velocities that are measured at the mitral leaflet tips by pulse wave Doppler, Tissue Doppler echocardiography which is performed to measure early (e') diastolic tissue velocities at the septal and lateral mitral annulus, and the mean of the septal and lateral E/e' ratio is used to estimate the PCWP[16,17]. 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 HF 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].

Patients with mild or moderate HF may appear normal on physical examination, with normal vital signs. Euvolemic patients with chronic dyspnoea, symptoms of HF, and normal cardiac filling pressures at rest may have abnormal hemodynamic responses during exercise, suggesting that the chronic symptoms are related to HF[18-21]. These patients with normal cardiac output at rest have an inability to increase cardiac output during exercise without an excessive increase in filling pressures, resulting in fatigue and intolerance. Elevated resting E/e' strongly supports the presence of high PCWP and thus HFpEF, but a normal resting E/e' does not exclude HFpEF[15,18]. Exercise stress echocardiography on a bicycle or a treadmill with imaging during exercise is recommended, but there are no universally adopted protocols[15]. Exercise echocardiography should be considered abnormal if the average E/e' ratio at peak stress increases to ≥15, with or without a peak tricuspid regurgitation (TR) velocity of >3.4 m/s[15]. An increase in only TR velocity should not be used to diagnose HFpEF because it might be a result of the normal hyperdynamic response to exercise (with increased pulmonary blood flow) without the LV diastolic dysfunction. For selected patients with suspected HF with uncertain diagnosis despite the evaluation, as described above, the clinical gold standard for the diagnosis of HF is the identification of an elevated PCWP on an invasive hemodynamic test (right heart catheterization with the PCWP assessed at rest or during exercise)[15,18]. The patient must have symptoms consistent with HF and PCWP ≥ 15 mmHg at rest or ≥ 25 mmHg during exercise for establishing a diagnosis of HF[18]. If these criteria are not fulfilled, further evaluation for other causes of dyspnoea is required. To summarize, echocardiography may help rule out HFpEF, although approaches to exclude HFpEF based solely on data at rest are of questionable accuracy, and furthermore, there is evidence that reinforces the value of exercise testing using invasive and non-invasive hemodynamic assessments to definitively confirm or rule out the diagnosis of HFpEF[18].

TREATMENT

The therapy for HFrEF aims to improve quality of life, reduce the rate of hospitalizations, as well as morbidity and mortality. Care for patients with HFrEF includes an overall approach - the treatment of possible causes and associated conditions (*e.g.*, hypertension, diabetes mellitus, and thyroid dysfunction, anemia) of HF, pharmacologic therapy, monitoring, education and cardiac rehabilitation, palliative care, device therapy and cardiac transplantation.

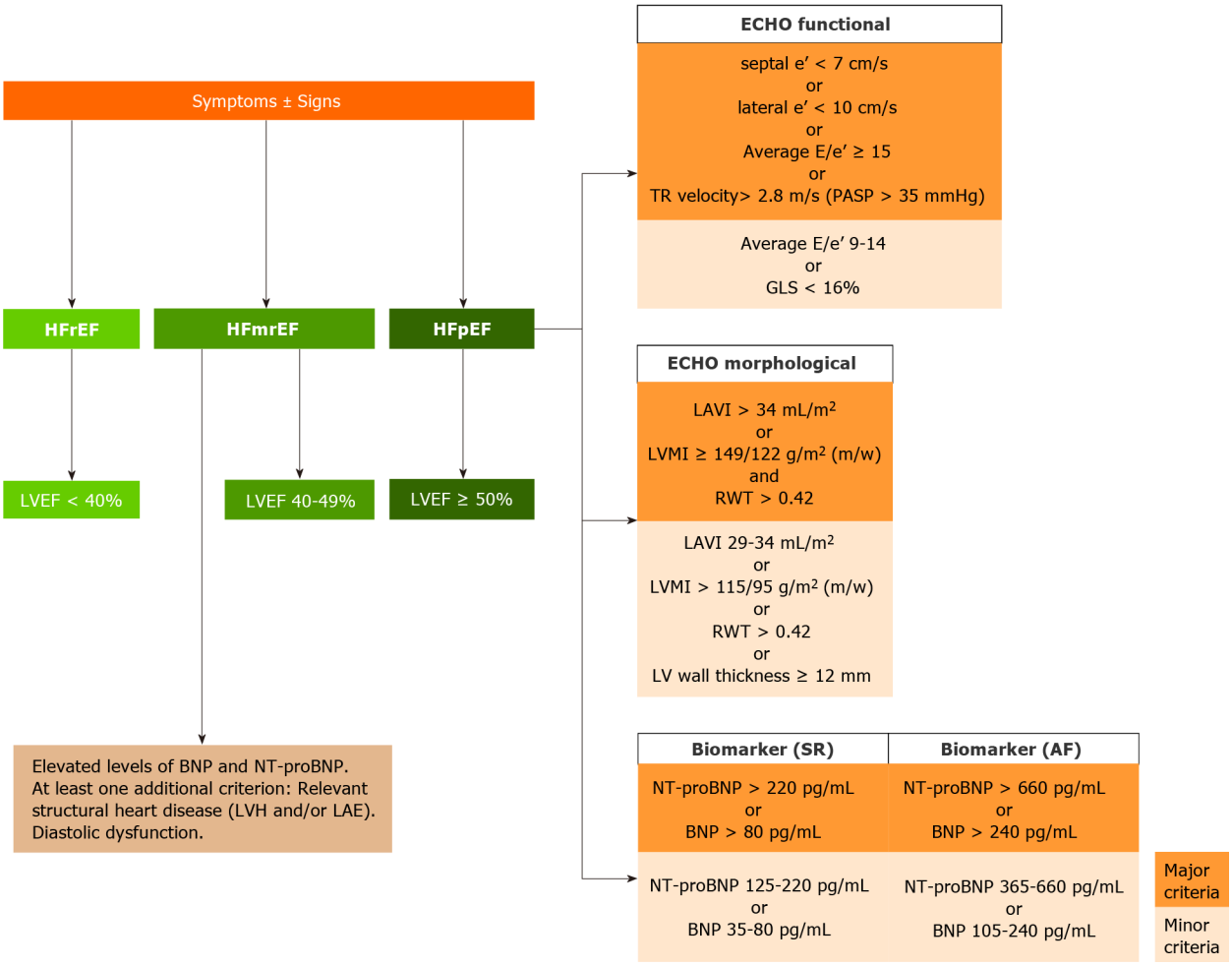

Figure 2 Heart failure – classification and criteria in diagnosis (data from[1,15]). HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; LVEF: Left ventricular ejection fraction; LVH: Left ventricular hypertrophy; LAE: Left atrial enlargement; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; LV: Left ventricle; TR: Tricuspid regurgitation; GLS: Global longitudinal strain; LAVI: Left atrial volume index; LVMI: Left ventricular mass index; RWT: Relative wall thickness; ECHO: Echocardiography.

Antagonism of neurohormonal activation is the foundation of the modern HF therapy. The pharmacological treatment aims to alleviate the symptoms and to improve the quality of life, prevent complications and the need for hospitalization, and thereby reduce high mortality. Diuretics are used to facilitate the symptoms of congestion. Meta-analyses show that diuretics, compared with placebo, appear to reduce the risk of death and reduce symptoms, and compared with an active control, appear to improve the functional capacity of patients with HFrEF[22,23]. The progression of the disease of the heart muscle itself can be prevented by acting on the reflex mechanisms that are activated in the body when HF occurs.

The first line of treatment is angiotensin converting enzyme inhibitors (ACEi) and beta-adrenergic receptor blockers (beta-blockers), regardless of the aetiology of HF[1,2,24]. 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]. The usage of beta-blockers showed an improvement of LVEF and a reduction of mortality and the number of hospitalizations[29]. Unlike ACEi, beta-blockers have no class effect and evidence of beneficial effects in the treatment of HF has been reported for bisoprolol, prolonged-release metoprolol, carvedilol, and nebivolol[30,31]. Therapy with ACEi and beta-blockers is complementary and can be started together. Beta-blockers are recommended as a start for clinically stable patients at a low dose, followed by titration to the maximum tolerated dose[1].

Mineralocorticoid receptor/aldosteron antagonists (MRA) - spironolactone and eplerenone are recommended in all symptomatic patients (who are on ACEi and beta-blocker therapy) with LVEF ≤ 35%[1,2]. Inhibition of aldosterone action results in

decreased endothelial inflammation and decreased stimulation of the sympathetic system and RAAS systems with an antifibrotic effect. Studies show reduction of all-cause mortality (for spironolactone 30%[32]) and lower rate of hospitalization in patients treated with MRA[33-35]. Possible side effects are hyperkalemia, hyponatremia, reversible increase in blood urea and creatinine levels in patients with impaired renal function, hypotension in patients with low blood pressure (although recent study shows that MRA treatment had little effect on systolic blood pressure in patients with HFrEF and therefore low systolic blood pressure is not a reason to withhold MRA therapy in patients with HFrEF[36]). Spironolactone binds to both androgen and progesterone receptors, so men can experience breast enlargement - gynecomastia, while women can develop excessive farsightedness - hirsutism, and postmenopausal bleeding[8]. Due to its selective binding to the mineralocorticoid receptor, eplerenone has no endocrine side effects, has a lower risk of hyperkalemia, and it is a better choice in diabetics[8]. Caution should be exercised in the use of MRA in patients with impaired renal function and serum potassium level greater than 5.0 mmol/L[1].

If symptomatic HF persists (NYHA class II or III), replacement of ACEi (or ARB if used) by angiotensin receptor neprilysin inhibitor (sacubutril) - ARNI (angiotensin receptor neprilysin inhibitor) is recommended to further reduce morbidity and mortality[1,24,37]. Neprylisin inhibits natriuretic peptides (NP), bradykinin, adrenomedullin, and the β-amyloid (Aβ) peptide[37]. The combination of the renin–angiotensin system and neprilysin inhibition showed to be superior to a separate approach [38], but in clinical trials, the combination of ACEi and neprilysin was associated with serious angioedema[39,40]. Combined molecule LCZ696 consisting of sacubutril and valsartan minimizes the risk of serious angioedema, and the mechanism of action is inhibition of the neprilysin *via* the active metabolite of sacubitril and blocking of the angiotensin II receptor *via* valsartan[41,42]. There is an increase in the number of peptides that neprilysin degrades, such as A-type natriuretic peptide (ANP) and BNP, which bind to NP receptors. This results in vasodilation, the enhancement of natriuresis and diuresis, increased glomerular filtration, the inhibition of renin and aldosterone release, decreased sympathetic activity, as well as antihypertrophic and antifibrotic effects[43]. Considering described mechanism of action, BNP concentrations rise with neprilysin inhibition and the clinical validity of measuring BNP in patients treated with sacubitril/valsartan has been questioned. The use of NT-proBNP is preferred and recommended in assessing the effectiveness of therapy, although either biomarker predicts the risk of major adverse outcomes in patients treated with ARNI[44]. Monitoring of blood pressure and renal function is necessary in these patients and accordingly the dose increases to the maximum tolerated dose. The long-term use of ARNI has possible side effects such as amyloid deposition and cognitive disfunction, and these side effects may be associated with specific polymorphisms in individuals[45,46]. One small study on healthy individuals showed increase of β-amyloid protein in the soluble rather than the aggregable form, which may indicate cerebral safety[47]. Long-term safety, especially in patients at risk of Alzheimer disease, needs to be assessed[1,46].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are an insulin-independent class of oral antihyperglycemic medication that are used in the treatment of type 2 diabetes. They reduce blood glucose by the inhibition of glucose reabsorption at the proximal tubule of the kidney which results in glycosuria and natriuresis[48]. Effects in lowering body weight and decreasing systolic blood pressure, as well as side effects such as genital tract infections, lower leg amputations, electrolyte disturbances, bone fractures are noted[48]. According to the latest recommendations on HF, empagliflozin should be considered in patients with type 2 diabetes mellitus (T2DM) in order to prevent or delay the onset of HF or prolong life, and canagliflozin and dapagliflozin should also be considered for patients with T2DM and either established cardiovascular (CV) disease or at high CV risk[49]. Newest studies show that SGLT2 inhibitors reduce the risk of cardiovascular death or hospitalization in patients with HFrEF regardless of the presence or absence of diabetes[50,51]. Beneficial effects of SGLT2 inhibitors may complement and improve the effects of first line HF therapy (increase in natriuresis, decreasing LV wall stress, preload, afterload and interstitial oedema), alongside with clinically important benefit such as improving renal function in HF patients[50,51]. Therefore, compelling evidence suggest that SGLT2 inhibitors should be added to the current recommended treatments of HFrEF, even in the absence of diabetes (Figure 3).

In addition to the maximum tolerated dose of betablocker, ACEi (or ARB), and the MRA, ivabradine should also be considered in symptomatic patients with increased heart rate (more than 70 / min), in sinus rhythm and EFLV < 35%, to reduce the risk of HF hospitalization or cardiovascular death (or in patients who are unable to tolerate or have contraindications for a beta-blocker)[1,24].

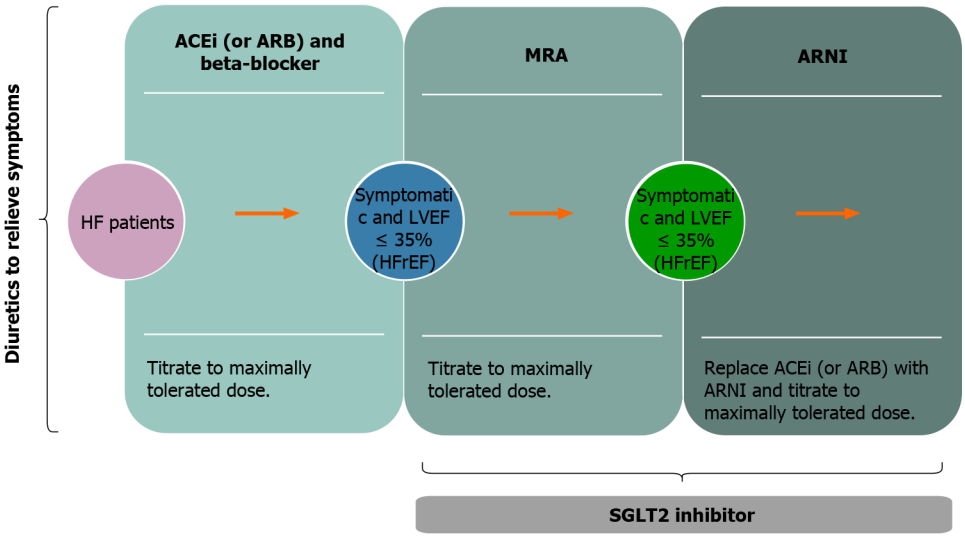

Figure 3 Heart failure medication therapy (data from[1,51]). HFrEF: Heart failure with reduced ejection fraction; ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; MRA: Mineralocorticoid receptor antagonist; ARNI: Angiotensin receptor neprilysin inhibitors; SGLT2: Sodium-glucose co-transporter-2; LVEF: Left ventricular ejection fraction.

In symptomatic patients (NYHA Class II-IV) with HFrEF who cannot tolerate ACEi nor ARB (or they are contra-indicated), hydralazine and isosorbide dinitrate may be considered to reduce the mortality[1,52]. Digoxin may be considered in symptomatic patients in sinus rhythm despite optimal medical therapy to reduce the risk of hospitalizations[1,53]. It is also used in patients with HF and atrial fibrillation (AF) to slow a rapid ventricular rate, but it is only recommended when adequate heart rate is not achieved with other therapeutic options[54,55]. Optimal ventricular rate for patients with HF and AF has not been well established but resting ventricular rate of 70-90/min is recommended based on current opinion (acceptable up to 110/min), rather than insisting on strict lower ventricular heart rate[56].

Non-dihydropyridine calcium-channel blockers (CCBs) are not recommended for the treatment of patients with HFrEF[1] (diltiazem and verapamil are considered to be unsafe in patients with HFrEF[57]). In case of compelling indications amlodipine and felodipine can be used in patients with HFrEF[1].

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) reduce the mortality and morbidity in patients with atherosclerotic disease, but there is no evidence of benefit or improvement of the prognosis in patients with HFrEF[58]. Patients who already receive statin because of coronary artery disease or hyperlipidemia should continue to use this therapy[1]. The n-3 polyunsaturated fatty acid (PUFAs) is not a routinely used supplement in patients with HFrEF since the randomized trial demonstrated minimal to no benefit[59].

Novel therapeutic approaches

The effect of a novel oral soluble guanylate cyclase stimulator – vericiguat was tested in patients with HFrEF and the result of the new randomized trial showed that the incidence of death from cardiovascular causes or hospitalization for HF was lower among subjects who received vericiguat in comparison to those who received placebo (HF hospitalizations were significantly reduced, while cardiovascular deaths were not significantly diminished)[60].

Omecamtiv mecarbil is a cardiac-specific myosin activator that improves cardiomyocyte contraction which is being studied for a potential role in the treatment of left ventricular systolic HF[61]. The latest trial showed a significant reduction of HF event or death from cardiovascular causes in subjects who received omecamtiv mecarbil twice daily in contrast to those who received the placebo[62].

The effect of the anticoagulant therapy in HF patients in sinus rhythm is being assessed since HF is associated with activation of thrombin-related pathways, which predicts a poor prognosis. Studies with rivaroxaban (factor Xa inhibitor) hypothesized that the treatment could reduce thrombin generation and improve outcomes for patients with worsening chronic HF and underlying coronary artery disease[63,64]. Rivaroxaban did not reduce HF hospitalization but did reduce the rate of stroke[63]. Thromboembolic events occurred frequently in patients with HF, coronary artery

disease, and sinus rhythm. A post-hoc analysis revealed that rivaroxaban may reduce the risk of thromboembolic events in this population, but these events are not the major cause of morbidity and mortality in patients with recent worsening of HF where rivaroxaban had no effect[64]. Rivaroxaban at dose 2.5 mg twice daily in addition to aspirin may be considered for ambulatory patients with coronary artery disease (CAD) and chronic HF in NYHA class I/II with an LVEF > 30%, in order to reduce the risk of stroke and CV death[49,64]. For chronic HF patients in NYHA class III/IV and recent HF hospitalization, initiation of treatment with rivaroxaban is not recommended, as no benefit was shown[49].

The treatment of comorbidities that are present in chronic HF patients is an important part of holistic approach and improves outcomes of these patients. Iron deficiency is common in patients with and without anemia and has unfavorable clinical and prognostic consequences in patients with HFrEF. Important clinical trials have been conducted with ferric carboxymaltose (FCM)[65-67], and the treatment with FCM may result in the improvement of functional capacity, symptoms and quality of life (whether FCM is associated with an improved outcome in these high-risk patients needs further study). The trial including iron deficient patients hospitalized for acute HF showed that intravenous FCM compared to placebo was associated with reduction of total HF hospitalizations and CV death[68].

To conclude, there are important advances in the medicament treatment of HFrEF and therapeutic development is accelerated. These new therapeutic options improve clinical outcomes and functional status[69]. Accordingly, new working definition of HF with recovered left ventricular ejection fraction (HFrecEF) has been proposed[69,70]. HFrecEF is a complex clinical entity and definition includes: (1) Documentation of a LVEF < 40% at baseline, combined with (2) a ≥ 10% absolute improvement in LVEF; and (3) A second measurement of LVEF > 40%[69,70]. The proportion of patients with HFrecEF varies widely (10%-40%) and should be followed every 6 mo to 1 year, with imaging obtained every 3-5 years to monitor LV function[70]. HFpEF has a significant morbidity and mortality and so far, no treatment has clearly demonstrated an improvement of outcome in HFpEF, but rather it is limited to symptom relief, which effectively improves the quality of life[13,71,72]. The emphasis is on treatment of comorbidities - hypertension, atrial fibrillation, obesity, diabetes mellitus, renal disease, obstructive lung disease, or ischemic heart disease. Regular exercise program is an important part in the treatment of these patients[13].

Device therapy

Implantable cardioverter-defibrillator (ICD) is effective in correcting potentially lethal ventricular arrhythmias. Some antiarrhythmic drugs might reduce the rate of tachyarrhythmias and sudden death, however they do not reduce overall mortality and may even increase it[1]. An ICD is recommended in secondary prevention to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing hemodynamic instability, and who are expected to survive for more than one year with good functional status[1,73,74]. ICD therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in selected patients at least 40 days after myocardial infarction with LVEF of 35% or less, symptomatic while receiving optimal medical therapy, and who have reasonable expectation of survival for more than one year with good functional status[1,24,75,76]. There is no benefit in patients who had an ICD implanted within 40 d after a myocardial infarction[77]. Decision about ICD implantation should be made for each patient individually, taking into consideration patient's opinion and their quality of life, the LVEF (survival benefit) and other diseases that can be cause of death within the following year[1,73,74]. ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy if they are not candidates for CRT, a ventricular assist device, or cardiac transplantation[1,78,79].

Cardiac resynchronization therapy (CRT) is recommended for symptomatic patients in sinus rhythm, with left bundle branch block (LBBB) QRS morphology, QRS ≥ 150 ms (and in patients with QRS duration of 130–149 ms) and EFLV ≤ 35% despite optimal medical therapy to improve symptoms and reduce morbidity and mortality[1,2,80-82]. For patients with ECG non-LBBB QRS morphology and QRS ≥ 150 msec CRT should be considered and CRT may be considered in patients with QRS 130–149 ms non-LBBB QRS morphology (in sinus rhythm)[1,2,80,83]. CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing in order to reduce morbidity, although no clear effect on mortality was observed (this also includes individualized decision for patients with atrial fibrillation)[84-86].

