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DIASTOLIC LEFT VENTRICULAR DYSFUNCTION AND HEART FAILURE WITH PRESERVED EJECTION FRACTION IN ELDERLY

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Rezumat. Disfuncția diastolică a ventriculului stâng și insuficiența cardiacă cu fracția de ejecție păstrată la vârstnici

Insuficiența cardiacă cu fracția de ejecție păstrată este denumită „insuficiență cardiacă diastolică" și este mai răspândită în rândul vârstnicilor, mai frecventă la femei. Prognosticul pacienților cu insuficiență cardiacă congestivă din cauza disfuncției diastolice este mai favorabil, decât la pacienții cu disfuncție sistolică, însă morbiditatea rămâne ridicată cu eșecuri în tratament și respitalizări frecvente. Astfel, diagnosticul de insuficiență cardiacă cu fracție de ejecție păstrată (ICpEF) la vârstnici (≥ 85 de ani) este unul complicat și reprezintă o provocare la pacienții euvolemici cu dispnee, din motivul lipsei criteriilor bazate pe dovezi. Disfuncția diastolică a VS este un parametru frecvent (58%), dar fără nicio specificitate pentru ICpEF, abordarea acesteia ar trebui să fie concentrată pe etiologia bolii de bază, precum și pe tulburarea funcției diastolice ventriculare stângi.

Cuvinte cheie: Insuficiență cardiacă congestivă, funcție sistolică a ventriculului stâng, funcție diastolică.

Summary

Congestive heart failure with preserved left ventricular systolic function is termed "diastolic heart failure" and is more prevalent in the older population, may account for one half of the older population with congestive heart failure, and may be more common in women than men. The prognosis of patients with congestive heart failure due to diastolic dysfunction is less ominous than in patients with systolic dysfunction yet the morbidity can be high with frequent treatment failures and hospital readmissions.

Conclusions: Thus, the diagnosis of heart failure with preserved ejection fraction (HFpEF) on elderly (≥ 85 years old) patients is cumbersome. Diagnosis of heart failure with preserved ejection fraction is challenging in euvolemic patients with dyspnea, and no evidence-based criteria are available. Diastolic LV dysfunction is very common parameter (58 %), but without any specificity for HFpEF, its treatments should be focused on the underlying disease etiology as well as on the derangement in left ventricular diastolic function.

Key words: Congestive heart failure, preserved left ventricular systolic function, diastolic function.

Резюме. Диастолическая дисфункция левого желудочка и сердечная недостаточность с сохранной фракцией выброса у пожилых.

Сердечная недостаточность с сохранной фракцией выброса, так называемая «диастолическая сердечная недостаточность», наиболее распространена среди людей пожилого возраста, чаще среди женщин. Прогноз пациентов с застойной сердечной недостаточностью вызванной диастолической дисфункцией является более благоприятным, чем у пациентов с систолической дисфункцией, однако заболеваемость остаётся высокой, с неудачами в лечении и частыми повторными госпитализациями. Таким образом, диагностика сердечной недостаточности с сохранной фракцией выброса у пожилых (≥ 85 лет) является сложной и представляет собой проблему у эуволемичных пациентов с одышкой из-за отсутствия критериев основанных на доказательной базе. Диастолическая дисфункция ЛЖ является частым (58%), но неспецифичным параметром для сердечной недостаточности с сохранной фракцией выброса, подход к ней должен быть ориентирован на этиологию основного заболевания, а также на нарушение диастолической функции ЛЖ.

Ключевые слова: Застойная сердечная недостаточность, систолическая функция левого желудочка, диастолическая функция.

Introduction

The clinical syndrome of congestive heart failure (CHF) is traditionally associated with inadequate myocardial contraction, volume overload and impaired ventricular filling. Accordingly, CHF therapy has been directed toward augmentation of contractile function with positive inotropic agents or alteration in preload and afterload with vasodilators and diuretics [1].

Recently it has been recognized that left ventricular (LV) diastolic impairment may occur without systolic dysfunction and may develop coincident with or before abnormalities of systolic function. Diastolic dysfunction is increasingly recognized as a cause of CHF. Meta-analyses of earlier studies of this disorder suggest that 40%–50% of patients with the congestive heart failure syndrome have preserved left ventricular systolic function, with current estimates ranging up to 74%. Among patients ≥ 65 years of age with congestive heart failure, 55% of all subjects and 67% of women had normal systolic function.

