Shortness of breath in clinical practice: A case for left atrial function and exercise stress testing for a comprehensive diastolic heart failure workup

Pupalan Iyngkaran, Nagesh S Anavekar, Christopher Neil, Liza Thomas, David L Hare

Abstract

The symptom cluster of shortness of breath (SOB) contributes significantly to the outpatient workload of cardiology services. The workup of these patients includes blood chemistry and biomarkers, imaging and functional testing of the heart and lungs. A diagnosis of diastolic heart failure is inferred through the exclusion of systolic abnormalities, a normal pulmonary function test and normal hemoglobin, coupled with diastolic abnormalities on echocardiography. Differentiating confounders such as obesity or deconditioning in a patient with diastolic abnormalities is difficult. While the most recent guidelines provide more avenues for diagnosis, such as incorporating the left atrial size, little emphasis is given to understanding left atrial mechanics.
and the role of exercise testing to build a comprehensive argument for the diagnosis of diastolic heart failure in a patient presenting with SOB.

Key words: Diastolic heart failure; Exercise stress test; Left atrium; Shortness of breath; Work-up

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Shortness of breath is a common clinical complaint. Etiologies such as systolic heart failure, obstructive airways disease or anemia have clear and reproducible physiological changes detectable through routine diagnostic tests. Diastolic heart failure (DHF) is often a diagnosis of exclusion. In the absence of directly demonstrating an elevation of left ventricular end diastolic pressures at rest or exercise, DHF is inferred by a combination of symptoms and resting echocardiography findings. We discuss the importance of a wider consideration, e.g., left atrium function and exercise stress testing, in DHF work-up.

Iyngkaran P, Anavekar NS, Neil C, Thomas L, Hare DL. Shortness of breath in clinical practice: A case for left atrial function and exercise stress testing for a comprehensive diastolic heart failure workup. World J Methodol 2017; 7(4): 117-128
Available from: URL: http://www.wjgnet.com/2222-0682/full/v7/i4/117.htm DOI: http://dx.doi.org/10.5662/wjm.v7.i4.117

INTRODUCTION

Most cardiological services are faced with a large number of referrals to diagnose and manage the symptom cluster of dyspnea or shortness of breath (SOB). Broadly the etiologies can be cardiac, respiratory, haematological, due to obesity or physical deconditioning. When a cardiac cause is considered likely, imaging modalities such as echocardiography and occasionally cardiac magnetic resonance imaging can rule out systolic heart failure or heart failure with reduced ejection fraction (SHF/HFrEF). Diastolic heart failure or heart failure with preserved ejection fraction (DHF/HFpEF) can be inferred, but requires greater analysis. Exercise stress protocols are also receiving greater attention for diagnosis of HFpEF.

To understand the controversies in DHF it is important to go back to the basics. HF is defined as "a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress"[45]. From this, four points are important in the work-up of patients suspected with DHF syndrome: (1) Chronic functional SOB, is the main reason for seeking medical care, however asymptomatic structural changes can also be detected. The correlation of changes at rest and with exercise with or without symptoms are yet to be adequately clarified; (2) in presentations with acute SOB admissions, risk stratifying diastolic abnormalities to a clinical course is also problematic[23]; for example are the observed changes age related or evidence of diastolic dysfunction contributing to DHF; (3) three conditions must be satisfied to rule in the diagnosis of HFpEF: Clinical symptoms of heart failure; normal or mildly abnormal systolic function [left ventricular ejection fraction (LVEF) > 50%]; and demonstration of diastolic abnormalities in left ventricular (LV) relaxation and filling, and stiffness manifesting as increased LV filling pressures (invasively measured as LV end diastolic pressure > 16 mmHg (LVEDP) or mean pulmonary capillary wedge pressure or mean left atrial (LA) pressure > 12 mmHg), at rest or with exercise[24]; and (4) demonstrating altered LV pathophysiology in the "resting state" are better established, while evaluation of dynamic diastolic changes (i.e., during exercise) and alterations in left atrium (LA) metrics (i.e., volume or function parameters), have not be given enough emphasis.

The incidence of HFpEF appears to be increasing relative to HFrEF. Combined data among HF presentations reveals an average prevalence of 54% (range 40%-71%)[5]. The etiology and pathophysiological basis also appears different. Patients tend to be older with greater burden of co-morbidities[6,7]. Cardiovascular and non-cardiovascular mortality is increased, although lower than HFrEF. However, survival trends are improving with HFrEF but not HFpEF[8-11]. There have been numerous publications and guideline updates that provide a synopsis of pathophysiology[12-14], clinical correlation and pathways for assessment of DHF[1-3,15] and management[16]. This review is focused on establishing the importance of LA function and exercise testing in the workup of a patient presenting with SOB. We also explore the rationale for including LA metrics under the umbrella of the DHF syndrome focusing on published work using echocardiography as the imaging modality (DHF and HFpEF are used interchangeably, where DHF is used in context of the syndrome and HFpEF in the scientific commentary).

LEFT ATRIAL ANATOMY, PHYSIOLOGY AND FUNCTION IN HEALTH AND DISEASE

The LA is predominately composed of overlapping and varyingly aligned layers of muscle fibers that have marked variation in thickness but is overall, significantly thinner than the LV. The left coronary artery and oblique vein, which drain into the coronary sinus, are the main arterial and venous blood vessels. Specifics on LA anatomy have been previously detailed[17,18]. The LA has four important mechanical functions across three phases (Figure 1): (1) A reservoir (phase) to receive blood and store kinetic energy (as pressure) for LV filling that coincides with mitral valve closure to opening...
atrioventricular connectivity are established. There and electromechanical coupling passive and active Through LA and LV preload, afterload, contractility is a compensation to maintain stroke volume (SV). filling or preload has significant LA contribution and by LV characteristics and morphology. The fourth, LV stiffness (compliance) are predominately determined three, LV relaxation, distensibility (restoring force) and four parameters used to define diastolic function, LV diastole coincides with LA systolic phase. Of the LV and diastole

