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Phenotyping heart failure by echocardiography: imaging of ventricular function and haemodynamics at rest and exercise

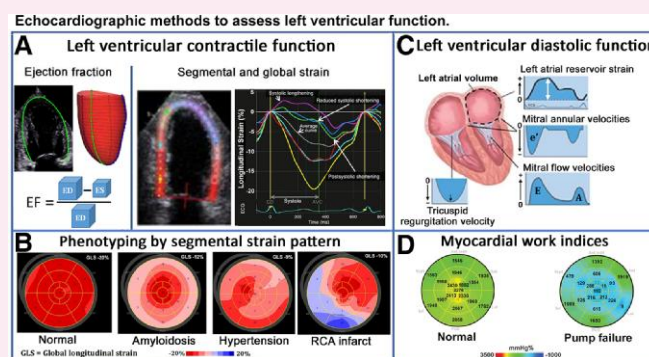
Otto A. Smiseth ^{1*}, Erwan Donal ², Espen Boe ³, Jong-Won Ha ⁴, Joao F. Fernandes ⁵, and Pablo Lamata ⁵

¹Division of Cardiovascular and Pulmonary Diseases, Institute for Surgical Research, Oslo University Hospital and University of Oslo, Oslo, Norway; ²Department of Cardiology, CHU Rennes and Inserm, LTSI, University of Rennes, Rennes, France; ³Department of Cardiology, Oslo University Hospital, Rikshospitalet, Sognsvannsveien 20, Oslo, Norway; ⁴Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; and ⁵Department of Biomedical Engineering, School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK

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Traditionally, congestive heart failure (HF) was phenotyped by echocardiography or other imaging techniques according to left ventricular (LV) ejection fraction (LVEF). The more recent echocardiographic modality speckle tracking strain is complementary to LVEF, as it is more sensitive to diagnose mild systolic dysfunction. Furthermore, when LV systolic dysfunction is associated with a small, hypertrophic ventricle, EF is often normal or supernormal, whereas LV global longitudinal strain can reveal reduced contractility. In addition, segmental strain patterns may be used to identify specific cardiomyopathies, which in some cases can be treated with patient-specific medicine. In HF with preserved EF (HFpEF), a diagnostic hallmark is elevated LV filling pressure, which can be diagnosed with good accuracy by applying a set of echocardiographic parameters. Patients with HFpEF often have normal filling pressure at rest, and a non-invasive or invasive diastolic stress test may be used to identify abnormal elevation of filling pressure during exercise. The novel parameter LV work index, which incorporates afterload, is a promising tool for quantification of LV contractile function and efficiency. Another novel modality is shear wave imaging for diagnosing stiff ventricles, but clinical utility remains to be determined. In conclusion, echocardiographic imaging of cardiac function should include LV strain as a supplementary method to LVEF. Echocardiographic parameters can identify elevated LV filling pressure with good accuracy and may be applied in the diagnostic workup of patients suspected of HFpEF.

Graphical Abstract



(A) Calculation of ejection fraction and strain. (B) Systolic strain pattern for different phenotypes. RCA, right coronary artery. (C) Parameters of diastolic function. (D) Myocardial work index by echocardiography. Adapted from Chan *et al.*²²

* Corresponding author. E-mail: otto.smiseth@gmail.com

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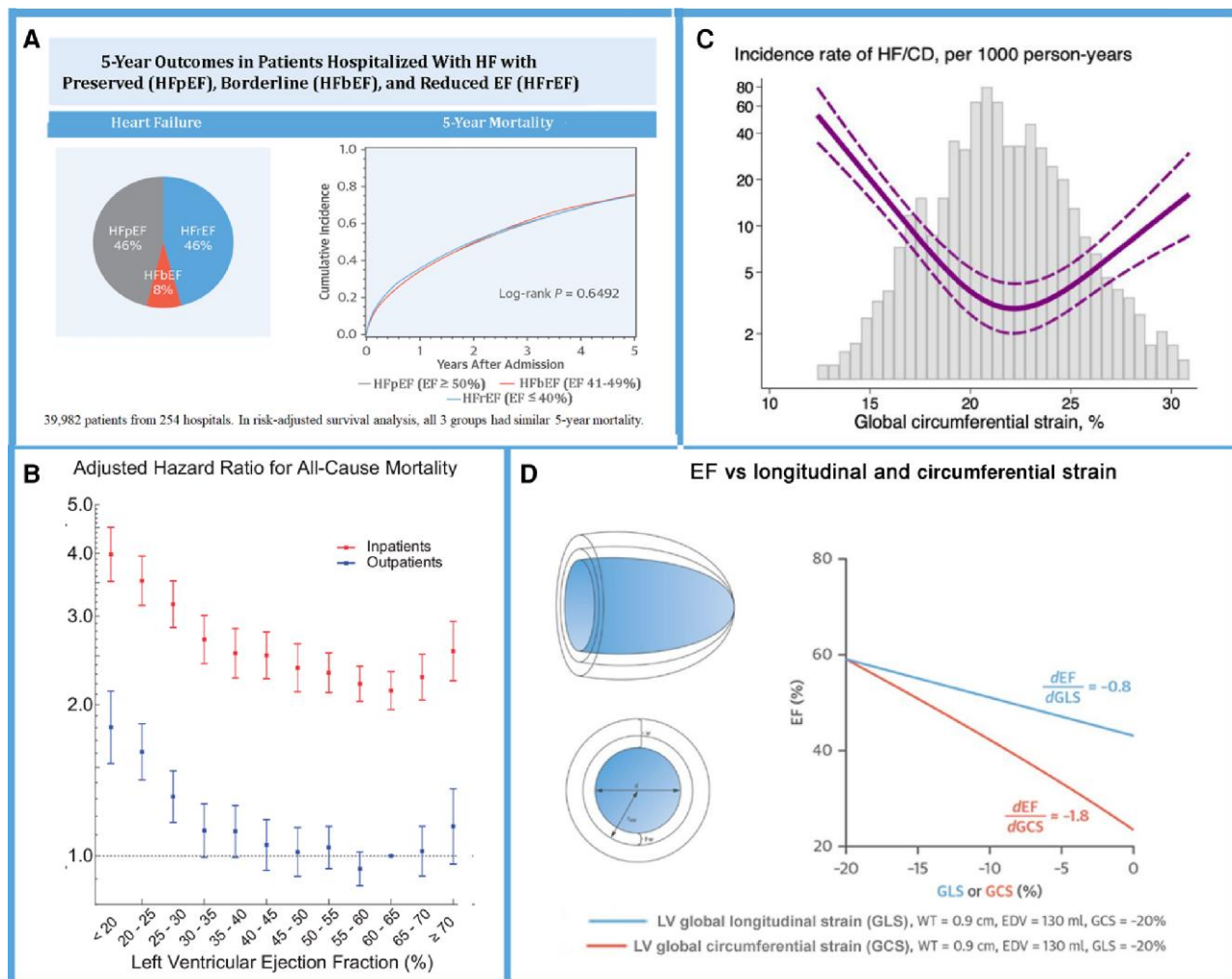


