

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

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**Author contributions:** Iyngkaran P wrote the paper; all authors read, agreed on arguments raised and provided feedback on paper.

**Conflict-of-interest statement:** All co-authors have secured independent and governmental research funding. None pose a conflict of interest for this review.

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Manuscript source: Invited manuscript

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Received: March 10, 2017

Peer-review started: March 17, 2017

First decision: May 23, 2017

Revised: June 29, 2017

Accepted: November 22, 2017

Article in press: November 22, 2017

Published online: December 26, 2017

### 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 function, which contributes to at least 25% of diastolic left ventricular filling; additionally, exercise stress testing to elicit symptoms and test the dynamics of diastolic parameters, especially when access to the "gold standard" invasive tests is lacking, presents clinical translational gaps. It is thus important in diastolic heart failure workup to understand 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

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**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.

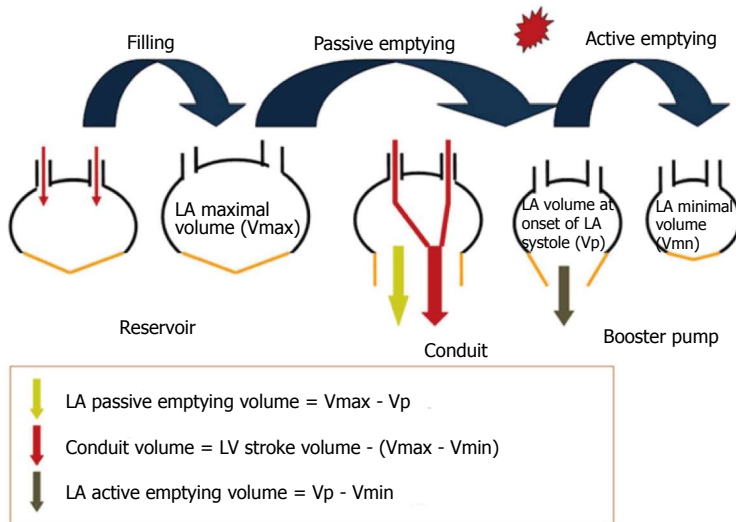
To understand the controversies in DHF it is important to go back to the basics. HF is defined as "a clinical syndrome characterized by typical symptoms (*e.g.*, breathlessness, ankle swelling and fatigue) that may be accompanied by signs (*e.g.*, elevated jugular venous pressure, pulmonary crackles 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"<sup>[1]</sup>. 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<sup>[2,3]</sup>; 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<sup>[2,4]</sup>; 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 been 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%)<sup>[5]</sup>. The etiology and pathophysiological basis also appears different. Patients tend to be older with greater burden of co-morbidities<sup>[6,7]</sup>. Cardiovascular and non-cardiovascular mortality is increased, although lower than HFrEF. However, survival trends are improving with HFrEF but not HFpEF<sup>[8-11]</sup>. There have been numerous publications and guideline updates that provide a synopsis of pathophysiology<sup>[12-14]</sup>, clinical correlation and pathways for assessment of DHF<sup>[1-3,15]</sup> and management<sup>[16]</sup>. 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<sup>[17,18]</sup>. 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



**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*<sup>[21]</sup>, 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 upto 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)<sup>[19-25]</sup>.