Figure 1  Phases of left atrial function. Left atrial preload is determined by blood flowing from the pulmonary vein. In this initial filling phase the LA acts a reservoir storing blood during left ventricular systole against a closed mitral valve. During LV diastole, diastasis and as the mitral valve opens it acts as a conduit, passively using stored energy to empty into the LV. Finally, in LV end diastole the LA contracts and actively empties blood completing the LV filling cycle. Reprinted from Karayannis et al[21], with permission of the publisher (Copyright © 2007, Springer Science + Business Media. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation). LA: Left atrial; LV: Left ventricle; Vp: Left atrial volume before atrial contraction; Vmax: Maximal volume (as defined at left ventricular end-systolic phase); Vmin: Left atrial minimal volume (as defined at left ventricular end-diastolic phase).

and ventricular events of isovolumic contraction, ejection and isovolumic relaxation; (2) a conduit (phase) for transiting blood (in early diastole) from the pulmonary veins to the LV after a pressure gradient develops to open the mitral valve and also passively during diastasis and is dependent on LV relaxation and preload; (3) a pump (contractile phase) to provide a "booster" depending on the preload, afterload, intrinsic contractility and electromechanical coupling (term defines the time between atrial electrical activation and mechanical activation (19)) to augment LV filling in late diastole; and (4) a suction effect to refill itself in early systole.

The LA contributes up to 30% of LV filling (The three phases can contribute around 40%, 35% and 25% respectively). LA flow from the pulmonary veins is continuous while LV filling is intermittent. The LA also acts as a volume sensor and regulates fluid balance by, neurohormonal function with production and regulation of natriuretic peptides, by regulatory (barometer) function via mechanoreceptors, and by interaction with renin angiotension aldosterone system/pathway (RAAS)[19-25].

LV and diastole
LV diastole coincides with LA systolic phase. Of the four parameters to define diastolic function, three, LV relaxation, distensibility (restoring force) and stiffness (compliance) are predominantly determined by LV characteristics and morphology. The fourth, LV filling or preload has significant LA contribution and is a compensation to maintain stroke volume (SV). Through LA and LV preload, afterload, contractility and electromechanical coupling passive and active atrioventricular connectivity are established. There are several publications that describe and evaluate LV aspects of DHF are cited[1,3,12,13,19,26,27]. Diastole is described in four phases and these phases can be related to phasic LA events (Figure 2)[28]: (1) Isovolumic relaxation during LA reservoir period; (2) rapid early filling; (3) diastasis during LA conduit phase; and (4) late filling, during atrial contraction phase.

Left atrial remodelling
When there is pressure and volume overload the process of atrial remodeling starts. In 220 healthy patients, age related LA indexed volumes changed only beyond the eight-decade[29]. In contrast, and without increasing LA size, changes in phasic atrial volumes and augmentation of LA contraction occur earlier, corresponding with age related alterations in LV diastolic relaxation[30,31]. Changes in the indexed LA volume (LAVi) appear to parallel the grade of diastolic diastolic dysfunction (DD)[32]. Atrial arrhythmias is an independent precipitant of atrial remodeling. The response of atrial cell to external stress incites hypertrophy, fibrosis and subsequently LA dilatation and hypococontractility[21]. LA dysfunction may alter the reservoir and conduit functions of the atrium and reduce the ability to absorb increases in LVEDP being transmitted to the pulmonary vasculature, for which there is a threshold similar to LV Frank-Starling mechanics[32]. Loss of phasic LA pump function can also lead to symptoms by reducing late LV diastolic filling, which is more marked when there is preexisting systolic impairment[25,33]. Pressure load to the LA can be seen in mitral stenosis and or increased LVEDP. Volume loading occurs in mitral regurgitation, intracardiac shunts or arteriovenous fistulae and high cardiac output states. These have to be factored in using LA metric when
Iyngkaran P et al. Diastolic heart failure workup

ROLE OF ATRIUM IN DHF WORKUP

In a patient with SOB, echocardiography will firstly confirm LV systolic function (i.e., normal or mildly impaired ventricle [LVEF > 50%]). A body of evidence is developing however to suggest that “sub clinical” systolic dysfunction such as reduced longitudinal LV shortening are present, and occur before the alteration seen in LVEF. At this stage the clinical context for DHF is evolving. Cardiac imaging with echocardiography however does not directly measure LVEDP and infers this by changes in volume, blood and tissue velocities. Invasive measures (LV pressure tracing or pressure volume data) and natriuretic peptides can provide direct information on myocardial stretch and hence diastolic abnormalities[22,38,39]. However, the noninvasively evaluated e/e’ (ratio of early diastolic transmural velocity to early diastolic tissue velocity) serves as a surrogate of LV EDP.

Some patients manifest symptoms during exercise and this similarly can be assessed[27,34-37]. There is no single non-invasive index that confirms or rules out the diagnosis, however using a combination of parameters, this can be achieved (Figure 3). Furthermore it is unclear if any one parameter provides greater weight than another.

Left atrium as a biomarker

There is a volume of data to support LA enlargement and adverse cardiovascular outcomes independent of age, gender and the major comorbid cardiovascular risk factors[22,38,39]. In fact LA dilatation should be considered pathological before the eight decade[28]. Among 2042 residents in Olmstead County, Minnesota over 45 years of age, LAVi predicted all cause mortality, as did the grade of DD[40]. From the same community, retrospective analysis of 1160 participants (> 65 years) followed for 3.8 ± 2.7 years, LAVi > 32 mL/m² predicted risk for first cardiovascular event (P = 0.003)[41]. Several studies with 851 and 1495 patients over 65 years of age, found that measures of LA size predicted new development of HF[42,43]. This risk was also demonstrated in 483 younger participants (mean age 47 years) followed for 6.8 years, where Leung et al showed that LAVi > 24 mL/m² was the only independent echocardiographic predictor of cardiovascular death, congestive heart failure, myocardial infarction, stroke and atrial fibrillation. Using a variety of methods, studies show an increase in cardiac and all cause mortality in a general population[44,45], following myocardial infarction[46,47], and with dilated cardiomyopathy[48]; predicts ischemic heart disease[49,50], atrial fibrillation and stroke[40,41,44,49-56].

Alteration in LA mechanics (function), with or without LA dilatation, correlate with disease states such as
hypertension, diabetes and renal impairment, and to adverse outcomes. In 1802 participants of the Dallas Heart study imaged with magnetic resonance imaging, decreasing LA emptying fraction was independently associated with mortality but not LAVi. In HF the reservoir and conduit functions are inversely related with Doppler parameters of DD and LVEDP. As HF progresses atrial contractility also gradually declines. Early changes in LA mechanics, correlations with comorbidities and disease severity and recovery with treatments, have been demonstrated for hypertension, atrial fibrillation and valvular heart disease, using a variety of methods.

