Use of echocardiography to distinguish between the various causes of shortness of breath

Value of echocardiography in chronic dyspnoea

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Summary

In chronic dyspnoea, cardiac and pulmonary aetiologies predominate, but multiple causes are present in up to one third of patients. Because of the multiple possible aetiologies, the evaluation of chronic dyspnoea remains challenging. Initial diagnostic testing should include at least a complete blood count, chest x-ray and an electrocardiogram. If there is an ongoing suspicion of a cardiac origin, echocardiography comes into play. Echocardiography is the first-line diagnostic imaging test for detecting myocardial, valvular or pericardial disease as an aetiology for chronic dyspnoea. In addition, echocardiography may aid in the diagnosis of thromboembolic disease and in pulmonary artery hypertension. Echocardiography also provides additional important information such as the severity and extent of the disease. In our review we will discuss the different causes of chronic dyspnea and we will highlight the strengths and limitations of echocardiography when evaluating these disorders. When interpreted together with the clinical presentation, echocardiography is a fundamental diagnostic tool for the evaluation of patients with chronic dyspnoea and contributes to directing further management.

Key words: echocardiography, chronic dyspnoea, heart failure, diastolic dysfunction, coronary artery disease, valvular heart disease, pericardial diseases

Introduction

Chronic dyspnoea is defined as shortness of breath lasting longer than one month [1]. The underlying causes can be classified into cardiac, pulmonary and other disorders which include anaemia, deconditioning or anxiety [2] (table 1). Cardiac and pulmonary pathologies as the cause for dyspnoea clearly predominate: for 85% of all cases of shortness of breath the causes are asthma, congestive heart failure, myocardial ischaemia, chronic obstructive pulmonary disease (COPD), interstitial lung disease, pneumonia or psychogenic disorders [3]. However, it is often not easy to distinguish between the various causes of shortness of breath, and the aetiology is multifactorial in up to one third of patients [1].

Before echocardiography, initial diagnostic testing in patients with chronic dyspnoea should include pulse oximetry, complete blood count, basic metabolic panel, chest x-ray and an electrocardiogram (ECG). The diagnostic yield of the clinical history, physical examination and chest x-ray was examined in 85 subjects with chronic dyspnoea by Pratter et al. [4] in 1989. Overall, the diagnosis could be reached with these three tools in two thirds of the patients (56 out of 85 cases). The clinical diagnostic impression was more accurate (81%, 47 out of 58 cases) in common diseases like asthma, COPD, interstitial lung disease or cardiomyopathy, whereas accuracy dropped drastically to 33% (9 out of 27 cases) with less common causes of dyspnoea. Thus, further tests such as echocardiography are clearly necessary to make a diagnosis or to confirm a clinical suspicion. In addition, echocardiography provides information on disease severity and more precise information on disease aetiology.

According to the European Society of Cardiology (ESC) [5], transthoracic echocardiography is appropriate when a cardiac origin of the dyspnoea is suspected. Figure 1 shows an algorithm for the assessment of heart failure according to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. In summary, the probability of heart failure should first be evaluated on the basis of the patient's prior clinical history, physical examination and resting ECG. If at least one element is abnormal, plasma

Table 1: Causes of chronic dyspnea. Adapted from Wahls SA et al. [1].

Cardiac	Noncardiac/nonpulmonary
Myocardial disease	Thromboembolic disease
Cardiac arrhythmias	Pulmonary hypertension
Pericardial disease	Deconditioning
Valvular heart disease	Obesity
	Severe anaemia
Pulmonary	Gastroesophageal reflux disease
Chronic obstructive pulmonary disease	Metabolic conditions
Asthma	Liver cirrhosis
Interstitial lung disease	Thyroid disease
Pleural effusion	Neuromuscular disorders
Malignancy	Chest wall deformities
Bronchiectasis	Upper airway obstruction
	Psychogenic causes