Diastolic function is defined as it describes the filling of the heart during diastole. The left ventricle is filled with blood initially by a pressure gradient between the left atrium (LA) and the left ventricle. Especially, ventricles of young healthy individuals also create suction in very early phase of filling due to a rapid expansion of the LV. There is a time between passive and active filling of the left ventricle where only little filling occurs, the so-called diastasis. Therefore diastolic dysfunction is understood as impaired left ventricular relaxation with increased stiffness of the LV and elevated filling pressures. Diastolic LV dysfunction is very common in, but not specific for HFpEF. It often co-exists with or is even caused by other cardiovascular abnormalities.

Cardiovascular changes with Physiologic Aging versus Cardiovascular Disease in the Elderly

Heart Rate

Resting heart rate is not generally affected by aging; however, decreased heart rate in response to exercise and stress (esp. beta-adrenergically mediated) is characteristic of healthy aging. The clinical consequence of this is decreasing in maximal heart rate on treadmill and heart rate response to fever, hypovolemia and postural stress. The response to beta-adrenergic blockade (as well as stimulation) is also reduced with healthy aging. Daytime bradycardia with heart rates < 40 bpm and sinus pauses of over 3 seconds are not seen with healthy aging.

Atrioventricular Conduction

Time for conduction through the atrioventricular (AV) node is increased with healthy aging. Therefore, the P-R interval on the ECG increases with age and the upper limit of normal for people > 65 is 210-220 milliseconds (not 200 ms). Second and third degree AV block are not normal consequences of aging. Right bundle branch block is seen more frequently in older compared to younger populations but has not been shown to identify increased risk for further conduction abnormalities. A gradual leftward shift of the QRS axis is observed with aging and left anterior hemiblock is seen with increasing frequency in older populations. Isolated left anterior hemiblock is not an independent predictor of cardiovascular morbidity or mortality in otherwise healthy elderly. Combined right bundle branch block and left anterior fascicular block is associated with cardiovascular disease in 75% of older patients and only 25% with this finding have otherwise normal hearts. Left bundle branch block is not associated with normal aging and is associated with cardiovascular disease and risks for cardiac events.

Arrhythmias

Atrial premature contractions increase with age and are frequent in up to 95% of older healthy volunteers at rest and during exercise in the absence of detectable cardiac disease. Atrial fibrillation is usually associated with coronary, hypertensive, valvular, sinus node disease or thyrotoxicosis but may occur in older patients with no other detectable diseases (1/5 of older men and 1/20 of older women with atrial fibrillation). Similarly, isolated and even multiform ventricular ectopy has been reported in up to 80 % of older men and women without detectable cardiac disease. The prevalence of chronic atrial fibrillation rises from < 1 per 1000 people at 25 - 35 years of age to about 40 per 100 at ages 80-90 (Framingham data, Baltimore Longitudinal Study, Cardiovascular Health Study). Chronic atrial fibrillation has been shown to be an important risk factor for cerebrovascular accidents (strokes) and control of rate is associated with better exercise tolerance [2].

Hypertension

The prevalence of hypertension, especially systolic, increases with aging in men and women. This increase in systolic pressure is thought to be due to thickening of the arterial wall which makes it less distensible and less able to buffer the rise in pressure that occurs with cardiac ejection. These changes result in an elevated systolic blood pressure with a relatively unchanged diastolic blood pressure. A large body of data have now demonstrated that cardiovascular morbidity and mortality increase with increasing [3].

Coronary Artery Disease

It has long been recognized that the prevalence of coronary artery disease rises with increasing age and that multi-vessel disease in older patients with coronary artery disease is more common. The age-related

increase in coronary artery disease occurs in women as well as men but begins at a later age in women. The approach to diagnosis in the elderly is similar to that in the younger patient. The history may be somewhat more difficult to interpret because exercise may be limited by other factors (arthritis, pulmonary disease, etc.) and chest discomfort may be atypical because of the prevalence of diabetes (10% of the elderly) and the greater preponderance of women in the older populations. ECG criteria for the diagnosis of coronary artery disease are also not as reliable in women of any age as in men. Nuclear imaging (usually thallium) with or without pharmacological stress is often used to overcome the limits of ECG interpretation, but again is not as good in women as men (estimated 20% false positives). Because of high prevalence of coronary artery disease in the elderly, the goal of diagnostic testing may be quantifying the amount of ischemia rather than to diagnosing its presence and perfusion, imaging allows localization, quantification and differentiation between infarcted and ischemic myocardium [4, 5, 6]. Pharmacological stress testing combined with echocardiography may also have some advantages in the older patient since it can provide assessment of valvular function, left ventricular function, and the presence and extend of wall motion abnormalities suggestive of ischemia or infarction. Angiography is of value for both assessment and as a prelude to interventions. Slightly greater rate of complications are seen in older patients than in younger (local bleeding, stroke) but remains low. This should be recognized and should not preclude procedures.