Patients with severe symptoms despite optimal medical and device therapy are potentially eligible for mechanical circulatory support - mechanical ventricular assist VAD); left - sided (LVAD) or right - sided (RVAD), biventricular (BiVAD)[1,87]. Heart transplantation is the last line of treatment for patients with the end-stage chronic HF [1,88]. These patients need to be motivated, well informed, emotionally stable, capable of complying with the intensive treatment required postoperatively and in order for transplantation to be successful and increase survival, proper selection criteria need to be applied[88].

ROLE OF CARDIAC REHABILITATION IN PATIENTS WITH CHRONIC HF

Although survival after diagnosis of HF has improved, the prognosis in such patients remains poor and quality of life severely reduced. The meta-analysis (2019), including over 1.5 million all-type HF patients, estimated the 1, 2, 5 and 10-year survival to be 87%, 73%, 57% and 35%, respectively[89]. Analysis about long-term outcomes among patients hospitalized with HF (including all three groups – HFrEF, HFmrEF, HFpEF; 2017) shown very high 5-year mortality rate of 75%, regardless of LVEF[90].

Chronic HF reduces the ability of physical activity in patients, which has detrimental effects on their daily life activities and reduces quality of life. Patients with HF have limited exercise capacity because of dyspnea and fatigue, so these symptoms make patients fearful of being active, moreover because exercise-induced dyspnea can be interpreted as worsening of their disease. In patients with stable HF, exercise training can relieve symptoms, improve the exercise capacity and quality of life, as well as reduce disability, hospitalization and mortality[91-93]. The Cochrane systematic review (2014) reported that exercise-based cardiac rehabilitation (CR) compared to no exercise control shows improvement in health-related quality of life (HRQoL) and hospital admission among people with HF, as well as possible reduction in mortality over long term[94]. A single large randomized controlled trial (RCT) with medically optimized and stable patients with systolic HF (LVEF ≤ 35%) showed a modest and non-significant reduction in the primary composite outcome of all-cause mortality or all-cause hospitalization, but improvement in self-reported health status compared with usual care without training that persisted over time[95,96]. Recent systematic review and meta-analysis (2019)[97], a meta-analysis of randomized trials (2018)[98] and the Cochrane meta-analysis (2019)[99] that included a total of 5783 patients, predominantly HFrEF (NYHA class II and III receiving center-based exercise-based CR programs) but also patients with HFpEF, showed that exercise rehabilitation reduced hospital admissions overall, as well as for HF, and clinically important improvement in HRQoL was shown. In patients with HFpEF clinically relevant improvements in exercise capacity can be achieved, without significant changes in LV function or structure[100,101], regardless of training modality[102].

In practice, it is reasonable to advise patients to avoid stimuli that cause worsening of the disease symptoms. There are many pathophysiological mechanisms of exercise intolerance in HF: cardiac (systolic and/or diastolic dysfunction, reduced stroke volume, elevated filling pressures, secondary pulmonary hypertension and right ventricle disfunction, mitral regurgitation, reduced chronotropic reserve), ventilatory system (exaggerated minute ventilation relative to CO_2 production, ventilation/perfusion mismatch, alveolar edema), skeletal muscle (reduced muscle mass, reduced enzymes for oxidative metabolism and generation of ATP), endothelial function (reduced nitric oxide, increased reactive oxygen compounds, reduced vasodilatory response), neurohumoral system (increased sympathetic activity, low vagal activity, increased levels of pro-inflammatory cytokines)[103]. However, in chronic HF, poor exercise tolerance and quality of life can be successfully improved by dosed and tailored exercise training (ET)[96,104-107]. 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 disfunction. ET in HF also results in reduction of reactive oxygen species and a concomitant increase in nitric oxide signaling, a reduction in Angiotensin II type 1 receptor signaling and a restoration of the imbalance of Angiotensin converting enzyme (ACE) and ACE2 expression, as well as a decrease in circulating pro-inflammatory cytokines, all of which contribute to the improvement of autonomic imbalance[103,108].

The guidelines of the European Society of Cardiology[1], American College of Cardiology/American Heart Association[2] and Canadian Cardiovascular Society[109] have included evidence-based recommendations for the use of exercise training in the management of chronic HF. Exercise training (or regular physical activity) is safe and effective in the improvement of symptoms and functional capacity (Class I, level of evidence A)[1,2,109], the reduction of the risk of hospitalization from HF (Class I, level of evidence A)[1] and in the improvement of exercise duration, HRQoL and reduction of mortality (Class IIa, level of evidence B)[2].

A consensus document of the HF 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, psychosocial support, as well as exercise training and physical activity counseling. In addition to adopting a change in lifestyle that includes daily life activities (*e.g.*, housework, gardening, walking, recreation, proper nutrition), conducting structured physical activity and ET is important for further maintenance of stable condition of these patients. Implementation of ET requires appropriate patient selection, training protocol identification, intensity level determination, and progression monitoring. ET is recommended for stable New York Heart Association (NYHA) class I–III HF patients[110]. Early mobilization of patients after an episode of acute HF is also recommended. 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 cardiopulmonary exercise test (CPET) and initiating regular ET. Exercise modalities 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. When clinical stabilization is achieved, it is necessary to assess whether there are contraindications for conducting rehabilitation (Table 2). This includes reassessment of the patient's condition and functional evaluation (history, clinical examination, electrocardiogram, ultrasound of the heart and CPET, and if the patient is unable to perform, then six-minute walking test)[110].

The choice of exercise modality should take into account patients associated diseases, work habits, preferences and abilities, limitations as well as the availability of rehabilitation itself. Determining the appropriate level of ET intensity is key in achieving the desired effects, while simultaneously having control over the potential risks associated with these patients. There is no general agreement on modalities of exercise, instead an individual approach is recommended, with careful clinical assessment, taking into consideration patient's preferences[110,111]. Exercise protocols can be different depending on the variables: intensity (aerobic and anaerobic), type (endurance, resistance, strength), method (continuous and intermittent/interval), application (systemic, regional area, respiratory muscles), control (supervised and non-supervised), setting (hospital and rehabilitation center or home-based). Three exercise modalities in different combinations have been proposed[110,111].

Aerobic/endurance training

Metabolic function can be assessed by maximum oxygen uptake which depends on the ability of the respiratory and cardiovascular systems to deliver oxygen from the atmosphere to the muscle and the ability of the working muscles to utilize oxygen. The volume of oxygen (VO2) measured in patients with chronic HF at the end of the exercise test is not the maximum VO2 value because such patients cannot reach it. Instead of the term VO2max we use the term VO2peak, by symptom-limited CPET. The CPET will give insight into the degree of cardiac impairment and will objectively measure VO2peak and help to determine training intensity and perform training adjustments[110]. The most used and evaluated exercise modality, the cornerstone of cardiac rehabilitation programs, is moderate continuous exercise (MCE)[112-114]. The intensity of training is thus usually prescribed relative to VO2peak, and the recommended intensity is 40%-50% at the beginning, with an increase during the exercise process to 70%-80% of VO2peak[110]. CPET is not always available in everyday clinical practice, so indirect methods have been proposed to assess the intensity of ET. 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. The intensity of physical training of 60% VO2peak corresponds to RPE from 12 to 13, and from 85% VO2peak corresponds to RPE 16[110]. High-intensity interval

Table 2 Contraindications for exercise training and screening for increased risk for exercise training (data from[110])

Contraindications to exercise training	Increased risk for exercise training
Progressive worsening of exercise tolerance or dyspnea at rest over previous 3–5 d	> 1.8 kg increase in body mass over the previous 1-3 d
Significant ischemia during low-intensity exercise (< 2 METs, < 50 W)	Concurrent, continuous, or intermittent dobutamine therapy
Uncontrolled diabetes	Decrease in systolic blood pressure with exercise
Recent embolism	NYHA functional class IV
Thrombophlebitis	Complex ventricular arrhythmia at rest or appearing with exertion
	Supine resting heart rate > 100 b.p.m.
	Pre-existing co-morbidities limiting exercise tolerance

NYHA: New York Heart Association.

training (HIIT) programs have been considered as a valuable exercise modality for low-risk HF patients[111,115]. HIIT is not superior to moderate continuous training (MCT) in changing left ventricular remodeling or aerobic capacity[115] but the recent meta-analysis showed that improves VO2peak and should be considered as a component of care of HFrEF patients[116]. Aerobic training dominates among cardiac rehabilitation programs, as in patients with chronic HF because it has the highest level of evidence, and proven beneficial effects for this type of activity[110,111].

Resistance/strength training

Muscle contraction is performed against a specific opposite force and thus generating resistance (*e.g.*, lifting weights). It gradually overloads the musculoskeletal system, strengthens and tones the muscles and it is suggested as an anabolic intervention due to the risk of muscle mass loss[110]. A meta-analysis showed that resistance exercise as a single intervention can increase muscle strength, aerobic capacity, and quality of life in HFrEF patients, and may offer an alternative approach, especially for those unable to participate in aerobic training[117]. It can be used as an adjunct to aerobic training which is the mainstay in HF patients.

As HF patients suffer from easy fatiguability, the initiation of a resistance/strength training (RST) program 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.

Respiratory training

The review of trials using inspiratory muscle training in patients with chronic HF suggested that such an intervention may improve the functional capacity and quality of life, especially in those with inspiratory muscle weakness[118]. Such additional exercises in combination with standard aerobic training might be useful.

There are limited data about ET for a special group of patients with chronic HF and implanted ICD or CRT. Evidence show that physical activity and exercise can be safely applied with adequate supervision[119,120] and it was confirmed in the larger RCT analysis of patients with ICD and HF[121]. It has been shown that physical activity can almost double the improvement in functional capacity and quality of life in CRT patients[122,123] and ET resulted in reduction of a number of ICD activations in the exercise group[120,121]. Moreover, non-sustained ventricular tachycardia in the presence of an ICD is not a contraindication for aerobic training[121]. Patients with an

ICD should begin training under medical supervision, and the HR must be monitored if it is possible to reach a HR close to the programmed intervention zone of the device. Patients who have symptomatic arrhythmias or ICD discharge should be directed to exercise modalities in which brief loss of consciousness due to ICD discharge may be less harmful (*e.g.*, avoiding swimming or climbing)[110]. Medical staff caring for such patients should be specially educated in understanding the possible challenges and problems associated with such patients.

Although progress has been made in rehabilitating patients with chronic HF, further RCT with large number of patients are needed to assess the effect and benefit from each training modality. Education of medical staff on the beneficial effects of physical exercise in patients with chronic HF and involvement of more patients in cardiac medical rehabilitation programs are crucial in order to provide complete care to chronic HF patients. A small part of patients with chronic HF participates in cardiac rehabilitation programs (the data vary, only 2.6% retrospectively[124], and in one observational study only 10% of eligible HF patients received cardiac rehabilitation referral at discharge after hospitalization for HF[125]), and this is partly due to the fact that chronic HF is not yet an indication for rehabilitation in many countries, at least not as a first diagnosis. Developing adequate and effective training methods and highlighting the beneficial effects of such an approach will result in improving the quality of life and providing better medical care to patients with chronic HF.

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.

REFERENCES

1 **Ponikowski P**, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129-2200 [PMID: 27206819 DOI: 10.1093/eurheartj/ehw128]

2 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147-e239 [PMID: 23747642 DOI: 10.1016/j.jacc.2013.05.019]

3 **Borovac JA**, D'Amario D, Bozic J, Glavas D. Sympathetic nervous system activation and heart failure: Current state of evidence and the pathophysiology in the light of novel biomarkers. *World J Cardiol* 2020; **12**: 373-408 [PMID: 32879702 DOI: 10.4330/wjc.v12.i8.373]

4 **Inamdar AA**, Inamdar AC. Heart Failure: Diagnosis, Management and Utilization. *J Clin Med* 2016; **5** [PMID: 27367736 DOI: 10.3390/jcm5070062]

5 **Ziaeian B**, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016; **13**: 368-378 [PMID: 26935038 DOI: 10.1038/nrcardio.2016.25]

6 **Choi HM**, Park MS, Youn JC. Update on heart failure management and future directions. *Korean J Intern Med* 2019; **34**: 11-43 [PMID: 30612416 DOI: 10.3904/kjim.2018.428]

7 **Zile MR**, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM Jr, Abraham WT, Smart FW, Stevenson LW, Kueffer FJ, Bourge RC. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation* 2008; **118**: 1433-1441 [PMID:

18794390 DOI: 10.1161/CIRCULATIONAHA.108.783910]

8 **Pazos-López P**, Peteiro-Vázquez J, Carcía-Campos A, García-Bueno L, de Torres JP, Castro-Beiras A. The causes, consequences, and treatment of left or right heart failure. *Vasc Health Risk Manag* 2011; **7**: 237-254 [PMID: 21603593 DOI: 10.2147/VHRM.S10669]

9 **Le Jemtel TH**, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007; **49**: 171-180 [PMID: 17222727 DOI: 10.1016/j.jacc.2006.08.046]

10 **The Criteria Committee of the New York Heart Association**. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th edition. Boston, Mass: Little & Brown; 1994: 253-256

11 **Hunt SA**, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; **119**: e391-e479 [PMID: 19324966 DOI: 10.1161/CIRCULATIONAHA.109.192065]

12 **Madsen BK**, Hansen JF, Stokholm KH, Brøns J, Husum D, Mortensen LS. Chronic congestive heart failure. Description and survival of 190 consecutive patients with a diagnosis of chronic congestive heart failure based on clinical signs and symptoms. *Eur Heart J* 1994; **15**: 303-310 [PMID: 8013501 DOI: 10.1093/oxfordjournals.eurheartj.a060495]

13 **Henning RJ**. Diagnosis and treatment of heart failure with preserved left ventricular ejection fraction. *World J Cardiol* 2020; **12**: 7-25 [PMID: 31984124 DOI: 10.4330/wjc.v12.i1.7]

14 **Reddy YNV**, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. *Circulation* 2018; **138**: 861-870 [PMID: 29792299 DOI: 10.1161/CIRCULATIONAHA.118.034646]

15 **Pieske B**, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019; **40**: 3297-3317 [PMID: 31504452 DOI: 10.1093/eurheartj/ehz641]

16 **Paulus WJ**, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; **28**: 2539-2550 [PMID: 17428822 DOI: 10.1093/eurheartj/ehm037]

17 **Nagueh SF**, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; **29**: 277-314 [PMID: 27037982 DOI: 10.1016/j.echo.2016.01.011]

18 **Obokata M**, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. *Circulation* 2017; **135**: 825-838 [PMID: 28039229 DOI: 10.1161/CIRCULATIONAHA.116.024822]

19 **Maron BA**, Cockrill BA, Waxman AB, Systrom DM. The invasive cardiopulmonary exercise test. *Circulation* 2013; **127**: 1157-1164 [PMID: 23479667 DOI: 10.1161/CIRCULATIONAHA.112.104463]

20 **Andersen MJ**, Olson TP, Melenovsky V, Kane GC, Borlaug BA. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ Heart Fail* 2015; **8**: 41-48 [PMID: 25342738 DOI: 10.1161/CIRCHEARTFAILURE.114.001731]

21 **Borlaug BA**, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010; **3**: 588-595 [PMID: 20543134 DOI: 10.1161/CIRCHEARTFAILURE.109.930701]

22 **Faris RF**, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane Database Syst Rev* 2012; CD003838 [PMID: 22336795 DOI: 10.1002/14651858.CD003838.pub3]

23 **Faris R**, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002; **82**: 149-158 [PMID: 11853901 DOI: 10.1016/s0167-5273(01)00600-3]

24 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017; **70**: 776-803 [PMID: 28461007 DOI:

10.1016/j.jacc.2017.04.025]

25 **Packer M**, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Rydén L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999; **100**: 2312-2318 [PMID: 10587334 DOI: 10.1161/01.cir.100.23.2312]

26 Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet* 1993; **342**: 821-828 [PMID: 8104270 DOI: 10.1016/0140-6736(93)92693-N]

27 **Køber L**, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995; **333**: 1670-1676 [PMID: 7477219 DOI: 10.1056/NEJM199512213332503]

28 **Garg R**, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995; **273**: 1450-1456 [PMID: 7654275 DOI: 10.1001/jama.273.18.1450]

29 **Bristow MR**, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996; **94**: 2807-2816 [PMID: 8941106 DOI: 10.1161/01.cir.94.11.2807]

30 **Heidenreich PA**, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1997; **30**: 27-34 [PMID: 9207617 DOI: 10.1016/s0735-1097(97)00104-6]

31 **Choi KH**, Lee GY, Choi JO, Jeon ES, Lee HY, Lee SE, Kim JJ, Chae SC, Baek SH, Kang SM, Choi DJ, Yoo BS, Kim KH, Cho MC, Park HY, Oh BH. The mortality benefit of carvedilol *vs* bisoprolol in patients with heart failure with reduced ejection fraction. *Korean J Intern Med* 2019; **34**: 1030-1039 [PMID: 30317846 DOI: 10.3904/kjim.2018.009]

32 **Pitt B**, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341**: 709-717 [PMID: 10471456 DOI: 10.1056/NEJM199909023411001]

33 **Pitt B**, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**: 1309-1321 [PMID: 12668699 DOI: 10.1056/NEJMoa030207]

34 **Zannad F**, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; **364**: 11-21 [PMID: 21073363 DOI: 10.1056/NEJMoa1009492]

35 **Girerd N**, Collier T, Pocock S, Krum H, McMurray JJ, Swedberg K, Van Veldhuisen DJ, Vincent J, Pitt B, Zannad F. Clinical benefits of eplerenone in patients with systolic heart failure and mild symptoms when initiated shortly after hospital discharge: analysis from the EMPHASIS-HF trial. *Eur Heart J* 2015; **36**: 2310-2317 [PMID: 26093641 DOI: 10.1093/eurheartj/ehv273]

36 **Serenelli M**, Jackson A, Dewan P, Jhund PS, Petrie MC, Rossignol P, Campo G, Pitt B, Zannad F, Ferreira JP, McMurray JJV. Mineralocorticoid Receptor Antagonists, Blood Pressure, and Outcomes in Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail* 2020; **8**: 188-198 [PMID: 31926854 DOI: 10.1016/j.jchf.2019.09.011]

37 **McMurray JJ**, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition *vs* enalapril in heart failure. *N Engl J Med* 2014; **371**: 993-1004 [PMID: 25176015 DOI: 10.1056/NEJMoa1409077]

38 **Rademaker MT**, Charles CJ, Espiner EA, Nicholls MG, Richards AM, Kosoglou T. Combined neutral endopeptidase and angiotensin-converting enzyme inhibition in heart failure: role of natriuretic peptides and angiotensin II. *J Cardiovasc Pharmacol* 1998; **31**: 116-125 [PMID: 9456286 DOI: 10.1097/00005344-199801000-00017]

39 **Kostis JB**, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 2004; **17**: 103-111 [PMID: 14751650 DOI: 10.1016/j.amjhyper.2003.09.014]

40 **Packer M**, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, Swedberg K. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002; **106**: 920-926 [PMID: 12186794 DOI: 10.1161/01.cir.0000029801.86489.50]

41 **Gu J**, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, Maahs S, Ksander G, Rigel DF, Jeng AY, Lin TH, Zheng W, Dole WP. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol* 2010; **50**: 401-414 [PMID: 19934029 DOI: 10.1177/0091270009343932]

42 **Hegde LG**, Yu C, Renner T, Thibodeaux H, Armstrong SR, Park T, Cheruvu M, Olsufka R, Sandvik ER, Lane CE, Budman J, Hill CM, Klein U, Hegde SS. Concomitant angiotensin AT1 receptor

antagonism and neprilysin inhibition produces omapatrilat-like antihypertensive effects without promoting tracheal plasma extravasation in the rat. *J Cardiovasc Pharmacol* 2011; **57**: 495-504 [PMID: 21297495 DOI: 10.1097/FJC.0b013e318210fc7e]

43 **Mangiafico S**, Costello-Boerrigter LC, Andersen IA, Cataliotti A, Burnett JC Jr. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. *Eur Heart J* 2013; **34**: 886-893c [PMID: 22942338 DOI: 10.1093/eurheartj/ehs262]

44 **Myhre PL**, Vaduganathan M, Claggett B, Packer M, Desai AS, Rouleau JL, Zile MR, Swedberg K, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. B-Type Natriuretic Peptide During Treatment With Sacubitril/Valsartan: The PARADIGM-HF Trial. *J Am Coll Cardiol* 2019; **73**: 1264-1272 [PMID: 30846338 DOI: 10.1016/j.jacc.2019.01.018]

45 **Krittanawong C**, Kitai T. Pharmacogenomics of angiotensin receptor/neprilysin inhibitor and its long-term side effects. *Cardiovasc Ther* 2017; **35** [PMID: 28489317 DOI: 10.1111/1755-5922.12272]

46 **Vodovar N**, Paquet C, Mebazaa A, Launay JM, Hugon J, Cohen-Solal A. Neprilysin, cardiovascular, and Alzheimer's diseases: the therapeutic split? *Eur Heart J* 2015; **36**: 902-905 [PMID: 25636748 DOI: 10.1093/eurheartj/ehv015]

47 **Langenickel TH**, Tsubouchi C, Ayalasomayajula S, Pal P, Valentin MA, Hinder M, Jhee S, Gevorkyan H, Rajman I. The effect of LCZ696 (sacubitril/valsartan) on amyloid-β concentrations in cerebrospinal fluid in healthy subjects. *Br J Clin Pharmacol* 2016; **81**: 878-890 [PMID: 26663387 DOI: 10.1111/bcp.12861]

