Comprehensive data integration - Toward a more personalized assessment of diastolic function

Loncaric, Filip; Čikeš, Maja; Sitges, Marta; Bijnens, Bart

Source / Izvornik: **Echocardiography, 2020, 37, 1926 - 1935**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1111/echo.14749

Title: Comprehensive data integration – towards a more personalized assessment of diastolic function
Running head: Towards a personalised approach in diastology

First authors:
Filip Loncaric[1], MD

Co-authors:
Maja Cikes[2], MD, PhD, Marta Sitges[1,3], MD, PhD, Bart Bijnens[1,4,5], PhD

Affiliations:
1-Institute of Biomedical Research August Pi Sunyer (IDIBAPS), Barcelona, Spain. CERCA Programme / Generalitat de Catalunya.
2- University of Zagreb School of Medicine, University Hospital Centre Zagreb, Department of Cardiovascular Diseases, Zagreb, Croatia
3- Institut Clínic Cardiovascular, Hospital Clínic, Universitat de Barcelona; CIBERCV, Instituto de Salud Carlos III (CB16/11/00354)
4- ICREA, Barcelona, Spain
5- KULeuven, Leuven, Belgium

Correspondence:
Filip Loncaric, MD
IDIBAPS-Institut d'Investigacions Biomèdiques August Pi i Sunyer
Carrer del Rosselló, 149, 08036 Barcelona

Abstract

Background and aim: The main challenge of assessing diastolic function is the balance between clinical utility, in the sense of usability and time-efficiency, and overall applicability, in the sense of precision for the patient under investigation. In this review, we aim to explore the challenges of integrating data in the assessment of diastolic function and discuss the perspectives of a more comprehensive data integration approach.

Methods: Review of traditional and novel approaches regarding data integration in the assessment of diastolic function.

Results: Comprehensive data integration can lead to improved understanding of disease phenotypes and better relation of these phenotypes to underlying pathophysiological processes - which may help affirm diagnostic reasoning, guide treatment options, and reduce limitations related to previously unaddressed confounders. The optimal assessment of diastolic function should ideally integrate all relevant clinical information with all available structural and functional whole cardiac cycle echocardiographic data – envisioning a personalized approach to patient care, a high-reaching future goal in medicine.

Conclusion: Complete data integration seems to be a long-lasting goal, the way forward in diastology, and machine learning seems to be one of the tools suited for the challenge. With perpetual evidence that traditional approaches to complex problems may not the optimal solution, there is room for a steady and cautious, and inherently very exciting paradigm shift towards novel diagnostic tools and workflows to reach a more personalized, comprehensive and integrated assessment of cardiac function.

Keywords: diastolic function, diastolic dysfunction

Introduction

The task to non-invasively assess left ventricular (LV) diastolic function and filling pressures has been an ongoing challenge since the emergence of cardiac ultrasound imaging. The tension lies in the complexity of diastolic dysfunction as a pathology opposed to a very real-life clinical need to assess it in a fast and simple workflow. Besides the difficult task of balancing specificity and sensitivity in the assessment, various proposed guidelines and algorithms also face the challenge of linking arbitrarily separated grades of dysfunction with clinical outcomes and treatment indications. Oversimplification of such algorithms has resulted in misclassifications of a large proportion of patients, whereas more complex algorithms, incorporating increased decision points and parameters, have proved to have low clinical utility in the real-world practical setting. Achieving a universal approach to the assessment of diastolic function therefore seems to be an intricate task that can hardly be approached with traditional algorithms, either simplified or complex. The optimal assessment of diastolic function and filling pressures should ideally integrate all relevant clinical information with all available structural and functional echocardiographic data, not a pre-selected set of parameters. The described assessment envisions a personalized approach to patient care, a high-reaching future goal in medicine.

In this review, we aim to explore the challenges of integrating data in the assessment of diastolic function and discuss the perspectives of a more comprehensive data integration approach.