Figure 2 EF as a prognostic indicator: (A) 5-year mortality was similar in HF patients with preserved, borderline, and reduced LVEF. Modified from Shah et al.⁵ (B) A U-shaped relationship was observed between LVEF and adjusted hazard ratios in patients with HF (number of echocardiograms = 40 616). Error bars, 95% confidence interval.⁶ (C) A U-shaped relationship was observed between LV GCS and the incidence rate of HF and/or CD (2874 patients).⁷ (D) Relationships between EF and LV strains, showing a much flatter slope for GLS vs. EF than for GCS vs. EF. CD, cardiovascular death; EF, ejection fraction; GCS, global circumferential strain; GLS, global longitudinal strain. EDV, end-diastolic volume; WT, wall thickness. Adapted from Stokke et al.⁸

As suggested by recent data from a large retrospective study of a general population, elevated GCS was independently associated with a higher risk of HF/cardiac death when LVEF was above 50% (Figure 2C).⁷ These observations, suggesting a role for measuring LV GCS clinically, need to be tested in future prospective studies.

Measurement of radial strain by STE is challenging because fewer speckles are present, and similar to circumferential strain, radial strains increase markedly from the outer to the inner layers of the LV wall due to a geometrical effect. There is also a transmural gradient for longitudinal strain, but it is much smaller than for circumferential and radial strains due to a larger radius of curvature in the long axis.¹⁶

Strain imaging may also be used to measure LV twist and torsion, but so far, this application has been limited to research studies.¹⁷ The strain rate is another parameter that is feasible by STE but has so far not been implemented in clinical routine.

As explained in this section, myocardial strain imaging is a useful supplement to EF in HF diagnostics. Measurement of GLS should be

considered in every patient who is evaluated for potential systolic dysfunction. For diagnosing specific cardiomyopathies, LV strain provides valuable diagnostic information that cannot be obtained by measuring EF or by visual assessment of contractile function. In addition, GLS is a strong prognostic marker.

Other parameters of systolic function

Cardiac output is an important parameter of systolic function, which is expressed as the amount of blood pumped out in the aorta per time unit. Cardiac output can be measured using the Doppler velocity–time integral combined with the LV outflow tract diameter to measure stroke volume, which is then multiplied by the heart rate. Peak systolic mitral annular velocity (s') using tissue Doppler and mitral annular plane