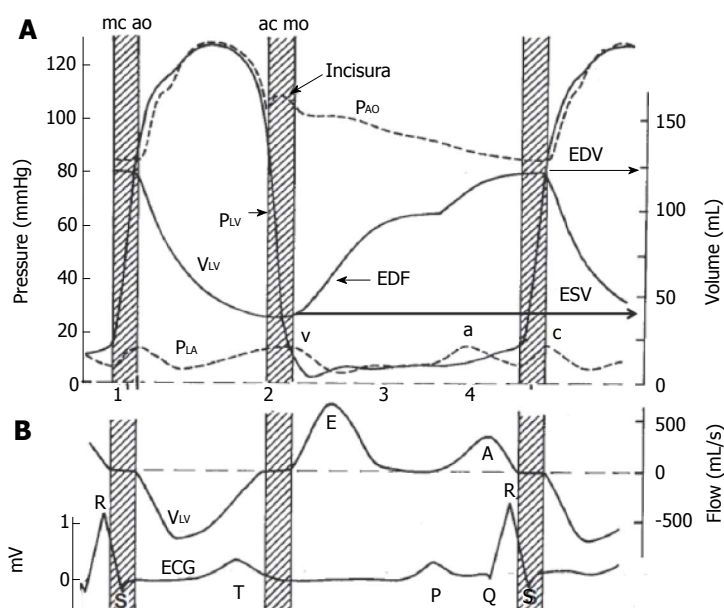
### LV and diastole

LV diastole coincides with LA systolic phase. Of the four parameters used to define diastolic function, three, LV relaxation, distensibility (restoring force) and stiffness (compliance) are predominately 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<sup>[1,3,12,13,19,26,27]</sup>. Diastole is described in four phases and these phases can be related to phasic LA events (Figure 2)<sup>[28]</sup>: (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<sup>[29]</sup>. 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<sup>[30,31]</sup>. Changes in the indexed LA volume (LAVi) appear to parallel the grade of diastolic dysfunction (DD)<sup>[22]</sup>. 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 hypocontractility<sup>[21]</sup>. 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<sup>[32]</sup>. 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<sup>[25,33]</sup>. 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



**Figure 2** Describes the volume and flow relationships in the left atrium and left ventricle throughout one cardiac cycle, *i.e.*, systole and diastole. A: Pressure (P) and volume (V) are presented for the Aorta (Ao), left atrium (LA) and left ventricle (LV). Systole: During the early phase between mitral valve closure (mc) and aortic valve opening (ao) is the isovolumic contraction phase (stripped bar), where there is increase in PLV (solid line) without change in VLV (solid line). This is followed by ventricular contraction with a rise in PLV and PAO (upper dashed line), that peaks mid cycle, and a reduction in VLV. Diastole: At the end of LV contraction, and when the PLV is lower than the aorta the aortic valve closes (ac), followed by a period of isovolumic LV relaxation (stripped bar), where there is reduction in PLV without a change in VLV. The Incisura or dirotic notch describes the small backflow of blood into the LV. Early diastolic point of early diastolic filling. In diastole PLA is generated early by the reservoir and conduit atrial function (v wave - lower dashed line) and corresponds with early diastolic filling (EDF) and a late atrial contraction or booster function (a wave) and contributes to late diastolic filling. Ventricular volumes are as end diastolic or end systolic (EDV or ESV; solid line). Cardiac sounds are shown as 1-4; B: Diagram showing relationship between electrical conduction and blood flow with an additional catheter in the LV. Systolic blood flow out of the ventricle (V LV), is followed by early diastolic blood flow into the LV (E wave), baste blood flow into the LV during LA contraction (A wave). A standard ECG lead II shows LA depolarization, LV depolarization, and LV repolarization (P wave, QRS complex, and T wave, respectively) (Published in Ref 28, figure provided courtesy of Dr. John V. Tyberg and Dr. Henk E. D. J. ter Keurs. Permission required). ECG: Electrocardiogram.

evaluating DD.

