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Prognostic markers in the pathology of cardiac failure: echocardiography and autonomic nervous system dysfunction

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Abstract

Introduction: Chronic heart failure is a major health problem worldwide and despite the therapeutic advances, the mortality and morbidity still remain high. Echocardiography is the gold standard for left ventricular function assessment and may provide prognostic information for predicting future heart failure events. *Patients and Methods*: We analyzed the main echocardiographic markers used for the prognostic of chronic heart failure patients such as the ejection fraction, diastolic impairment and the collapse of inferior vena cava. Also, another parameter is studied, recently recognized as a marker for future cardiac events: autonomic nervous dysfunction. The current paper makes a comprehensive approach of the echocardiographic markers recommended for the diagnosis and follow-up of heart failure adapted to what we really find in our everyday practice with a correct patient management in a clinical and biological context. Even though left ventricle ejection fraction is the most often used parameter for cardiac failure follow-up and prognostic, new and more accurate parameters should be used: Tissue Doppler Imaging and Heart rate recovery – which may become a therapeutic target in the era of cardiac rehabilitation. *Conclusions*: There is no stand-alone marker for the assessment of cardiac failure; each of the parameters presented has its advantages and its pitfalls. Echocardiography allows a morphologic study, which should always be correlated with clinical and functional studies (exercise stress test and autonomic nervous system dysfunction).

Keywords: echocardiography, heart rate recovery, heart failure, autonomic nervous system.

Introduction

Heart failure is a complex syndrome consisting in structural and functional abnormalities, which alter the ventricular ejection and ventricular filling as well. Its main symptoms are dyspnea, a lower exercise tolerance and edemas, sometimes with a significant reduction in functional capacity and quality of life. Despite the therapeutic advances in patients with chronic heart failure, the mortality and morbidity still remain high [1, 2]. Even though systolic dysfunction is a target of more aggressive medical therapy with many drug trials focused upon [3], diastolic failure (commonly known as preserved ejection fraction heart failure) is also a main concern for prognostic as it represents 50% of the presentations mostly in the elderly [4]. According to ACC/AHA (*American College of Cardiology/American Heart Association*) and ESC (*European Society of Cardiology*) [5, 6], echocardiography is the gold standard for left ventricular function assessment and may provide prognostic information for predicting future heart failure events [7].

The purpose of the current paper is combining a literature and guideline approach with a practical diagnostic algorithm of one of the most common illnesses in cardiology: heart failure. This algorithm should not only be composed by a morphological description using echocardiography but pathophysiology should always be considered when evaluating the disease, as these two parameters are interdependent.

Patients and Methods

Echocardiography currently relies upon 2–7 MHz ultrasound for a characterization of the structure and function of the heart with M-mode, two-dimensional spectral Doppler and color Doppler modalities. In our Cardiology Department's Laboratory of Cardiovascular Noninvasive Investigations, we use for imaging acquisition ACUSON Sequoia C512 Ultrasound System with a 1.5–4.0 MHz adult cardiac sector probe. We present our clinical experience revealed in an analysis of 30 heart failure patients admitted in our Department of Internal Medicine in the past six months. From the study group, 23 were aged 50 or more with a clear predominance of a preserved ejection fraction heart failure (19 cases). In fact, only one of the younger patients had a dilated ischemic cardiomyopathy, the other six were hypertensive with a diastolic impairment. For the elderly, ischemic heart disease was the dominant underlying disease, which caused the wall movement abnormalities and lowering the ejection fraction. Each of them underwent the same echocardiographic imaging algorithm with the measurement of several parameters as presented below.

Left ventricle ejection fraction

Left ventricle ejection fraction is measured using Simpson's biplane discs method (Figure 1) – slicing the left ventricle from apex to mitral valve in small sections. An end diastole (just before the aortic valve opens – corresponding on the R wave on ECG) and end systole (before mitral valve opens – T wave on ECG) volume in a 2-chamber and 4-chamber 2D views (it may be done in a single plane but for accuracy two perpendicular planes are preferred) are measured, with a careful delineation of the endocardium and excluding papillary muscle from the cavity measurements.

Left cardiac chambers size

Left cardiac chambers size 2D and M-mode imaging are the modalities of choice, resulting in 2D and volumetric measurements – similar to Simpson's principle. M-mode in a long-axis parasternal view at the tip of the mitral valve, intersecting both ventricles allows the assessment edge to edge of the end-diastolic and end-systolic diameters and wall thicknesses.