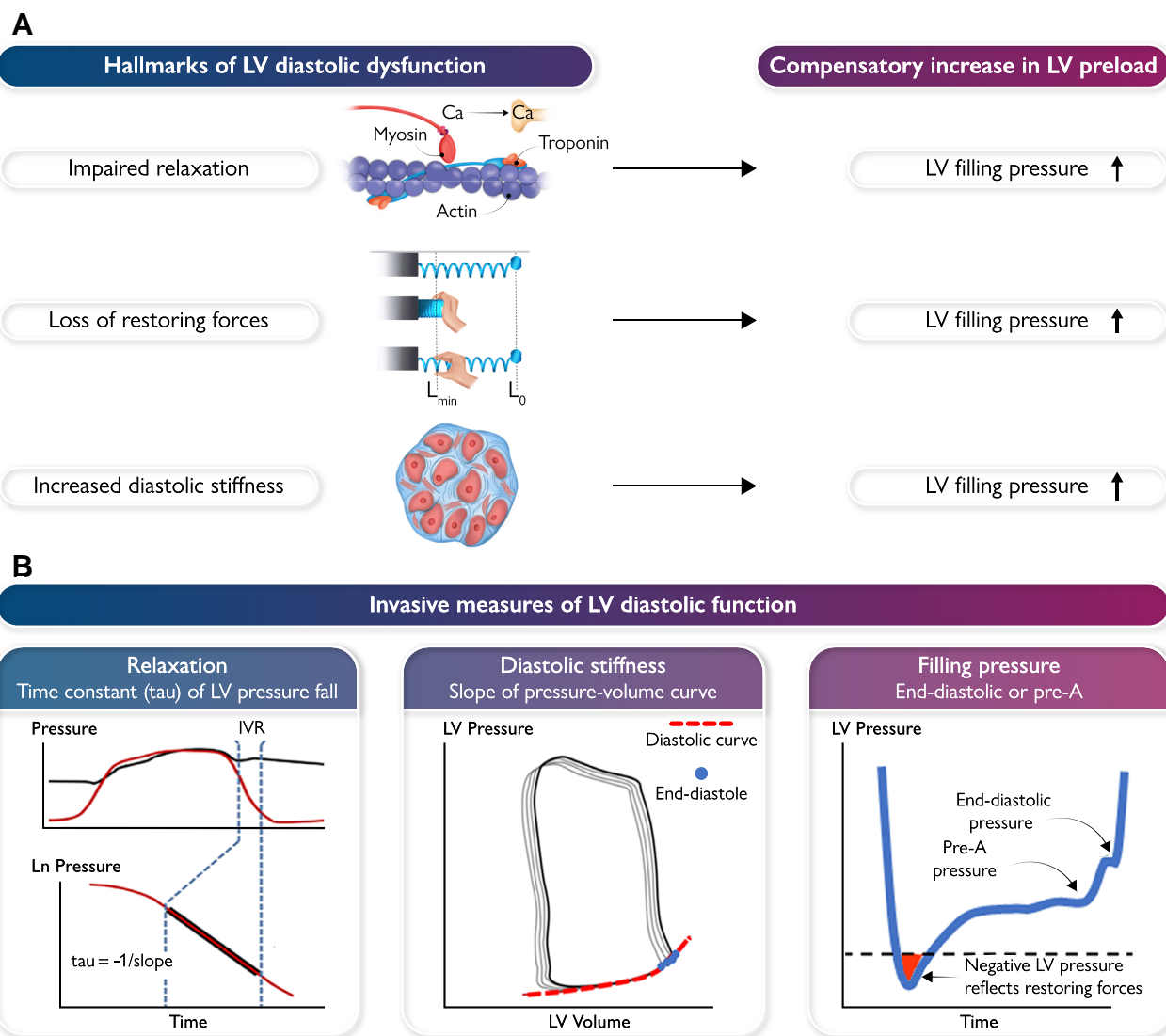


Figure 4 (A) The three fundamental mechanisms of LV diastolic dysfunction are impaired myocardial relaxation, loss of restoring forces, and increased passive elastic stiffness. Each one of these mechanisms may impair LV filling, and as a compensatory mechanism, there is elevated LV filling pressure. Based on Opdahl et al.²⁷ L_{\min} , minimum length of the compressed spring; L_0 , unstressed length. (B) Illustration of invasive methods for measuring diastolic function. The left panel shows calculation of the time constant of LV isovolumic pressure fall (τ).²⁸ The middle panel shows LV diastolic stiffness calculated as the slope of the diastolic PV curve. The right panel shows the measurement of LV filling pressure.

During congestive HF (right panel), there was loss of diastolic suction, as indicated by elevated minimum LV pressure, and increased transmitral flow during exercise was attributed to a marked increase in LA pressure. Figure 7B shows data from two patients, one with slightly negative LV early diastolic pressures during exercise and one with marked elevation of early and late diastolic pressures, indicating diastolic dysfunction.

A non-invasive diastolic stress test with measurement of E/e' and peak TR velocity as markers of LV filling pressure during exercise can be added in the setting of suspected HFpEF and normal resting LV filling pressure (Figure 8A).³⁴ Candidates for the test are patients with Grade I diastolic dysfunction and signs of delayed myocardial relaxation as indicated by septal $e' < 7$ or lateral $e' < 10$ cm/s. Criteria for positive diastolic stress test are signs of elevated filling pressure, as shown in

Figure 8A. For further details of the test, it is referred to Ha et al.³⁵ In some cases, an invasive diastolic stress test may be needed for a conclusive diagnosis of HFpEF, as illustrated in Figure 8B.

The LA as a mirror of LV function

Imaging of the LA provides important diagnostic information in patients suspected of HF, as summarized in Figure 9. In the absence of atrial arrhythmias, an enlarged LA is often the result of long-standing elevation of LV filling pressure. The recommended upper normal limit for LAVi by 2D echocardiography is 34 mL/m². However, ~10% of apparently heart-healthy individuals have LAVi above 34 mL/m².⁴⁰ LA volume can also be quantified by 3D echocardiography and cardiac magnetic