## ROLE OF ATRIUM IN DHF WORKUP

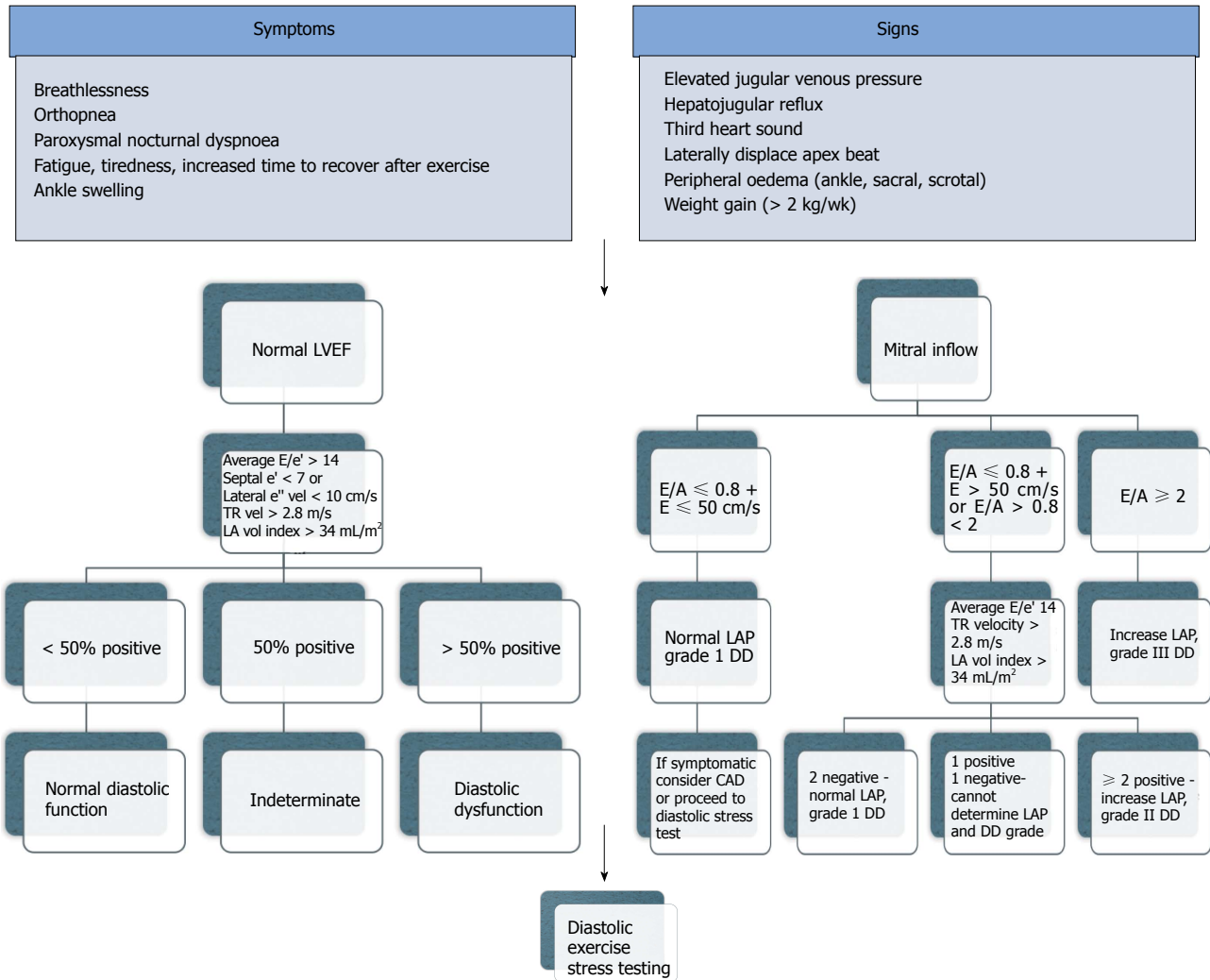
In a patient with SOB, echocardiography will firstly confirm LV systolic function (*i.e.*, normal or mildly impaired ventricle (LVEF > 50%). A body of evidence is developing however to suggest that "sub clinical" systolic dysfunction such as reduced longitudinal LV shortening are present, and occur before 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<sup>[15]</sup>. However, the noninvasively evaluated  $e/e'$  (ratio of early diastolic transmitral 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<sup>[27,34-37]</sup>. 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<sup>[22,38,39]</sup>. In fact LA dilatation should be considered pathological before the eight decade<sup>[28]</sup>. Among 2042 residents in Olmstead County, Minnesota over 45 years of age, LAVi predicted all cause mortality, as did the grade of DD<sup>[40]</sup>. From the same community, retrospective analysis of 1160 participants (> 65 years) followed for  $3.8 \pm 2.7$  years, LAVi > 32 mL/m<sup>2</sup> predicted risk for first cardiovascular event ( $P = 0.003$ )<sup>[41]</sup>. Several studies with 851 and 1495 patients over 65 years of age, found that measures of LA size predicted new development of HF<sup>[42,43]</sup>. 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/m<sup>2</sup> 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<sup>[44,45]</sup>, following myocardial infarction<sup>[46,47]</sup>, and with dilated cardiomyopathy<sup>[48]</sup>; predicts ischemic heart disease<sup>[41,49,50]</sup>, atrial fibrillation and stroke<sup>[40,41,44,49-56]</sup>.