Functional mitral insufficiency

Functional mitral insufficiency (Figure 2) can be evaluated both in 2D for valve movement abnormalities, status of papillary muscles and also in color Doppler which integrates the findings, allowing a direct view of the regurgitating flow and a measurement of its area, of vena contracta, of flow convergence (PISA) – parameters taking into account for classifying its severity.

Diastolic impairment

Ventricular diastole is an active process, which results in a rapid fall of the left ventricle pressure at the end of ventricular systole. Measuring the mitral valve inflow is the current modality used for diastolic function assessment in a routine echocardiographic scan, although pulmonary vein flow and left atrial size are indirect markers in practice. The transmitral pattern obtained with PW (Pulsed Wave) Doppler sample volume at mitral cusps opening from apical four-chamber view consists in an E wave for the fast ventricular filling and A wave for atrial contraction; the E wave is higher in a normal heart with an E/A ratio above 1. In diastolic impairment (Figure 3), a lower E wave and a higher A wave are found (a common finding in old age). As the heart failure worsens, the left atrium pressures increase even more with a pseudo-normalization pattern (E/A ratio 1–2), which can be differentiated from a normal one using Tissue Doppler Imaging.

The deceleration time from the top of E wave until the base is another marker for diastolic function assessment, and it becomes longer as the left atrial pressure increases. A short isovolumetric relaxation time and dominant early diastolic inflow velocities are found in the presence of impaired left ventricular compliance and elevated end-diastolic pressures [8].

Tissue Doppler Imaging

It is measured in a 4-chamber view by placing the sample either on the septal or lateral annulus of the mitral valve and it reflects the shortening and elongation of myocardial fibbers in longitudinal plane with three waves: S' – peak systolic, E' – early, A' – late diastolic velocities derived from septal and lateral mitral annulus movements. E' wave indicates left ventricle relaxation, independently of atrial pressures and an E/E' ratio higher than 15 is correlated with dyspnea and pulmonary congestion.

The inferior vena cava in inspiration

The evaluation of inferior vena cava collapse during inspiration (Figure 4) is used as a marker for right heart chambers pressures and volumes and as a guide for therapeutic decision for diuretics and hospitalization. It is measured in a subcostal view by rotating the probe anti-clockwise, keeping the right atrium in the centre, preferably in M-mode, during inspiration and expiration for a correct assessment of its size.

Pulmonary arterial pressure

Pulmonary arterial pressure by convention is measured in a 4-chamber view using the right atrium-right ventricle gradient as a substitute with the continuous Doppler sample placed at the tip of tricuspid valve leaflets. The peak velocity obtained allows to derive a pressure gradient (Figure 5).

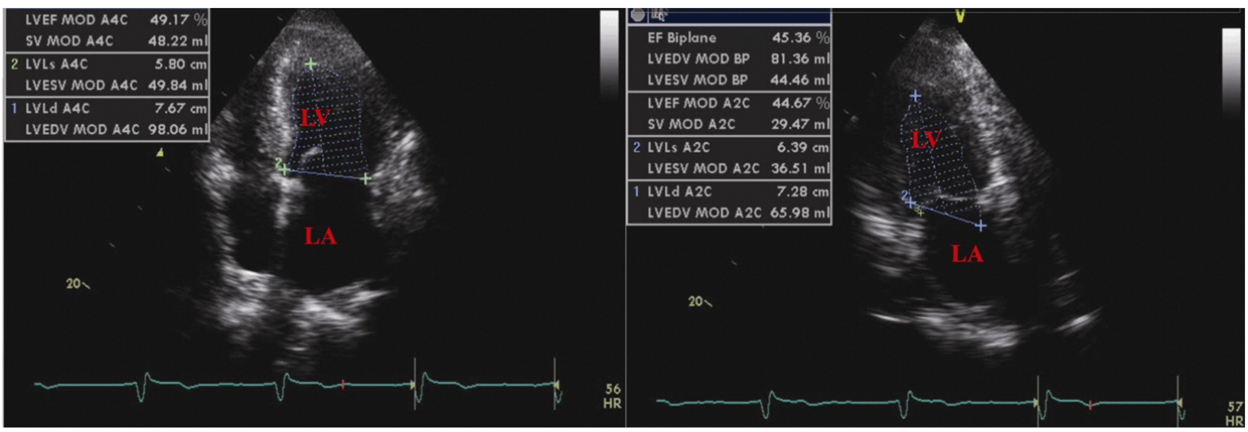

Figure 1 – ***Left ventricle ejection fraction assessment using Simpson's biplane method in apical four and two chambers view. LA: Left atrium; LV: Left ventricle; LVEF: Left ventricle ejection fraction; LVESV: Left ventricle end systolic volume; LVEDV: Left ventricle end diastolic volume.***