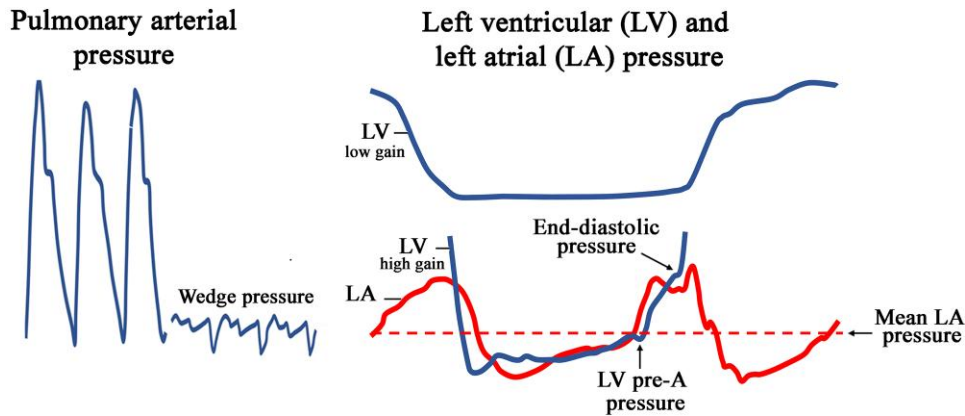
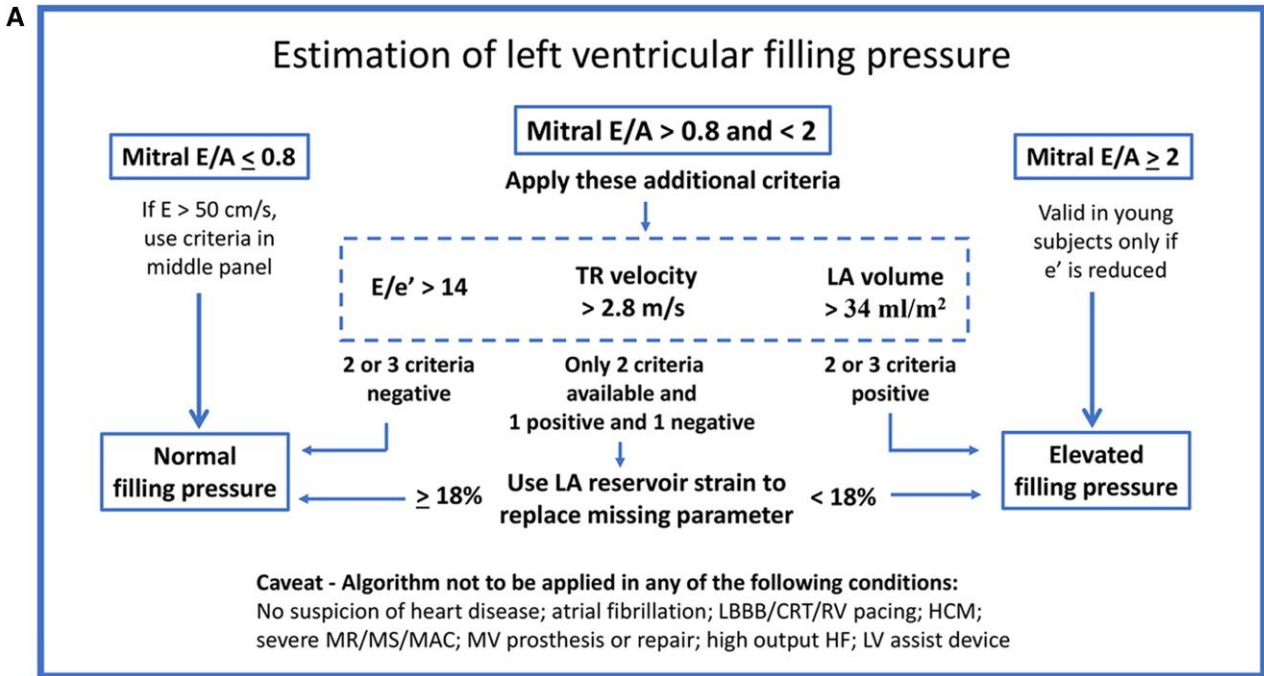


Figure 5 Definitions of LV filling pressure. The left panel shows recordings of pulmonary arterial pressure along with PCWP. The right panel shows simultaneous recordings of LV and LA pressure, and LV pre-A pressure and LVEDP are indicated. The horizontal dashed line indicates mean LA pressure.



B Criteria for normal and abnormal LV diastolic function

Parameters	Cutoffs for abnormal	
1. Septal e' or lateral e'	< 7 cm/s < 10 cm/s	Diastolic function is normal if > one half (3 of 4 or 2 of 3) of values are normal
2. Average E/e' ratio	> 14	Diastolic function is abnormal if > one half (3 of 4 or 2 of 3) of values are abnormal
3. LA volume index	> 34 ml/m ²	The study is inconclusive if 2 of 4 parameters meet cutoff criteria
4. Peak TR velocity	> 2.8 m/s	

C Criteria for grading of LV diastolic dysfunction according to filling pattern and filling pressure

	Grade I	Grade II	Grade III
Mitral flow velocities			
Mitral E/A ratio	≤ 0.8	> 0.8 to < 2	≥ 2
LV filling pressure	Normal or low	Elevated	Elevated