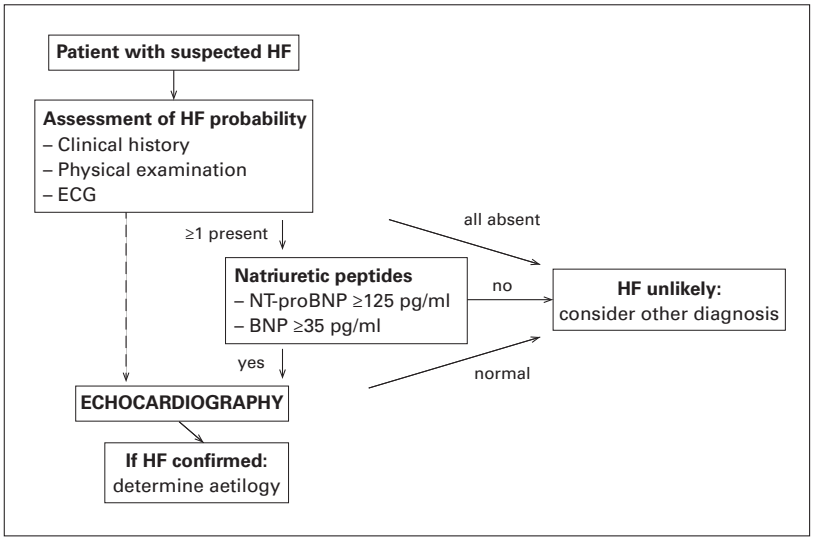

Figure 1: Flow chart for the assessment of heart failure (HF) according to the ESC guidelines 2016. Adapted from Ponikowski P et al. [5] Clinical history: for example history of coronary artery disease, arterial hypertension, exposure to cardiotoxic drug / radiation, use of diuretics, orthopnoea, paroxysmal nocturnal dyspnoea. Physical examination: for example rales, bilateral ankle oedema, heart murmur, jugular venous dilatation, laterally displaced apical beat. ECG: any abnormality.

natriuretic peptides should be measured, to identify those who need echocardiography (if the level of natriuretic peptides is above the exclusion threshold or if circulating natriuretic peptide levels cannot be assessed).

Cardiac causes of dyspnoea include systolic dysfunction (which may be caused by myocardial ischaemia, valvular diseases or cardiomyopathies) primary diastolic dysfunction, pericardial diseases, congenital heart diseases, pulmonary hypertension and cardiac masses. Most of these disorders are reliably detectable by echocardiography. We will discuss each of the conditions separately, highlighting the strengths and limitations of echocardiography and, when appropriate, comparing it with other imaging tools.

Evaluation of left ventricular systolic function

Assessment of left ventricular systolic function is the most frequent reason for ordering echocardiography, and reduced systolic function is the most apparent finding causing dyspnoea. Even though not optimal, the most widely measured parameter reflecting systolic function is left ventricular ejection fraction (LVEF). Over past decades, measurement of LVEF has evolved from a purely visual assessment to complex, computer assisted tracing of the left ventricular cavity throughout the cardiac cycle.

The simplest approach to measuring LVEF is so-called eyeballing. Whether visual estimation of left ventricular ejection fraction is equivalent to other methods has been examined in a number of studies. Overall, the intra- and inter-observer variability of visual estimates of LVEF is higher than for other techniques [6]. However, visual estimation of LVEF is still widely applied to confirm quantitative measures of LVEF. Also, visual estimation may still provide a rough estimate of LVEF in patients with very poor image quality where tracing of the left ventricular cavity is not possible.

The most widely used method for measuring LVEF is the simplified Simpson's method to estimate ventricular volume from two orthogonal apical views [7]. This method is time consuming, and relies on geometric assumptions and on good image quality. The most common error is apical foreshortening, which leads to underestimation of left ventricular volumes. Simpson's method has been shown to correlate well with other methods used for estimation of LVEF, such as magnetic resonance imaging [8]. However, it should be remembered that on an individual patient basis, the measurement variability can be quite high This needs to be taken into account for clinical decision making, which often uses discrete LVEF cutoffs, for example as indications for the implantation of implantable cardioverter-defibrillators or cardiac resynchronisation. For example, in an analysis of echocardiography data from the TIME-CHF study [9], about one fifth of all patients would have been re-assigned to an LVEF category (above or below 30%) clinically on a second reading.

Given the shortcomings of visual estimation or of Simpson's measurement of LVEF that mainly depends on image quality, ultrasound contrast agents have been used and shown to result in less inter-observer variability and better correlation to other techniques such as cardiac magnetic resonance imaging (CMR) [8]. However, as a drawback, use of contrast agents necessarily involves an intravenous line, and measurements still rely on geometric assumptions. In this respect, three-dimensional echocardiography (3DE) is a major step forward. A systematic review and meta-analysis have assessed the performance of 3DE in measuring left ventricular volumes and LVEF [10]. The authors concluded that, compared with traditional 2D, 3DE is more precise for measuring left ventricular volumes and LVEF. However, perhaps even more than two-dimensional imaging, 3DE does depend on good image quality.