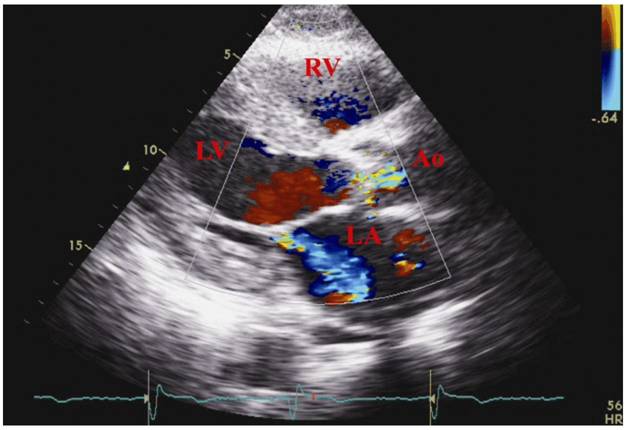

Figure 2 – ***Second-degree mitral regurgitation in a patient with left ventricle dysfunction and ischemic heart disease. LA: Left atrium; LV: Left ventricle; RV: Right ventricle; Ao: Ascending aorta.***

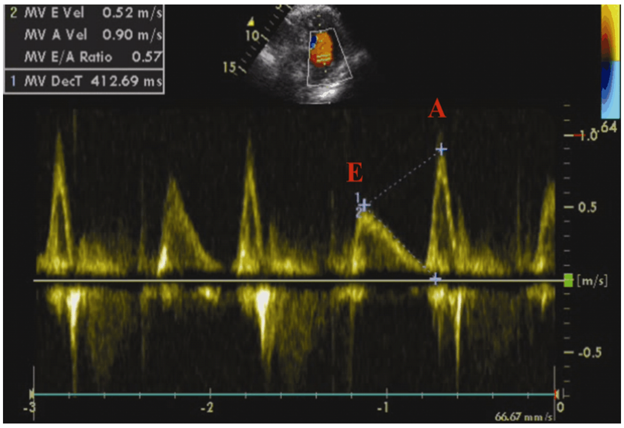

Figure 3 – ***Diastolic impairment with a low E wave and a high A wave. E: Rapid ventricular filling wave; A: Atrial systolic wave.***

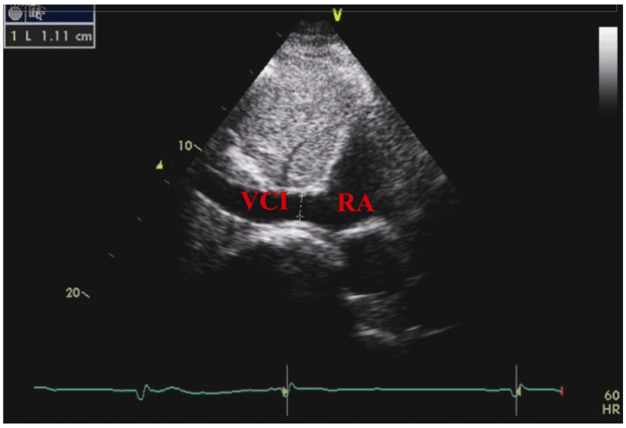

Figure 4 – ***Less than 50% collapse of inferior vena cava during inspiration in a patient with chronic heart failure and increased pressures in right atrium. VCI: Inferior vena cava; RA: Right atrium.***

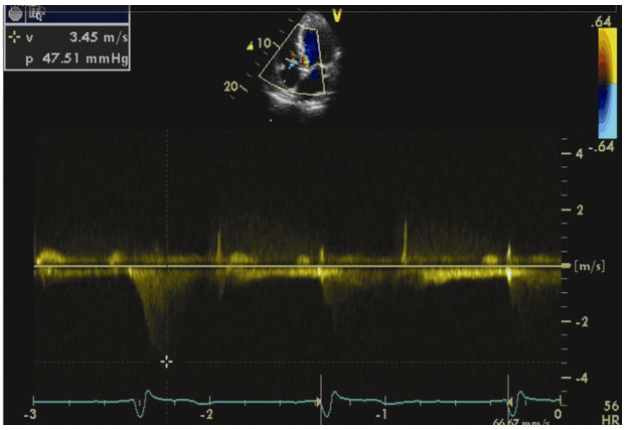

Figure 5 – ***Pulmonary hypertension evaluated in an apical four-chamber view Continuous Wave Doppler using tricuspid regurgitation.***

All the previous described parameters are not stand-alone for the patient with heart failure, they should always be interpreted in the clinical context and with biological parameters. For example, an aggressive diuretic therapy cannot be started in fragile and elderly, dehydrated with low potassium levels despite high right chambers pressures.