**Left atrium as a barometer**

LA changes particularly the LAVi reflects the chronicity and cumulative effects of changes in LV filling pressures. While the LAVi does not reflect acute changes in LV pressures it can be used as a barometer for chronically elevated LV filling pressures. This change can persist for some time after pressures have normalized. Increased LA volume can also be seen in athletes, bradycardia, anemia, high output states, atrial arrhythmias and mitral valve disease, independent of diastolic dysfunction. When these conditions are excluded LAVi > 34 mL/m² should alert treating physicians to the possibility of DD and raised LV filling pressures.

The new guidelines are a positive step forward, and the authors for the first time acknowledged LA size, a surrogate for chronically elevated LVEDP and LA dysfunction. They fall short however as there are confounders for the abnormalities and none of the factors can be conclusively correlated to symptoms, where exercise testing could.

**Figure 3 How to diagnose heart failure with preserved ejection fraction.** From the 2016 consensus statements of HF, the diagnosis of HF requires 4 important factors: (1) the presence of symptoms and/or signs of HF; (2) a "preserved" EF (defined as LVEF ≥ 50% or 40%-49% for HfmrEF; (3) elevated levels of natriuretic peptides (BNP > 35 pg/mL and/or NT-proBNP > 125 pg/mL); (4) objective evidence of other cardiac functional and structural alterations underlying HF; and (5) In case of uncertainty, a stress test or invasively measured elevated LV filling pressure may be needed to confirm the diagnosis. However in clinical practice many patients present predominately with a symptom such as SOB. The new guidelines are a positive step forward, and the authors for the first time acknowledged LA size, a surrogate for chronically elevated LVEDP and LA dysfunction. They fall short however as there are confounders for the abnormalities and none of the factors can be conclusively correlated to symptoms, where exercise testing could. A: Atrial filling velocity; BNP: Brain natriuretic peptides; E: Early filling velocity; e': Early mitral annular tissue doppler velocity; EF: Ejection fraction; HfmrEF: Heart failure mid-range ejection fraction; LA: Left atrium; LAP: Left atrial pressure; LV: Left ventricle; LVEDP: Left ventricular end diastolic pressure; NT-proBNP: N Terminal Brain Natriuretic peptide; TR: Tricuspid regurgulation (adapted from References 1 and 3).

Breathlessness
Orthopnea
Paroxysmal nocturnal dyspnoea
Fatigue, tiredness, increased time to recover after exercise
Akle swelling

Elevated jugular venous pressure
Hepatogugular reflux
Third heart sound
Laterally displaced apex beat
Peripheral oedema (ankle, sacral, scrotal)
Weight gain (> 2 kg/wk)
diastolic filling abnormalities due to atrioventricular interdependence\cite{40}.

**IMAGING THE LEFT ATRIUM**

Conventional echocardiography is sufficient to assess atrial size, but a combination of conventional and novel techniques are required to assess atrial mechanical functions.

**Left atrial size assessment**

M-mode and 2D echocardiography measuring the antero-posterior diameter, as performed in early studies, is now agreed to be an inadequate measure of LA size. Both the American and European Society of Echocardiography are in consensus that LAV using either the ellipsoid model or Simpson’s method in two and four chamber apical views is more accurate as LA enlargement occurs asymmetrically. When the LAV is indexed (LAVi) it provides the strongest association, most sensitive predictor and risk stratification tool for cardiovascular outcomes\cite{2,3,22,38,55}. A detailed description of LAV is highlighted below\cite{35}.

**LA passive volumes consist of:** (1) Preatrial contraction volume (Vpreatrial), measured at the onset of the P-wave on an electrocardiogram (ECG); (2) minimal LA volume (Vmin), measured at the closure of the mitral valve in end-diastole; and (3) maximal LA volume (Vmax), measured just before the opening of the mitral valve in end-systole.

**LA active volumes are:** (1) LA reservoir volume (Vmax - Vpreatrial); (2) LA conduit volume (LV total SV - LA reservoir volume); (3) LA passive emptying volume (Vmax - Vpreatral); and (4) LA contractile volume (Vpreatrial - Vmin).

Physiological associations of LA size have been noted with body size and gender, but these differences are not apparent once indexed to BSA. Age related changes are seen at the extremes but not with normal aging. Based on the sensitivity and specificity for predicting cardiac events, population studies have shown mean LAVi by biplane Simpsons or area length methods was between 20-23 ± 6-7 mL/m$^2$. In the guidelines, 1 standard deviation (SD) from the mean > 28 mL/m$^2$ is considered LA enlargement and 2 SD from the mean > 34 mL/m$^2$ for DD\cite{31,40,44,51,53}. In the guidelines, 1 standard deviation (SD) from the mean > 28 mL/m$^2$ is considered LA enlargement and 2 SD from the mean > 34 mL/m$^2$ for DD\cite{31,40,44,51,53}. Pressure load to the LA can be seen in mitral stenosis and or increased LV diastolic compliance, altered hemodynamics and mitral valve disease. Peak transmitial A wave velocity, velocity time integral and atrial fraction can be used to measure LA contractile function and has been beneficial in following correction of atrial fibrillation with cardioversion, cathether ablation or surgery\cite{53,71-78}. The atrial ejection force can be calculated with several assumptions of the density of blood and a circular mitral annulus area, where diameter is measured in 4-chamber view. This has found correlation with return of atrial function post cardioversion, adverse cardiovascular remodeling and cardiovascular events\cite{79,80}, although significant technical limitations persist\cite{20}. Importantly all Doppler measurements can only be performed in sinus rhythm.

Tissue Doppler imaging of intrinsic myocardial velocity (e.g., mitral annulus), can provide regional and when averaged from several sites, global function. It is a low-velocity and high amplitude signal and has the advantage of being load independent. Tissue Doppler has deficiencies of angle dependency (acquisition angle - long axis), is dependent on cardiac motion and myocardial properties such as tethering and annular sampling site. A’ values has been shown to be a useful surrogate of global LA function, while all parameters (S’, E’ and A’) provide useful prognostic information\cite{30,31,81-86}.