Figure 6 (A) Algorithm for assessing LV filling pressure by echocardiography. According to a consensus document from EACVI.³¹ LBBB, left bundle branch block; RV, right ventricular; CRT, cardiac resynchronization therapy; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MAC, mitral annular calcification; MV, mitral valve.³¹ (B) Criteria for normal and abnormal LV diastolic function. (C) Criteria for grading of diastolic dysfunction. According to a consensus document.³¹

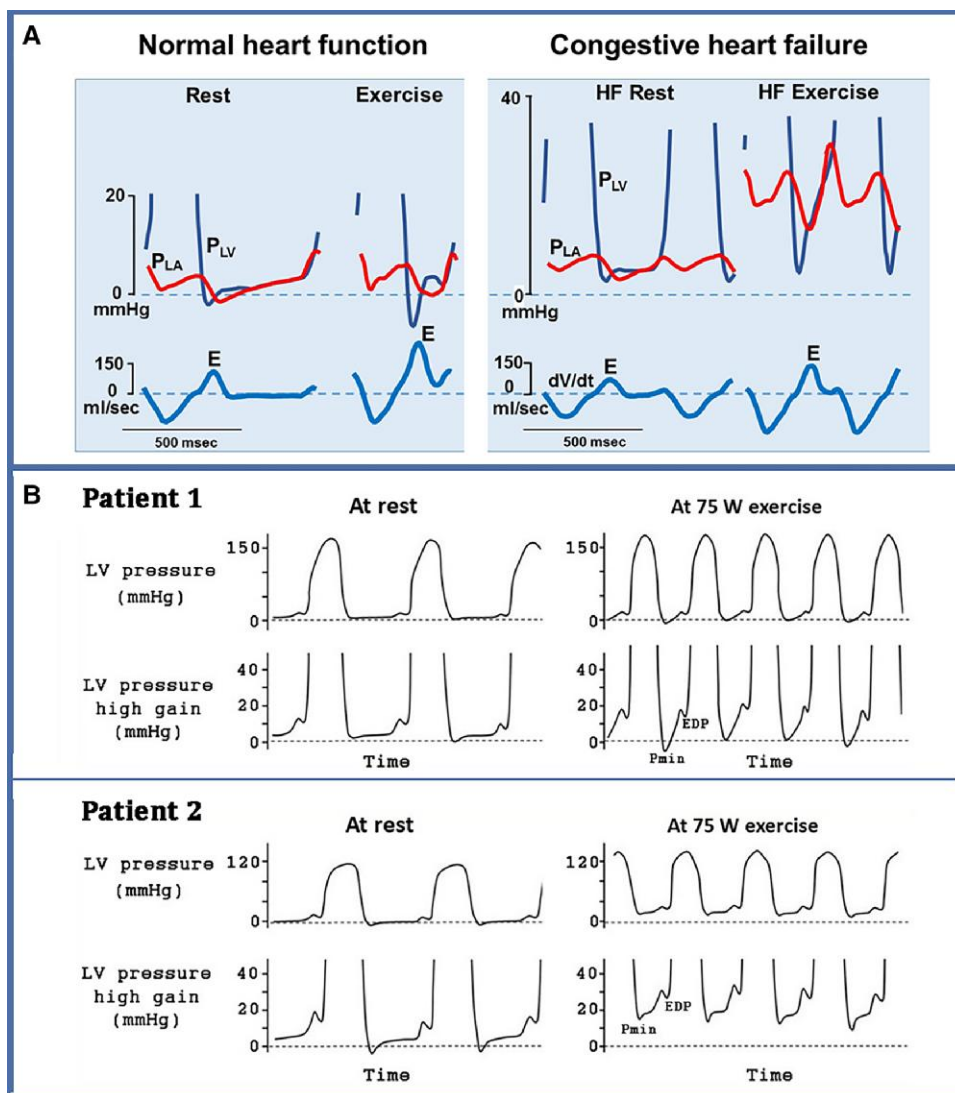


Figure 7 (A) Loss of diastolic suction in the failing heart: experimental study showing a normal heart (left panel), which generates markedly negative diastolic pressure during exercise, causing LV filling by suction. Thereby, the normal heart can increase mitral *E* with no rise in LA pressure. During HF (right panel), LV minimum pressure does not decrease during exercise and transmitral flow increases by elevation of LA pressure. Transmitral flow rate was measured as dV/dt. Adapted from Cheng *et al.*³¹ (B) Recordings from two patients 1 year after percutaneous coronary intervention but no coronary stenosis at the time of the study. Patient A responds to bicycle exercise with mild elevation of LVEDP and a fall in minimum LV pressure (P_{min}), indicating maintained diastolic suction. In Patient B, however, LVEDP approaches 30 mmHg during exercise and there is a marked elevation of minimum LV pressure, indicating loss of diastolic suction. To maintain LV filling during exercise, Patient B would require marked elevation of LA pressure. Adapted from Hong *et al.*³³

resonance (CMR) (of note, values derived from 3D echocardiography and CMR are usually greater than those derived from 2D echocardiography).

When using LA strain to assess diastolic function, elevated LV filling pressure is reflected in reductions in LA reservoir and pump strains (Figure 9C). Recent studies have shown that LA strain has a stronger correlation with invasive LV filling pressure than LAVi.³⁹ There are small age- and sex-related differences in normal values for LA reservoir and pump strains.³⁶ Values for LA reservoir strain < 19–23% are considered abnormally low.