Assessing diastolic function – the quest for a universal approach

The majority of current ideas and pitfalls surrounding non-invasive assessment of diastolic function were recognized and defined in the seminal work from Appleton, Hatle and Popp [1], relating distinct transmitral flow velocity patterns to LV diastolic function. The observed flow patterns were more related to myocardial dysfunction and hemodynamic status than the type of underlying disease, setting ground for future classification of diastolic dysfunction into grades (**Figure 1)**. Although these grades are pathophysiologically interpretable, the patterns of mitral inflow represent a dynamic continuum, changing with regard to disease progression, medical therapy or alterations in hemodynamic status. Ongoing research showed that the correlation of mitral inflow parameters and pressure measurements is influenced by overall cardiac function, resulting in the fact that transmitral flow parameters do not correlate with LV filling pressures in patients with preserved ejection fraction, whereas they do in reduced LV function [2]. Interpreting any surrogate diastolic parameter is inherently complex, as most Doppler patterns demonstrate varying dependency on the inotropic state, volume loading, ventricular relaxation, chamber compliance and left atrial pressure, as well as on additional factors such as age, heart rate, blood pressure, mitral valve pathology, amongst others **[3–6]**. Therefore, to correctly interpret findings and assess function, it is crucial to recognize a wider pattern including clinical history, diagnostic data, echocardiographic patterns and their dynamic changes.

To address these challenges and resolve the ambiguity of the pseudonormalisation pattern, various additional tests and parameters were suggested over time – the alteration of loading conditions with a Valsalva test [7], the addition of pulmonary venous velocity curves [8–10] or tissue Doppler imaging (TDI) [2,11,12] – ultimately resulting in more complex algorithms. As an example, with the addition of the ratio between early diastolic transmitral flow and TDI velocities of the mitral ring (i.e. E/e') the assessment of diastolic function in patients with preserved EF was somewhat simplified. However, this addition ultimately created a new grayzone in the intermediate range of the ratio, where further assessment and parameters were mandatory to assess underlying diastolic function (e.g. pulmonary flow velocities or the Valsalva manoeuvre). [2] This need for a wide combination of parameters in non-invasive diastolic function assessment, together with alterations of algorithms in specific patient populations, was thus emphasised in the ASE/EACVI 2009 guidelines for diastolic assessment [13]. Besides parameters of diastolic function and associated measurements (i.e. mitral inflow velocities, Valsalva manoeuvre, pulmonary venous flow, TDI velocities etc.), morphologic and functional correlates of diastolic dysfunction (i.e. LV hypertrophy, left atrial (LA) volume, LA function and pulmonary artery systolic and diastolic pressures) were also considered. However, the incorporation of complexity backfired, resulting in a burdensome, sophisticated and multipart algorithm reflective of the complex underlying pathology, but nevertheless with limited applicability in the clinical setting. The revised 2016 guidelines [14] hence aimed to reduce and simplify the required measurements for diastolic dysfunction assessment, selecting only four diastolic function and diastolic function-influenced parameters for the task (i.e. E/A, E/e', tricuspid regurgitation velocity and LA indexed volume). The algorithm flow was modified offering a two-step decision tree now classifying a new subset of patients with indeterminate function, thus increasing specificity and reducing the diagnosis of first grade dysfunction [15]. A major limitation of the guidelines was still the lack of consideration of age – where age influences the findings of diastolic parameters. [16] Recent efforts have been made in addressing the challenges of age-appropriate interpretation of diastolic patterns by applying age-specific multivariate reference regions for echocardiographic parameters commonly used in the evaluation of LV diastolic function [17], or general population age-based normative values [18], demonstrating age-specific ranges to be prognostically relevant and suggesting that such approaches in the classification of LV filling patterns could lead to more consistent diagnostic algorithms.

Several studies [19,20] demonstrated that the 2016 guidelines proved to have higher sensitivity in estimating the filling pressures in patients with reduced EF as compared to the 2009 guidelines, while the low sensitivity was still present in patients with normal EF and normal filling pressures. However, more data integration - combining demographic and clinical variables with non-invasive echocardiographic parameters - showed an incremental value when diagnosing elevated filling pressures. [21] On the other hand, stratification into diastolic grades has been strained by the lack of relationship to cardiovascular outcomes, complicating the clinical utility of undergoing complex algorithms to identify a diastolic class. While various diastolic parameters proved predictive of clinical outcomes in studies [22–26], combining parameters in classifications to define grades showed no consistent relation to outcomes [27,28] – showing worse outcomes in moderate/severe compared to mild diastolic dysfunction [29], or only in severe dysfunction [30]. A universal diastolic grading approach therefore evidently lacked clear clinical value.