Deformation analysis with strain and the speed of deformation with strain rate imaging can quantify regional and global function independent of tethering. Values however show regional variation\cite{63,73}. Positive values are seen with chamber dilatation and wall stretch and negative values with contraction. Similarly this method has shown correlations with clinical outcomes and prognosis such as maintenance of sinus rhythm and atrial mechanics in atrial fibrillation\cite{67-71,87}. New York Heart Association Functional Class\cite{87}, LA contractile function\cite{65}, hypertensive heart disease\cite{64,66} and valvar heart disease\cite{19}.

**EXERCISE DIASTOLOGY**

SOB and exercise intolerance due to HFpEF, should demonstrate an increased LVEDP with exercise. The
proven exercise protocols are stress echocardiography, combined stress echocardiography and cardiopulmonary stress test, and right heart catheterization with exercise. HFpEF is a systemic condition with an interaction of the primary cause coupled with secondary pathophysiological changes in the LV and LA. The continuity of the vasculature places the cardiac and peripheral endothelial beds at risk of injury when chronically exposed to risk factors. This loss of compliance or efficiency can see disproportionate rises in LV filling pressures, which can be buffered for, e.g., by changes in atrial function. Thus a combination of deficits in arterial-ventricular-atrial function will be present in symptomatic individuals where a rise in LVEDP or LA pressure is the common denominator.

Burgess et al.[91] studied 37 patients at baseline and after supine cycle ergometry, and found that the e/e’ of > 13 correlates with an elevated LVEDP during exercise. In another 166 patients post-exercise e/e’ > 13 was highly specific (90%) for stratifying an exercise capacity of < 8 METs or > 8 METs. Nedeljkovic et al.[99] studied 87 patients with HTN, exertional SOB and normal resting LV function with combined exercise stress echocardiography cardiopulmonary testing to identify masked HFpEF found correlations between e/e’ > 15 and reduced peak VO2 and other parameters with high sensitivity and specificity. Maeder et al.[30] identified 14 patients with diagnosed HFpEF and matched controls, who subsequently underwent supine cycle ergometer exercise, found that patients with HFpEF achieved a similar pulmonary capillary wedge pressure (PCWP) to asymptomatic controls at a much lower workload. However, contrary to Burgess et al.[91], the e/e’ did not reflect the hemodynamic changes during exercise in HFNEF patients.

Pulmonary artery pressures, which can act as a surrogate for elevated left sided filling pressures can also be used. This spectral Doppler method measures the tricuspid regurgitation (TR) jet velocity and applies the formula 4V² + right atrial pressure (V = Doppler velocity of regurgitant jet). Standardized measures of right atrial pressure are readily available from guideline and textbooks. While the non-invasive stress test is practical and translatable, translational gaps persists partly due discrepancies in role of e:e’ found in Burgess et al.[91] and Maeder et al.[30], identifying a suitable adjunct for pulmonary artery pressures when TR is absent, and establishing values that constitute elevated pressures across the spectrum of resting diastolic profiles, and baseline pulmonary artery pressures.

### Table 1 Imaging modalities and their correlations with components of atrial function

| LA function | Volumetric | Spectral Doppler | Tissue Doppler and deformation indexes |
|-------------|------------|-----------------|---------------------------------------|
|             | LA volume fraction | Transmirtal flow | PV flow | Composite indexes | TDI | Strain (cm) | Strain rate |
| Global      | LA EF ([LAmx - LAmn]/LAmx) | - | - | LAFI | - | - | - |
| Reservoir   | Expansion index ([LAmx - LAmn]/LAmx) | - | S | - | S’ | S | S |
| Conduit     | Passive EF ([LAmx - LAmx]/LAmx) | E | D | - | E | e-pos | E |
| Contractile (Booster) | Active EF ([LAmx - LAmx]/LAmx) | A | PVa | Ejection force (AEF) | LAKE | A’ | a-neg | A |

Table modified from Ref[22,34-36,88-98]. ε: Strain; A/A’: Atrial contraction velocity/tissue Doppler velocity; AEF: Atrial ejection force AEF = 0.5 × 1.06 g/cm³ × mitral annulus area (peak A velocity). Mass of blood is calculated as the product of the density of blood (ρ = 1.06 g/cm³) and volume of blood passing through mitral annulus; AFF: Atrial filling fraction, the ratio of the velocity time integral of the mitral A wave to the total diastolic transmital flow; E/E’: Early diastole velocity/tissue Doppler velocity; EF: Emptying fraction; LA: Left atrial; LAEF: Left atrial emptying fraction; LAFE: Left atrial functional index; LAKE: Left atrial kinetic energy; LAmx: Maximum left atrial volume; LAmn: Minimum left atrial volume; neg: Negative; pos: Positive; preA: Preatrial contraction; PV: Pulmonary venous; Pva: Pulmonary venous reversal velocity; S/S’: Ventricular systole velocity/tissue Doppler velocity; TDI: Tissue Doppler imaging.

### RATIONALE AND ARGUMENTS FOR FUTURE CLINICAL STUDIES OF DHF

**Clinical correlation of atrial derived parameters**

The current understanding of diastology does not allow us to definitively correlate symptoms to the varying changes in diastolic profiles. In addition no single parameter can be used to determine the diagnoses. In the process of grading diastolic abnormalities changes in the mitral valve velocity profiles and tissue Doppler occur as a normal part of aging. With the advent of exercise diastology and the inclusion of left atrial volume in the most recent guidelines, highlights the importance of looking for evidence that LV filling pressures are elevated in a patient with SOB. We thus feel that an important first step is to document an increase in intracardiac pressures and the subsequent steps should go on to explore the causes for this both in the LV and LA. The bases for the later is that many of the atrial derived parameters are used to define LV diastolic function, with little emphasis on how changes in LA function could alter this.
Terminology
DHF syndrome is a broad categorisation of a complex syndrome with multiple contributors where the end result is SOB and clinical impairment. Unlike SHF where the entirety of the syndrome is coupled with an impairment of LV myocardial contractility, in HFrEF it remains unclear how the interplay between degrees of LV stiffness and LA dynamics contributes to symptoms. Thus terminology in HFrEF should reflect the atrioventricular interaction in LV diastole. Lets explore several hypothetical case examples: (1) HfPEF - With predominantly impaired LV relaxation. In this scenario a patient would have clinical symptoms and signs, abnormal LV diastolic parameters, has demonstrated elevation of LVEDP (at rest or exercise), without significant LA abnormalities, and a shift of LVEDP and volume curve to the left; and (2) HFrEF - Secondary to atrial dysfunction/atrial fibrillation. In this scenario the patients have similar presentation as above, however despite rate control, remains symptomatic. Restoration of sinus rhythm correlates with clinical improvement of symptoms. Part of establishing the terminology requires an improved understanding of all aspects of LV and LA abnormalities.