Apart from the variability of the measurements, one should also be aware that LVEF is influenced by heart rate, preload, afterload and contractility. Thus, LVEF within a normal range does not necessarily indicate normal systolic function. For example, chronic severe

mitral regurgitation leads to a decrease in afterload and thus LVEF can be normal even if systolic dysfunction as a consequence of long-standing left ventricular volume overload is present. Hence, LVEF is not an ideal measurement of systolic function. There is an unmet clinical need for additional tools to better assess systolic function. Newer echocardiographic techniques have helped identify myocardial mechanical abnormalities in patients with cardiac disease and preserved LVEF (≥50%). Specifically, speckle-tracking imaging of myocardial deformation has allowed for a more refined assessment of ventricular systolic and diastolic function, and may allow the detection of subtle myocardial abnormalities that do not impact LVEF [11]. Conversely, the finding of reduced LVEF or systolic dysfunction does not automatically explain the origin of chronic dyspnoea. The demonstration of increased filling pressure or pulmonary systolic pressure is essential to conclude causality between the echocardiographic findings and the symptoms.

Evaluation of left ventricular diastolic dysfunction

Diastolic dysfunction with an increase in left atrial pressure (LAP) is the common mechanism responsible for dyspnoea in patients with heart failure as a consequence of left-sided heart disease, irrespective of the presence or severity of systolic dysfunction. The approach to the evaluation of diastolic dysfunction depends on the presence of reduced ejection fraction. In patients with a normal ejection fraction, heart failure with preserved ejection fraction (HFpEF) is a possible cause for dyspnoea. According to current guidelines [5], the diagnosis of HFpEF requires the following conditions to be fulfilled: (1) The presence of symptoms and signs of heart failure; (2) normal or "preserved" LVEF (≥50%); (3) elevated levels of natriuretic peptides (BNP ≥35 pg/ml, NT-proBNP ≥125 pg/ml); and (4) at least one additional criterion representing objective evidence of relevant structural heart disease (left ventricular hypertrophy, dilated left atrium) or evidence of diastolic dysfunction. However, it should be noted that the cut-off point of 50% is arbitrary, as many clinical studies considered patients with an LVEF between 40 and 49% as having HFpEF [12]. Remarkably for the first time, 2016 guidelines describe an LVEF between 40 and 49% as heart failure with mid-range ejection fraction (HFmrEF). In patients with HFpEF as a possible cause of dyspnoea, assessment as to whether diastolic dysfunction is present or not is the first step. Although a large number of indices that reflect diastolic function have been developed, it should be noted that in general there is a large overlap of values in normal subjects and those with diastolic dysfunction. Therefore, a diagnosis of diastolic dysfunction should never be based on single measurements. Current guidelines recommend the measurement of early mitral inflow peak velocity (E), septal and lateral annulus tissue velocities (e'), peak tricuspid regurgitation velocity (TR velocity) and left atrial volume. The diagnosis of diastolic dysfunction is then based on whether a majority of the measured parameters falls into the abnormal range (fig. 2). Following this, additional parameters are then used to assess whether LAP is elevated at the time of investigation. With regards to additional criteria for structural heart disease, left ventricular mass index (LVMI) ≥115 g/m^2 for males and ≥95 g/m^2 for females should be considered pathological. Echocardiographic assessment of left ventricular mass is done with either the linear method or 2D-based formulas [7]. The linear method, which uses linear measurement from the parasternal window at the level of the mitral valve leaflet tips, is fast, widely used and a simple method to screen for left ventricular hypertrophy. However, this method tends to overestimate left ventricular mass in subjects with hypertrophy that is limited to the base of the left ventricle. In contrast to the linear methods, 2D-based formulas, such as the area length and truncated ellipsoid methods, underestimate mass in basal septal hypertrophy. Apart from these technical considerations, the indexing of left ventricular mass allows comparisons in subjects with different body sizes, but can lead to underestimation of hypertrophy in obese patients.