48 **Simes BC**, MacGregor GG. Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: A Clinician's Guide. *Diabetes Metab Syndr Obes* 2019; **12**: 2125-2136 [PMID: 31686884 DOI: 10.2147/DMSO.S212003]

49 **Seferovic PM**, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, de Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; **21**: 1169-1186 [PMID: 31129923 DOI: 10.1002/ejhf.1531]

50 **Packer M**, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; **383**: 1413-1424 [PMID: 32865377 DOI: 10.1056/NEJMoa2022190]

51 **Zannad F**, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020; **396**: 819-829 [PMID: 32877652 DOI: 10.1016/S0140-6736(20)31824-9]

52 **Cohn JN**, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; **314**: 1547-1552 [PMID: 3520315 DOI: 10.1056/NEJM198606123142404]

53 **Digitalis Investigation Group**. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; **336**: 525-533 [PMID: 9036306 DOI: 10.1056/NEJM199702203360801]

54 **Vamos M**, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. *Eur Heart J* 2015; **36**: 1831-1838 [PMID: 25939649 DOI: 10.1093/eurheartj/ehv143]

55 **Bavishi C**, Khan AR, Ather S. Digoxin in patients with atrial fibrillation and heart failure: A meta-analysis. *Int J Cardiol* 2015; **188**: 99-101 [PMID: 25900519 DOI: 10.1016/j.ijcard.2015.04.031]

56 **Mulder BA**, Van Veldhuisen DJ, Crijns HJ, Tijssen JG, Hillege HL, Alings M, Rienstra M, Groenveld HF, Van den Berg MP, Van Gelder IC; RACE II investigators. Lenient vs. strict rate control in patients with atrial fibrillation and heart failure: a post-hoc analysis of the RACE II study. *Eur J Heart Fail* 2013; **15**: 1311-1318 [PMID: 23759284 DOI: 10.1093/eurjhf/hft093]

57 **Goldstein RE**, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation* 1991; **83**: 52-60 [PMID: 1984898 DOI: 10.1161/01.cir.83.1.52]

58 **Kjekshus J**, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J; CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357**: 2248-2261 [PMID: 17984166 DOI: 10.1056/NEJMoa0706201]

59 **Tavazzi L**, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G; Gissi-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients

with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**: 1223-1230 [PMID: 18757090 DOI: 10.1016/S0140-6736(08)61239-8]

60 **Armstrong PW**, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM; VICTORIA Study Group. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2020; **382**: 1883-1893 [PMID: 32222134 DOI: 10.1056/NEJMoa1915928]

61 **Liu LC**, Dorhout B, van der Meer P, Teerlink JR, Voors AA. Omecamtiv mecarbil: a new cardiac myosin activator for the treatment of heart failure. *Expert Opin Investig Drugs* 2016; **25**: 117-127 [PMID: 26587768 DOI: 10.1517/13543784.2016.1123248]

62 **Teerlink JR**, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sørensen T, Böhm M, Bonderman D, Cleland JGF, Corbalan R, Crespo-Leiro MG, Dahlström U, Echeverria LE, Fang JC, Filippatos G, Fonseca C, Goncalvesova E, Goudev AR, Howlett JG, Lanfear DE, Li J, Lund M, Macdonald P, Mareev V, Momomura SI, O'Meara E, Parkhomenko A, Ponikowski P, Ramires FJA, Serpytis P, Sliwa K, Spinar J, Suter TM, Tomcsanyi J, Vandekerckhove H, Vinereanu D, Voors AA, Yilmaz MB, Zannad F, Sharpsten L, Legg JC, Varin C, Honarpour N, Abbasi SA, Malik FI, Kurtz CE; GALACTIC-HF Investigators. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. *N Engl J Med* 2021; **384**: 105-116 [PMID: 33185990 DOI: 10.1056/NEJMoa2025797]

63 **Zannad F**, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghiade M, Lam CSP, Mehra MR, Neaton JD, Nessel CC, Spiro TE, van Veldhuisen DJ, Greenberg B; COMMANDER HF Investigators. Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. *N Engl J Med* 2018; **379**: 1332-1342 [PMID: 30146935 DOI: 10.1056/NEJMoa1808848]

64 **Greenberg B**, Neaton JD, Anker SD, Byra WM, Cleland JGF, Deng H, Fu M, La Police DA, Lam CSP, Mehra MR, Nessel CC, Spiro TE, van Veldhuisen DJ, Vanden Boom CM, Zannad F. Association of Rivaroxaban With Thromboembolic Events in Patients With Heart Failure, Coronary Disease, and Sinus Rhythm: A Post Hoc Analysis of the COMMANDER HF Trial. *JAMA Cardiol* 2019; **4**: 515-523 [PMID: 31017637 DOI: 10.1001/jamacardio.2019.1049]

65 **Anker SD**, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**: 2436-2448 [PMID: 19920054 DOI: 10.1056/NEJMoa0908355]

66 **van Veldhuisen DJ**, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, Zakin L, Cohen-Solal A; EFFECT-HF Investigators. Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency. *Circulation* 2017; **136**: 1374-1383 [PMID: 28701470 DOI: 10.1161/CIRCULATIONAHA.117.027497]

67 **Ponikowski P**, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. *Eur Heart J* 2015; **36**: 657-668 [PMID: 25176939 DOI: 10.1093/eurheartj/ehu385]

68 **Ponikowski P**, Kirwan BA, Anker SD, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Haboubi T, Keren A, Khintibidze I, Kragten H, Martinez FA, McDonagh T, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Jankowska EA. Rationale and design of the AFFIRM-AHF trial: a randomised, double-blind, placebo-controlled trial comparing the effect of intravenous ferric carboxymaltose on hospitalisations and mortality in iron-deficient patients admitted for acute heart failure. *Eur J Heart Fail* 2019; **21**: 1651-1658 [PMID: 31883356 DOI: 10.1002/ejhf.1710]

69 **Bueno H**, Moura B, Lancellotti P, Bauersachs J. The year in cardiovascular medicine 2020: heart failure and cardiomyopathies. *Eur Heart J* 2021; **42**: 657-670 [PMID: 33388764 DOI: 10.1093/eurheartj/ehaa1061]

70 **Wilcox JE**, Fang JC, Margulies KB, Mann DL. Heart Failure With Recovered Left Ventricular Ejection Fraction: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2020; **76**: 719-734 [PMID: 32762907 DOI: 10.1016/j.jacc.2020.05.075]

71 **Ilieșiu AM**, Hodorogea AS. Treatment of Heart Failure with Preserved Ejection Fraction. *Adv Exp Med Biol* 2018; **1067**: 67-87 [PMID: 29498023 DOI: 10.1007/5584_2018_149]

72 **Wintrich J**, Kindermann I, Ukena C, Selejan S, Werner C, Maack C, Laufs U, Tschöpe C, Anker SD, Lam CSP, Voors AA, Böhm M. Therapeutic approaches in heart failure with preserved ejection fraction: past, present, and future. *Clin Res Cardiol* 2020; **109**: 1079-1098 [PMID: 32236720 DOI: 10.1007/s00392-020-01633-w]

73 **Connolly SJ**, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; **101**: 1297-1302 [PMID: 10725290 DOI: 10.1161/01.cir.101.11.1297]

74 **Connolly SJ**, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann D, Gent M, Roberts RS. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics *vs* Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator

Study. *Eur Heart J* 2000; **21**: 2071-2078 [PMID: 11102258 DOI: 10.1053/euhj.2000.2476]
75 **Moss AJ**, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877-883 [PMID: 11907286 DOI: 10.1056/NEJMoa013474]
76 **Desai AS**, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA* 2004; **292**: 2874-2879 [PMID: 15598919 DOI: 10.1001/jama.292.23.2874]
77 **Steinbeck G**, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, Kornacewicz-Jach Z, Sredniawa B, Lupkovics G, Hofgärtner F, Lubinski A, Rosenqvist M, Habets A, Wegscheider K, Senges J; IRIS Investigators. Defibrillator implantation early after myocardial infarction. *N Engl J Med* 2009; **361**: 1427-1436 [PMID: 19812399 DOI: 10.1056/NEJMoa0901889]
78 **Steinberg BA**, Al-Khatib SM, Edwards R, Han J, Bardy GH, Bigger JT, Buxton AE, Moss AJ, Lee KL, Steinman R, Dorian P, Hallstrom A, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Inoue LY, Sanders GD. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities: results from a combined analysis of 4 randomized clinical trials. *JACC Heart Fail* 2014; **2**: 623-629 [PMID: 25306452 DOI: 10.1016/j.jchf.2014.06.007]
79 **Miller RJ**, Howlett JG, Exner DV, Campbell PM, Grant AD, Wilton SB. Baseline Functional Class and Therapeutic Efficacy of Common Heart Failure Interventions: A Systematic Review and Meta-analysis. *Can J Cardiol* 2015; **31**: 792-799 [PMID: 26022990 DOI: 10.1016/j.cjca.2014.12.031]
80 **Cleland JG**, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, Sherfesee L, Wells GA, Tang AS. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013; **34**: 3547-3556 [PMID: 23900696 DOI: 10.1093/eurheartj/eht290]
81 **Linde C**, Gold MR, Abraham WT, St John Sutton M, Ghio S, Cerkvenik J, Daubert C; REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction Study Group. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Eur Heart J* 2013; **34**: 2592-2599 [PMID: 23641006 DOI: 10.1093/eurheartj/eht160]
82 **Moss AJ**, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; **361**: 1329-1338 [PMID: 19723701 DOI: 10.1056/NEJMoa0906431]
83 **Woods B**, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, Klein H, Sculpher M, Plummer CJ, Cowie MR. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart* 2015; **101**: 1800-1806 [PMID: 26269413 DOI: 10.1136/heartjnl-2015-307634]
84 **Curtis AB**, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, Sutton MS; Biventricular vs Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013; **368**: 1585-1593 [PMID: 23614585 DOI: 10.1056/NEJMoa1210356]
85 **Brignole M**, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011; **32**: 2420-2429 [PMID: 21606084 DOI: 10.1093/eurheartj/ehr162]
86 **Tang AS**, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; **363**: 2385-2395 [PMID: 21073365 DOI: 10.1056/NEJMoa1009540]
87 **Stewart GC**, Givertz MM. Mechanical circulatory support for advanced heart failure: patients and technology in evolution. *Circulation* 2012; **125**: 1304-1315 [PMID: 22412091 DOI: 10.1161/CIRCULATIONAHA.111.060830]
88 **Banner NR**, Bonser RS, Clark AL, Clark S, Cowburn PJ, Gardner RS, Kalra PR, McDonagh T, Rogers CA, Swan L, Parameshwar J, Thomas HL, Williams SG. UK guidelines for referral and assessment of adults for heart transplantation. *Heart* 2011; **97**: 1520-1527 [PMID: 21856726 DOI: 10.1136/heartjnl-2011-300048]
89 **Jones NR**, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail* 2019; **21**: 1306-1325 [PMID: 31523902 DOI: 10.1002/ejhf.1594]
90 **Shah KS**, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol* 2017; **70**: 2476-2486 [PMID: 29141781 DOI: 10.1016/j.jacc.2017.08.074]
91 **Piepoli MF**, Davos C, Francis DP, Coats AJ; ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004; **328**: 189 [PMID: 14729656 DOI: 10.1136/bmj.37938.645220.EE]

92 **van Tol BA**, Huijsmans RJ, Kroon DW, Schothorst M, Kwakkel G. Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis. *Eur J Heart Fail* 2006; **8**: 841-850 [PMID: 16713337 DOI: 10.1016/j.ejheart.2006.02.013]

93 **Piepoli MF**. Exercise training in chronic heart failure: mechanisms and therapies. *Neth Heart J* 2013; **21**: 85-90 [PMID: 23239451 DOI: 10.1007/s12471-012-0367-6]

94 **Taylor RS**, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014; CD003331 [PMID: 24771460 DOI: 10.1002/14651858.CD003331.pub4]

95 **O'Connor CM**, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301**: 1439-1450 [PMID: 19351941 DOI: 10.1001/jama.2009.454]

96 **Flynn KE**, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP; HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301**: 1451-1459 [PMID: 19351942 DOI: 10.1001/jama.2009.457]

97 **Taylor RS**, Long L, Mordi IR, Madsen MT, Davies EJ, Dalal H, Rees K, Singh SJ, Gluud C, Zwisler AD. Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis. *JACC Heart Fail* 2019; **7**: 691-705 [PMID: 31302050 DOI: 10.1016/j.jchf.2019.04.023]

98 **Taylor RS**, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, O'Connor C, Whellan D, Keteyian SJ, Coats A, Davos CH, Dalal HM, Dracup K, Evangelista L, Jolly K, Myers J, McKelvie RS, Nilsson BB, Passino C, Witham MD, Yeh GY, Zwisler AO; ExTraMATCH II Collaboration. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail* 2018; **20**: 1735-1743 [PMID: 30255969 DOI: 10.1002/ejhf.1311]

99 **Long L**, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ, Taylor RS. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev* 2019; **1**: CD003331 [PMID: 30695817 DOI: 10.1002/14651858.CD003331.pub5]

100 **Fukuta H**, Goto T, Wakami K, Kamiya T, Ohte N. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev* 2019; **24**: 535-547 [PMID: 31032533 DOI: 10.1007/s10741-019-09774-5]

101 **Leggio M**, Fusco A, Loreti C, Limongelli G, Bendini MG, Mazza A, Coraci D, Padua L. Effects of exercise training in heart failure with preserved ejection fraction: an updated systematic literature review. *Heart Fail Rev* 2020; **25**: 703-711 [PMID: 31399956 DOI: 10.1007/s10741-019-09841-x]

102 **Mueller S**, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, Pieske-Kraigher E, Beckers P, Bobenko A, Hommel J, Van de Heyning CM, Esefeld K, von Korn P, Christle JW, Haykowsky MJ, Linke A, Wisløff U, Adams V, Pieske B, van Craenenbroeck EM, Halle M; OptimEx-Clin Study Group. Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *JAMA* 2021; **325**: 542-551 [PMID: 33560320 DOI: 10.1001/jama.2020.26812]

103 **Downing J**, Balady GJ. The role of exercise training in heart failure. *J Am Coll Cardiol* 2011; **58**: 561-569 [PMID: 21798416 DOI: 10.1016/j.jacc.2011.04.020]

104 **Belardinelli R**, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; **99**: 1173-1182 [PMID: 10069785 DOI: 10.1161/01.cir.99.9.1173]

105 **Chicco AJ**, McCune SA, Emter CA, Sparagna GC, Rees ML, Bolden DA, Marshall KD, Murphy RC, Moore RL. Low-intensity exercise training delays heart failure and improves survival in female hypertensive heart failure rats. *Hypertension* 2008; **51**: 1096-1102 [PMID: 18259016 DOI: 10.1161/HYPERTENSIONAHA.107.107078]

106 **Piepoli MF**, Capucci A. Exercise training in heart failure: effect on morbidity and mortality. *Int J Cardiol* 2000; **73**: 3-6 [PMID: 10748303 DOI: 10.1016/s0167-5273(99)00220-x]

107 **Morris JH**, Chen L. Exercise Training and Heart Failure: A Review of the Literature. *Card Fail Rev* 2019; **5**: 57-61 [PMID: 30847247 DOI: 10.15420/cfr.2018.31.1]

108 **Haack KK**, Zucker IH. Central mechanisms for exercise training-induced reduction in sympatho-excitation in chronic heart failure. *Auton Neurosci* 2015; **188**: 44-50 [PMID: 25458427 DOI: 10.1016/j.autneu.2014.10.015]

109 **Ezekowitz JA**, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Rajda M, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, LeBlanc MH, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. *Can J Cardiol* 2017; **33**: 1342-1433 [PMID: 29111106 DOI: 10.1016/j.cjca.2017.08.022]

110 **Piepoli MF**, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T, McMurray J, Pieske B, Piotrowicz E, Schmid JP, Anker SD, Solal AC, Filippatos GS, Hoes AW, Gielen S, Giannuzzi P, Ponikowski PP. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail* 2011; **13**: 347-357 [PMID: 21436360 DOI: 10.1093/eurjhf/hfr017]

111 **Pelliccia A**, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesselink JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M; ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021; **42**: 17-96 [PMID: 32860412 DOI: 10.1093/eurheartj/ehaa605]

112 **Gayda M**, Ribeiro PA, Juneau M, Nigam A. Comparison of Different Forms of Exercise Training in Patients With Cardiac Disease: Where Does High-Intensity Interval Training Fit? *Can J Cardiol* 2016; **32**: 485-494 [PMID: 26927863 DOI: 10.1016/j.cjca.2016.01.017]

113 **Canadian Cardiovascular Society Heart Failure Management Primary Panel**, Moe GW, Ezekowitz JA, O'Meara E, Howlett JG, Fremes SE, Al-Hesayen A, Heckman GA, Ducharme A, Estrella-Holder E, Grzeslo A, Harkness K, Lepage S, McDonald M, McKelvie RS, Nigam A, Rajda M, Rao V, Swiggum E, Virani S, Van Le V, Zieroth S; Canadian Cardiovascular Society Heart Failure Management Secondary Panel, Arnold JM, Ashton T, D'Astous M, Dorian P, Giannetti N, Haddad H, Isaac DL, Kouz S, Leblanc MH, Liu P, Ross HJ, Sussex B, White M. The 2013 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: focus on rehabilitation and exercise and surgical coronary revascularization. *Can J Cardiol* 2014; **30**: 249-263 [PMID: 24480445 DOI: 10.1016/j.cjca.2013.10.010]

114 **European Association of Cardiovascular Prevention and Rehabilitation Committee for Science Guidelines**; EACPR, Corrà U, Piepoli MF, Carré F, Heuschmann P, Hoffmann U, Verschuren M, Halcox J; Document Reviewers, Giannuzzi P, Saner H, Wood D, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, McGee H, Mendes M, Niebauer J, Zwisler AD, Schmid JP. Secondary prevention through cardiac rehabilitation: physical activity counselling and exercise training: key components of the position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur Heart J* 2010; **31**: 1967-1974 [PMID: 20643803 DOI: 10.1093/eurheartj/ehq236]

115 **Ellingsen Ø**, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, Larsen AI, Hole T, Mezzani A, Van Craenenbroeck EM, Videm V, Beckers P, Christle JW, Winzer E, Mangner N, Woitek F, Höllriegel R, Pressler A, Monk-Hansen T, Snoer M, Feiereisen P, Valborgland T, Kjekshus J, Hambrecht R, Gielen S, Karlsen T, Prescott E, Linke A; SMARTEX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure) Group. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. *Circulation* 2017; **135**: 839-849 [PMID: 28082387 DOI: 10.1161/CIRCULATIONAHA.116.022924]

116 **Gomes Neto M**, Durães AR, Conceição LSR, Saquetto MB, Ellingsen Ø, Carvalho VO. High intensity interval training *vs* moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. *Int J Cardiol* 2018; **261**: 134-141 [PMID: 29572084 DOI: 10.1016/j.ijcard.2018.02.076]

117 **Giuliano C**, Karahalios A, Neil C, Allen J, Levinger I. The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure - A meta-analysis. *Int J Cardiol* 2017; **227**: 413-423 [PMID: 27843045 DOI: 10.1016/j.ijcard.2016.11.023]

118 **Ribeiro JP**, Chiappa GR, Neder JA, Frankenstein L. Respiratory muscle function and exercise intolerance in heart failure. *Curr Heart Fail Rep* 2009; **6**: 95-101 [PMID: 19486593 DOI: 10.1007/s11897-009-0015-7]

119 **Fitchet A**, Doherty PJ, Bundy C, Bell W, Fitzpatrick AP, Garratt CJ. Comprehensive cardiac rehabilitation programme for implantable cardioverter-defibrillator patients: a randomised controlled trial. *Heart* 2003; **89**: 155-160 [PMID: 12527665 DOI: 10.1136/heart.89.2.155]

120 **Vanhees L**, Kornaat M, Defoor J, Aufdemkampe G, Schepers D, Stevens A, Van Exel H, Van Den Beld J, Heidbüchel H, Fagard R. Effect of exercise training in patients with an implantable cardioverter defibrillator. *Eur Heart J* 2004; **25**: 1120-1126 [PMID: 15231370 DOI: 10.1016/j.ehj.2004.04.034]

121 **Piccini JP**, Hellkamp AS, Whellan DJ, Ellis SJ, Keteyian SJ, Kraus WE, Hernandez AF, Daubert JP, Piña lL, O'Connor CM; HF-ACTION Investigators. Exercise training and implantable cardioverter-defibrillator shocks in patients with heart failure: results from HF-ACTION (Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing). *JACC Heart Fail* 2013; **1**: 142-148 [PMID: 23936756 DOI: 10.1016/j.jchf.2013.01.005]

122 **De Marco T**, Wolfel E, Feldman AM, Lowes B, Higginbotham MB, Ghali JK, Wagoner L, Kirlin PC, Kennett JD, Goel S, Saxon LA, Boehmer JP, Mann D, Galle E, Ecklund F, Yong P, Bristow MR. Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial sub-study. *J Card Fail* 2008; **14**: 9-18 [PMID: 18226768 DOI: 10.1016/j.cardfail.2007.08.003]

123 **Davids JS**, McPherson CA, Earley C, Batsford WP, Lampert R. Benefits of cardiac rehabilitation in patients with implantable cardioverter-defibrillators: a patient survey. *Arch Phys Med Rehabil* 2005; **86**: 1924-1928 [PMID: 16213232 DOI: 10.1016/j.apmr.2005.04.009]

124 **Park LG**, Schopfer DW, Zhang N, Shen H, Whooley MA. Participation in Cardiac Rehabilitation Among Patients With Heart Failure. *J Card Fail* 2017; **23**: 427-431 [PMID: 28232047 DOI: 10.1016/j.cardfail.2017.02.003]

125 **Golwala H**, Pandey A, Ju C, Butler J, Yancy C, Bhatt DL, Hernandez AF, Fonarow GC. Temporal Trends and Factors Associated With Cardiac Rehabilitation Referral Among Patients Hospitalized With Heart Failure: Findings From Get With The Guidelines-Heart Failure Registry. *J Am Coll Cardiol* 2015; **66**: 917-926 [PMID: 26293762 DOI: 10.1016/j.jacc.2015.06.1089]

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MINIREVIEWS

Large eustachian valve fostering paradoxical thromboembolism: passive bystander or serial partner in crime?