Future clinical studies
The premise of any future study should be based on consolidating the diagnosis with this point in mind: “In a patient with SOB and normal LVEF the diagnosis of HFpEF can only be consolidated by reproducibly demonstrating an elevation of LVEDP or LA pressure before treatment, that this elevation is outside a physiological norm and correlates with the patients symptoms”. The premise of therapeutic studies while not the aim of this paper should also focus on atrioventricular pathophysiological derangements. From this point we can explore the steps in cardiac investigations.

Screening: (1) Firstly all patients should have a screening echocardiogram; and (2) epidemiology studies are still needed to correlate the chronology of diastolic parameters with time and symptoms.

Demonstrating increased LVEDP: Firstly, we need to demonstrate an increase in LVEDP, and secondly we need to demonstrate the abnormality in the atrioventricular context. An important question then is should exercise stress testing be a routine part of DHF work-up? Due to cost, availability and the sheer volume of patients’ invasive tests seem unrealistic, however non-invasive exercise echocardiography could screen patients needing an invasive test. Secondly, what parameters to use? (1) Pulmonary artery pressure elevations detected by exercise stress echocardiography can be a surrogate for LVEDP. Excluding other causes for pulmonary hypertension is important. When TR is absent patients could go onto an invasive exercise right heart study; and (2) The role of e/e’ and other variations in spectral and tissue Doppler parameters requires further attention. There is conflicting data from studies in the former and a lack of data for the latter[36,90]. Thirdly, natriuretic peptides: Are secreted in response to atrial (atrial natriuretic peptides) or ventricular (brain natriuretic peptides) stretch. These factors have different biological properties such as chamber secreted and half-life can be exploited for diagnosis and monitoring. In clinical translation its utility with exercise stress echocardiography as a surrogate for an invasive right heart study derived LVEDP is yet to be defined[95].

Atrial function: Is difficult to assess both at baseline and with exercise, as there are no clinically friendly tools. As many of the echocardiographic derived DHF parameters correlate with atrial mechanics, understanding how these parameters change with LA disease will better inform LV diastology. Several examples: From an invasive study in dogs undergoing exercise, it is observed that reservoir and booster functions increase but not conduit function[96]; in 50 HFpEF patients, using late diastolic mitral annular velocity and calculated left atrial reserve index, found reduced LA function with exercise that could contribute to symptoms in addition to LV systolic and diastolic abnormalities[97]. An improved understanding could also help inform future therapies targeting the LA.

Reliability in monitoring: Issues that need to be addressed are inter and intraobserver variability and the correlation of diastolic parameters following treatment and with changes in clinical status over time[98].

Diastolic compensation and chronology: For patients who have abnormal baseline diastology who do not demonstrate increases in LVEDP with exercise, we will need to find satisfactory means to exclude HFpEF from the diagnosis. This will require improved understanding of diastolic compensation in the chronology of myocardial cellular function, where a different result could be elicited with different conditions.

CONCLUSION
SOB is a common symptom presentation to cardiology clinics. Clinical workup can point toward coronary artery disease, HFrEF, respiratory causes or anemia. There is also a sizable group where differentiation is required between deconditioning, obesity or HFpEF. Thus diagnosis of HFpEF has and still remains difficult where no one parameter we have is “a smoking gun”. Baseline echocardiographic parameters have translated into flow diagrams published in the latest guidelines. There remain however important gaps in the understanding of this syndrome: (1) Diastolic function is complex in that it requires functional mechanics of both the atrium and ventricle, where less importance has been placed in understanding LA function; (2) exercise stress echocardiography is underutilized in the diagnostic
REFERENCES

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. Authors' Task Force Members; Document Reviewers. 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 J Heart Fail 2016; 18: 891-975 [PMID: 27207191 DOI: 10.1002/ejhf.952]

2. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskaempf FA, Rademakers FE, Marino P, Smeiseth OA, De Keulenenaer G, Leite-Moreira AB, Borbély A, Edes I, Handoko ML, Heymann 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 and echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007; 28: 2539-2550 [PMID: 17428822 DOI: 10.1093/eurheartj/ehl037]

3. Nagues SF, Smeiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edwards T, Flachskaempf FA, Giliberte TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD; Houston, Texas; Oslo, Norway; Phoenix, Arizona; Nashville, Tennessee; Hamilton, Ontario, Canada; Uppsala, Sweden; Ghent and Liège, Belgium; Cleveland, Ohio; Novara, Italy; Rochester, Minnesota; Bucharest, Romania; and St. Louis, Missouri. 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. Eur Heart J Cardiovasc Imaging 2016; 17: 1321-1360 [PMID: 27428299 DOI: 10.1002/ejci.2016.01.011]

4. Kovács SJ. Diastolic function in heart failure. Clin Med Insights Cardiovasc Med 2015; 9: 49-55 [PMID: 25922587 DOI: 10.4137/CMC.S1874]

5. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation 2009; 119: 3070-3077 [PMID: 19506115 DOI: 10.1161/CIRCULATIONAHA.108.81944]

6. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis 2005; 47: 320-332 [PMID: 16003647 DOI: 10.1016/j.pcad.2005.02.010]

7. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355: 251-259 [PMID: 16855265 DOI: 10.1056/NEJMoa052256]

8. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011; 13: 18-28 [PMID: 20685685 DOI: 10.1093/ejhf/hfq121]

9. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015; 175: 996-1004 [PMID: 25895156 DOI: 10.1001/jamainternmed.2015.0924]

10. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012; 33: 1756-1757 [PMID: 21821494 DOI: 10.1093/eurheartj/ehr254]

11. Gottlieber JS, McClelland RL, Marshall R, Shemanski L, Farber CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002; 137: 631-639 [PMID: 12379062 DOI: 10.7326/0003-4819-137-8-200210150-00006]

12. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2014; 11: 507-515 [PMID: 24958077 DOI: 10.1038/nrcardio.2014.83]

13. Kovács Á, Papp Z, Nagy L. Causes and pathophysiology of heart failure with preserved ejection fraction. Heart Fail Clin 2014; 10: 389-398 [PMID: 24975903 DOI: 10.1016/j.hfc.2014.04.002]

14. Phan TT, Shivu GN, Abozgoua K, Sanderson JE, Frennea M. The pathophysiology of heart failure with preserved ejection fraction: from molecular mechanisms to exercise haemodynamics. Int J Cardiol 2012; 158: 337-343 [PMID: 21794933 DOI: 10.1016/j.ijcard.2011.06.113]

15. Flachskaempf FA, Biering-Sorensen T, Solomon SD, Duvernoy O, Bjermer T, Smeiseth OA. Cardiac Imaging to Evaluate Left Ventricular Diastolic Function. JACC Cardiovasc Imaging 2015; 8: 1071-1093 [PMID: 26381769 DOI: 10.1016/j.jcmg.2015.07.004]

16. Nanayakkara S, Kaye DM. Management of heart failure with preserved ejection fraction: a review. Clin Ther 2015; 37: 2186-2198 [PMID: 26385583 DOI: 10.1016/j.clinthera.2015.08.005]

17. Corradi D, Maestri R, Macchi E, Callegari S. The atria: from morphology to function. J Cardiovasc Med 2011; 12: 223-235 [PMID: 20812935 DOI: 10.1111/j.1540-8167.2010.01887.x]

18. Ho SY, Sanchez-Quintana D, Cabrera JA, Anderson RH. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. J Cardiovasc Electrophysiol 1999; 10: 1525-1533 [PMID: 10571372]

19. Todaro MC, Choudhuri I, Belohlavek M, Jahangir A, Carej S, Oreo L, Khandheria BK. New echocardiographic techniques for evaluation of left atrial mechanics. Eur J Heart Fail 2012; 14: 973-984 [PMID: 22909795 DOI: 10.1002/ejhf.174]

20. Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiology correlates, and prognostic implications. Am J Cardiol 2008; 156: 1056-1064 [PMID: 19032999 DOI: 10.1016/j.amjcard.2008.07.021]

21. Rossi A, Gheorghiade M, Tripopiasidis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction: structure, function, and significance. Circ Heart Fail 2014; 7: 1042-1049 [PMID: 25413975 DOI: 10.1161/CIRCHEARTFAILURE.114.001276]

22. Hoft BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol 2014; 63: 493-505 [PMID: 24291276 DOI: 10.1016/j.jacc.2013.10.055]

23. Blumke GG, Meleod CJ, Barnes ME, Seward JB, Peetlikka PA, Bastiansen PM, Tsang TS. Left atrial function: physiology, assessment, and clinical implications. Eur J Echocardiogr 2011; 12: 421-430 [PMID: 21568866 DOI: 10.1093/eurheartj/ejq175]

24. Patel DA, L>jive J, Milani RV, Shah S, Gilliland Y. Clinical implications of left atrial enlargement: a review. Ochsner J 2009; 9: 191-196 [PMID: 21603443 DOI: 10.1513/ajnl.2009.3030]

25. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TS. Left atrial size: physiologic determinants and clinical applications. Am J Cardiol 2006; 47: 2357-2363 [PMID: 17428822 DOI: 10.1016/j.ijcard.2011.06.113]
Iyngkaran P et al. Diastolic heart failure workup

16781359 DOI: 10.1016/j.jacc.2006.02.048

Asrar Ul Haq M, Matha V, Rudd N, Hare DL, Wong C. Heart failure with preserved ejection fraction - unmasking the diagnosis mystique. Am J Cardiol 2014; 110: 190-113 [PMID: 25360383]

Asrar Ul Haq M, Goh CY, Levinger E, Wijl C, Hare DL. Clinical utility of exercise training in heart failure with reduced and preserved ejection fraction. Clin Med Insights Cardiovasc Med 2015; 9: 1-9 [PMID: 25698883 DOI: 10.4137/CMC.S21372]

Mitchell JR, Wang J. Expanding application of the Wiggers diagram to teach cardiovascular physiology. Adv Physiol Educat 2014; 38: 170-175 [PMID: 24913453 DOI: 10.1152/advanc.00123.2013]

Barnes ME, Gersh BJ, Takemoto Y, Rosales AG, population 2010; [PMID: ]

Boyd AC, Schiller NB, Leung D, Ross DL, Thomas L. Atrial dilation and altered function are mediated by age and diastolic function but not before the eighth decade. JACC Cardiovasc Imaging 2011; 4: 234-242 [PMID: 21414570 DOI: 10.1016/j.jcmg.2010.11.018]

Spencer KT, Mor-Avi V, Gorcsan J 3rd, DeMaria AN, Kimball TR, Monaghan MJ, Perez JE, Weintert L, Bednarz J, Edelman K, Kwan OL, Glasscock B, Hancock J, Baumann C, Lang RM. Effects of aging on left atrial reservoir, conduit, and booster pump function: a multi-institutional acoustic quantification study. Heart 2001; 85: 272-277 [PMID: 11178264]

Thomas L, Levett K, Boyd A, Leung DY, Schiller NB, Ross DL. Compensatory changes in atrial volumes with normal aging: is atrial enlargement inevitable? J Am Coll Cardiol 2002; 40: 1630-1635 [PMID: 12427416]

Blondheim DS, Osipov A, Meisel SR, Frimerman A, Shochat M, Shoton A. Relation of left atrial size to function as determined by transesophageal echocardiography. Am J Cardiol 2005; 96: 457-463 [PMID: 16504483 DOI: 10.1016/j.amjcard.2005.03.101]

Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights. Mayo Clin Proc 2001; 76: 832-836 [PMID: 11486801 DOI: 10.4103/0002-9149.101460-6]

Bailey KR, Seward JB. Prediction of risk for first age-related cardiovascular events in patients originally diagnosed with lone atrial fibrillation in 1655 older men and women. Mayo Clin Proc 2001; 76: 476-475 [PMID: 11357793 DOI: 10.4065/76.2008.0108]