The optimal cut-off to differentiate between normal and elevated LV filling pressures was 18% for LA reservoir strain and 8% for pump strain, when defining PCWP > 12 mmHg as elevated, and 16 and 6%,

respectively, when using PCWP ≥ 15 mmHg as a criterion for elevated filling pressure.³⁹ The association between LA strain and LV filling pressure was strongest in patients with reduced LVEF. In the most recent EACVI consensus document on imaging of patients suspected of HFpEF, it is recommended to include LA reservoir strain as a parameter of LV filling pressure (Figure 6A).

Diastolic stiffness by cardiac shear wave elastography

Increased LV diastolic stiffness is a cardinal feature of HFpEF, but previously, no non-invasive parameter of diastolic stiffness was available.

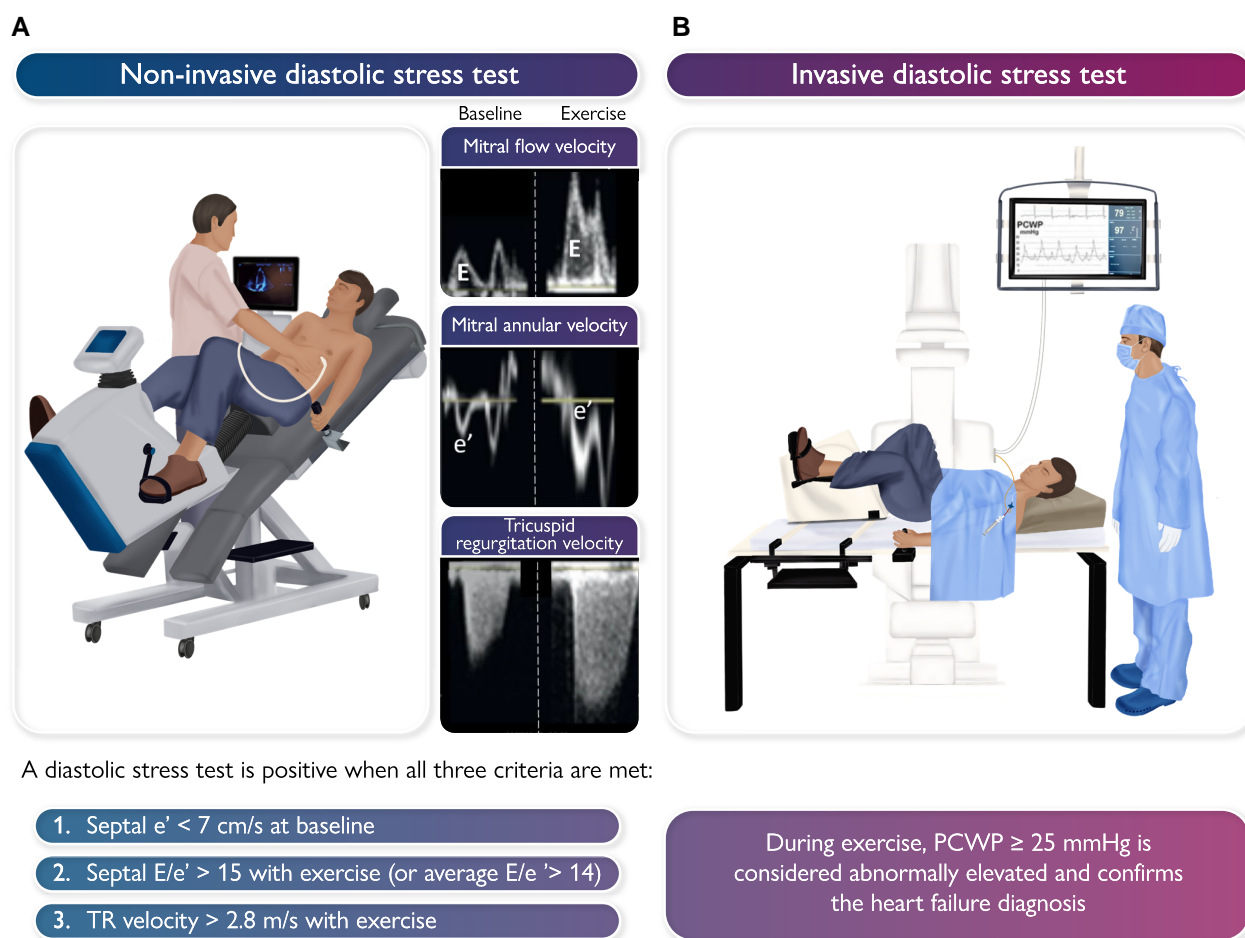


Figure 8 (A) Illustration of a non-invasive diastolic stress test using echocardiography. The inserted traces show mitral flow velocity, mitral annular velocity, and tricuspid regurgitant velocity at rest and during exercise. (B) Illustration of an invasive diastolic stress test with bicycle exercise during right heart catheterization. During the test, PCWP as measure of LV filling pressure is recorded.

Cardiac shear wave elastography was recently proposed as a method to assess LV stiffness.