Novel imaging techniques like speckle tracking echocardiography (STE) are also increasingly in focus, as they can offer a wealth of embedded information on the systolic and diastolic function, and provide insight into patterns of myocardial mechanics that correlate with diastolic parameters and cardiovascular outcomes. [14,31] The wealth of data that can be obtained using these techniques is still under research and therefore clinically underused [32]. Analysis of single-beat STE based LV and LA volume and strain peak velocity and timing measurements resulted in patient groups with increasing severity of diastolic dysfunction and LV filling pressures (validated by invasive measurements), proving that information derived from STE variables can indeed be useful for assessment of diastolic dysfunction. [38]. Moreover, STE indices of diastolic function showed to be an important discriminator between heart failure phenogroups [34]. Deformation data also carries immense information in exercise testing, especially in the subset of patients with diastolic dysfunction that may have normal hemodynamic profile at rest but symptoms of heart failure or dyspnoea in effort. Typically, the data from these exercise tests is complex to integrate and therefore conclusions are reduced to the comparison of only selected measurements at rest and exercise.

Assessing function in challenging patients - the limitations of a universal approach

The described overview of non-invasive diastolic function assessment shows, consistently and somewhat paradoxically, that a universal approach is feasible only by sacrificing precise assessment in special patient populations where non-invasive parameters and the corresponding patterns are influenced by related comorbidities. For example, mitral valve disease or regional deformation impairment due to ischemic disease or genetic-sarcomere mutations can alter the mitral inflow pattern, TDI velocity profile and the related ratios, resulting in diastolic patterns not reflective of the level of diastolic dysfunction. These pitfalls can be demonstrated through the comparison of the patients presented in **Figures 1-3.** Patterns related to increasing grades of diastolic dysfunction are clearly defined using the guideline-recommended echocardiographic measurements in four hypertensive patients shown in **Figure 1**. The patient histories, signs and symptoms are supplemental, describing increased comorbidities, worse symptoms and a need for more medical therapy in higher grade dysfunction. The STE LV and LA strain parameters concur, showing overall decreased LV global longitudinal strain in grade I and II, and a more heterogenic regional LV deformation with basal impairment in grade III. LA strain adds incremental value to the finding of LA enlargement, reflecting underlying atrial functional dynamics [33]. Impaired LV relaxation in grade I dysfunction results in a reduction of LA conduit strain, while the pump function is augmented to maintain to LV stroke volume. In more advanced diastolic dysfunction, we can observe a steady reduction in all components of LA strain. The cases are more challenging in **Figure 2.** Patients present with relatively similar guideline-defined patterns – E/A < 0.8 in the first two patients, similar septal e' velocities and E/e', lack of quantifiable tricuspid regurgitation and an enlarged LA. However, in these individuals the clinical and STE data provide a crucial framework for interpreting underlying patient phenotypes. The first case is a patient presenting with elevated blood pressure at examination, which can influence the relaxation of the LV. This can be objectively quantified with the LV deformation curves, showing a post-systolic motion in the basal septum (i.e. a pattern associated with elevated blood pressure and reflecting delayed LV relaxation [33,34]); whereas the LA strain reflects a relatively preserved atrial function. Integration of clinical and echo data in the second case reveals long-standing moderate primary mitral regurgitation-related LV hypertrophy and preserved EF. Due to these confounders, the utility of the E/A, E/E', and LA enlargement for diastolic assessment has to be taken with caution. STE imaging gives some insight, showing a shift in atrial dynamics, with augmented contractile strain and decreased conduit strain. Additional parameters are needed to assess cardiac function (e.g. IVRT and difference in pulmonary and mitral A wave duration).

Finally, in the last case, the clinical history and STE data provide important insight – showing severe hypertrophy and severe regional deformation impairment of the anterolateral wall related to the diagnosis of hypertrophic cardiomyopathy, which is paired with systolic anterior motion and mild mitral regurgitation. In hypertrophic cardiomyopathy individual variables have moderate correlation with LV filling pressures, and regional abnormalities in deformation can influence mitral annulus motion [14]**.** LA strain again shows a signal of LV relaxation impairment, however additional parameters are needed to assess the diastolic function.

The described clinical cases outline the challenges of a universal, algorithmic assessment of diastolic dysfunction. These challenges can be approached either with numerous alterations to a general algorithm in specific diseases, as suggested in the 2009 and 2016 guidelines, or with comprehensive data integration that can incorporate and weigh all information relevant to the positioning of patients in the spectrum of cardiac function abnormalities. The latter seems more attractive and intuitive, and is indeed, as shown above, applied in everyday workflows using clinical reasoning and experience. Due to complex relations of diastolic parameters, confidence in assessment of specific patients can only be achieved through the integration of the complete clinical assessment and complete available data – from clinical to echocardiographic (**Figure 3**).