In literature, there is no clear definition of the normal value for the ventricular ejection fraction, but in our current practice, we consider it preserved when it is higher than 55%, correlated with wall motion abnormalities and the existence of an obstacle in the ejection such as aortic stenosis (where a value of 50% is already considered dysfunction). We found that many elderly, even with a preserved ejection fraction may have symptoms as worse as some with a 40% value; in fact, all of the 19 elderly with a preserved ejection fraction heart failure had the main symptom dyspnea even though no changes of the ejection fraction; moreover, we find cases with a 35% ejection fraction and dilated left and right cardiac chambers, which perform their usual activity without complains of fatigue (such was the case of the 45-year-old patient with an ischemic dilated cardiomyopathy), therefore this parameter is far from ideal for the assessment of clinical severity. An increase in the left cardiac chambers area or diameters, are especially important for patients with dilated ischemic cardiomyopathy and atrial fibrillation. A left atrium area of over 20 cm^2 puts the patient in a high-risk group for thrombus formation and subsequent embolism and is a decisive factor when choosing between aspirin and oral anticoagulation for CHADS (Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke) score of 1.

In our every day practice, mitral insufficiency is a common finding, present in people with otherwise no cardiovascular illnesses (24 of the study group). All changes when it comes to an ischemic mitral regurgitation, for example after a myocardial infarction, and the parameters used to evaluate it have much lower cut-off values for considering the regurgitation severe than in non-ischemic cases. None of the parameters (vena contracta, PISA, regurgitant orifice area) are fully reliable, that is why when assessing a mitral valve deficiency all of them should be measured and the decision for operation should be taken in a clinical context.

When it comes to diastolic impairment, an abnormal mitral valve inflow pattern is also a common finding in patients aged over 50 and the current tendency is to consider it as a normal variant in elderly. On the other hand, a restrictive pattern with a small A wave and a E/A ratio >2 is a cornerstone in deciding for intensified diuretic therapy (just like for severe tricuspid regurgitation) in a severe dilated cardiomyopathy. Also, a dilated inferior vena cava with poor inspiration collapse and dilated hepatic veins are indicators for high right cavities pressure and recommend prompt depletisation.

Discussion

Left ventricle ejection fraction is probably still the most often used parameter and has an excellent predictive rate as proved in the CHARM (Candesartan in Heart Failure Reduction in Mortality) study [9] on 7599 patients followed for 38 months, showing that a value below 32% doubles the mortality through acute decompensation. Unfortunately, despite its everyday use, this parameter is affected by extrinsic factors such as preload, afterload and heart rate, and some authors consider that ejection fraction is largely driven by the degree of ventricular dilatation [10].

Left atrial volume increases as a response to high filling pressures, and a volume above 32 mL/m^2 was considered a poor prognostic marker for 1160 patients in a four-year period [11]. Also, an end-diastole left ventricular diameter is an independent predictor of cardiac mortality [12] and an end-systolic ventricular volume indexed with body surface over 25 mL/m^2 may be used as an indicator for hospitalization in left ventricle dysfunction associated with stable coronary disease [13]. Moreover, Hinderliter *et al.* reported on their analysis on 212 patients that left ventricular and atrial size and function are significant predictors of all cause mortality in patients with heart failure, independent of NT-proBNP (amino-terminal pro-brain-type natriuretic peptide) values [14].

Functional mitral insufficiency is a frequent finding in ischemic and dilated cardiomyopathy because of geometry alteration of left ventricle and papillary muscle relocation towards the apex and posterior, but with a normal anatomic mitral valve and that is why a valve should be assessed first in 2D. The dP/dT parameter using continuous Doppler has a predictive value with an increase in mortality when below 600 mmHg [15], but the fact is ischemia is the most important factor to be taken into account when establishing the prognosis of the patient.