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Abstract

Catheter-based closure of patent foramen ovale (PFO) is more effective than medical therapy in the prevention of recurrent stroke[1]. It is likely that a proportion of patients evaluated for potential transcatheter PFO closure has actually different anatomical variants particularly common in the right atrium such as eustachian valve, Chiari network, Thebesian valve and Crista Terminalis. Notably, the eustachian valve may represent an increased risk factor for left circulation thromboembolism beyond that associated with PFO size and shunting. Such patients may benefit the most from percutaneous closure procedure.

Key Words: Eustachian valve; Chiari's network; Patent foramen ovale; Right-to-left shunt; Paradoxical embolism; Echocardiography

Core Tip: Eustachian valve is usually considered to be a benign finding in the absence of associated cardiac anomalies. Moreover, eustachian valve is frequently found in adult patients with septal abnormalities mainly patent foramen ovale. It may actively facilitate the mechanism of paradoxical embolism by directing the blood from the inferior vena cava towards the interatrial septum *via* patent foramen ovale into the left atrium. Therefore, the presence of such anatomic variant may represent per se an increased risk factor for left circulation thromboembolism.

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INTRODUCTION

Bartolomeo Eustachio (San Severino Marche, Macerata 1507 (?)–Fossato di Vico, Perugia, Italy, 1574), also known by his latin name of Eustachius, was an Italian anatomist and one of the founders of human and comparative anatomy. He had a comprehensive humanistic education, in the course of which he acquired an excellent knowledge of Greek, Hebrew and Arabic. Eustachio's greatest contributions to anatomical science passed through many vicissitudes which kept his real merit from being recognized until long after his death. His greatest work, which he was unable to publish, is the "De dissensionibus et controversiis anatomicis" illustrated in the Anatomical Engravings (Tabulae). Engraved on copper plates, these tables illustrated the results of the dissections of Eustachio and were completed in 1552 but discovered only in the early eighteenth century-after 162 years-in the possession of a descendant of Pier Matteo Pini to whom Eustachio had bequeathed them. They were later purchased by Pope Clement XI for 600 scudi and presented to Giovanni Maria Lancisi, his physician and the successor to Eustachio in the chair of anatomy at the Sapienza in Rome. Lancisi published the plates in 1714, together with the eight smaller ones that had already appeared in 1564[2,3] (Figure 1). Although devoid of Eustachio's planned text, the plates alone assured him a distinguished position in the history of anatomy. The fact that his book became a bestseller more than a century after his death shows the extent of the religious restrictions on anatomists all through the Renaissance. In his work on the azygos vein and its ramifications (Opuscula Anatomica, 1564), Eustachio described the thoracic duct and particularly the "valvula venae cavae inferioris" (known as Eustachian Valve) that lies at the junction of the inferior vena cava and right atrium which serves to direct the blood through the foramen ovale into the left atrium, indicating a careful and relatively advanced knowledge of heart's structure. His description of the fetal circulation was the most complete up to his time. This constitutes the most important distinctive structural difference between the circulatory apparatus of the adult and the child.

Incomplete regression of the right sinus valve of sinus venosus results in a spectrum of vestiges such as Chiari network, eustachian valve (EV), Thebesian valve of the coronary sinus and crista terminalis.

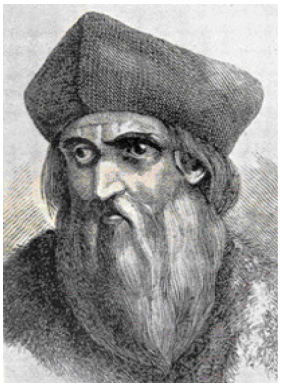
In particular, EV is a remnant of the embryonic valve of inferior vena cava (IVC), which in fetal heart directs oxygenated blood (by the placenta) towards the foramen ovale into the systemic circulation. It appears as a crescent-like membrane which extends from the IVC to the lower part of the fossa ovalis. There is a large variability in size, shape, thickness, texture and in the extent to which EV encroaches on neighboring structures such as the atrial septum. Its average length is 3.6 mm ranging from 1.5 to 23 mm[4]. Over time, EV disappears completely represented only by a thin ridge or, most commonly, it appears as a crescentic fold of endocardium arising from the anterior rim of the IVC orifice. The lateral horn of the crescent tends to meet the lower end of the crista terminalis, while the medial horn joins the thebesian valve, a semicircular valvular fold at the orifice of the coronary sinus (Figure 2). Sometimes, EV may persist as a mobile, elongated structure projecting deeply into the right atrial cavity, showing an undulating motion in real time echocardiography and, when it is quite large, it may be confused with right atrial tumors, thrombi, or vegetations.

The superior vena cava, on the contrary, does not have any homologous valve.

WHAT IS THE EUSTACHIAN VALVE PREVALENCE AND THE ANATOMICAL PATTERNS?

The prevalence of EV in the general population is not known, as the diagnostic criteria vary in different studies. Yater[5] reported a rate of approximately 60% of persisting EV in adults in a group of 120 consecutive necropsies. Limacher *et al*[4] found an incidence of approximately 70% in children of various ages. On transoesophageal echocardiography (TEE) a persisting EV was found in 4.2% of the patients and its prevalence was similar in men and in women[6]. The features and the physiology of the EV have been well described by 2D/3D echocardiography[7,8].

Three different anatomical patterns have been described: (1) Chiari network, found in 2%-3% of normal hearts at autopsy[9], is a reticolous and filamentous membrane with attachment to the upper wall of the right atrium along the ridge connecting the vena cava and atrial septum; it often appears as a web-like structure with a variable number of thread-like components[10]; (2) Eustachian ridge (ER), also known as ''sinus septum'' is prominently located between the fossa ovalis and the coronary



Bartolomeo Eustachio

San Severino Marche (Macerata), 1507? –
Fossato di Vico (Perugia), August 27 1574

Figure 1 Bartolomeo Eustachio, also known by his latin name of Eustachius, was a distinguished physician of the Renaissance period, professor of anatomy at the medical faculty of Collegio della Sapienza in Rome and one of the founders of the science of modern human anatomy.

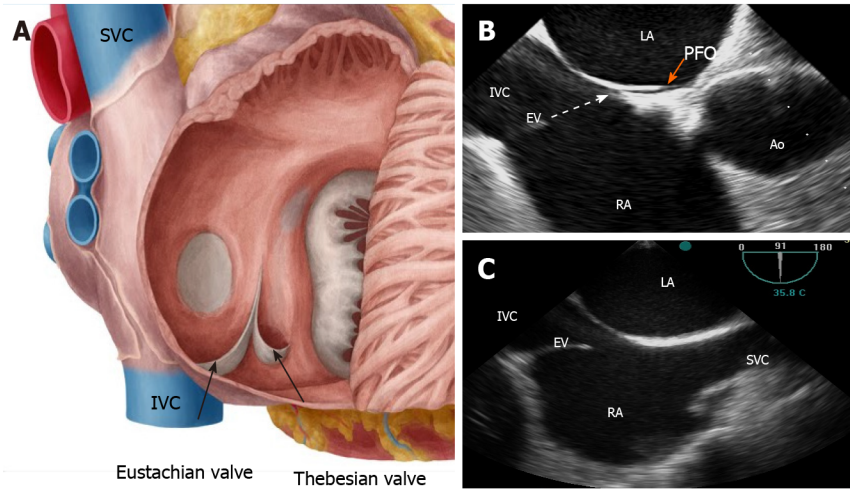


Figure 2 Anatomical illustration (A) and two-dimensional transesophageal echocardiogram in sagittal (B) and in bicaval (C) views showing the specific orientation of the eustachian valve directing the blood (white dotted arrow) toward the interatrial septum and patent foramen ovale (orange arrow). SVC: Superior vena cava; IVC: Inferior vena cava; RA: Right atrium; LA: Left atrium; EV: Eustachian valve; Ao: Aorta; PFO: Patent foramen ovale.

sinus ostium; the medial portion of the EV takes insertion on this structure and continues in the tendon of Todaro, which runs on the ER towards the central fibrous body[11]; and (3) EV, so called "valvula venae cavae inferioris", which is characterized by a mobile and fenestrated membrane without any anatomic connection[12] (Figures 3, 4 and Supplementary Videos 1, 2), often misdiagnosed as an intra-atrial thrombus.

CLUES FROM CLINICAL FEATURES ASSOCIATED WITH INCREASED RISK OF PARADOXICAL EMBOLISM

A persisting EV in the absence of other structural heart diseases is believed to have no pathological importance.

Nevertheless, EV is frequently found in adult patients with septal abnormalities, mainly patent foramen ovale (PFO) but also atrial septal defect (ASD) and it may participate in the mechanism of paradoxical embolism, by maintaining an embryonic right atrial flow pattern into adult life and directing the blood from the IVC *via* PFO into the left atrium (LA). Therefore, the presence of a prominent and large EV may increase the chance of paradoxical embolization beyond that associated with PFO size and the amount of shunting.

There are several reports documenting cyanosis in patients with ASD without an increase in right heart pressures but in whom the congenital defect was associated

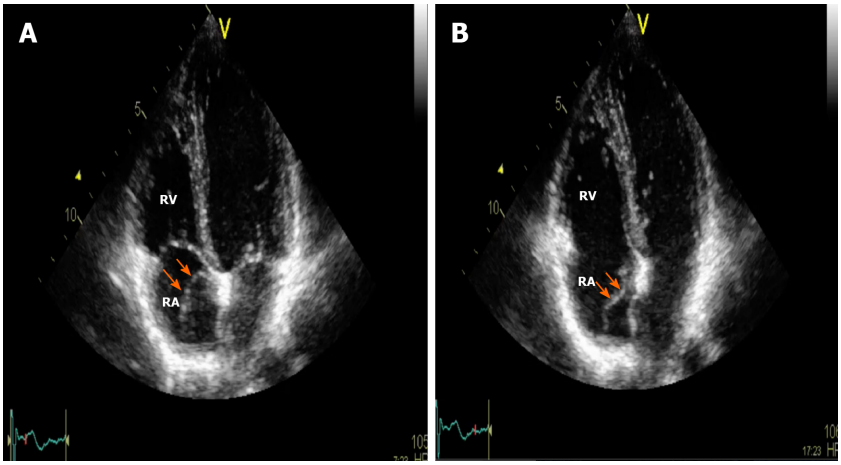


Figure 3 Two-dimensional transthoracic echocardiogram in apical four-chamber views showing the eustachian valve as a mobile, elongated structure (orange arrows) projecting into the right atrial cavity, showing an undulating motion during cardiac cycles. A: Systole; B: Diastole. RA: Right atrium; RV, right ventricle.

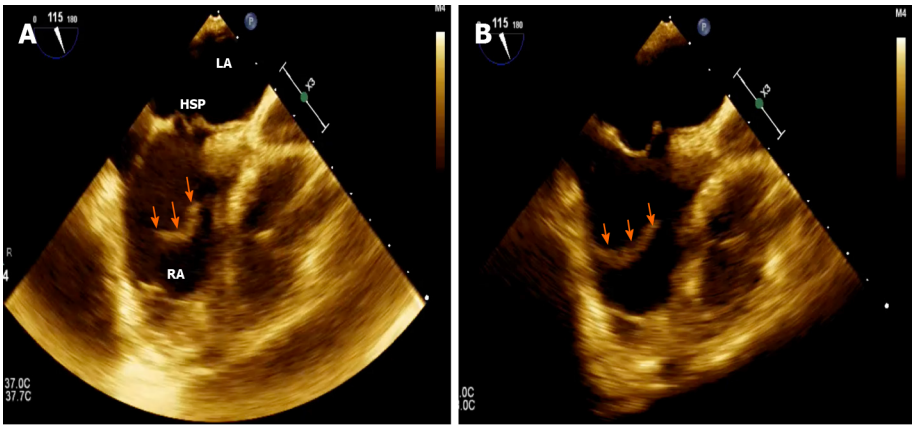


Figure 4 Two-dimensional transesophageal echocardiogram bicaval views. A: systolic frame; B: diastolic frame showing a prominent elongated eustachian valve (orange arrows) without any anatomic connection pointing towards the hypermobile septum primum. RA: Right atrium; LA: Left atrium; HSP: hypermobile septum primum.

with a prominent EV, the valve thus being implicated as the possible source of the right to left shunt[13]. The findings support the hypothesis that patients with a cryptogenic stroke (CS) and ASD or PFO combined with a prominent EV may benefit from interventional closure of the interatrial communication.

A persistent EV, particularly a prominent one, has been frequently observed in cases of platypnea-orthodeoxia syndrome[14,15].

Furthermore, a large ER or a prominent EV may pose issues with device placement because those right atrial structures limit the space available over the fossa ovalis on the right atrial side and may cause a PFO device to sit away from the fossa ovalis. The disc may rest on the ER or EV and result in the PFO tunnel being held open with a persistent residual shunt. Comprehensive assessment on 2D/3D TEE imaging is needed to accurately assess how such structures will impact on device choice and size.

In addition, EV has the potential to interfere with manipulation of the guidewire and it can be caught in the device during deployment, interfering with the occluder position or enhancing an embolic risk if drawn across the septum into the LA. A report of a case series showed the practicability of using a steerable ablation catheter to deflect the EV away from the interatrial septum during the procedure[16].

Complications related to the presence of EV may occur such as obstruction of the inferior vena cava, thrombosis and possibly subsequent pulmonary embolism.

Occasionally, the EV crosses the floor of the right atrium from the orifice of the IVC and inserts into the lower portion of the interatrial septum adjacent to the atrioventricular valves. Higher insertion of a very prominent EV mimicking the echocardiographic appearance of divided right atrium is very rare[17]. Such a config-

uration of a large EV may also mimic a right atrial cystic tumor[18].

A SUMMARY OF ARGUMENTS SUPPORTING THE GUILTINESS OF EUSTACHIAN VALVE AS A SERIAL PARTNER IN CRIME

EV redirects flow from the IVC to the interatrial septum through a right-to-left shunt into the LA thus explaining the left circulation paradoxical thromboembolism event

Indeed, a multivariate analysis showed that the presence of prominent EV or Chiari's network was independently related to CS and have been included in risk prediction models to identify patients at the highest risk of paradoxical embolism[19]. In particular, the OR for EV or Chiari's network as factors related to CS was 4.47 in univariate analysis (P = 0.002) and 4.71 in multivariate analysis (P = 0.009).

EV predicts the prognosis and outcomes following percutaneous PFO closure

Large EV can predict the occurrence of residual shunt in patients who underwent PFO closure for cryptogenic cerebral ischemia[20]. Inglessis *et al*[21] found that the detection of EV on transthoracic echocardiography (hazard ratio: 9.04; 95% confidence interval: 2.07 to 39.44; P < 0.0034) was significantly associated with the occurrence of cerebrovascular events after PFO closure. Interestingly, the 3 patients with a prominent EV who suffered a recurrent event had persistent residual shunt after PFO closure.

EV may be nidus for thrombus formation

In situ or from adhesion of embolic material from another distant source (lower extremity deep vein thrombosis). In this setting, PFO patients with hypercoagulable states are at very high risk.

EV may be nidus for tumors

Rare (myxomas, cystic tumors, fibroelastic papillomas).

EV may interfere with the device placement

Presence of either EV or Chiari's network may hinder the passage of wires, reduce the available space in the right atrium or even interfere with device placement[22].

EV may interfere to IVC cannulation

A detailed echocardiographic right atrial anatomy inspection can help suggesting an alternative plan and prevent complications during surgery[23].

EV may mimic ASD rim

EV may potentially complicate a simple percutaneous ASD device closure: the free end can be confused in fact with superior rim on TEE bicaval view[24,25]. During surgery, EV could be mistaken for the true septum and inadvertently incorporated into the patch. This causes iatrogenic right to left shunt due to diversion of the IVC blood flow into the LA[26].

CONCLUSION

Echocardiography plays a key role in the identification and understanding of the eustachian valve and the other right atrial structural abnormalities, in order to avoid misdiagnosis and to prevent complications during interventional patent foramen ovale and before atrial septal defect closure procedures.

Large prominent eustachian valve has been found guilty at all the degrees of judgment and represents an important risk factor fostering paradoxical thromboembolism in patients with right-to-left shunting *via* patent foramen ovale. Bartolomeo Eustachio, the papal anatomist, would never have thought that his valve could have been identified as a serial partner in crime.

REFERENCES

1 **Ahmad Y**, Howard JP, Arnold A, Shin MS, Cook C, Petraco R, Demir O, Williams L, Iglesias JF, Sutaria N, Malik I, Davies J, Mayet J, Francis D, Sen S. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials. *Eur Heart J* 2018; **39**: 1638-1649 [PMID: 29590333 DOI: 10.1093/eurheartj/ehy121]

2 **Conforti M**. The Biblioteca Lancisiana and the 1714 edition of Eustachi's anatomical plates. Maria Pia Donato and Jill Kraye. In: Donato MP, Kraye J, editors. Conflicting duties: Science, Medicine and Religion in Rome, 1550-1750, London, Warburg Institute; 2009: 303-317

3 **Simpson D**. The papal anatomist: Eustachius in renaissance Rome. *ANZ J Surg* 2011; **81**: 905-910 [PMID: 22507418 DOI: 10.1111/j.1445-2197.2011.05793.x]

4 **Limacher MC**, Gutgesell HP, Vick GW, Cohen MH, Huhta JH. Echocardiographic anatomy of the eustachian valve. *Am J Cardiol* 1986; **57**: 363-365 [PMID: 3946237 DOI: 10.1016/0002-9149(86)90930-6]

5 **Yater WM**. Variations and anomalies of the venous valves of the right atrium of the human heart. *Arch Pathol* 1929; **7**: 418-441

6 **Marek D**, Sovova E, Kocianova E. The prevalence of eustachian valve on transoesophageal echo examination. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2011; **155**: 283-285 [PMID: 22286815 DOI: 10.5507/bp.2011.025]

7 **Okamoto M**, Beppu S, Nagata S, Park YD, Masuda Y, Sakakibara H, Nimura Y. [Echocardiographic features of the eustachian valve and its clinical significance (author's transl)]. *J Cardiogr* 1981; **11**: 271-276 [PMID: 7264390]

8 **Maeno YV**, Boutin C, Benson LN, Nykanen D, Smallhorn JF. Three-dimensional transesophageal echocardiography for secundum atrial septal defects with a large eustachian valve. *Circulation* 1999; **99**: E11 [PMID: 10338469 DOI: 10.1161/01.cir.99.20.e11]

9 **Werner JA**, Cheitlin MD, Gross BW, Speck SM, Ivey TD. Echocardiographic appearance of the Chiari network: differentiation from right-heart pathology. *Circulation* 1981; **63**: 1104-1109 [PMID: 7471371 DOI: 10.1161/01.cir.63.5.1104]

10 **Chiari H**. Uber netzbildungen im rechten vorhof des herzens. *Beitr Pathol Anat* 1897; **22**: 1-10

11 **Faletra FF**, Ho SY, Auricchio A. Anatomy of right atrial structures by real-time 3D transesophageal echocardiography. *JACC Cardiovasc Imaging* 2010; **3**: 966-975 [PMID: 20846634 DOI: 10.1016/j.jcmg.2010.03.014]

12 **De Dominicis E**, Ometto R, Frigiola A, Menicanti L, Arfiero S, Vincenzi M. [Echocardiographic aspects of persistence of the right valve of the venous sinus]. *G Ital Cardiol* 1985; **15**: 80-83 [PMID: 4007356]

13 **Morishita Y**, Yamashita M, Yamada K, Arikawa K, Taira A. Cyanosis in atrial septal defect due to persistent eustachian valve. *Ann Thorac Surg* 1985; **40**: 614-616 [PMID: 4074009 DOI: 10.1016/s0003-4975(10)60359-1]

14 **Blanche C**, Noble S, Roffi M, Testuz A, Müller H, Meyer P, Bonvini JM, Bonvini RF. Platypnea-orthodeoxia syndrome in the elderly treated by percutaneous patent foramen ovale closure: a case series and literature review. *Eur J Intern Med* 2013; **24**: 813-817 [PMID: 24007641 DOI: 10.1016/j.ejim.2013.08.698]

15 **Teupe CH**, Groenefeld GC. Platypnea-orthodeoxia due to osteoporosis and severe kyphosis: a rare cause for dyspnea and hypoxemia. *Heart Int* 2011; **6**: e13 [PMID: 22049312 DOI: 10.4081/hi.2011.e13]

16 **McMahon CJ**, Pignatelli RH, Rutledge JM, Mullins CE, Grifka RG. Steerable control of the eustachian valve during transcatheter closure of secundum atrial septal defects. *Catheter Cardiovasc Interv* 2000; **51**: 455-459 [PMID: 11108680 DOI: 10.1002/1522-726x(200012)51:4<455:aid-ccd17>3.0.co;2-e]