Valvular Diseases

The frequency of aortic stenosis increases with age and it is the most clinically significant valvular lesion in the elderly. The most common cause of aortic regurgitation in the elderly is aortic root dilation secondary to the age-related rise in blood pressure and increased peripheral resistance. Mitral regurgitation accounts for 2/3 of mitral valve disease in the elderly [7, 8].

In contrast, the diagnosis of HFpEF is cumbersome, especially in patients presenting in an out-patient clinic with exertional dyspnoea and multiple comorbidities but without obvious physical signs of fluid overload [9, 10, 11]. More specifically, diastolic LV dysfunction is a consequence of impaired LV suction due to impaired systolic relaxation and reduced diastolic compliance. Causes of impaired relaxation are related to factors intrinsic and extrinsic to cardiomyocytes. The intrinsic factors include impaired inactivation processes (disturbed intracellular calcium homeostasis, myofilament function and cell energetics), whereas the extrinsic factors include pressure volume overload, ventricular dyssynchrony and abnormal activity of soluble cardio-active factors (angiotensin, endothelin, nitric oxide). Decreased compliance of the LV is due to extracellular matrix or cytoskeletal abnormalities. Interestingly, none of the above mechanisms of diastolic dysfunction seems to be specific for HFpEF or HFrEF (Heart Failure with reduced Ejection Fraction).

Pulmonary pressures increase with ageing and are correlated with systemic vascular stiffening—both common risk factors for HFpEF. Pulmonary hypertension in HFpEF appears to be due to both elevated left heart pressures and high pulmonary vascular resistance, which may develop in response to the former. In early-stage of HFpEF, pulmonary vasodilation with exercise is preserved and exertional pulmonary hypertension is passive and secondary primarily to high left heart pressures. It may represent a novel therapeutic target in HFpEF, although unbalanced pulmonary arterial vasodilation in such patients may lead to pathologic elevations in left heart pressures or even frank pulmonary oedema, and further study is required to define the possible role of pulmonary vasodilators in HFpEF [12, 13, 14].

Four sets of guidelines for the diagnosis of HFpEF have so far been published. They all require the simultaneous and obligatory presence of signs and/or symptoms of HF, evidence of normal systolic LV function and diastolic LV dysfunction or of surrogate markers of diastolic dysfunction such as LV hypertrophy, LA enlargement, atrial fibrillation, or elevated plasma natriuretic peptides (NP) levels [15, 16, 17].

The first set of guidelines was provided by the Working Group on Myocardial Function of the European Society of Cardiology [18].

A second set of guidelines was provided by the NHLBI Framingham Heart Study and combined signs and symptoms of HF, normal LVEF (>50%), and invasive evidence of diastolic LV dysfunction [19].

A third set of guidelines was proposed by Yturralde and Gaasch from the Lahey Clinic [20]. They implement their assessment with a scoring system of major and minor criteria and use LV hypertrophy and LA enlargement as surrogate markers of diastolic LV dysfunction.

Finally, the last set of guidelines was provided by the Heart Failure and Echocardiography Associations of the European Society of Cardiology [21, 22, 23, 24].

In accordance to this last set of guidelines, the diagnosis of HFpEF required of symptoms and/or signs of HF, a preserved EF (defined as LVEF ≥50%), elevated levels of NPs (BNP >35 pg/mL and/or NT-proBNP >125 pg/mL) and objective evidence of other cardiac functional and structural alterations underlying.