Diastolic impairment assessed through transmitral flow patterns seems to add incremental value to QRS duration in determining the prognosis in chronic heart failure patients [16]. A restrictive filling pattern with E/A ratio >2, a DT <150 ms is indicative of poor prognostic [17]. All these wave alteration are due to extensive stiffness, scaring and other structural changes in myocardial tissue, which lead to an abnormal increase in the filling pressures and redistribution of flow during diastole [18]. From TDI – derived mitral annular E' velocity Wang *et al.* reported an incremental value for mortality compared to standard clinical and echocardiographic measurements [19] and Nikitin *et al.* demonstrated on a study on 185 patients with chronic heart failure and systolic dysfunction despite maximal pharmacological treatment, that the strongest independent predictor of prognosis is S' velocity measured using TDI [20]. The advantage of using this method consist in a less dependency on the quality of the echocardiographic images, it does not require tracing of endocardial contours (like in assessment of volumes or ejection fraction) and has a better interobserver variability (4–8%) than for the ejection fraction (19–20%) [21]. Also, this modality seems to be preferred to the classical mitral inflow pattern for patients with preserved ejection fraction cardiac failure [22].

Pellicori *et al.* [23], in a study on almost 700 patients of which 568 had heart failure show that the IVC_{max} correlates well with natriuretic peptide levels and other markers of systemic congestion, such as jugular venous pressure and, that increased values are independently associated with the composite endpoint of heart failure admission, cardiovascular death and overall mortality.

Pulmonary arterial pressure may be increased in heart failure being associated with poor outcomes [24] and is approximated using tricuspid regurgitation. Pulmonary arterial hypertension (Figure 5) with values higher than 45 mmHg is a strong predictor of mortality and is independent of NT-proBNP, another powerful predictor in heart failure, and could also be one of the mechanisms by which heart failure progresses and also a target for therapy [25].

Heart failure and autonomic system dysfunction

All the parameters of cardiac function (contractility, relaxation, heart rate) reflect the balance between the sympathetic stimulating system and inhibiting parasympathetic one [26]. In cardiac failure, there is an imbalance between sympathetic and parasympathetic tone leading to an increase stimulation of beta-adrenergic receptors by down-regulation and a decrease in the vagal tone, which appears early in cardiac dysfunction, resulting in a lower effort tolerance. The nervous system abnormalities appear to be caused by an alteration of calcium metabolism at myocyte level [27].

Abnormal heart rate recovery upon stopping the exercise stress test is considered a marker of nervous autonomic system dysfunction and, in the past few years, more and more clinicians have become aware of its prognostic value for cardiovascular mortality, which remains significant even in a submaximal exercise [28]. Heart rate recovery is the difference between maximal heart rate achieved during exercise and first and second minute of recovery. There is no standard definition for abnormal heart rate recovery, which makes the comparison between studies very difficult. Still, the most used definition is less than 12 beats per minute (bpmin) in the first minute and 11 bpmin in the second minute. There are authors which believe a more through division is necessary (30, 60, 90 and 120 s – Thomas *et al.*) and some consider also the type of recovery (active or passive) modifying the cut-off value at 18 bpmin for passive and 12 bpmin for active one [29].

Either way, the value of heart rate recovery as a cardiovascular prognostic marker has been studied in many groups of patients at risk or already having cardiovascular disease. Even though the dysautonomies are a well-known occurrence in heart failure, there are few studies of correlation between the sympathetic and parasympathetic imbalance and echocardiographic findings in these patients. Retrospective data on 712 patients with ischemic heart disease and dilated cardiomyopathy and an ejection fraction below 45% report for a subgroup with lowest heart rate recovery (<4 bpmin one minute) which had the highest NYHA (*New York Heart Association*) class, an increase in all cause mortality [30]. Garacholou *et al.* [31] have studied diastolic function on 2826 patients, and it appears that diastolic impairment and lower exercise tolerance and age correlate best with autonomic system dysfunction. Their findings are consistent with the ones of Phan *et al.* [32], which launch the hypothesis that chronotropic dysfunction may appear as an adaptation process for assuring the diastolic filling.

Knowing the increasing importance of this parameter – heart rate recovery as marker of autonomic nervous system dysfunction – in assessing the outcome for heart failure patients, and its possibility to become a therapeutic target, new studies that find connections with echocardiographic findings in heart failure are necessary.

Conclusions

Echocardiography is currently the most available, cheap, repeatable method for investigating a cardiovascular patient, being performed not only by cardiologist but also by internal medicine and imaging specialists. The parameters described outline the routine determinations for a heart failure patient, which should always-interpreted taking into consideration the whole picture, and adapted for each patient. In the era of cardiac rehabilitation (which improves cardiac prognosis) with great impact on cardiac autonomic dysfunction improvement, new data such as heart rate recovery and exercise capacity should be included for the assessment of cardiac insufficiency.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

All authors equally contributed in the present study.

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