17 **Martínez-Quintana E**, Rodríguez-González F, Marrero-Santiago H, Santana-Montesdeoca J, López-Gude MJ. Cor triatriatum dexter versus prominent Eustachian valve in an adult congenital heart disease patient. *Congenit Heart Dis* 2013; **8**: 589-591 [PMID: 22469336 DOI: 10.1111/j.1747-0803.2012.00648.x]

18 **Malaterre HR**, Kallee K, Périer Y. Eustachian valve mimicking a right atrial cystic tumor. *Int J Card Imaging* 2000; **16**: 305-307 [PMID: 11219602 DOI: 10.1023/a:1026521306831]

19 **Nakayama R**, Takaya Y, Akagi T, Watanabe N, Ikeda M, Nakagawa K, Toh N, Ito H. Identification of High-Risk Patent Foramen Ovale Associated With Cryptogenic Stroke: Development of a Scoring System. *J Am Soc Echocardiogr* 2019; **32**: 811-816 [PMID: 31130417 DOI: 10.1016/j.echo.2019.03.021]

20 **Scacciatella P**, Butera G, Meynet I, Giorgi M, D'Amico M, Pennone M, Alunni G, Frisenda V, Pelloni E, Marra S. Percutaneous closure of patent foramen ovale in patients with anatomical and clinical high-risk characteristics: long-term efficacy and safety. *J Interv Cardiol* 2011; **24**: 477-484 [PMID: 21539612 DOI: 10.1111/j.1540-8183.2011.00652.x]

21 **Inglessis I**, Elmariah S, Rengifo-Moreno PA, Margey R, O'Callaghan C, Cruz-Gonzalez I, Baron S, Mehrotra P, Tan TC, Hung J, Demirjian ZN, Buonanno FS, Ning M, Silverman SB, Cubeddu RJ, Pomerantsev E, Schainfeld RM, Dec GW Jr, Palacios IF. Long-term experience and outcomes with transcatheter closure of patent foramen ovale. *JACC Cardiovasc Interv* 2013; **6**: 1176-1183 [PMID: 24262618 DOI: 10.1016/j.jcin.2013.06.013]

22 **Onorato E**, Pera IG, Melzi G, Rigatelli G. Persistent redundant Eustachian valve interfering with

Amplatzer PFO occluder placement: anatomico-clinical and technical implications. *Catheter Cardiovasc Interv* 2002; **55**: 521-524 [PMID: 11948904 DOI: 10.1002/ccd.10141]

23 **Sarupria A**, Bhuvana V, Mani M, Kumar AS. Large Eustachian valve: an incidental finding yet perplexing. *Ann Card Anaesth* 2014; **17**: 309-310 [PMID: 25281632 DOI: 10.4103/0971-9784.142073]

24 **Raut MS**, Maheshwari A, Dubey S, Shivnani G, Makhija A, Mohanty A. Eustachian valve - Masquerading ASD rim. *Indian Heart J* 2016; **68**: 368-369 [PMID: 27316494 DOI: 10.1016/j.ihj.2016.03.026]

25 **Krishnamoorthy KM**, Gopalakrishnan A, Kumar DS, Sivasankaran SS. Eustachian valve-Masquerading ASD rim. *Indian Heart J* 2017; **69**: 422-423 [PMID: 28648449 DOI: 10.1016/j.ihj.2017.04.011]

26 **Desnick SJ**, Neal WA, Nicoloff DM, Moller JH. Residual right-to-left shunt following repair of atrial septal defect. *Ann Thorac Surg* 1976; **21**: 291-295 [PMID: 773318 DOI: 10.1016/s0003-4975(10)64313-5]

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ORIGINAL ARTICLE

Retrospective Study

Effect of trabeculated myocardial mass on left ventricle global and regional functions in noncompaction cardiomyopathy

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Abstract

BACKGROUND

Left ventricular (LV) noncompaction cardiomyopathy is a rare cardiomyopathic subtype that has been recognized in recent years and is being diagnosed at an increased rate. There is no consensus regarding the diagnosis of the disease, and increased trabeculation rates that meet the existing diagnostic criteria may even be present in healthy asymptomatic people. This indicates that differentiating criteria for diagnosis are needed.

AIM

To examine the increase in myocardial trabeculation and the change in left ventricular global and regional functions.

METHODS

This retrospective study included 65 patients (28 females, 37 males) diagnosed with LV noncompaction cardiomyopathy who underwent cardiac magnetic resonance imaging between January 2011 and August 2016 and had a noncompacted/compacted myocardial thickness ratio of over 2.3 in more than one segment in the left ventricle. The distribution and ratios of trabeculations in apical, midventricular, and basal regions were examined in short-axis images obtained from cardiac magnetic resonance. In addition, by using short-axis cine images, regional ejection fraction (EF) and global EF were calculated using the Simpson method in the left ventricle at apical, basal, and midventricular levels.

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RESULTS
While the number of trabeculated segments were similar at the apical (3.2 ± 1.0) and midventricular levels, a statistically significant level of involvement was not observed at the basal level (0.4 ± 0.9) ($P > 0.05$). The highest noncompacted/compacted (trabeculation) ratio was observed at the apical level (3.9 ± 1.4), while this ratio was higher at the anterior (59%-89.4%) and lateral (62%-84.8%) segments ($P > 0.05$). Global EF was positively correlated with apical, midventricular, and basal regional EF ($P < 0.05$). However, there was no significant correlation between regional EF and the number of trabeculated segments or trabeculation ratio in all three regions; nor was there a significant correlation between regional EF and the number of trabeculated segments or trabeculation ratio in the entire LV ($P > 0.05$).

CONCLUSION
No global or regional relationship was observed between LV dysfunction and trabeculation rate or the number of trabeculated segments. This limits the usefulness of change in LV functions in the differentiation between normal and pathological trabeculation.

Key Words: Isolated noncompaction of the ventricular myocardium; Cardiomyopathies; Magnetic resonance imaging; Stroke volume; Magnetic resonance imaging; Ventricular function

Core Tip: With the advancements in cardiac magnetic resonance, there is increased frequency of left ventricular noncompaction cardiomyopathy diagnosis; meanwhile, increased trabeculation that meet diagnostic criteria may also be observed in healthy asymptomatic individuals. This suggests the need for new diagnostic criteria of the disease. In this regard, our retrospective study investigates the impact of the number of trabeculated segments and the trabeculation ratio on regional and global left ventricular functions.

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INTRODUCTION

Left ventricular noncompaction cardiomyopathy (LVNC) is a form of cardiomyopathy that has been classified as primary genetic cardiomyopathy by the World Health Organization since 2006[1,2]. It is characterized by phenotypically prominent trabeculations, deep intertrabecular recesses, and thick noncompacted endocardium *vs* thin compacted epicardium. Etiologic factors of the disease are not fully clear. Genetic transmission may occur in sporadic or familial forms[3,4]. Several hypotheses have been prepared to explain the development mechanism of LVNC. However, there is a consensus of ideas that the left ventricle is the result of abnormal morphogenesis. In the 8th wk of gestation, myocardial trabeculations begin to be compacted starting from the basal region of the heart (compaction: Compacting of the trabeculations)[5]. Ventricular compaction advances from the epicardium towards the endocardium, from the base of the heart towards the apex and from the septum towards the free wall [6]. In the fetal heart, ventricular myocardial compaction is completed in the 4th mo. If the compaction process is interrupted, non-compaction cardiomyopathy occurs and the clinical manifestation varies depending on the stage of interruption. In addition, autopsy studies have shown that prominent trabeculations arising from the embryonal development process can also be found in high rates in the hearts of normal people and can be observed in the apex[7-9].

The actual prevalence of non-compaction cardiomyopathy is not fully known; however, one single-study in the literature reported that it varies between 0.014%-1.3% [10]. The most important diagnostic parameter is the ratio of non-compacted layer in relation to compacted layers of myocardium; this ratio should be over 2 in echocardiography and over 2.3 in cardiac magnetic resonance (CMR) imaging[11,12]. Different criteria have been proposed for diagnosis, the most important of which is to decide whether the trabeculations observed in imaging are normal, a normal variant, or pathological. The existing diagnostic criteria based on echocardiographic and CMR findings have certain limitations[13]. Recent studies have shown that increased trabeculation ratios may also be present in healthy asymptomatic individuals, leading to increased rates of LVNC diagnosis and indicating that new diagnostic criteria are needed. In addition, LVNC may be complicated by heart failure and result in cardiac transplantation, while the existing diagnostic criteria cannot determine or predict this process[6,14].

In this retrospective study, we aimed to investigate the effect of increased myocardial trabeculation on left ventricular global and ejection fraction (EF). In this regard, changes in EF can be included among the diagnostic criteria of the disease, preventing misdiagnosis, and can be used in the follow-up of the disease.

MATERIALS AND METHODS

Patient population

A total of 65 patients between ages 18-65 who were diagnosed with LVNC and referred to our department between January 2011 and August 2016 were included in our study. Patients were diagnosed by experienced cardiologists according to Jenni echocardiographic criteria. In the retrospective evaluations, the most important inclusion criteria independent from age and gender was CMR noncompacted/compacted myocardium ratio (NC/C) of 2.3 or higher. Exclusion criteria were as follows: Presence of contraindications for CMR, presence of other cardiomyopathies and congenital or non-congenital heart disease, and history of neuromuscular disease.

CMR protocol

The cardiac magnetic resonance imaging (MRI) protocol for LVNC in our clinic was applied to the patient group. Imaging was conducted in supine position with a 1.5 Tesla (Philips Achieva; Philips Medical Systems, Amsterdam, Netherlands) MRI device. The SENSE-XL-Torso cardiac coil was placed on the anterior chest wall, and a signal acquisition system using electrocardiogram and respiratory trigger was applied. Initially, cardiac survey imaging was performed for the coronal, axial, and sagittal planes with Single Shot Balanced transcription factor E sequence. From the survey images, the plane formed between the mitral valve and apex in the axial plane and long axis two-chamber cine images from the Balanced transcription factor E sequence were obtained. Long axis four-chamber cine and short-axis (SA) cine images were obtained from these images. Since equal breath-hold is important for image quality, patients were asked to hold their breath at the end of expiration.

Imaging analysis

Cardiac MRI images were retrospectively evaluated by two radiologist who were experienced with cardiac images together using the standard approach on a Philips workstation. In the analyses, first the segment's non-trabeculated segment ratio was measured according to the American Heart Association's 16-segment model based on the ratio of trabeculated segment to non-trabeculated segment in the left ventricle (LV) at end-diastole[15]. Segments above the 2.3 cutoff value in all three SA planes (apical, mid, and basal), and the segment with the highest ratio in each axis was determined when making measurements. When distinguishing segmentation, the papillary muscle level was specified for the midventricular segment, the superior of the papillary muscles for the basal segment, and inferior of the papillary muscles as the apical segment. When determining the basal regions, the short axis section where more than half of the lumen was surrounded by myocardium was chosen. According to the current protocol, trabeculations were determined as regions with muscular structure moving together with the inner myocardium border, extending towards the cardiac region, and not accompanying the papillary muscles at the end of systole. The border between compacted and trabeculated myocardium in each segment was chosen outside of the line where trabeculation was not prominent (Figure 1). In the second step, systolic function analysis was performed separately for all three axes and

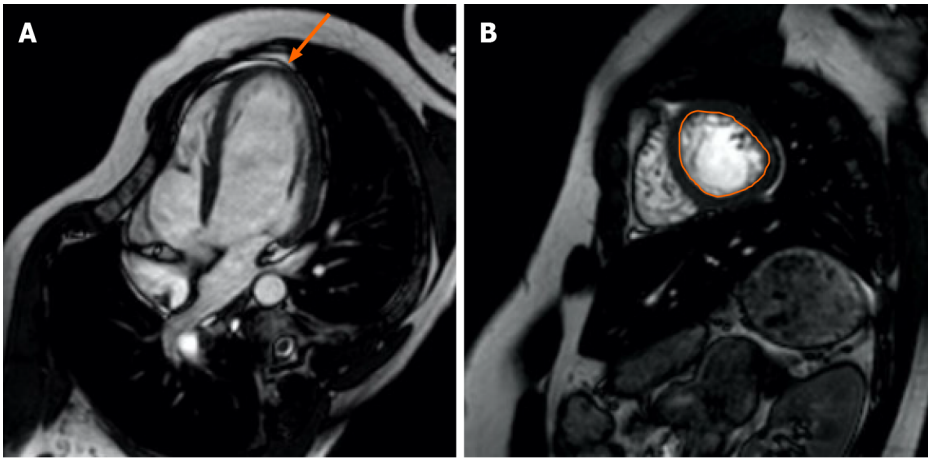

Figure 1 Cardiac magnetic resonance imaging appearance of left ventricular non-compaction. Cardiac magnetic resonance of a 21-year-old male patient with left ventricular noncompaction cardiomyopathy. The end-diastolic appearance of compacted and noncompacted myocardium in the left ventricle of a patient with left ventricular noncompaction cardiomyopathy. A: In four-chamber cine images, trabeculated myocardium and deep intertrabecular recesses are more prominent in the apical and mid-ventricular regions (arrow); B: In short-axis cine, the boundaries between the trabeculated myocardial mass and the non-trabeculated myocardial mass are seen at the midventricular region.

globally for the entire LV. Simpson method was used for analysis. In the calculation of EF values, diastole and end-systolic endocardial boundaries were drawn manually for all three axes in short axis images, and finally, global EF values were calculated by drawing systole and end-diastolic endocardial boundaries in all sections from the apex to the base. The narrowest and widest ventricular cavity size was used at the mid-ventricular region to determine the systole and end-diastolic phases, respectively. Endocardial boundaries were drawn using the difference between the hyperintensity of the blood-filled cavity and the moderate intensity of the myocardium[16]. Papillary muscles were included in the ventricular cavity since they did not affect mass and cavity volume change in EF measurements.

Statistical analysis

Statistical analyses were performed using the SPSS 22.0 package program (Armonk, NY, United States). Mean, standard deviation, median, lowest-highest frequency, and percentage values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. Mann-Whitney *U* test was used in the analysis of quantitative independent data. Chi-square test was used to analyze qualitative independent data, and Fischer's exact test was used when Chi-square test conditions were not met. Spearman's rank correlation coefficient was used for correlation analysis.

RESULTS

We reviewed the electronic medical records and the baseline clinical characteristics, and cardiovascular compliments (congestive heart failure, syncope, embolic events, and any arrhythmias) of the patient population are summarized in Table 1. Also, in the study group none of the patients had diabetes mellitus and dyslipidemia. However, 5 patients had hypertension.

All patients who were included in the study met echocardiographic and CMR diagnostic criteria. All 65 patients had trabeculation ratio over 2.3 in at least three segments and at least two regions (apical, midventricular, basal). The number of trabeculated segments were high and similar at apical (3 ± 1) and midventricular (3 ± 1.4) regions, while there was no statistically significant involvement in basal regions. According to segmental distribution, trabeculation was most frequently observed in the apical-lateral (93.9%) and apical-anterior (89.4%) segments ($P < 0.001$). The highest trabeculation ratio was seen in the apical region (3.6 ± 1.4) (Tables 2 and 3).

There was a positive correlation between global EF and apical, midventricular, and basal EFs ($P < 0.05$). In addition, there was a positive correlation between the EFs of all three regions ($P < 0.05$) (Figure 2).

Table 1 Clinical characteristics of the study population

Clinical characteristics	mean ± SD, *n* (%)
Age in yr	31.09 ± 10.22
Male gender, *n* (%)	37 (56.9)
Syncope	5 (7.7)
Arrhytmia	2 (3.1)
Embolic events	1 (1.5)
CHF	0
Asymptomatic	57 (87.7)

CHF: Chronic heart failure; SD: Standard deviation.

Table 2 The highest values of the trabeculation ratio for apical, midventricular, basal regions, and global left ventricle and the distribution of the total number of trabeculated segments

	Min-Max	Media	mean ± SD
Highest ratio			
Apical, global	0.4-9.0	3.6	3.9 ± 1.4
Midventricular	1.7-6.5	3.2	3.3 ± 0.9
Basal	2.0-4.0	2.6	2.7 ± 0.6
Number of segments			
Total	0.0-11.0	7.0	6.3 ± 2.2
Apical total	0.0-4.0	3.0	3.2 ± 1.0
Mid total	0.0-5.0	3.0	2.8 ± 1.4
Basal total	0.0-3.0	0.0	0.4 ± 0.9

In cardiac magnetic resonance short axis images, the highest trabeculation ratio was observed in the apical region in the measurements made according to Simpson method. Similarly, the number of trabeculated segments s observed more prominently in the apical and midventricular regions. SD: Standard deviation.

There was no correlation between global EF and total number of segments involved and highest trabeculation rates for all three apical, midventricular, and basal regions ($P > 0.05$). No correlation was found between the regional EF values of the apical, midventricular, and basal regions and the number of trabeculated segments and the highest trabeculation ratio in these regions ($P > 0.05$) (Tables 4 and 5).

DISCUSSION

Noncompaction cardiomyopathy is a form of cardiomyopathy characterized by a bilayered compacted and noncompacted myocardium model with prominent myocardial trabeculations and intertrabecular recesses[17]. While it may be isolated, it may also be accompanied by multiple cardiac malformations[18]. Although there is no consensus regarding the etiopathogenesis of the disease, genetic studies have identified certain sarcomeric and non-sarcomeric cardiomyopathy genes[19,20]. Usually, the LV is affected alone[21]. While clinical presentation may occur at all ages, it usually manifests in childhood[19]. The disease may be asymptomatic, or symptoms may vary depending on the severity of involvement, symptoms of the accompanying syndrome, and congenital heart diseases[18]. In the literature, the most common clinical findings related to LVNC include heart failure, arrhythmias, and systemic embolic events[18]. The compaction process in the fetal heart occurs from the epicardium towards the endocardium, from the base of the heart towards the apex, and from the septum towards the lateral, and severity of the phenotype varies

Table 3 Segmental distribution of trabeculations in the apical, midventricular, and basal regions of the left ventricle

	n	%
Apical		
Septal	31	47.0
Anterior	56	84.8
Lateral	62	93.9
Inferior	59	89.4
Midventricular		
Anterior	42	63.6
Anterolateral	52	78.8
Inferolateral	49	74.2
Inferior	30	45.5
Inferoseptal	7	10.6
Anteroseptal	3	4.5
Basal		
Anterior	7	10.6
Anterolateral	10	15.2
Inferolateral	7	10.6
Inferior	2	3.0
Inferoseptal	0	0.0
Anteroseptal	1	1.5

$P < 0.01$ Mc Nemar test. Trabeculations were commonly observed in the apical-lateral segment, and there were no patients with a noncompacted/compacted myocardial ratio above 2.3 in the basal-inferoseptal segment.

Table 4 Comparison of highest trabeculation ratio and ejection fraction in global and regional left ventricular function

		Highest trabeculation ratio		
		Apical	**Midventricular**	**Basal**
Global EF	r	0.072	-0.054	-0.128
	P value	0.573	0.687	0.707
Apical EF	r	0.028		
	P value	0.825		
Midventricular EF	r		-0.022	
	P value		0.873	
Basal EF	r			-0.91
	P value			0.789

There was no correlation between global ejection fraction (EF) and highest trabeculation ratios of apical, midventricular, and basal regions ($P > 0.05$). There was no correlation between apical EF and apical highest ratio, between midventricular EF and midventricular highest ratio, or between basal EF and basal highest ratio ($P > 0.05$).

depending on the time of interruption[21]. In our study, trabeculations were observed more commonly in the apical and midventricular regions, consistent with the fetal compaction process.

In order to diagnose LVNC, the main defined structural features must be revealed with imaging. The most important parameter in diagnosis is the ratio of the noncompacted layer to the compacted layers. This ratio must be more than 2 in echocardi-

Table 5 Comparison of global and regional (apical, midventricular, and basal) number of trabeculated segments and ejection fraction in left ventricular function

		Number of segments			
		Total	Apical	Midventricular	Basal
Global EF	r	0.075	-0.034	0.146	-0.169
	P value	0.555		0.246	0.179
Apical EF	r	0.120	0.048		
	P value	0.340	0.704		
Midventricular EF	r	0.173		0.225	
	P value	0.168		0.072	
Basal EF	r	0.083			-0.229
	P value	0.510			0.066

It was observed that the number of trabeculated segments had no significant effect on regional and global left ventricular functions. There was no correlation between global ejection fraction (EF) and total number of trabeculated segments at apical, midventricular, and basal regions ($P > 0.05$). There was no correlation between apical EF and apical segment number, midventricular EF and midventricular segment number, or basal EF and basal segment number ($P > 0.05$).