Previous studies using pulsed Doppler echocardiography have demonstrated a pattern of abnormal left ventricular relaxation associated with increasing age. Specifically, aging is associated with decreased peak velocity of early diastolic mitral inflow, increased peak velocity of late diastolic inflow, increased isovolumic relaxation time and early diastolic deceleration time. Abnormal relaxation can progress to significantly elevated left atrial pressure – characterized by increased early peak velocity and shortened isovolumic relaxation time and deceleration time – as part of the disease processes. Left ventricular diastolic dysfunction is highly prevalent, occurring in one half to two thirds of elderly patients with congestive heart failure in association with normal systolic function. Left ventricular hypertrophy which is commonly related to systemic arterial hypertension and ischemic heart disease are the two major causes of abnormal left ventricular diastolic function in the elderly. Recently, newer echocardiographic techniques have been described that allow more accurate evaluation of left ventricular diastolic function.

How to establish if diastolic dysfunction is present in a patient with a normal ejection fraction and no known cardiac disease

The echocardiographic evaluation for diastolic dysfunction includes:

- blood flow Doppler measurements of the mitral inflow velocity patterns (E: early diastolic; A: late diastolic), pulmonary vein flow patterns and E/A ratio;
- tissue Doppler (TD) measurements of the left ventricular annular flow E' and E/E' ratio;
- echocardiographic calculation of the left ventricle (LV) mass index and left atrial (LA) volume index.

5 Steps to identify diastolic dysfunction

- Step 1: Left Ventricle Ejection Fraction
- Step 2: Mitral Valve Inflow - E Wave
- Step 3: PW TISSUE
- Step 4: Tricuspid Regurgitation
- Step 5: Left Atrium Size

In the case of a patient with a normal ejection fraction we used the following cut-off values to assess the number of abnormal parameters (Table 1).

• If you have none, or only one abnormal parameter the patient has NORMAL diastolic function

• If you have three or more abnormal parameters, the patient has diastolic dysfunction

• If you have only two abnormal parameters, the patient has indeterminate diastolic dysfunction

Treatment of Left Ventricular diastolic dysfunction

Preserved ejection fraction heart failure is not a single, homogeneous disease but a protean syndrome with complex pathophysiology, dependent on the dominant etiology associated with various comorbidities.

f the elevation of filling pressures in the left ventricle is the common denominator of this syndrome responsible for dyspnea and hydrosaline retention, reflecting the need to control volemia using diuretics, HFpEF is primarily etiological. Thus, there is probably no uniform treatment for HFpEF, as the choices of therapies must be tailored to the etiology and therefore the dominant pathophysiological process. Precise phenotypic analysis, taking into account clinical, etiological and biological factors, echocardiographic parameters, comorbidity, or even the results of myocardial MRI and diphosphonate scans, is therefore necessary in order to achieve a pathophysiological

Table 1

Diagnosing of diastolic dysfunction in patient with normal ejection fraction

PATIENTS WITH NORMAL EF AND NO KNOWN CARDIAC DISEASE	
Parameter	**Abnormal Cut-Off Value**
Average E/e'	> 14
Septal OR Lateral e'	Septal < 7cm/s OR Lateral < 10cm/s
TR Velocity	> 2.8 m/s
LA Volume Index	> 34 mL/m^2

Number of Abnormal Parameters	**Diastolic Function**
1 Abnormal Value	Normal Diastolic Function
2 Abnormal Values	Indeterminate Diastolic Dysfunction
3+ Abnormal Values	Diastolic Dysfunction

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classification of different forms of HFpEF and to propose appropriate treatment.

The main etiopathogenesis are formed by barometric overloads, dominated by hypertensive heart disease, volumetric overload, obesity and kidney failure, myocardial impairment with, on the one hand, cardiomyopathy specific to metabolic syndrome and diabetes and, on the other hand, hypertrophic and restrictive cardiomyopathies, not to mention ischemic heart disease [25,26,27,28]. A new approach used information tools usually dedicated to genotyping. "Phenomapping" has enabled, based on clinical and paraclinical data collected in patients with HFpEF, to individualize 3 large phenotypic groups that are distinguished by their prognosis and could justify attitudes therapeutic scans [29, 30].

The first group probably corresponds to the early forms of the disease, patients being younger, rarely diabetic, with lower levels of natriuretic type B peptides, unaltered kidney function, left ventricular mass, volume of the left atrium, left ventricular filler pressures and lower lung pressure compared to the other two groups. Logically it is the one who has the best prognosis and should respond best to the treatments.

The second group is characterized by a high prevalence of obesity, high blood pressure, diabetes, obstructive sleep apnea, and has the highest hemodynamic heart rate, a chart consistent with the consequences obesity and metabolic syndrome, its prognosis is intermediate.