Russi A, Cicioira M, Zanolli L, Sandrini R, Golia G, Zardini P, Enriquez-Sarano M. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol 2002; 40: 1425 [PMID: 12392832 DOI: 10.1016/S0735-1097(02)03507-5]

Ossareh A, Bursi F, Bailey KR, Redder GS, Wright RS, Park SW, Bailey KR, Popp RL. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. Circulation 2003; 107: 2207-2212 [PMID: 12695291 DOI: 10.1161/01.CIR.0000066318.21784.43]

Beinart R, Boyko V, Schwammenthal E, Kuperstein R, Sagie A, Hod H, Mateszky S, Behar S, Eldar M, Feinberg MS. Long-term prognostic significance of left atrial volume in acute myocardial infarction. J Am Coll Cardiol 2004; 44: 327-334 [PMID: 15261927 DOI: 10.1016/j.jacc.2003.06.062]

Laukanka JA, Kuri S, Erinen J, Huttunen M, Salonen JT. Left atrium size and the risk of cardiovascular death in middle-aged men. Arch Intern Med 2005; 165: 1788-1793 [PMID: 16087829 DOI: 10.1001/archinte.165.15.1788]

Moller JE, Hillsis GS, Oh JK, Seward JB, Reeder GS, Wright RS, Park SW, Bailey KR, Popp RL. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. Circulation 2003; 107: 2207-2212 [PMID: 12695291 DOI: 10.1161/01.CIR.0000066318.21784.43]

Bailey KR, Seward JB. Prediction of risk for first age-related cardiovascular events in patients originally diagnosed with lone atrial fibrillation in 1655 older men and women. Mayo Clin Proc 2001; 76: 832-836 [PMID: 11486801 DOI: 10.4103/0002-9149.101460-6]

Barnes ME, Miyasaka Y, Seward JB, Gersh BJ, Rosales AG, Bailey KR, Petty GW, Wibbers DO, Tsang TS. Left atrial volume in the prediction of ischemic stroke in an elderly cohort without atrial fibrillation.Mayo Clin Proc 2004; 79: 1008-1014 [PMID: 15301328 DOI: 10.4065/79.8.1008]

Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Taketomo Y, Diamond PM, Marra MA, Gersh BJ, Wibbers DO, Petty GW, Seward JB. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clin Proc 2001; 76: 476-475 [PMID: 11357793 DOI: 10.4065/76.5.467]

Di Tullio MR, Sacco RL, Sciaccia RM, Honma S. Left atrial size and the risk of ischemic stroke in an ethnically mixed population. Stroke 1999; 30: 2019-2024 [PMID: 10512901 DOI: 10.1161/01.STR.30.10.2019]

Benjamin EJ, D’Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation 1995; 92: 835-841 [PMID: 7641364 DOI: 10.1161/01.CIR.92.4.835]

Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation 1994; 89: 724-730 [PMID: 8313561 DOI: 10.1161/01.CIR.89.2.724]

Caplan LR, D’Cruz I, Hier DB, Reddy H, Shah S. Atrial size, atrial fibrillation, and stroke. Ann Neurol 1986; 19: 158-161 [PMID: 3968758 DOI: 10.1002/ana.410190208]

Leischik R, Littwitz H, Dwornik B, Garg P, Zhu M, Sahn DJ, Horlitz
Bailey KR, Casaclang Kimura G. Correlation between left ventricular end diastolic pressure and peak left atrial wall strain during left ventricular systole. J Am Soc Echocardiogr 2009; 22: 847-851 [PMID: 19506602 DOI: 10.1016/j.echo.2009.04.026]

Sirbu C, Herbots L, D’hooge J, Claus P, Marciniak A, Langeland T, Bijnen B, Rademakers FE, Sutherland GR. Feasibility of strain and strain rate imaging for the assessment of regional left atrial deformation: a study in normal subjects. Eur J Echocardiography 2006; 7: 199-208 [PMID: 16054869 DOI: 10.1016/j.euje.2005.06.001]

Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, Ballo P. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. J Am Soc Echocardiogr 2011; 24: 898-908 [PMID: 21665431 DOI: 10.1016/j.echo.2011.04.014]

Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, Marino E, Galderisi M. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. Cardiovasc Ultrasound 2009; 7: 6 [PMID: 19200402 DOI: 10.1186/1476-7120-7-6]

Kokubu N, Yuda S, Tsuchishita K, Hashimoto A, Nakata T, Miura T, Ura N, Nagao K, Tsuzuki C, Wabayahashi C, Shimamoto K. Noninvasive assessment of left atrial function by strain rate imaging in patients with hypertension: a possible beneficial effect of renin-angiotensin system inhibition on left atrial function. Hypertens Res 2007; 30: 13-21 [PMID: 17460367 DOI: 10.1291/hypres.30.13]

Saha SK, Anderson PL, Caracoglio G, Kiotsokagoulo A, Wilansky S, Govind S, Mori N, Sengupta PP. Global left atrial strain correlates with CHADS2 score risk in patients with atrial fibrillation. J Am Soc Echocardiogr 2011; 24: 506-512 [PMID: 21477990 DOI: 10.1016/j.echo.2011.02.012]

Kuppahtally SS, Akoum N, Burgon NS, Badger TJ, Khomvongski EG, Vijayakumar S, Rao SN, Blauer J, Fish EN, Dibella EV, Macleod RS, McGann C, Litwin SE, Marrouche NF. Left atrial strain and diastolic pressure: noninvasive assessment of atrial systolic function. J Am Coll Cardiol 2013; 62: 163-170 [PMID: 23688727 DOI: 10.1016/j.jacc.2012.09.014]

Choong CY, Herrmann HC, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. J Am Coll Cardiol 1987; 10: 800-808 [PMID: 2958532 DOI: 10.1016/S0735-1097(87)80273-5]

Klein AL, Burstow DJ, Taji AJ, Zachariah PK, Bailey KR, Seward JB. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. Mayo Clin Proc 1994; 69: 212-224 [PMID: 8133658 DOI: 10.4330/wjc.v2.i7.163]

Manning WJ, Silverman DI, Katz SE, Riley MF, Doherty RM, Munson JT, Douglas PS. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. J Am Coll Cardiol 1994; 23: 1535-1540 [PMID: 8195510 DOI: 10.1016/0735-1097(94)90562-1]