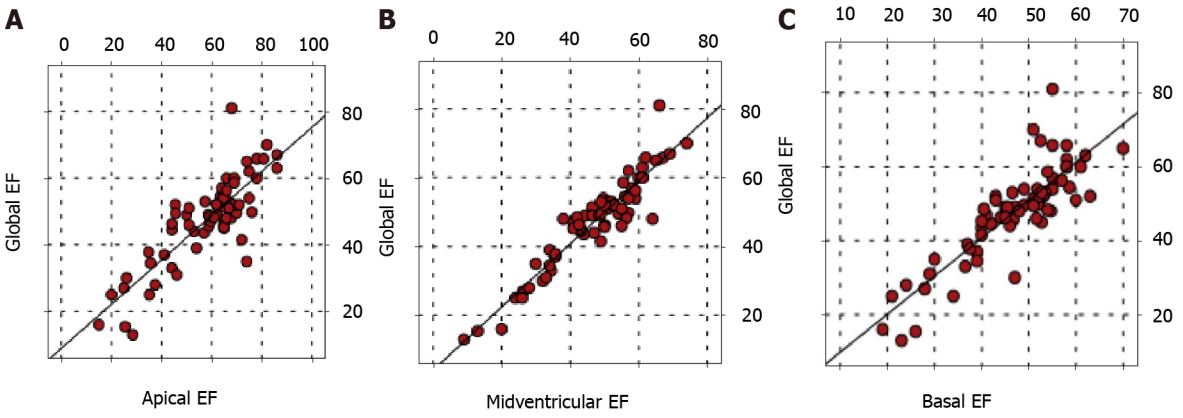

Figure 2 Comparison of left ventricular global function and regional (apical, midventricular, basal) functions. (Spearman correlation) A positive correlation was found between left ventricular global ejection fraction (EF) and EF at apical, midventricular, and basal regions ($P < 0.05$). A: Apical EF; B: Midventricular EF; C: Basal EF.

ography, and more than 2.3 in CMR. Echocardiography and CMR are the main imaging modalities used to diagnose the disease. Echocardiography is widely used due to its availability, common use, low cost, and absence of radiation exposure[22]. Chin *et al*[11] initially proposed evaluating the ratio of X to Y for echocardiographic diagnosis, in which X refers to the distance from the epicardial surface to the deepest part of the trabecular recess, and Y is the distance from the epicardial surface to the peak of the trabeculation. An X/Y ratio up to 0.5 at end-diastole is enough for diagnosis. Chin *et al*[11] also acknowledged the relationship between the clinical presentation of the disease and genetically transmitted cardiac diseases[11].

Jenni *et al*[23] specified diagnostic criteria as NC/C > 2 measured at end-systole and recommended additional morphological criteria including visualization of deep perfused intertrabecular recesses on color flow Doppler, involvement predominately in the lateral, apical, or inferior walls of the LV, and absence of additional cardiac anomaly[23]. The contribution of Stöllberger *et al*[12] to echocardiographic diagnostic criteria was > 3 trabeculations apically to the LV papillary muscles, apart from aberrant bands and false tendons[12]. However, there are many studies on the pitfalls of echocardiographic diagnostic criteria. One such was a study by Ottaviani *et al*[24], who measured trabeculations in the explanted hearts of 105 patients diagnosed as LVNC by echocardiography and who underwent orthotopic heart transplant. NC/C ratio was found as 1.7/1 ± 0.2, demonstrating the discordance between echocardiography and pathology[24]. Echocardiography has several limitations, such as such as

being operator dependent, inadequate apex evaluation, difficulty in distinguishing the bilayer appearance, and inadequate short axis imaging. Therefore, the weak correlation between the existing echocardiographic diagnostic criteria has led to the increased use of CMR in diagnosis[25]. CMR is a highly sensitive method in the diagnosis of LVNC and stands out with its ability to provide three-dimensional data, functional imaging, and tissue characterization with late gadolinium enhancement imaging[26,27]. However, its diagnostic criteria for the disease are not fully established [28].

Regarding CMR based diagnostic criteria, Petersen *et al*[27] conducted a study evaluating trabeculation distribution and NC/C ratios in different patient groups, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, as well as 7 patients with LVNC; they concluded that trabeculation ratio > 2.3 (NC/C > 2.3) measured in end-diastole SA supported non-compaction cardiomyopathy diagnosis with 86% sensitivity and 99% sensitivity[27]. Fazio *et al*[29] performed end-diastole measurements in 8 patients diagnosed with LVNC and reported that it would be more appropriate to increase NC/C ratio to 2.5[29]. Other CMR-based criteria are more quantitative measurements, based on the measurement of trabeculated mass developed by Jacquier *et al*[30] and Grothoff *et al*[31]. Jacquier *et al*[30] conducted a CMR imaging study on trabeculation mass and reported that the trabeculated LV mass should be more than 25% of the total LV mass, and the noncompacted myocardial mass should be > 15 g/m^2[30,31].

Ventricular myocardium in LVNC has varying morphology ranging from increased spongiosis to dysplastic appearance. Changes in coronary microcirculation together with myocardial abnormalities are thought to play a role in the development of fibrosis. Late gadolinium enhancement may reveal findings of subendocardial and trabecular fibrosis. Although fibrosis may emerge as a follow-up parameter due to increased fibrosis occurrence in adult patients and advanced disease, recent studies have shown that late contrast enhancement may also occur in normally compacted myocardium[32,33]. Similar to a study by Nucifora *et al*[34], the presence and prevalence of myocardial fibrosis may be associated with EF but is insufficient for diagnosis and follow-up[34]. Thanks to advances in high resolution imaging, the sensitive imaging techniques can be used to detect even the slight variations in myocardial morphology within normal limits. Dawson *et al*[35] conducted a study to determine the anatomic norm of trabeculation and evaluated normal hearts of 120 healthy volunteers using CMR. Similar to LVNC, they demonstrated the highest volume of trabeculated myocardium was at a young age and in the apical anterior segments end-diastolic, however, the study needs to be supported by large cohort studies to determine normal limits[35]. The increasing prevalence of the disease indicates the need for strict diagnostic guidelines that can distinguish between normal and pathological trabeculation. LVNC is associated with systolic dysfunction and may clinically progress to heart failure. However, the factors affecting global and regional systolic left ventricular functions and their relationship with the LV noncompacted myocardial mass are not clearly known. Therefore, studies have been conducted to examine the relationship between the change in LV systolic function and the distribution and extent of trabeculation.

In our study, we investigated the relationship between and global and regional EF of apical, midventricular, and basal regions and the trabeculation ratio and number of trabeculated segments of these regions in 65 patients diagnosed with LVNC. We did not find any concordance between EF and trabeculated segment number and ratio for all three regions or global LV. Choudhary *et al*[36] investigated the relationship between LV systolic function and global and regional LVNC mass. Contrary to our study, a significant inverse correlation was found between global EF and NC/C ratios in basal, apical, and midventricular regions in end-systolic measurements, and a significant inverse correlation was observed between end-systolic NC/C ratio and regional EF[36]. Dellegrottaglie *et al*[37] used qualitative and quantitative methods such as wall motion score and fractional wall thickening to measure regional systolic function in 16 adult patients. In measurements of regional systolic functions, an inverse relationship was found between NC/C ratio and fractional wall thickening, and a direct relationship with wall motion score. In other words, a positive correlation was found between regional function and NC/C myocardial ratio. While no significant correlation could be found between the number of noncompacted segments and left ventricular EF, it was considered an indicator of global left ventricular dysfunction[37].

Choi *et al*[38] conducted a study on 145 people [24 isolated LVNC, 33 non-isolated LVNC, 30 dilated cardiomyopathy with noncompaction, 27 dilated cardiomyopathy, and 31 healthy controls] and, similar to our study, did not find a significant correlation

between left ventricular trabeculation volumes and EF in isolated LVNC patients compared to the control group[38].

Fazio *et al*[29] evaluated the relationship between ventricular dysfunction and the number of noncompacted segments in noncompaction cardiomyopathy and found that 122 of 238 patients (mean EF 44.39%) diagnosed with isolated LVNC had ventricular dysfunction with mean EF as 34.6%. However, they did not find a correlation between the number of affected segments and systolic dysfunction[29].

The severity and extent of myocardial involvement in patients with LVNC varies according to the stage of the disease and is heterogeneous. While some studies have found a significant relationship between trabeculation ratio and change in global ventricular function, other studies did not find a significant correlation between ventricular function and the ratio and frequency of trabeculation, as in our study. In addition, most of the studies conducted to date have focused on the relationship between trabeculation volume and global LV systolic function (EF). The limited number of studies on the impact to segmental function report varying results. In our study, we did not find a significant relationship between segmental function and the number of trabeculated segments or trabeculation ratio ($P > 0.05$).

The main limitations of this study are the lack of control group and its retrospective design. In addition, cardiac biopsies and genetic factors were not available for the included patients. Histopathological findings and genetic factors could help to provide more accurate diagnoses for LVNC.

CONCLUSION

In conclusion, there is a need for large cohort studies that include healthy subjects in order to utilize changes in left ventricular function as a criterion in the diagnosis of LVNC. There is not enough evidence yet for the use of segmental and global functions in the diagnosis and follow-up of the disease.

ARTICLE HIGHLIGHTS

Research background

The frequency of left ventricular noncompaction cardiomyopathy (LVNC) diagnosis is increasing day by day due to inadequate diagnostic criteria. In addition, the criteria used cannot determine the prognosis and stage of the disease.

Research motivation

New cardiac magnetic resonance (CMR) criteria that can be used in the diagnosis of LVNC can explain when the increased trabeculation rate in healthy individuals can be called disease. In this context, left ventricular function changes due to increased trabeculation may be a parameter.

Research objectives

In our study, it was aimed to evaluate the relationship between LV global and regional function and trabeculation increase. A new parameter that can be used in diagnosis and follow-up will increase the diagnostic specificity of LVNC.

Research methods

The distribution and ratios of trabeculations in apical, midventricular, and basal regions were examined in CMR. In addition, by using short-axis cine images, regional ejection fraction (EF) and global EF were calculated with the Simpson method in the left ventricle (LV) at apical, basal, and midventricular levels.

Research results

Global EF was correlated with apical, midventricular, and basal regional EF, but there was no significant correlation between global EF and the number of trabeculated segments or trabeculation ratio in the global LV. Also, there was no significant correlation between regional EF and the number of trabeculated segments or trabeculation ratio in all three regions.

Research conclusions

Global and regional EF changes may be new diagnostic criteria in the diagnosis of LVNC and in the follow-up of the disease.

Research perspectives

Studies on the relation of LV segmental functions with trabeculation are limited. Studies with larger cohorts and control groups should be conducted.

REFERENCES

1 **Elliott P**, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kühl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008; **29**: 270-276 [PMID: 17916581 DOI: 10.1093/eurheartj/ehm342]

2 **Maron BJ**, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006; **113**: 1807-1816 [PMID: 16567565 DOI: 10.1161/CIRCULATIONAHA.106.174287]

3 **Oechslin E**, Jenni R. Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? *Eur Heart J* 2011; **32**: 1446-1456 [PMID: 21285074 DOI: 10.1093/eurheartj/ehq508]

4 **Finsterer J**, Stöllberger C, Blazek G, Sehnal E. Familal left ventricular hypertrabeculation (noncompaction) is myopathic. *Int J Cardiol* 2013; **164**: 312-317 [PMID: 21788087 DOI: 10.1016/j.ijcard.2011.07.012]

5 **Stöllberger C**, Winkler-Dworak M, Blazek G, Finsterer J. Left ventricular hypertrabeculation/noncompaction with and without neuromuscular disorders. *Int J Cardiol* 2004; **97**: 89-92 [PMID: 15336813 DOI: 10.1016/j.ijcard.2003.08.014]

6 **Boyd MT**, Seward JB, Tajik AJ, Edwards WD. Frequency and location of prominent left ventricular trabeculations at autopsy in 474 normal human hearts: implications for evaluation of mural thrombi by two-dimensional echocardiography. *J Am Coll Cardiol* 1987; **9**: 323-326 [PMID: 3805522 DOI: 10.1016/s0735-1097(87)80383-2]

7 **Zambrano E**, Marshalko SJ, Jaffe CC, Hui P. Isolated noncompaction of the ventricular myocardium: clinical and molecular aspects of a rare cardiomyopathy. *Lab Invest* 2002; **82**: 117-122 [PMID: 11850525 DOI: 10.1038/Labinvest.3780404]

8 **Wengrofsky P**, Armenia C, Oleszak F, Kupferstein E, Rednam C, Mitre CA, McFarlane SI. Left Ventricular Trabeculation and Noncompaction Cardiomyopathy: A Review. *EC Clin Exp Anat* 2019; **2**: 267-283 [PMID: 31799511]

9 **Bartram U**, Bauer J, Schranz D. Primary noncompaction of the ventricular myocardium from the morphogenetic standpoint. *Pediatr Cardiol* 2007; **28**: 325-332 [PMID: 17632682 DOI: 10.1007/s00246-006-0054-8]

10 **Stanton C**, Bruce C, Connolly H, Brady P, Syed I, Hodge D, Asirvatham S, Friedman P. Isolated left ventricular noncompaction syndrome. *Am J Cardiol* 2009; **104**: 1135-1138 [PMID: 19801037 DOI: 10.1016/j.amjcard.2009.05.062]

11 **Chin TK**, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium. A study of eight cases. *Circulation* 1990; **82**: 507-513 [PMID: 2372897 DOI: 10.1161/01.cir.82.2.507]

12 **Stöllberger C**, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. *Am J Cardiol* 2002; **90**: 899-902 [PMID: 12372586 DOI: 10.1016/s0002-9149(02)02723-6]

13 **Tamborini G**, Pepi M, Celeste F, Muratori M, Susini F, Maltagliati A, Veglia F. Incidence and characteristics of left ventricular false tendons and trabeculations in the normal and pathologic heart by second harmonic echocardiography. *J Am Soc Echocardiogr* 2004; **17**: 367-374 [PMID: 15044872 DOI: 10.1016/j.echo.2003.12.020]

14 **Aras D**, Tufekcioglu O, Ergun K, Ozeke O, Yildiz A, Topaloglu S, Deveci B, Sahin O, Kisacik HL, Korkmaz S. Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. *J Card Fail* 2006; **12**: 726-733 [PMID: 17174235 DOI: 10.1016/j.cardfail.2006.08.002]

15 **Cerqueira MD**, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging

Committee of the Council on Clinical Cardiology of the American Heart Association. *Int J Cardiovasc Imaging* 2002; **18**: 539-542 [PMID: 12135124 DOI: 10.1161/hc0402.102975]

16 **Chuang ML**, Hibberd MG, Salton CJ, Beaudin RA, Riley MF, Parker RA, Douglas PS, Manning WJ. Importance of imaging method over imaging modality in noninvasive determination of left ventricular volumes and ejection fraction: assessment by two- and three-dimensional echocardiography and magnetic resonance imaging. *J Am Coll Cardiol* 2000; **35**: 477-484 [PMID: 10676697 DOI: 10.1016/s0735-1097(99)00551-3]

17 **Singh DP**, Patel H. Left Ventricular Non-compaction Cardiomyopathy. 2020 Jul 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021 [PMID: 30725710]

18 **van Waning JI**, Caliskan K, Hoedemaekers YM, van Spaendonck-Zwarts KY, Baas AF, Boekholdt SM, van Melle JP, Teske AJ, Asselbergs FW, Backx APCM, du Marchie Sarvaas GJ, Dalinghaus M, Breur JMPJ, Linschoten MPM, Verlooij LA, Kardys I, Dooijes D, Lekanne Deprez RH, IJpma AS, van den Berg MP, Hofstra RMW, van Slegtenhorst MA, Jongbloed JDH, Majoor-Krakauer D. Genetics, Clinical Features, and Long-Term Outcome of Noncompaction Cardiomyopathy. *J Am Coll Cardiol* 2018; **71**: 711-722 [PMID: 29447731 DOI: 10.1016/j.jacc.2017.12.019]

19 **Tariq M**, Ware SM. Importance of genetic evaluation and testing in pediatric cardiomyopathy. *World J Cardiol* 2014; **6**: 1156-1165 [PMID: 25429328 DOI: 10.4330/wjc.v6.i11.1156]

20 **Dellefave LM**, Pytel P, Mewborn S, Mora B, Guris DL, Fedson S, Waggoner D, Moskowitz I, McNally EM. Sarcomere mutations in cardiomyopathy with left ventricular hypertrabeculation. *Circ Cardiovasc Genet* 2009; **2**: 442-449 [PMID: 20031619 DOI: 10.1161/CIRCGENETICS.109.861955]

21 **Sedmera D**, Pexieder T, Vuillemin M, Thompson RP, Anderson RH. Developmental patterning of the myocardium. *Anat Rec* 2000; **258**: 319-337 [PMID: 10737851 DOI: 10.1002/(SICI)1097-0185(20000401)258:4<319::AID-AR1>3.0.CO;2-O]

22 **Mavrogeni SI**, Markousis-Mavrogenis G, Vartela V, Manolopoulou D, Abate E, Hamadanchi A, Rigopoulos AG, Kolovou G, Noutsias M. The pivotal role of cardiovascular imaging in the identification and risk stratification of non-compaction cardiomyopathy patients. *Heart Fail Rev* 2020; **25**: 1007-1015 [PMID: 31784859 DOI: 10.1007/s10741-019-09898-8]

23 **Jenni R**, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart* 2001; **86**: 666-671 [PMID: 11711464 DOI: 10.1136/heart.86.6.666]

24 **Ottaviani G**, Segura AM, Rajapreyar IN, Zhao B, Radovancevic R, Loyalka P, Kar B, Gregoric I, Buja LM. Left ventricular noncompaction cardiomyopathy in end-stage heart failure patients undergoing orthotopic heart transplantation. *Cardiovasc Pathol* 2016; **25**: 293-299 [PMID: 27135206 DOI: 10.1016/j.carpath.2016.03.004]

25 **Kohli SK**, Pantazis AA, Shah JS, Adeyemi B, Jackson G, McKenna WJ, Sharma S, Elliott PM. Diagnosis of left-ventricular non-compaction in patients with left-ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria? *Eur Heart J* 2008; **29**: 89-95 [PMID: 17993472 DOI: 10.1093/eurheartj/ehm481]

26 **Diwadkar S**, Nallamshetty L, Rojas C, Athienitis A, Declue C, Cox C, Patel A, Chae SH. Echocardiography fails to detect left ventricular noncompaction in a cohort of patients with noncompaction on cardiac magnetic resonance imaging. *Clin Cardiol* 2017; **40**: 364-369 [PMID: 28267213 DOI: 10.1002/clc.22669]

27 **Petersen SE**, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, Watkins H, Neubauer S. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol* 2005; **46**: 101-105 [PMID: 15992642 DOI: 10.1016/j.jacc.2005.03.045]

28 **Arbustini E**, Weidemann F, Hall JL. Left ventricular noncompaction: a distinct cardiomyopathy or a trait shared by different cardiac diseases? *J Am Coll Cardiol* 2014; **64**: 1840-1850 [PMID: 25443708 DOI: 10.1016/j.jacc.2014.08.030]

29 **Fazio G**, Novo G, D'Angelo L, Visconti C, Sutera L, Grassedonio E, Galia M, Ferrara F, Midiri M, Novo S. Magnetic resonance in isolated noncompaction of the ventricular myocardium. *Int J Cardiol* 2010; **140**: 367-369 [PMID: 19111359 DOI: 10.1016/j.ijcard.2008.11.080]

30 **Jacquier A**, Thuny F, Jop B, Giorgi R, Cohen F, Gaubert JY, Vidal V, Bartoli JM, Habib G, Moulin G. Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. *Eur Heart J* 2010; **31**: 1098-1104 [PMID: 20089517 DOI: 10.1093/eurheartj/ehp595]

31 **Grothoff M**, Pachowsky M, Hoffmann J, Posch M, Klaassen S, Lehmkuhl L, Gutberlet M. Value of cardiovascular MR in diagnosing left ventricular non-compaction cardiomyopathy and in discriminating between other cardiomyopathies. *Eur Radiol* 2012; **22**: 2699-2709 [PMID: 22772366 DOI: 10.1007/s00330-012-2554-7]

32 **Dursun M**, Agayev A, Nisli K, Ertugrul T, Onur I, Oflaz H, Yekeler E. MR imaging features of ventricular noncompaction: emphasis on distribution and pattern of fibrosis. *Eur J Radiol* 2010; **74**: 147-151 [PMID: 19328640 DOI: 10.1016/j.ejrad.2009.01.015]

33 **Sato Y**, Matsumoto N, Matsuo S, Kunimasa T, Yoda S, Tani S, Kasamaki Y, Kunimoto S, Saito S. Myocardial perfusion abnormality and necrosis in a patient with isolated noncompaction of the ventricular myocardium: evaluation by myocardial perfusion SPECT and magnetic resonance imaging. *Int J Cardiol* 2007; **120**: e24-e26 [PMID: 17583365 DOI: 10.1016/j.ijcard.2007.04.049]

34 **Nucifora G**, Aquaro GD, Pingitore A, Masci PG, Lombardi M. Myocardial fibrosis in isolated left ventricular non-compaction and its relation to disease severity. *Eur J Heart Fail* 2011; **13**: 170-176

[PMID: 21208941 DOI: 10.1093/eurjhf/hfq222]

35 **Dawson DK**, Maceira AM, Raj VJ, Graham C, Pennell DJ, Kilner PJ. Regional thicknesses and thickening of compacted and trabeculated myocardial layers of the normal left ventricle studied by cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2011; **4**: 139-146 [PMID: 21193690 DOI: 10.1161/CIRCIMAGING.110.960229]

36 **Choudhary P**, Hsu CJ, Grieve S, Smillie C, Singarayar S, Semsarian C, Richmond D, Muthurangu V, Celermajer DS, Puranik R. Improving the diagnosis of LV non-compaction with cardiac magnetic resonance imaging. *Int J Cardiol* 2015; **181**: 430-436 [PMID: 25569272 DOI: 10.1016/j.ijcard.2014.12.053]

37 **Dellegrottaglie S**, Pedrotti P, Roghi A, Pedretti S, Chiariello M, Perrone-Filardi P. Regional and global ventricular systolic function in isolated ventricular non-compaction: pathophysiological insights from magnetic resonance imaging. *Int J Cardiol* 2012; **158**: 394-399 [PMID: 21345500 DOI: 10.1016/j.ijcard.2011.01.063]

38 **Choi Y**, Kim SM, Lee SC, Chang SA, Jang SY, Choe YH. Quantification of left ventricular trabeculae using cardiovascular magnetic resonance for the diagnosis of left ventricular non-compaction: evaluation of trabecular volume and refined semi-quantitative criteria. *J Cardiovasc Magn Reson* 2016; **18**: 24 [PMID: 27142637 DOI: 10.1186/s12968-016-0245-2]

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ORIGINAL ARTICLE

Retrospective Study

Modes of failure with fractional flow reserve guidewires: Insights from the manufacturer and user facility device experience database

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Author contributions: Khalid N, Panday Y, and Kayani WT designed and performed the research and wrote the paper; Khalid U, Kamran H, and Wermers JP contributed to the analysis; Chhabra L and Alam M provided clinical advice; Jneid H and Kayani WT supervised the report.