Alteration in LA mechanics (function), with or without LA dilatation, correlate with disease states such as



**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 regurgitation (adapted from References 1 and 3).

hypertension, diabetes and renal impairment, and to adverse outcomes<sup>[57,58]</sup>. 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<sup>[59]</sup>. 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<sup>[60-62]</sup>. Early changes in LA mechanics, correlations with comorbidities and disease severity and recovery with treatments, have been demonstrated for hypertension<sup>[63-65]</sup>, atrial fibrillation<sup>[66-70]</sup> and valvular heart disease, using a variety of methods<sup>[19,22]</sup>.

**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/m<sup>2</sup> should alert treating physicians to the possibility of DD and raised LV filling pressures<sup>[15]</sup>.

To summarize the data, firstly LA size is a marker of health in a population; secondly a change in size highlights a remodeling process that predicts adverse outcomes; and thirdly alterations in LA size and mechanics potentially is caused by alterations in LV

diastolic filling abnormalities due to atrioventricular interdependence<sup>[40]</sup>.

## 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<sup>[2,3,22,38]</sup>. A detailed description of LAV is highlighted below<sup>[55]</sup>.

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

**LA active volumes are:** (1) LA reservoir volume ( $V_{max} - V_{min}$ ); (2) LA conduit volume (LV total SV - LA reservoir volume); (3) LA passive emptying volume ( $V_{max} - V_{preA}$ ); and (4) LA contractile volume ( $V_{preA} - V_{min}$ ).

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 method was between  $20-23 \pm 6-7 \text{ mL/m}^2$ , giving a normal value of  $22 \pm 6 \text{ mL/m}^2$ <sup>[31,40,44,51,53]</sup>. In the guidelines, 1 standard deviation (SD) from the mean  $> 28 \text{ mL/m}^2$  is considered LA enlargement and 2 SD from the mean  $> 34 \text{ mL/m}^2$  for DD<sup>[3,18,21]</sup>. 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 evaluating DD and LA changes. Factoring these conditions LAVi has been shown to strongly correlate with the degree of DD and even differentiate between normal and pseudonormal filling patterns<sup>[19,20,22,50,71,72]</sup>.

### Left atrial function assessment

The gold standard test atrial volume loop is invasive

and not routinely available. Four established echocardiographic parameters can provide information on the varying phases of LA function with advantages and disadvantages (Table 1).

2D volumetric analysis (the volume method) is the simplest but requires skill in obtaining the images and is time consuming. It uses LA volume at their maximum, minimum and just before LA systole to determine functions.

Spectral (pulsed wave) Doppler of transmitral flow and pulmonary veins (sampled at mitral leaflet tips) are readily available, easy to use but only provides estimate of LA function. It is dependent on immediate loading conditions and can be affected by myocardial tethering acquisition angle, heart rates, atrial fibrillation, conduction system disease, age related reductions in LV diastolic compliance, altered hemodynamics and mitral valve disease. Peak transmitral 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, catheter ablation or surgery<sup>[53,71-78]</sup>. 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<sup>[79,80]</sup>, although significant technical limitations persist<sup>[20]</sup>. 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<sup>[20,31,81-86]</sup>.

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<sup>[63,73]</sup>. 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<sup>[67-71,87]</sup>, New York Heart Association Functional Class<sup>[97]</sup>, LA contractile function<sup>[63,65]</sup>, hypertensive heart disease<sup>[64,66]</sup> and valvular heart disease<sup>[19]</sup>.