The third group corresponds to the most advanced forms of the syndrome, patients being older, less often overweight, with higher levels of natriuretic peptides, frequently impaired kidney function, the duration of the RSQ left ventricular mass, left atrium volume, left ventricular filler pressures and higher pulmonary arterial pressure and lower cardiac output. Logically it is the one who has the worst prognosis and should respond poorly to treatments, which may partly explain the failures of therapeutic attempts.

Histopathologic evaluation reveals a maladaptive remodeling of the interstitium associated with aging, resulting in an increase in interstitial collagen content. The interstitium normally plays a crucial role in the generation of early diastolic suction. When there is a significant enough increase in myocardial collagen volume fraction, with its increased viscoelastic burden, this normal early diastolic suction is compromised and diastolic pressures increase. Left ventricular diastolic dysfunction ensues. Neurohumoral abnormalities associated with diastolic dysfunction include activation of the renin-angiotensin-aldosterone system, including increased elaboration of myocardial aldosterone. This excess of aldosterone appears to play a major role in the development of myocardial fibrosis. Recent observations in animal models and humans have demonstrated regression of interstitial collagen volume fraction in response to inhibition of the renin-angiotensin-aldosterone system by angiotensin-converting enzyme inhibitors and aldosterone inhibition with improvement in diastolic function. Therapeutic implications of these observations suggest targeting the maladaptive remodeling of the interstitium via inhibition of the renin-angiotensin-aldosterone system.

Effect of treatment on symptoms in heart failure with preserved ejection fraction.

Treatments for left ventricular diastolic dysfunction should focus on the underlying disease etiology as well as on the derangement in left ventricular diastolic function. Although calcium channel blockers and angiotensin—converting enzyme inhibitors have been used clinically to treat diastolic dysfunction, their effects on prognosis remain unproven. Unlike heart failure caused by systolic dysfunction, standardized by the neuro-hormonal consequences of alteration of the ejection fraction, its treatment is not based on any solid recommendations, the 6 major trials therapeutic studies, the last of which, the PARAGON-HF study, was unable to demonstrate a significant decrease in morbi-mortality [31, 32, 33, 34, 35, 36].

Diuretics will usually improve congestion, if present, thereby improving symptoms and signs of HF. The evidence that diuretics improve symptoms is similar across the spectrum of LVEF.

Evidence that beta-blockers and MRAs improve symptoms in these patients is lacking. There is inconsistent evidence for an improvement in symptoms in those treated with ARBs (only for candesartan was there an improvement in NYHA class) and ACEIs [37, 38].

There is some evidence that in patients in sinus rhythm nebivolol, digoxin, spironolactone and candesartan might reduce HF hospitalizations. For patients in AF, beta-blockers do not appear to be effective and digoxin has not been studied. The evidence in support of either ARBs or ACEIs is inconclusive [39, 40, 41].

Trials of ACEIs, ARBs, beta-blockers and MRAs have all failed to reduce mortality in patients with HFpEF. However, in older patients, Nebivolol reduced the combined endpoint of death or cardiovascular hospitalization, with no significant interaction between treatment effect and baseline LVEF [42, 43, 44].

Conclusions

1. Although widely prevalent, diagnosis of HFpEF remains challenging. A prior consensus statement on diagnosis of HFpEF relied solely on echo-

cardiographic data and natriuretic peptide levels, both of which have a low sensitivity.

2. Echocardiogram is indicated in all patients with HF symptoms. Preserved EF is defined as an EF >50%. HFpEF is suggested by normal EF, nondilated left ventricle with concentric remodeling, or left ventricular hypertrophy and left atrial enlargement.

3. Recommended echocardiographic criteria consist of functional markers (septal and lateral annular peak early diastolic velocities, tricuspid regurgitation velocity) and morphological markers (left atrial size and left ventricular mass index). Natriuretic peptide cut-offs have been specified based on underlying cardiac rhythm (sinus vs. atrial fibrillation).

4. If criteria for diastolic dysfunction during an exercise echocardiogram through E/e' ratio and tricuspid regurgitant velocity are not met, invasive hemodynamic assessment through a right heart catheterization at rest or at exercise is the next step.

5. The final step consists of establishing HFpEF etiology. This includes assessment of blood pressure control, chronotropic competence, arrhythmias and ischemia.

6. The treatment of HFpEF had an etiologic aspect without certain prognosis by death and cardiovascular hospitalization.

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