An enlarged left atrium is associated with adverse cardiovascular outcomes [13]. Historically, left atrial

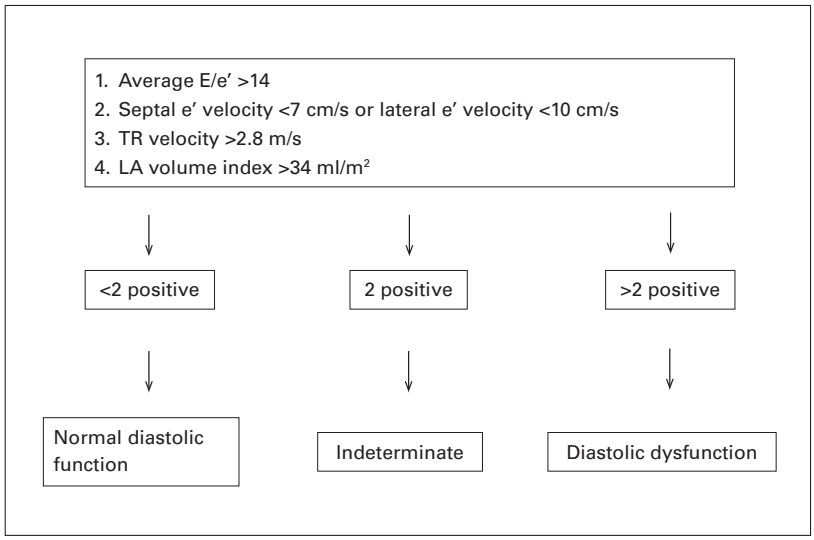

Figure 2: Diastolic dysfunction in normal ejection fraction. Adapted from Nagueh SF et al. [38]. E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; LA = left atrium; TR = tricuspid regurgitation

size was measured as the anteroposterior diameter derived from M-mode tracings from a parasternal window. However, it is important to realise that the left atrium often dilates asymmetrically along its long axis, and thus measurement in one dimension is inaccurate. Therefore, according to current guidelines the left atrial volume should be measured with the Simpson's method on two orthogonal planes from apical windows. Also, 3DE holds promises for assessing left atrial volume accurately [14, 15].

Lastly, patients with reduced ejection fraction invariably have diastolic dysfunction, and assessment is limited to determining whether there is elevated LAP, as shown in figure 3.

Evaluation of the right heart

Chronic dyspnoea caused by right heart disorders is not uncommon. Right ventricular function plays an important role in clinical outcomes of many cardiopulmonary diseases causing chronic dyspnoea. Therefore, in all studies the investigator should systematically evaluate the right heart as well as the left. The assessments should include measurement of right ventricular and right atrial size, and evaluation of right ventricular function as fractional area change (FAC) or tricuspid annular plane systolic excursion (TAPSE). In addition, systolic pulmonary artery pressure (SPAP) should be measured and right atrial pressure approximated [16].

The apical four-chamber view allows estimation of the right heart dimensions. To avoid foreshortening, the image plane should include the base and the apex of the right ventricle. Right ventricular dimensions at end-diastole are obtained at the base (diameter >42 mm), at mid-level (>35 mm) and longitudinally (>86 mm); this differs from measurement of right atrial dimensions, where most often the right atrial area is traced (>18 cm^2). Information for estimation of right atrial pressure is provided in subcostal views by measurement of inferior vena cava (IVC) size and collapse ability. In general, an IVC with diameter ≤2.1 cm that collapses >50% suggests normal right atrial pressure (range 0–5 mm Hg), whereas an IVC diameter >2.1 cm that collapses <50% suggests high right atrial pressure (10–20 mm Hg).

The assessment of right ventricular function is discussed in detail in the context of echocardiographic findings in pulmonary disease.