It is well established that the elastance or stiffness of the myocardium is related to how and at which velocity a shear wave is propagated along the myocardium. With technological advances in echocardiography, it has become possible to image the velocity of the shear wave along the myocardium. The technique is based on high-frame rate shear wave elastography and was introduced very recently in the human heart.⁴¹ The shear wave is based on a tissue displacement perpendicular to the wave propagation direction, which originates from a vibration at the onset region. This vibration can originate naturally upon valve closure—aortic and mitral valves when focusing on the LV—or might be induced mechanically by the probe or another external source.⁴² The shear wave velocity is then calculated from the M-mode along the myocardium from base to apex. When three LV imaging planes are acquired, it is possible to map the shear wave velocity on a LV bull's eye plot (Figure 10).⁴³

There have been several pre-clinical and clinical studies that clearly demonstrate the value of shear wave imaging for the evaluation of myocardial stiffness.⁴³ Nevertheless, shear wave velocity is a surrogate of myocardial stiffness and might be limited by confounding mechanical and/or haemodynamic factors. Therefore, it remains to be studied

the ideal setting for shear wave imaging accounting for these factors. And ultimately, it remains to be studied how shear wave velocity is related to global cardiac stiffness as quantified from the LVEDP–volume relationship.⁴²

Use of echocardiography to differentiate between specific cardiomyopathies

Cardiomyopathy is defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality.⁴⁴ The diagnosis is often challenging, and in many cases, echocardiography does not provide all the diagnostic information needed. Therefore, supplementary imaging by CMR, nuclear techniques, computed tomography (CT), and genetic testing is often needed.

With the introduction of therapies for several cardiomyopathies, it is increasingly important to be aware of echocardiographic features of the different phenotypes, such as amyloidosis, Fabry disease, and glycogen

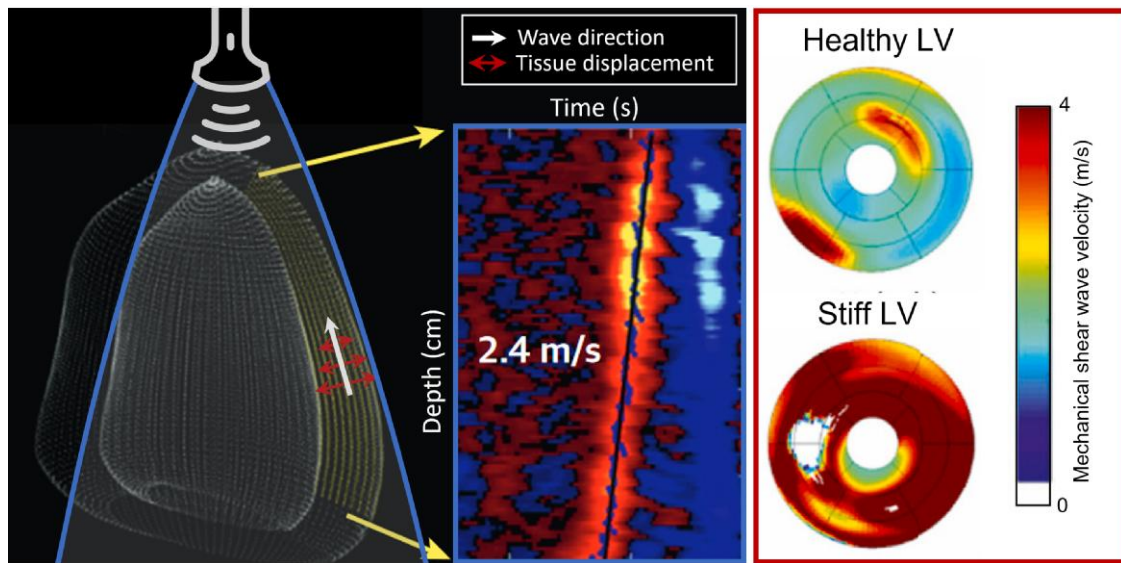


Figure 10 Schematic representation of mechanical shear wave velocity acquisition (left) and example of shear wave mapping for quantifying passive stiffness (right), based on Salles et al.⁴³ High-frame rate M-mode echocardiography along the myocardium captures the tissue displacement acceleration and deceleration originating from mitral valve closure. The slope of the peak displacement over time and over myocardial length gives the shear wave velocity. A stiff myocardium is characterized by a high shear wave velocity. LV, left ventricle.