## EXERCISE DIASTOLOGY

SOB and exercise intolerance due to HFpEF, should demonstrate an increased LVEDP with exercise. The

**Table 1** Imaging modalities and their correlations with components of atrial function<sup>1</sup>

LA function	Volumetric	Spectral Doppler			Tissue Doppler and deformation indexes		
	LA volume fraction	Transmitral flow	PV flow	Composite indexes	TDI	Strain ( $\epsilon$ )	Strain rate
Global	LA EF [(LAmax - LAmin)/LAmax]	-	-	LAFI	-	-	-
Reservoir	Expansion index [(LAmax - LAmin)/LAmin]	-	S	-	S'	S;	S
Conduit	Passive EF [(LAmax - LApre-A)/LAmax]	E	D	-	E'	e-pos	E
Contractile (Booster)	Active EF [(LApre-A - LAmin)/LApre-A]	E/A	PVa	Ejection force (AEF) LAKE	A'	a-neg	A
		AFF					

<sup>1</sup>Table modified from Ref<sup>[20,21]</sup>.  $\epsilon$ : Strain; A/A': Atrial contraction velocity/tissue Doppler velocity; AEF: Atrial ejection force Atrial ejection force =  $0.5 \times 1.06 \text{ g/cm}^3 \times \text{mitral annulus area (peak A velocity)}$ . Mass of blood is calculated as the product of the density of blood ( $\rho = 1.06 \text{ g/cm}^3$ ) 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 transmitral flow; E/E': Early diastole velocity/tissue Doppler velocity; EF: Emptying fraction; LA: Left atrial; LAEF: Left atrial emptying fraction; LAFI: Left atrial functional index; LAKE: Left atrial kinetic energy; LAmax: Maximum left atrial volume; LAmin: 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.

proven exercise protocols are stress echocardiography, combined stress echocardiography and cardiopulmonary stress test, and right heart catheterization with exercise<sup>[27,34-36,88-98]</sup>. 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<sup>[27]</sup>. 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.*<sup>[91]</sup> 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<sup>[91]</sup>. Nedeljkovic *et al.*<sup>[89]</sup> 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  $\dot{V}O_2$  and other parameters with high sensitivity and specificity. Maeder *et al.*<sup>[36]</sup> 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.*<sup>[91]</sup>, 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  $4V^2 + \text{right atrial pressure}$  ( $V = \text{Doppler velocity of regurgitant jet}$ ). 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 to discrepancies in role of  $e/e'$  found in Burgess *et al.*<sup>[91]</sup> and Maeder *et al.*<sup>[36]</sup>, 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.

## 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 HFpEF it remains unclear how the interplay between degrees of LV stiffness and LA dynamics contributes to symptoms. Thus terminology in HFpEF 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) HFpEF - 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<sup>[36,99]</sup>. 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<sup>[95]</sup>.

**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<sup>[96]</sup>; 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<sup>[97]</sup>. 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<sup>[100]</sup>.

**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.

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## CONCLUSION

SOB is a common symptom presentation to cardiology clinics. Clinical workup can point toward coronary artery disease, HFpEF, 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



work-up; (3) our understanding of the baseline and subsequent parameters in its reproducibility and clinical translation requires more study; (4) the terminology defining the major contributor to HFpEF into atrial or ventricular dysfunction, should be explored; and (5) the translation of diagnostic findings into the clinical context such as relieving LVEDP, addressing myocardial stiffness with antifibrotics, correcting or augmenting atrial function and perhaps even devices to improve atrioventricular electrical or mechanical functions. To satisfactorily deliver optimal treatments more studies are needed to consolidate on our understanding and to confidently provide the diagnosis of HFpEF in a patient presenting with SOB.

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P- Reviewer: Teragawa H S- Editor: Kong JX L- Editor: A  
E- Editor: Lu YJ



# World Journal of *Methodology*

*World J Methodol* 2017 December 26; 7(4): 112-150





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**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>.

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