Thomas L, Thomas SP, Hoy M, Boyd A, Schiller NB, Ross DL. Comparison of left atrial volume and function after linear ablation and after cardioversion for chronic atrial fibrillation. Am J Cardiol 2004; 93: 165-170 [PMID: 14715341 DOI: 10.1016/j.amjcard.2003.09.033]

Yu CM, Sanderson JE, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function. J Am Coll Cardiol 1997; 10: 174-179 [PMID: 10010753 DOI: 10.1016/S0735-1097(96)81132-7]
Iyngkaran P et al. Diastolic heart failure workup

diastolic function. J Am Coll Cardiol 1997; 30: 474-480 [PMID: 9247521 DOI: 10.1016/S0735-1097(97)88335-0]

87 Di Salvo G, Caso P, Lo Piccolo R, Fusco A, Martinello AR, Russo MG, D’Onofrio A, Severino S, Calabrò P, Pacileo G, Mininni N, Calabrò R. Atrial myocardialocardial properties predict maintenance of sinus rhythm after external cardioversion of recent-onset lone atrial fibrillation: a color Doppler myocardial imaging and transthoracic and transesophageal echocardiographic study. Circulation 2005; 112: 387-395 [PMID: 16006491 DOI: 10.1161/ CIRCULATIONAHA.104.463125]

88 Penicka M, Bartunk J, Trkalova H, Hrubakova H, Maruskova M, Karasek J, Kocka V. Heart failure with preserved ejection fraction in outpatients with unexplained dyspnea: a pressure-volume loop analysis. J Am Coll Cardiol 2010; 55: 1701-1710 [PMID: 20394874 DOI: 10.1016/j.jacc.2009.11.076]

89 Nedeljkovic I, Banovic M, Stepanovic J, Giga V, Djordjevic-Dikic A, Trifunovic D, Nedeljkovic M, Petrovic M, Dobric M, Dikic N, Zlatar M, Beleslin B. The combined exercise stress echocardiography and cardiopulmonary exercise test for identification of masked heart failure with preserved ejection fraction in patients with hypertension. Eur J Prev Cardiol 2016; 23: 71-77 [PMID: 26358991 DOI: 10.1177/204787315604836]

90 Oh JK, Park SJ, Nagheu SF. Established and novel clinical applications of diastolic function assessment by echocardiography. Circ Cardiovasc Imaging 2011; 4: 444-455 [PMID: 21772012 DOI: 10.1161/CIRCIMAGING.110.961623]

91 Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol 2006; 47: 1891-1900 [PMID: 16682317 DOI: 10.1016/ j.jacc.2006.02.042]

92 Mezzani A, Agostoni P, Cohen-Solal A, Corrà U, Jegier A, Kouidi E, Mazic S, Meurin P, Piepoli M, Simon A, Laethem CV, Vanhees L. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil 2009; 16: 249-267 [PMID: 19440156 DOI: 10.1097/ HJR.0b013e3282914e8]

93 Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Cardiopulmonary exercise testing variables reflect the degree of diastolic dysfunction in patients with heart failure-normal ejection fraction. J Cardiopulm Rehabil Prev 2010; 30: 165-172 [PMID: 20216325 DOI: 10.1097/HCR.0b013e3181d8cdad]

94 Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. J Am Coll Cardiol 2005; 46: 1883-1890 [PMID: 16286176 DOI: 10.1016/ j.jacc.2005.07.051]

95 Hamaasaki H. The Effects of Exercise on Natriuretic Peptides in Individuals without Heart Failure. Sports 2016; 4: 32 [DOI: 10.3390/ sports4020032]

96 Nishikawa Y, Roberts JP, Tan P, Klopfenstein CE, Klopfenstein HS. Effect of dynamic exercise on left atrial function in conscious dogs. J Physiol 1994; 481 ( Pt 2): 457-468 [PMID: 7738837 DOI: 10.1113/ jphysiol.1994.sp020454]

97 Tan YT, Wenzelburger F, Lee E, Nightingale P, Heftie G, Leyva F, Sanderson JE. Reduced left atrial function on exercise in patients with heart failure and normal ejection fraction. Heart 2010; 96: 1017-1023 [PMID: 20584857 DOI: 10.1136/hrt.2009.189118]

98 Pagel PS, Kehl F, Gare M, Hettrick DA, Kersten JR, Warltier DC. Mechanical function of the left atrium: new insights based on analysis of pressure-volume relations and Doppler echocardiography. Anesthesiology 2003; 98: 975-994 [PMID: 12657862 DOI: 10.1097/0 000542-20030400-00027]

99 Meris A, Amigoni M, Uno H, Thune JJ, Verma A, Køber L, Bourgou M, McMurray JJ, Velazquez EJ, Maggioni AP, Ghali J, Arnold JM, Zelenkofske S, Pfeffer MA, Solomon SD. Left atrial remodelling in patients with myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: the VALIANT Echo study. Eur Heart J 2009; 30: 56-65 [PMID: 19001474 DOI: 10.1093/eurheartj/ehn499]

100 Ristow B, Ali S, Whooley MA, Schiller NB. Usefulness of left atrial volume index to predict heart failure hospitalization and mortality in ambulatory patients with coronary heart disease and comparison to left ventricular ejection fraction (from the Heart and Soul Study). Am J Cardiol 2008; 102: 70-76 [PMID: 18572038 DOI: 10.1016/ j.amjcard.2008.02.099]

P- Reviewer: Teragawa H; S- Editor: Kong JX; L- Editor: A; E- Editor: Lu YJ
Author/s: Iyngkaran, P; Anavekar, NS; Neil, C; Thomas, L; Hare, DL

Title: Shortness of breath in clinical practice: A case for left atrial function and exercise stress testing for a comprehensive diastolic heart failure workup.

Date: 2017-12-26

Citation: Iyngkaran, P., Anavekar, N. S., Neil, C., Thomas, L. & Hare, D. L. (2017). Shortness of breath in clinical practice: A case for left atrial function and exercise stress testing for a comprehensive diastolic heart failure workup. World J Methodol, 7 (4), pp.117-128. https://doi.org/10.5662/wjm.v7.i4.117.

Persistent Link: http://hdl.handle.net/11343/255980

File Description: Published version

License: CC BY-NC