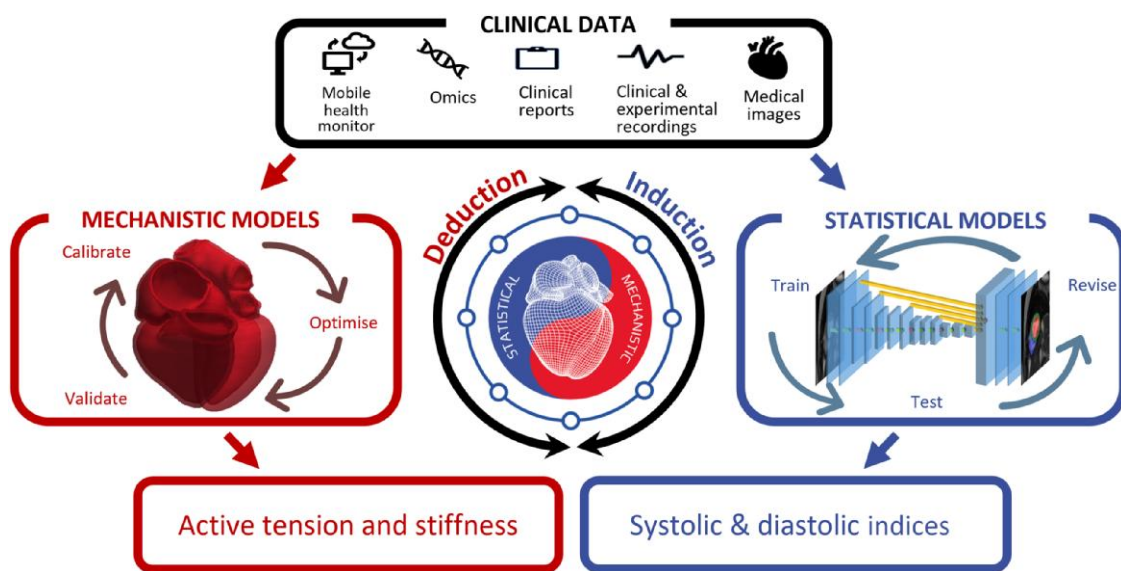


Figure 11 Use of digital twin technologies to extract cardiac functional biomarkers, by either mechanistic models that extract the parameters that rule LV systolic and diastolic function or statistical models that learn from previous examples to rank the disease stage (systolic and diastolic indices).⁵⁰

The RV is sensitive to changes in afterload, and assessment of the interplay between RV contractility and afterload is important. The ratio of end-systolic elastance (E_{es}) (ventricular contractility) to arterial elastance (E_a) (end-systolic pressure/stroke volume) is obtained invasively and is considered the gold standard of RV–pulmonary arterial coupling. The optimal E_{es}/E_a is between 1.5

and 2, where a ratio of <0.8 – 0.6 has been associated with worse outcomes.⁴⁹ Low values of the non-invasive surrogate, the TAPSE/PASP ratio, are associated with worse prognosis in both HFrEF and HFpEF.⁴⁹

When RV images by echocardiography are suboptimal, which occurs especially in obesity and chronic obstructive pulmonary disease,

or a specific diagnosis such as ARVC is suspected, further imaging with CMR is necessary.

A digital twin of systolic and diastolic performance

The ability to build a computational representation of patient-specific LV performance, i.e. its digital twin, offers new opportunities for better management of HF. A digital twin is a model, a simplified representation of reality, which brings a computer-enhanced ability to reason, either through deduction (using mechanistic models) or through induction (using statistic models).⁵⁰

Unveiling the hidden parameters that govern the heartbeat is one of the main values provided by a digital twin (Figure 11). Systole may be simplified into the ability to generate tension by myocytes. And there are two main mechanistic processes that govern filling, the active relaxation of myocytes and the passive storage of strain energy. The quest is then for the extraction of the temporal profile of active tension (generation and relaxation) and the stiffness of the myocardium. The way to estimate these key hidden parameters is the personalization of a mechanical model accounting for the 3D anatomy, material constitutive parameters, and cellular contraction and relaxation.⁵¹

Decaying active tension and myocardial stiffness become the fundamental properties able to dissect out the aetiology of impaired filling. These model-derived biomarkers may provide novel and more specific myocardial diagnostics than global pressure-volume loop-derived chamber stiffness.⁵² There are nevertheless a range of challenges that need careful consideration in the extraction of these LV functional biomarkers.

The first challenge is access to the right data, specifically filling pressure. In fact, one would need the pericardial pressure to get the actual pressure difference that drives diastolic filling. Taking informed guesses of filling pressure, the healthy stiffness of the human myocardium has been estimated at 1.2 ± 0.4 kPa.⁵² Novel methods to estimate filling pressure would be a promising strategy to get these needed data.

The second challenge is the choice of modelling assumptions that are suitable for the question asked and the data available. Cardiac mechanics is a multiscale process spanning through organ, tissue, cell, and ion levels. But the data for each patient are far too limited to personalize models at all those scales. Assumptions for the orientation of fibre bundles for tissue incompressibility or for reference configuration are part of the collection of model choices needed to hit the right level of complexity.^{51,52}

Even at the tissue level, myocardial tissue displays a non-linear behaviour that is difficult to parameterize with the limited range of deformation observed during a heartbeat. In other words, it is difficult to uncouple the linear and exponential parts of the constitutive material behaviour,⁵¹ and previous works mainly aim to estimate the linear one. The choice of metrics that fundamentally remove the interplay, such as energy cost function, is a promising strategy to address it.⁵³

Once the hidden parameters are unveiled, simulations hold the potential to predict long-term effects of concentric or eccentric remodelling. Digital twin technologies also encompass the ability to teach machines how to interpret medical images through statistical models, i.e. machine learning. These models extract the hidden patterns in the data to solve a task and have for example recently been used to extract HF severity via random forest models.⁵⁴ The main challenges here are related to statistical inductive inference, i.e. bounds of generality and robustness and the lack of interpretability or mechanisms that explain the inference.

Although digital twin technology is at an early stage, it holds promise as a future approach for a better understanding of mechanisms of HF and may serve as a means to refine phenotyping.

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Conflict of interest: O.A.S. is a co-inventor of 'Method for myocardial segment work analysis' and has received one speaker honorarium from GE Healthcare. O.A.S. and J.F.F. have filed patent on 'Estimation of blood pressure in the heart.'

Data availability

No new data were generated or analysed in support of this research.

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