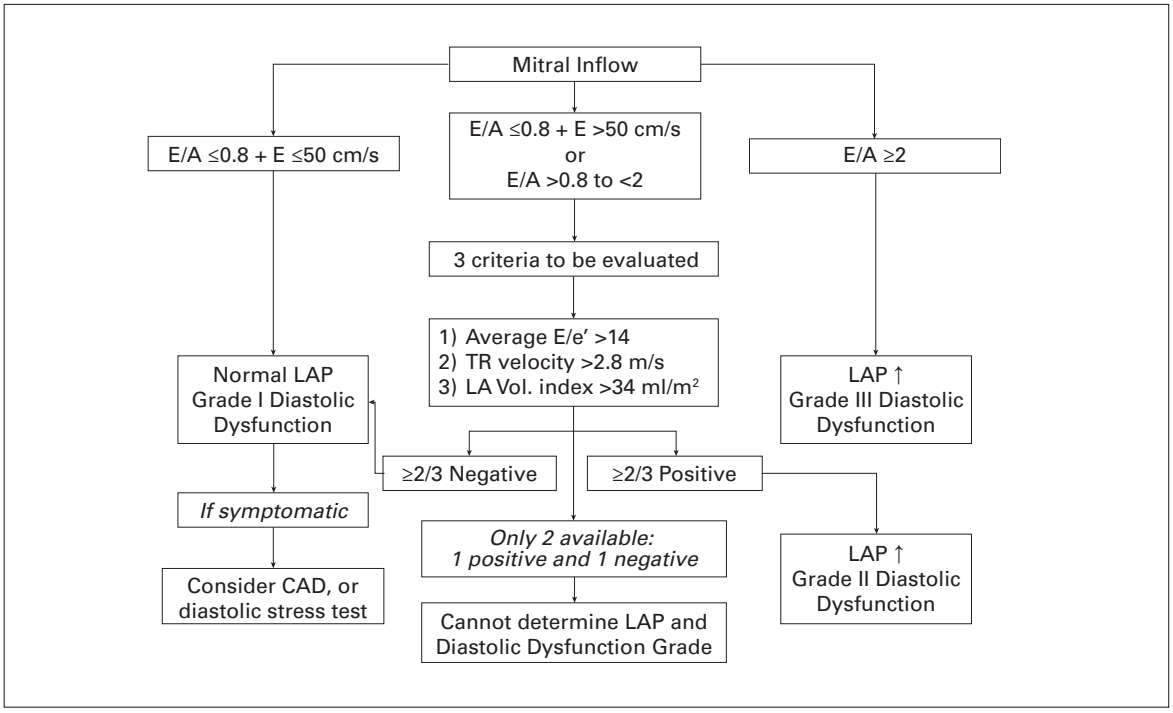

Figure 3: Algorithm for estimation of left ventricular filling pressures and grading left ventricular diastolic function in patients with depressed left ventricular ejection fraction (LVEF) and patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data. Adapted from Nagueh SF et al. [38]. CAD = coronary artery disease; E/A = ratio of early mitral inflow velocity to mitral diastolic inflow velocity; E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; LA = left atrial; LAP = LA pressure; TR = tricuspid regurgitatation

Aetiology of myocardial disease

Besides the detection of ventricular dysfunction causing dyspnoea, echocardiography can also detect the underlying aetiology. First and foremost, coronary artery disease needs to be considered in all patients with chronic dyspnoea, especially when regional wall motion abnormalities at rest or with stress (exercise or dobutamine infusion) are present. Regional wall motion assessment is usually performed by grading the contractility of individual myocardial segments. To provide a standardised classification, the left ventricle is divided into three levels (basal, mid, apical) and 16 segments [17].

Are patients with the primary symptom of dyspnoea at high risk of having coronary artery disease? In a recent study [18] of patients with dyspnoea (but no chest pain) referred for exercise echocardiography, 42% had echocardiographic evidence of ischaemia. During a 3-year follow-up, myocardial infarction, coronary revascularization or death occurred in one fifth of these patients. Hence, patients with dyspnoea have a high likelihood of ischaemia, and cardiac events during follow-up are frequent.

Less common entities, but important causes of chronic dyspnoea, for example non-compaction cardiomyopathy, hypertrophic obstructive cardiomyopathy or amyloidosis can also be identified with echocardiography (fig. 4).