Institutional review board statement: This study was conducted from a publicly available database, therefore, an approval from the institutional review board was not required.

Informed consent statement: Patients were not required to give informed consent for the study because the analysis used anonymous clinical data that were obtained from a freely accessible database.

Conflict-of-interest statement: We

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Abstract

BACKGROUND

Fractional flow reserve (FFR) measurement is commonly used in the cardiac catheterization laboratory to assess the functional significance of coronary arterial plaques. Robust real-world data on complications and modes of failure of FFR guidewires are limited.

AIM

To characterize these outcomes by analyzing the post-marketing surveillance data from the United States Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database for commonly used FFR guidewires.

METHODS

The MAUDE database was queried from January 2010 through April 2020 for 3

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FFR guidewires [PressureWire™ X (Abbott), Comet™ (Boston Scientific), and Verrata™ (Philips)] by searching for the following events: "Injury", "malfunction", "death", and "other". This yielded 544 reports. After excluding incomplete reports, 486 reports were analyzed.

RESULTS

Guidewire tip fracture was the most commonly reported mode of failure, in 174 (35.8%) cases followed by guidewire kinking (n = 152, 31.3%), communication failure (n = 141, 29.0%), and shaft fracture (n = 67, 13.8%). In total, 133 (27.4%) device failures resulted in patient adverse events. The most common adverse event was retained guidewire tip, in 71 (53.4%) cases, followed by freshly deployed stent dislodgment (n = 26, 19.6%) and coronary artery dissection (n = 23, 17.3%). Seven deaths were reported.

CONCLUSION

FFR guidewire failures can occur because of various mechanisms and cause patient adverse events. The MAUDE database serves as an important platform for improved collaboration among clinicians, device manufacturers, and regulators to improve device performance and optimize patient outcomes. Our analysis provides mechanistic insights of FFR guidewire failure and associated adverse events but cannot verify causality or provide a comparison among different guidewires.

Key Words: Fractional flow reserve; Coronary guidewire; Adverse events; Modes of failure; Food and Drug Administration; Manufacturer and user facility device experience

Core Tip: We analyzed post-marketing surveillance data from the Food and Drug Administration Manufacturer and User Facility Device Experience database to outline the most common adverse events and modes of failure encountered with Fractional Flow Reserve (FFR) coronary guidewires. Guidewire tip fracture was the most commonly reported mode of failure, in 35.8% of cases; retained guidewire tip was the most common patient complication (53.4% of cases). FFR is an important frontline measurement in the cardiac catheterization laboratory to assess intracoronary physiology. Our analysis demonstrates that in real-world practice, FFR guidewire failures can occur because of myriad mechanisms and result in patient complications.

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INTRODUCTION

Fractional flow reserve (FFR) is an essential measurement in the cardiac catheterization laboratory to assess intracoronary physiology. It is obtained by using a pressure sensing guidewire to calculate flow in the epicardial coronary arteries and determine the functional significance of stenosis. The benefits of an FFR-based revascularization strategy in coronary artery disease are well-established. Landmark clinical trials[1-5] have demonstrated that an FFR-guided decision to perform percutaneous coronary intervention reduces major adverse cardiovascular events and decreases the rate of urgent interventions. Likewise, physicians can safely defer revascularization for FFR-negative lesions[6], sparing patients the risk of invasive procedures and long-term antiplatelet therapy. FFR has considerable clinical advantages and is widely utilized.

Performing FFR requires the insertion of an additional guidewire into the patient's arterial system, which increases the risk of procedural complications. However, robust real-world data on the complications and modes of failure of commonly used FFR guidewires are limited. We aim to characterize these outcomes by analyzing the post-marketing surveillance data from the United States Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database for commonly used FFR guidewires.

MATERIALS AND METHODS

The MAUDE database is an electronic repository created by the FDA to capture major adverse events involving medical devices[7]. Reporting is either mandatory (manufacturers and device-user facilities) or voluntary (medical personnel, patients, and consumers). Developed in the 1990s, the database is updated monthly, with each report containing information on the device, event date, and event description by the provider and the manufacturer. The MAUDE database was queried from January 1, 2010, through April 1, 2020, for three commonly utilized FFR guidewires [Pressurewire™ X (Abbott), Comet™ (Boston Scientific), and Verrata™ (Philips)] by searching for the following events: "Injury", "malfunction", "death", and "other". This yielded 544 reports. Each report included a narrative description of the failure event and the results of a standardized inspection of the device if it was returned to the manufacturer. After excluding incomplete reports, duplicate reports, and older devices not in current use, 486 reports were included in the final analysis. This study was conducted from a publicly available database; therefore, an approval from the institutional review board was not required. Patients were not required to give informed consent for the study because the analysis used anonymous clinical data that were obtained from a freely accessible database. Although the MAUDE database is a passive monitoring framework, it can provide important insight into the most commonly reported complications associated with interventional devices. Reports on safety and monitoring of approved interventional devices based on this database have been previously reported[8].

RESULTS

Tables 1 and 2 show a complete list of reported modes of failure and adverse patient events, respectively, categorized by each FFR coronary guidewire. Percentages represent the proportion of total submitted MAUDE reports and do not reflect the incidence rates. Guidewire tip fracture occurred in 174 (35.8%) cases and was the most commonly reported mode of failure. Guidewire kinking was reported in 152 (31.3%) cases, communication failure in 141 (29.0%) cases, and shaft fracture in 67 (13.8%) cases. In total, 133 (27.4%) device failures resulted in adverse patient events. The most common adverse patient events were a retained guidewire tip, in 71 (53.4%) cases, followed by freshly deployed stent dislodgment in 26 (19.6%) cases and coronary artery dissection in 23 (17.3%) cases. Seven patient deaths were reported. The device-related adverse events were most commonly reported during physiologic evaluation of the left anterior descending (LAD) artery, accounting for 54.8% of the reported adverse events. The relative involvement of other target coronary arteries is demonstrated in Figure 1.

DISCUSSION

This study demonstrates the modes of failure of commonly used FFR guidewires and highlights the potential for adverse patient outcomes. Two general categories of guidewire failure can occur: structural failure and errors in signal communication. The most common structural failures reported in this study were distal tip fractures (35.8%), kinking (31.3%), peeled coating (18.3%), and shaft fractures (13.8%). A majority of devices in this study failed from more than one of the above mechanisms. Most structural failures were attributed to operator handling issues, defined as having occurred at any point after the device was removed from packaging. Structural failures add complexity for the operator, as demonstrated by 23% of reports noting the inability to advance the guidewire. Structural failures are also directly associated with patient harm: 53% of adverse patient events were related to fractured guidewire tips

Table 1 Summary of device modes of failure for fractional flow reserve coronary guidewires

Device mode of failure	Verrata™ (Philips), *n* = 199	Comet™ (Boston Scientific), *n* = 180	PressureWire™ X (Abbott), *n* = 107	Total, *n* = 486
Guidewire distal tip fracture	55 (27.6)	68 (37.8)	51 (47.7)	174 (35.8)
Guidewire kinking	37 (18.6)	103 (57.2)	12 (11.2)	152 (31.3)
Communication failure	64 (32.2)	59 (32.8)	18 (16.8)	141 (29.0)
Failure to advance guidewire	62 (31.2)	36 (20.0)	14 (13.1)	112 (23.0)
Peeled guidewire coating	6 (3.0)	83 (46.1)	0 (0)	89 (18.3)
Guidewire shaft fracture	25 (12.6)	22 (12.2)	10 (9.3)	67 (13.8)

Percentages represent proportion of reported events and do not reflect the incidence rates. Results reported as *n* (%).

Table 2 Summary of patient adverse events for fractional flow reserve coronary guidewires

Adverse patient events	Verrata™ (Philips), *n* = 58	Comet™ (Boston Scientific), *n* = 29	PressureWire™ X (Abbott), *n* = 46	Total, *n* = 133
Retained guidewire tip	27 (46.6)	22 (75.9)	22 (47.8)	71 (53.4)
Stent dislodgement	18 (31.0)	0 (0)	8 (17.4)	26 (19.6)
Vessel dissection	8 (13.0)	4 (13.8)	11 (23.9)	23 (17.3)
Death	2 (3.4)	2 (6.9)	3 (6.5)	7 (5.3)
Vessel perforation	3 (5.2)	1 (3.5)	2 (4.4)	6 (4.5)

Percentages represent proportion of reported events and do not reflect the incidence rates. Results reported as *n* (%).

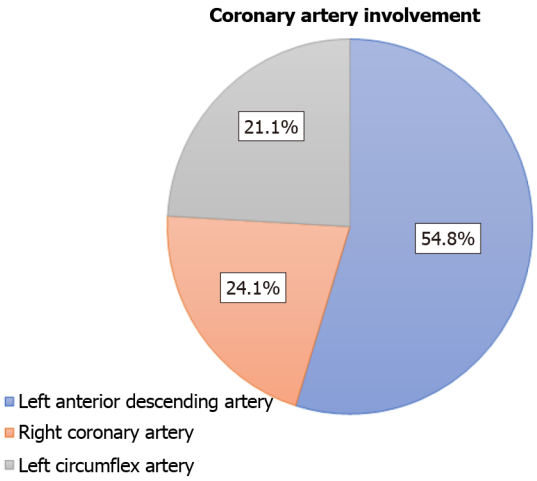

Figure 1 Adverse events stratified by target vessels for fractional flow reserve coronary guidewires.

that remained in the coronary arteries. Retained guidewire fragments increase the risk of dissection, embolization, and thrombus formation and necessitate further interventions[9]. All options, including percutaneous retrieval with a snare, surgical retrieval combined with coronary bypass, or stenting with antiplatelet therapy, increase the risk of further procedural complications and morbidity. Given the high incidence of guidewire fractures, operators should assess the integrity of the device upon removal and ensure that there are no retained pieces in the patient.

The other category of guidewire failure is an error in signal communication, which contributed to 29% of guidewire failures in this study. Pressure sensors at the tip of FFR guidewires transmit data to an external hub that processes information for clinician interpretation. In all three FFR guidewires assessed in this study, commu-

nication between the tip and hub occurs *via* internal cables threaded through the shaft of the guidewire. Errors in signal communication can manifest as the inability to zero the sensor, significant drift, or no signal detected by the hub. The currently available pressure wire sensors are either piezo-electric or optical; these pressure wires differ from routine workhorse wire, as they require integration of thin wires or optical fibers that transmit the pressure signals[10]. While the exact etiologies of communication errors of FFR guidewires were not captured in our data, they can occur after any structural failure that causes sensor or cable damage, or from manufacturing defects. Communication errors are important to detect, as they can result in inaccurate measurements, prolonged procedures, and the need for additional instrumentation.

FFR guidewires can cause patient adverse events. This study demonstrates that vessel dissection, vessel perforation, and stent dislodgement can occur with FFR guidewire use. These are clinically significant complications that must be recognized early and managed carefully to avoid further patient harm. The age of dislodged stents was not documented in the reports; however, operators should exercise caution when advancing or withdrawing an FFR guidewire across any freshly deployed stents. Seven deaths were reported among the cases reviewed. While this is noteworthy, there is not enough information to link the use of FFR guidewires with these deaths.

A majority of all reported events (54.8%) occurred in the LAD, followed by 24.1% in the right coronary artery and 21.1% in the left circumflex artery. A higher rate of reported failures in the LAD may be attributed to generally higher rates of FFR procedures performed in this vessel; however, this information was not captured in our data. Additionally, coronary characteristics such as tortuosity, calcification, and disease severity can also impact individual coronary outcomes. Without this information, the clinical significance of higher reported failures in the LAD is uncertain. Further studies that include data on coronary characteristics and operator technique would be useful to better determine whether FFR guidewires have higher failure rates in any one coronary artery.

Limitations

The MAUDE database has several inherent limitations that impact the interpretation of our study. Notably, only cases with adverse events are reported in the database, and reporting is partially voluntary. Successful cases are not reported, and there is no information on the overall frequency of the device use. Without this information, we cannot derive the incidence of failure rates associated with the use of these guidewires or compare outcomes among different devices. Adverse events may be reported both by users and manufacturers, leading to duplicate reports and difficulty in discriminating. Another notable limitation of the database is that data are provided in a non-standardized narrative form. Not all failed devices were returned to the manufacturer for standard inspections. Without standardized information on the clinical context of failure events, these data cannot be used to imply causality or comparison between procedures or devices.

CONCLUSION

The landmark clinical trials that support the routine frontline use of FFR did not specifically address adverse events related to the use of FFR guidewires. Consequently, the present study is important in understanding the common pitfalls of this widely used procedure. Our analysis demonstrates that real-world use of FFR is associated with complications and adverse patient outcomes. Knowledge of the methods of FFR guidewire failure is critical for operators to develop situational awareness, anticipate difficult situations, assess for common complications, and mitigate adverse patient events. Interpretation of MAUDE data also provides critical feedback to manufacturers and allows for collaboration among clinicians, device manufacturers, and regulators to improve devices and patient outcomes.

ARTICLE HIGHLIGHTS

Research background

Fractional flow reserve (FFR) measurement is an essential tool in the cardiac catheterization laboratory to assess the functional significance of coronary artery lesions. Robust real-world data on the commonly reported complications and modes of failure

associated with the FFR guidewires are scarce.

Research motivation

The landmark clinical trials that support routine physiologic lesion assessment with FFR did not specifically address adverse events associated with the use of FFR guidewires. Accordingly, this provided us the impetus to explore common shortcomings with one of the most common applied technology in the cardiac catheterization laboratory. With broadened global utilization of the FFR and newer iterations, standard reporting of adverse events and failure modes may improve patient selection, operator expertise and device technology.

Research objectives

The objective of our study was to investigate the most commonly reported adverse events and failure modes associated with commonly used FFR guidewires by analyzing the post-marketing surveillance data from the United States Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database.

Research methods

We queried the MAUDE database from January 2010 through April 2020 for 3 FFR guidewires [PressureWire™ X (Abbott), Comet™ (Boston Scientific), and Verrata™ (Philips)] by searching for the following events: "Injury", "malfunction", "death", and "other". The search yielded 544 reports. After excluding incomplete and duplicate reports, 486 reports were included in the final analysis.

Research results

The most commonly reported mode of failure was guidewire tip fracture described in 174 (35.8%) cases followed by guidewire kinking (n = 152, 31.3%), communication failure (n = 141, 29.0%), and shaft fracture (n = 67, 13.8%). One hundred thirty-three (27.4%) device failures caused patient adverse events. The most commonly reported adverse event was retained guidewire tip described in 71 (53.4%) cases, followed by freshly deployed stent dislodgment (n = 26, 19.6%) and coronary artery dissection (n = 23, 17.3%). Seven deaths were reported.

Research conclusions

FFR guidewire failures can occur because of myriad mechanisms and cause patient adverse events. Understanding the methods of FFR guidewire failure is critical for interventionalists to develop operational awareness, forebode challenging situations, evaluate common complications, and assuage adverse patient events. The MAUDE database serves as an important pulpit for improved collaboration among physicians, device manufacturers, and regulators to improve device performance and optimize patient outcomes.

Research perspectives

Intermediate coronary lesions are commonly encountered during cardiac catheterization and present a diagnostic dilemma. Physiologic testing using a pressure wire-based system is appropriate for these lesions. The introduction of newer nonhyperemic pressure-based indices of stenosis severity such as instant wave-Free Ratio (iFR) and coregistered iFR pressure mapping may augur a paradigm shift for functional lesion assessment. It is pivotal for interventionalists to familiarize themselves with the common pitfalls associated not only with the standard FFR system but also with the newer iterations.

REFERENCES

1 **Tonino PA**, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360**: 213-224 [PMID: 19144937 DOI: 10.1056/NEJMoa0807611]

2 **De Bruyne B**, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012; **367**: 991-1001 [PMID: 22924638 DOI: 10.1056/NEJMoa1205361]

3 **Li J**, Elrashidi MY, Flammer AJ, Lennon RJ, Bell MR, Holmes DR, Bresnahan JF, Rihal CS, Lerman LO, Lerman A. Long-term outcomes of fractional flow reserve-guided vs. angiography-guided percutaneous coronary intervention in contemporary practice. *Eur Heart J* 2013; **34**: 1375-1383 [PMID: 23344979 DOI: 10.1093/eurheartj/eht005]

4 **Smits PC**, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angerås O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med* 2017; **376**: 1234-1244 [PMID: 28317428 DOI: 10.1056/NEJMoa1701067]

5 **Ahn JM**, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, Kim JH, Chae IH, Yoon JH, Her SH, Seung KB, Chung WY, Yoo SY, Lee JB, Choi SW, Park K, Hong TJ, Lee SY, Han M, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park SJ; IRIS-FFR Investigators†. Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease: Data From a Prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation* 2017; **135**: 2241-2251 [PMID: 28356440 DOI: 10.1161/CIRCULATIONAHA.116.024433]

6 **Bech GJ**, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation* 2001; **103**: 2928-2934 [PMID: 11413082 DOI: 10.1161/01.cir.103.24.2928]

7 **FDA**. MAUDE database. [cited 10 January 2021]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm

8 **Khalid N**, Javed H, Rogers T, Hashim H, Shlofmitz E, Wermers JP, Chen Y, Musallam A, Khan JM, Torguson R, Bernardo NL, Waksman R. Adverse events with orbital atherectomy: an analytic review of the MAUDE database. *EuroIntervention* 2020; **16**: e325-e327 [PMID: 31422928 DOI: 10.4244/EIJ-D-19-00295]

9 **Al-Moghairi AM**, Al-Amri HS. Management of retained intervention guide-wire: a literature review. *Curr Cardiol Rev* 2013; **9**: 260-266 [PMID: 23116055 DOI: 10.2174/1573403x11309030010]

10 **Kern MJ**. Comparing FFR tools: New wires and a pressure microcatheter. *Cath Lab Digest* 2016; **24**: 5 [cited 10 January 2021]. Available from: https://www.cathlabdigest.com/article/Comparing-FFR-Tools-New-Wires-Pressure-Microcatheter

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CASE REPORT

Sliding with the sines − fatal hyperkalemia: A case report

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Abstract

BACKGROUND

Classic electrocardiographic manifestations of hyperkalemia starting with peaked symmetrical T-waves are widely recognized in daily clinical practice but little evidence is documented how quickly it can evolve in real-time.

CASE SUMMARY

An elderly diabetic and hypertensive male presented with acute renal failure and rhabdomyolysis. He experienced cardiac arrest with moderate hyperkalemia despite medical treatment and hemodialysis. Telemetry changes were retrospectively studied and found to have significant rhythm changes that occurred just less than 10 minutes prior to the cardiac arrest.

CONCLUSION

In hyperkalemia, telemetry rhythm can change instantaneously in a significant way. Rapidly rising potassium could be life threatening and may require more than medical treatment.

Key Words: Electrocardiogram; Arrhythmia; Hyperkalemia; Electrolyte imbalance; Cardiac arrest; Case report

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Specialty type: Cardiac and cardiovascular systems

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Core Tip: We present a case of acute rhabdomyolysis and renal failure where the patient experienced cardiac arrest with moderate hyperkalemia despite medical treatment and hemodialysis. This case illustrates how quickly the telemetry rhythm can change in a short period of time (9 min).

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INTRODUCTION

In rhabdomyolysis where massive tissue destruction could produce significant hyperkalemia, potassium levels are closely monitored and electrocardiographic changes would trigger immediate action even before the laboratory confirmation[1]. Rapidly rising potassium levels are more likely to present with cardiac rhythm changes but the pace of those changes is rarely reported in the literature.

CASE PRESENTATION

Chief complaints

A 76-year old male presented to emergency department with generalized weakness and encephalopathy.

History of present illness

His generalized weakness gradually started over a few months and recently he was getting weaker and also confused for a few days.

History of past illness

His past medical history was significant for hypertension, diabetes and old ischemic stroke with residual right sided weakness.

Personal and family history

He was a non-smoker and non-drinker, and he lived in a house.

Physical examination

He was somnolent but arousable. He had dry mucous membranes and mild right hemiparesis which was his baseline.

Laboratory examinations

Laboratory results were significant for serum potassium 6.7 mmol/L, serum creatinine 10.76 mg/dL, and serum creatine kinase 40673 U/L.

Imaging examinations

Computed tomography of the brain without contrast showed no acute changes. Electrocardiography (Figure 1) did not show any classic changes associated with hyperkalemia.

FINAL DIAGNOSIS

Patient was diagnosed as hyperkalemia with acute renal failure possibly due to rhabdomyolysis.