Valvular heart disease

Echocardiography has developed into the first-line diagnostic method for detecting valvular heart disease in recent decades. Aortic stenosis is usually easily diagnosed by using transthoracic imaging. However, in some cases image quality or difficulties in aligning the continuous wave Doppler beam correctly with the flow acceleration through the stenotic aortic valve can preclude grading of aortic valve stenosis when using the transthoracic approach. Thus, in patients with chronic dyspnoea with no other explanation except for a thickened aortic valve on transthoracic echocardiography, a further investigation with transoesophageal echocardiography should be considered. Echocardiography is the standard means for the evaluation of aortic stenosis severity; cardiac catheterisation is no longer recommended as a routine method [19]. Aortic stenosis jet and left ventricular outflow tract (LVOT) velocity measurements have a very low intra- and interobserver variability of 3–4% in an experienced laboratory [20]. Apart from severe aortic stenosis with normal LVEF and a mean gradient of 40 mm Hg or more, other conditions should be considered: severe low-flow low-gradient aortic stenosis (aortic valve area <1 cm^2, reduced LVEF) and paradoxical low-flow low-gradient severe aortic stenosis (aortic valve area <1 cm^2, low gradients, preserved ejection fraction and a small stroke volume <35 ml/m^2) [21]. Apart from valvular aortic stenosis, rare cases such as subvalvular aortic stenosis

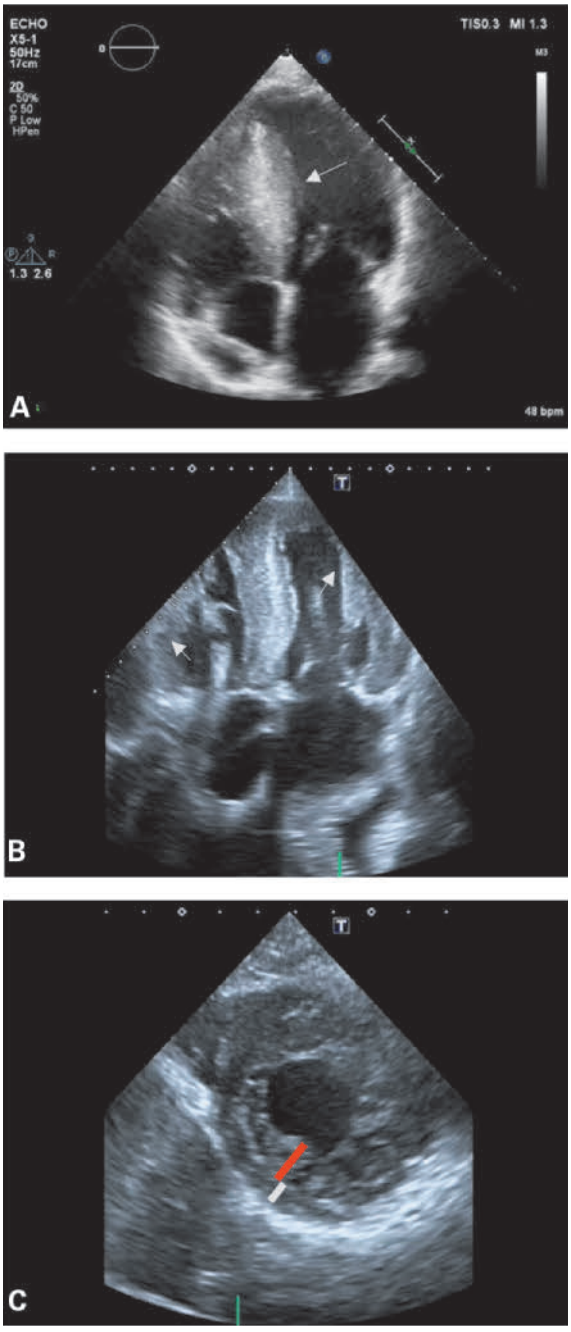

Figure 4: Examples of less common causes of chronic dyspnoea. (A) Hypertrophic obstructive cardiomyopathy; arrow denotes severely hypertrophic interventricular septum. (B) Amyloidosis; arrows denote diffusely thickened myocardium of both the left and right ventricle. (C) Non-compaction cardiomyopathy; non-compacted myocardium (red line) and thin layer of compacted myocardium (white line).

due to a subvalvular membrane or a "paradoxical" low flow / low gradient aortic stenosis may be present and should be considered in the differential diagnoses of chronic dyspnoea. Mitral regurgitation is the most frequent valvular lesion in adults. Evaluation of mitral regurgitation is critical in patients presenting with chronic dyspnoea and a heart murmur. Both the severity and aetiology of mitral regurgitation can be assessed with transthoracic echocardiography.

Constrictive pericarditis

In patients with chronic dyspnoea combined with signs of right heart failure, constrictive pericarditis is a differential diagnosis. As constrictive pericarditis is potentially reversible, accurate diagnosis is crucial. Constrictive pericarditis is characterised by impaired diastolic cardiac filling and elevated ventricular filling pressures due to a fibrotic, thickened and adherent pericardium [22]. Interestingly, it was one of the very first pathological conditions to be recognised [23]. The main causes in the developed world range from pericarditis to cardiac surgery and mediastinal irradiation. Most frequently the cause remains idiopathic or is, in developing countries, still mainly tuberculosis [24]. Echocardiographic recognition remains challenging, as in up to one fifth of cases the pericardium is not thickened and constrictive pericarditis is present with a normal pericardium [25].

Welch et al. [26] compared 130 patients with surgically confirmed constrictive pericarditis with 36 patients with restrictive myocardiopathy or severe tricuspid regurgitation in whom constrictive pericarditis was ruled out. Respiration-related ventricular septal shift, preserved/increased medial mitral annular E' velocity, and prominent hepatic vein expiratory diastolic flow reversals were independent predictors for the diagnosis of constrictive pericarditis. The combination of ventricular septal shift with either medial E' ≥9 cm/s or a hepatic vein reversal ratio ≥0.79 corresponded to a sensitivity of 87% and a specificity of 91% for diagnosing constrictive pericarditis. Therefore, when performing echocardiography on patients with chronic dyspnoea and the suspicion of constrictive pericarditis these specific assessments should always be included in the examination.

Echocardiography findings in pulmonary disease

Thus far we have focused on left ventricular diseases. However, shortness of breath is one of the characteristic features of pulmonary artery hypertension (PAH) [27]. Certain two-dimensional echocardiographic features suggest right ventricular pressure overload, for example right ventricular hypertrophy, a dilated right ventricle or a "D-shaped" left ventricular cavity due to leftward displacement of the interventricular septum. Doppler echocardiography is the primary tool for estimating pulmonary artery pressures by measuring tricuspid regurgitation velocity [28]. As a result of the asymmetrical shape of the right ventricle and because the contraction mainly occurs along the longitudinal plane [29], many investigators have tried to identify echocardiographic parameters for the proper evaluation of right ventricular function. Forfia et al. [30] showed that systolic displacement of the tricuspid annulus toward the right ventricular apex (longitudinal plane), referred to as tricuspid annular plane systolic excursion (TAPSE), closely correlates with right ventricular ejection fraction and reflects prognosis in PAH. The percentage right ventricular fractional area change (RVFAC), defined as (end-diastolic area minus end-systolic area)/end-diastolic area × 100, is another way to measure right ventricular systolic function [16]. A recent study showed that RVFAC is the best of commonly utilised echocardiographic 2D measures of right ventricular function and correlates best with MRI-derived right ventricular ejection fraction [31]. RVFAC was found to be an independent predictor of heart failure and mortality in patients after thrombolysis for pulmonary embolism [32]. To evaluate RVFAC a proper tracing of the endocardial border in apical four-chamber (A4C) view is required (fig. 5).

Any patient with unexplained PAH should be evaluated for chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH causes intermittent symptoms, mainly dyspnoea and exercise intolerance, which start when there is a functional loss of more than 60% of the pulmonary vasculature [33]. As a general rule, mean pulmonary artery pressure is lower in CTEPH than it is in PAH [34]; a possible explanation is the assumption that right ventricular adaptation may be poorer principally because of the older age of CTEPH patients. If the suspicion for CTEPH clinically and on echocardiography is high, the next diagnostic step is the detection of a mismatch perfusion defect on ventilation/perfusion scan [35].

We have already mentioned the difficulties of assessing right ventricular function. Despite their widespread application, TAPSE and RVFAC represent indirect and imperfect measurements. Deformation imaging using 2D-speckle tracking strain analysis appears to be a more robust technique to assess right ventricular function. In the setting of CTEPH, it was re-