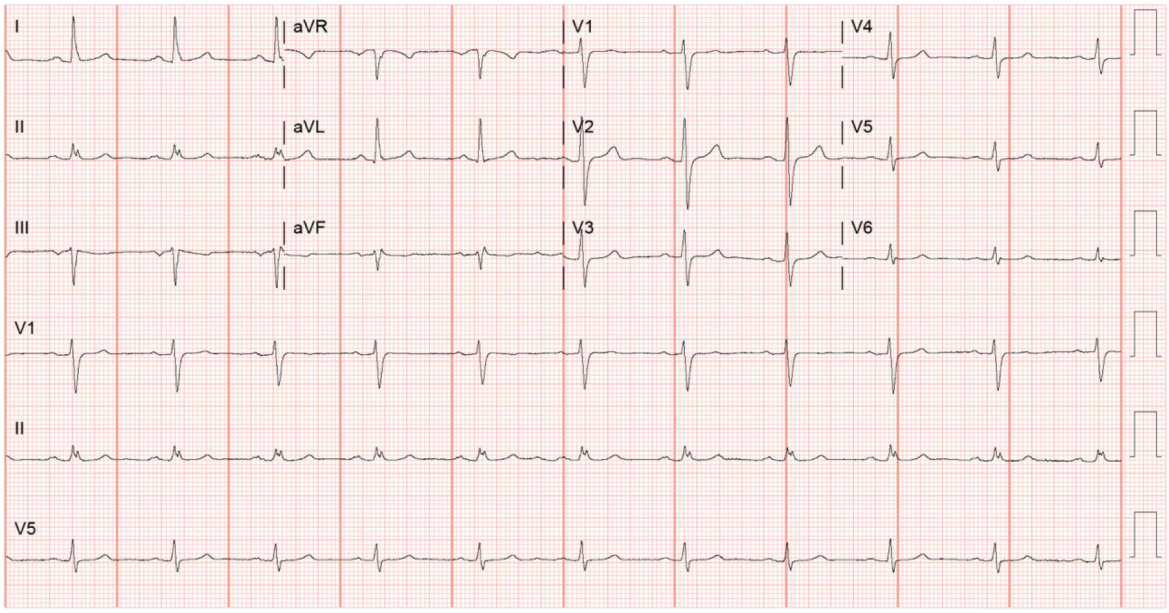

Figure 1 Electrocardiogram on admission. Twelve lead electrocardiogram without any hyperkalemic manifestations.

TREATMENT

Initial treatment

The patient received intravenous calcium gluconate, furosemide, dextrose, insulin, and sodium bicarbonate, and albuterol by nebulizer. Emergent hemodialysis was arranged and performed in the intensive care unit uneventfully, resulting in potassium decreasing to 4.0 mmol/L. CK also trended down to 37586 U/L the following day. Further daily hemodialysis sessions were provided for oliguria.

Progress during hospital stay

On the third hospital day, CK increased to 206297 U/L but the potassium level remained stable at 4.7 mmol/L. Six hours after the hemodialysis session of the day, the repeat potassium was 6.9 mmol/L. The telemetry rhythm strip (Figure 2A) showed no hyperkalemic manifestations. The patient was again administered calcium gluconate, dextrose, insulin and sodium polystyrene. Despite these efforts, two hours later the patient suffered a cardiac arrest with pulseless electrical activity. The patient was resuscitated and the repeat potassium level which was taken just before the cardiac arrest was 7.4 mmol/L. On review of the telemetry, significant changes associated with hyperkalemia were noted just 9 min before the cardiac arrest (Figure 2B-G). The potassium levels, creatine kinase levels and the treatments patient received are summarized in Table 1.

Electrocardiography following the resuscitation still showed the typical sine waves of hyperkalemia (Figure 3) with a repeat potassium level of 7.9 mmol/L.

OUTCOME AND FOLLOW-UP

The patient was intubated and continuous renal replacement therapy (CRRT) was initiated. Despite these interventions, the hyperkalemia and metabolic acidosis continued to worsen and he eventually expired from ventricular fibrillation refractory to multiple defibrillation attempts. Repeat 12 Lead electrocardiography before the last cardiac arrest showed more pronounced sine waves from hyperkalemia with corresponding potassium level of 7.1 mmol/L (Figure 4).

DISCUSSION

Traditionally, the electrocardiographic manifestations of hyperkalemia are sufficient to make emergent interventions indicated even prior to laboratory confirmation[1-4].

Table 1 Potassium levels, creatine kinase levels and treatments received

Timeline	Potassium levels (mmol/L)	CK levels (U/L)	Treatments received
Day 0	6.7	40673	IV calcium gluconate 1 g once
			Albuterol nebulization 10 mg once
			IV furosemide 40 mg once
			IV dextrose 50% 50 g once
			IV regular insulin 5 units once
			IV sodium bicarbonate 50 mEq once
			IV sodium bicarbonate 8.4% continuous infusion was started
Day 0 (2 h)	6.2	-	Hemodialysis initiated
Day 1	4.0, 4.2	37586	Daily intermittent hemodialysis continued
Day 2	4.2, 4.7	206297	Daily intermittent hemodialysis continued
Day 3, 4 AM	6.9	198294	IV calcium gluconate 1 g once
			IV dextrose 50% 25 g once
			IV regular insulin 5 units once
			PO sodium polystyrene 30 g once
Day 3, 6 AM	7.4	-	Cardiac arrest before result was out
			IV epinephrine 1mg × 3
			IV calcium chloride 1g × 2
			IV sodium bicarbonate 50 mEq × 3
			IV dextrose 50% 25 g once
			IV regular insulin 10 units once
			CRRT initiated after resuscitation

CK: Creatine kinase; IV: Intravenous; CRRT: Continuous renal replacement therapy.

Continuous electrocardiographic telemetry is typically sufficient for monitoring cardiac rhythm. However, this patient did not demonstrate the classic peaked, symmetrical T waves on telemetry despite significant hyperkalemia. The amplitudes of T waves in lead II (Figure 2A) were less than half the height of QRS complexes and it had similar morphology on telemetry for the first three days. If a 12-lead electrocardiogram had been recorded prior to cardiac arrest, it might have shown some peaked T waves in the other non-monitoring leads.

Hyperkalemia is also associated with atrioventricular conduction disturbances[5,6] and we observed the left bundle branch block morphology just 3 minutes prior to cardiac arrest (Figure 2F).

Hyperkalemia is generally classified as moderate for the level between 6.5 mmol/L to 8.0 mmol/L and severe for the level above 8.0 mmol/L. Rapidly progressive hyperkalemia is more likely to present with cardiac rhythm changes[7]. This patient only experienced moderate hyperkalemia but suffered cardiac arrest likely because of a rapidly rising potassium. Moreover, it is also notable that the sine waves were more dramatic with potassium level of 7.1 mmol/L (Figure 4) when he eventually demised than with potassium level of 7.9 mmol/L (Figure 3) from his first cardiac arrest.

Intravenous regular insulin 5 units with dextrose can reduce the potassium level by 0.54-1.04 mmol/L at one hour[3] and a systematic review showed regular insulin 10 units could reduce the potassium by average of 0.78 ± 0.25 mmol/L in an hour[8]. The beta-2 agonist, salbutamol 10 mg nebulization, is also another potent agent that can reduce the potassium by 0.62 ± 0.09 mmol/L after 120 min of administration[9] but with the possible side effect of severe tachycardia and is limited in patients with heart failure or coronary artery disease. However, all of these treatments influence the potassium level by intracellular transfer without actually reducing total body potassium. Intravenous loop diuretics are largely ineffective in relieving hyperkalemia in oliguric patients. Oral agents that increase gastrointestinal potassium excretion, in-

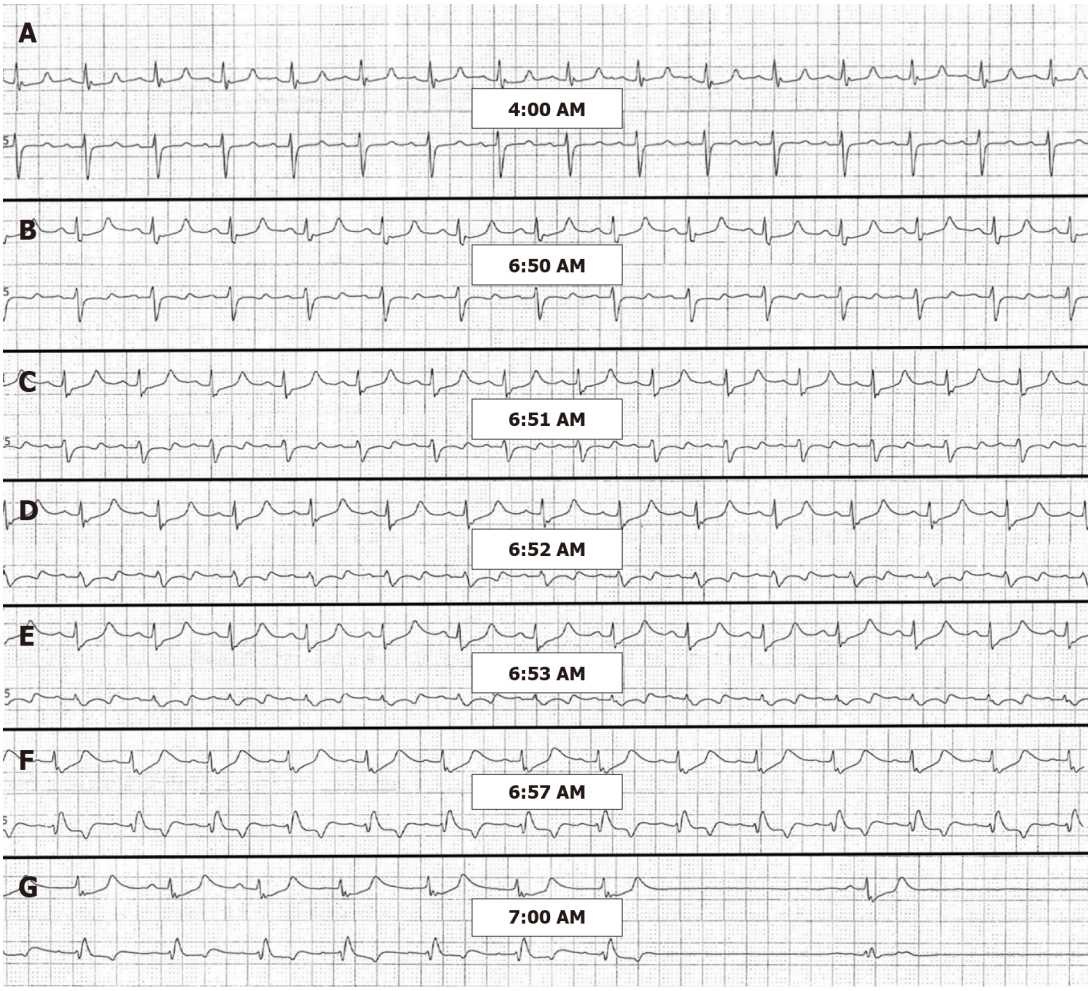

Figure 2 Telemetry strips (rate 25 mm/s). The upper rhythm is lead II and lower rhythm is lead V5. A: At 4:00 AM. when potassium level started rising. T wave amplitude measuring 2-2.5 mm in lead II. PR interval 0.16-0.20 s. QRS 0.1-0.12 s. QT prolongation from hypocalcemia; B: At 6:50 AM. T waves in lead II seems to be slightly taller, maybe about 0.5 mm (half small square) than Figure 2. Similar measurements for PR interval and QRS. Non-specific T waves changes in V5; C: At 6:51 AM. ST and T waves changes more pronounced in V5. ST depression by 0.5-1 mm in V5. QRS slightly widened beyond 0.12 s in both lead II and V5; D: At 6:52 AM. QRS widened more with further ST depression. Transitioning into sine wave, more obvious in lead V5; E: At 6:53 AM. Complete loss of original QRS morphology in lead V5 and transforming into sine waves. P waves still visible with PR interval 0.16 s in lead II; F: At 6:57 AM. QRS morphology in lead II deformed with marked ST depression, transitioning into sine waves. QRS in V5 is showing left bundle branch block morphology at the similar heart rate; G: At 7:00 AM. Sinus pause over 2 s and pulseless electrical activity cardiac arrest.

cluding sodium polystyrene, patiromer and sodium zirconium, have a slow onset of action. Sodium zirconium could potentially have incremental effect in treatment of hyperkalemia with potassium reduction of 0.41 mmol/L as early as 4 h after administration[10].

In addition to the above medical intervention, it is warranted to initiate renal replacement therapy in the setting of hyperkalemic emergency with rhabdomyolysis. Our patient, however, was already on daily hemodialysis with potassium level under control for two days. Nevertheless, his rebound hyperkalemia should have been managed aggressively with immediate hemodialysis rather than medical management and wait for another two hours for response.

After the medical management, potassium level should be repeated one to two hour after treatment. In our patient, it was scheduled to be repeated two hour after treatment which was reasonable. More aggressive approach to repeat the potassium at one hour or earlier might have shown worsening hyperkalemia which would have prompted more intervention.

Hemodialysis is the mainstay for the emergency management of hyperkalemia but daily intermittent hemodialysis may be inadequate as shown in this case. There is not enough evidence to suggest that continuous renal replacement therapy (CRRT) is superior to intermittent hemodialysis in management of rhabdomyolysis but CRRT has been found to remove myoglobin more effectively and is more practical in the setting of hypotension[11]. Early initiation of continuous veno-venous hemodialysis

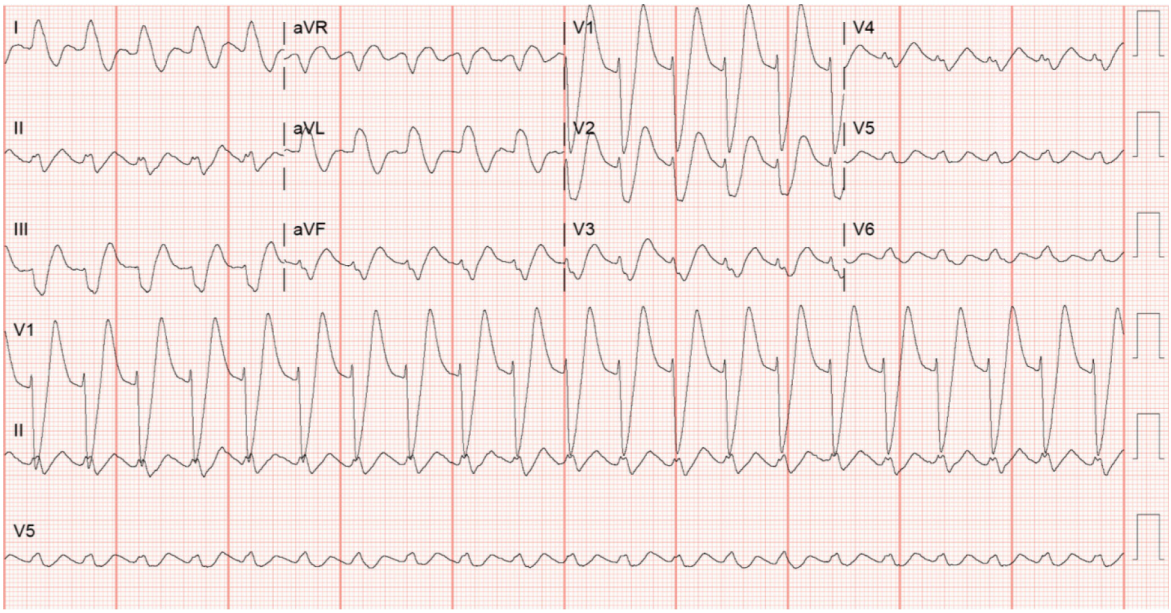

Figure 3 Electrocardiogram after resuscitation. Twelve lead electrocardiogram showing classic description of hyperkalemic manifestations, peaked T waves in V1, V2, widened QRS complexes, P waves not seen and sine waves in V4, V5, V6.

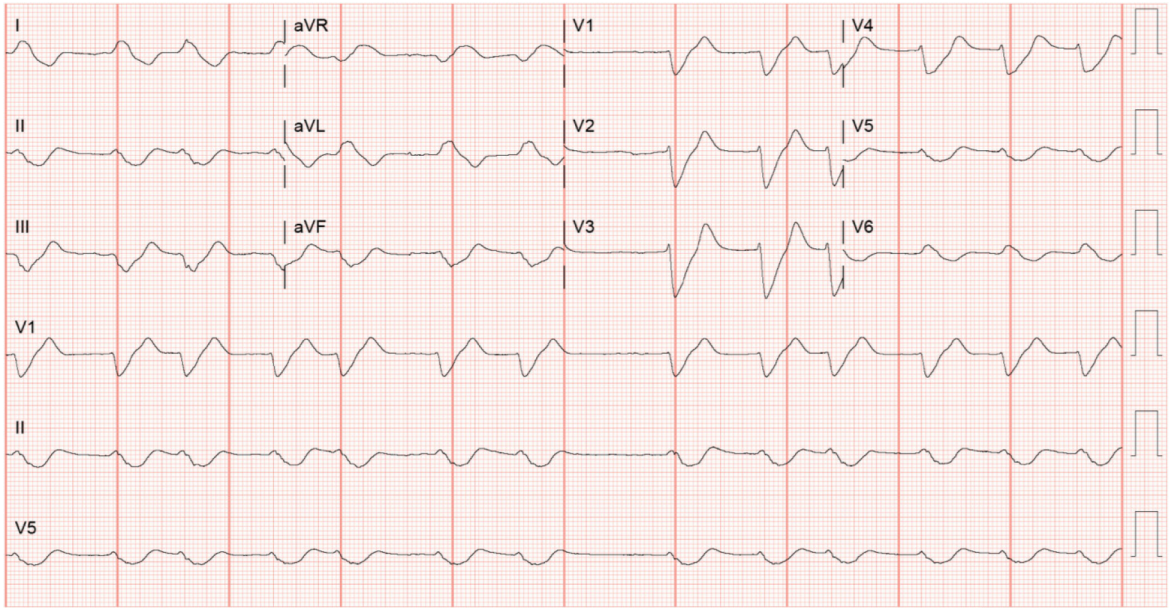

Figure 4 Electrocardiogram showing typical sine waves of hyperkalemia. Findings include loss of P waves, severe widening of QRS complexes resulting in fusion of QRS complexes and T waves, decrease in amplitudes of QRS complexes and T waves.

along with aggressive potassium monitoring may be necessary for severe cases of rhabdomyolysis.

CONCLUSION

Frequent 12-lead electrocardiograms in addition to the close attention to continuous telemetry monitoring are necessary for patient with hyperkalemia from rhabdomyolysis. Despite appropriate support with daily hemodialysis, this case demonstrates how rapidly acute hyperkalemia can worsen and cause an evolution of the cardiac rhythm. Timely intervention and reassessment for clinical response are critical in the management of hyperkalemia.

REFERENCES

1 **Merrill JP**, Levine HD, Somerville W, Smith S. Clinical recognition and treatment of acute potassium intoxication. *Ann Intern Med* 1950; **33**: 797-830 [PMID: 14771753 DOI: 10.7326/0003-4819-33-4-797]

2 **Rossignol P**, Legrand M, Kosiborod M, Hollenberg SM, Peacock WF, Emmett M, Epstein M, Kovesdy CP, Yilmaz MB, Stough WG, Gayat E, Pitt B, Zannad F, Mebazaa A. Emergency management of severe hyperkalemia: Guideline for best practice and opportunities for the future. *Pharmacol Res* 2016; **113**: 585-591 [PMID: 27693804 DOI: 10.1016/j.phrs.2016.09.039]

3 **Dépret F**, Peacock WF, Liu KD, Rafique Z, Rossignol P, Legrand M. Management of hyperkalemia in the acutely ill patient. *Ann Intensive Care* 2019; **9**: 32 [PMID: 30820692 DOI: 10.1186/s13613-019-0509-8]

4 **Coutrot M**, Dépret F, Legrand M. Tailoring treatment of hyperkalemia. *Nephrol Dial Transplant* 2019; **34**: iii62-iii68 [PMID: 31800081 DOI: 10.1093/ndt/gfz220]

5 **Davidson S**, Surawicz B. Ectopic beats and atrioventricular conduction disturbances. In patients with hypopotassemia. *Arch Intern Med* 1967; **120**: 280-285 [PMID: 6038287 DOI: 10.1001/archinte.120.3.280]

6 **Bashour T**, Hsu I, Gorfinkel HJ, Wickramesekaran R, Rios JC. Atrioventricular and intraventricular conduction in hyperkalemia. *Am J Cardiol* 1975; **35**: 199-203 [PMID: 1119378 DOI: 10.1016/0002-9149(75)90001-6]

7 **Surawicz B**, Chlebus H, Mazzoleni A. Hemodynamic and electrocardiographic effects of hyperpotassemia. Differences in response to slow and rapid increases in concentration of plasma K. *Am Heart J* 1967; **73**: 647-664 [PMID: 6024862 DOI: 10.1016/0002-8703(67)90174-3]

8 **Harel Z**, Kamel KS. Optimal Dose and Method of Administration of Intravenous Insulin in the Management of Emergency Hyperkalemia: A Systematic Review. *PLoS One* 2016; **11**: e0154963 [PMID: 27148740 DOI: 10.1371/journal.pone.0154963]

9 **Allon M**, Dunlay R, Copkney C. Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; **110**: 426-429 [PMID: 2919849 DOI: 10.7326/0003-4819-110-6-426]

10 **Peacock WF**, Rafique Z, Vishnevskiy K, Michelson E, Vishneva E, Zvereva T, Nahra R, Li D, Miller J. Emergency Potassium Normalization Treatment Including Sodium Zirconium Cyclosilicate: A Phase II, Randomized, Double-blind, Placebo-controlled Study (ENERGIZE). *Acad Emerg Med* 2020; **27**: 475-486 [PMID: 32149451 DOI: 10.1111/acem.13954]

11 **Zimmerman JL**, Shen MC. Rhabdomyolysis. *Chest* 2013; **144**: 1058-1065 [PMID: 24008958 DOI: 10.1378/chest.12-2016]

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