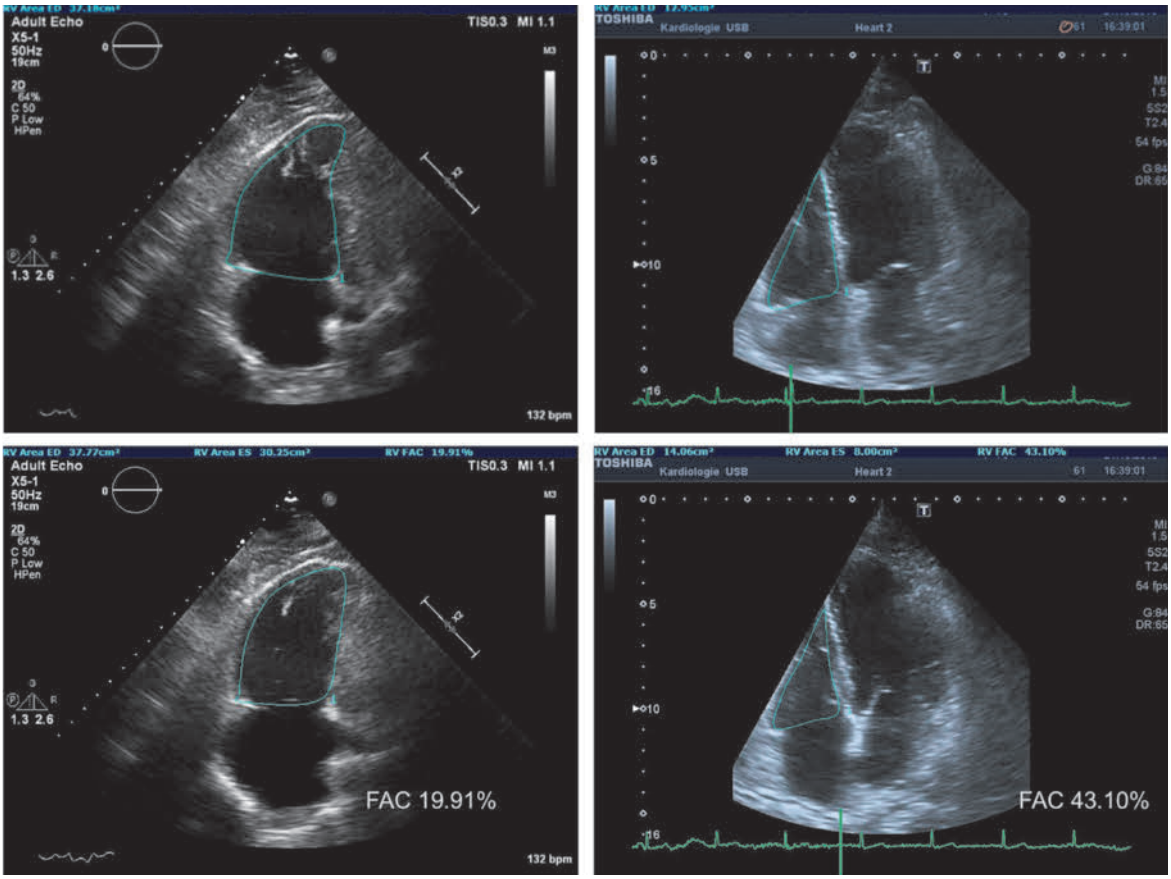

Figure 5: Examples of right ventricular fractional area change (FAC). The endocardial border is traced in apical 4-chamber (A4C) at end-diastole (top) and end-systole (bottom). Trabeculation, tricuspid leaflets, and chords are included in the chamber. Left: optimized view for the right ventricular chamber (RV), FAC 19.9%, dilated RV. Right: Normal subject, FAC 43.10%.

cently shown that greater right ventricular strain correlated with higher 6-minute walk time prior to pulmonary thromboendarterectomy. Several studies suggested an improvement of the 6-minute walk time after pulmonary thromboendarterectomy [36], leading to the assumption that right ventricular strain could represent a marker for functional improvement after the procedure [37].

In summary, we would like to emphasise that the mentioned alterations and diseases are just examples of the diagnostic value of echocardiography in patients with chronic dyspnoea. Certainly, other relevant disorders causing chronic dyspnoea, such as mitral stenosis or chronic pericardial effusion, which are missing from our discussion, may also be evaluated by means of echocardiography.

Conclusion

Chronic dyspnoea remains challenging to evaluate because of the many diverse causes for this symptom. Echocardiography is the first-line diagnostic imaging test to evaluate myocardial, valvular or pericardial disease as an aetiology for chronic dyspnoea. Echocardiography may aid in the diagnosis of thromboembolic diseases and pulmonary artery hypertension as well. When interpreted together with the clinical presentation, transthoracic echocardiography is a fundamental diagnostic tool for the evaluation of patients with chronic dyspnoea and contributes to directing further management.

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