Moving towards more comprehensive data integration of the whole cardiac cycle in the assessment of diastolic function

The addition of whole cardiac cycle data extracted from echocardiographic images (e.g. volume, blood-pool and myocardial velocity, strain or strain-rate curves) to the assessment of diastolic function serves as a step towards a more sophisticated data integration strategy. Heterogeneity of diastolic dysfunction is an appropriate challenge for machine learning (ML), especially unsupervised approaches [31], which aim to extract hidden patterns in available data and naturally cluster patients regardless of a priori knowledge or pre-defined clinical labels. Such algorithms have recently been used to approach diastolic dysfunction classification. Using recommended parameters for diastolic assessment, an unsupervised clustering approach identified unique patterns of diastolic dysfunction that showed a relationship to clinical outcomes, as opposed to current grading schemes. [32] Importantly, patients classified as indeterminate by guidelines were reclassified into an appropriate risk group. In other studies, a combination of variables (i.e. demographic, clinical, laboratory, ECG and echo) have been used to explore heart failure phenotypes that differ in outcomes and therapy response [35,36]; and also, to investigate HF phenogroups with data on invasive hemodynamics, altogether showing that the severity of diastolic dysfunction seems to be one of the main separating factors between these phenogroups [36,37]. Precise phenotyping of diastolic function inevitably influences patient care, for example, optimal patient management requires differentiation between abnormal relaxation, when heart rate reduction is beneficial, and decreased compliance, when the latter is not the case. [38] The distinction can be found through comprehensive data assessment incorporating a wide set of parameters, stepping out of the scope of simplified algorithms of classification. ML approaches can aid in standardizing echocardiographic evaluation using unlabelled variables without a priori algorithms, isolating prognostic phenotypes not visualized by guideline algorithms.

In disease exploration, both the traditional consensus-based and the described ML approaches are constrained to a limited number of key disease markers and clinical variables, such as selected peak value or timing measurements. These might not capture the full complexity, and subtle changes of the underlying diseases. Specifically, spatiotemporal patterns of myocardial velocity curves, defined by peak and timing values throughout the whole cardiac cycle, are reflective of regional and global dysfunction in systole and diastole [39], and reveal intricate changes in myocardial mechanics in specific cardiac pathologies [40]. Similarly to when a clinician integrates these data based on previous experience and knowledge, novel machine learning techniques offer the possibility to incorporate information embedded in the velocity data of the whole cardiac cycle, with the aim to extract the maximum amount of information reflective of cardiac function and disease from cardiac images. This approach could also be used to analyze the complex changes occurring between rest and exercise echocardiography. Moreover, pathology related information is contained not only in the amplitude and profile of a velocity curve, but likewise in the timings and durations of different cardiac phases (e.g. isovolumic contraction or early diastole) [40]. Temporal differences, due to inter-patient variability in heart rate or intra-patient variability between rest and exercise, result in a challenging interpretation of the relationship between cardiac phases (e.g. when assessing a shift in the onset of systole/diastole due to dysfunction, see **Figure 4**). Since the timings of cardiac phases can easily be defined with echocardiographic (valve flows) and ECG (onset of atrial contraction) data, time alignment of echo data is feasible as part of the ML approach [39,41–43]. Velocity data can be time aligned to a common temporal reference within a patient cohort and quantitatively compared between patients. Data on the corrected differences in timings can be preserved, and used as an additional parameter in later analysis.

An important matter to assess is if the theoretical advantage of whole-cardiac cycle data integration adds any real advantages in disease exploration. To address this question, a ML approach integrating spatiotemporal information from rest and exercise echocardiographic data (including velocity, strain and strain rate curves, respectably) was used to create spatiotemporal-rest-exercise representations of the LV function. [39] This comprehensive whole cardiac cycle data proved more successful than traditional measurements (e.g. peak amplitudes of systolic and early diastolic velocities, selected peaks and timings of strain and strain rate measurements, or echocardiographic variables such as LV end-diastolic volumes and LA indexed size) in identifying HFpEF, objectively showing that indeed, traditional measurements do not exploit all available diagnostic data and represent just a single value from the information-filled cardiac cycle. Time-alignment also proved useful here and in other studies [39], improving the characterization of a HFpEF population, showing that the largest variability of cardiac data is found within the diastolic cardiac phase, especially during exercise.

A further illustration of the utility of the integration of whole cardiac cycle data lies in the valuable possibility of ML to provide patient membership probabilities, in favour of categorical clinical diagnoses, to diseased (i.e. HF) or healthy groups. For example, hypertensive and breathless patients have been categorized belonging to a transition zone of the HFpEF spectrum, thus demonstrating possible culprits of clinical diagnostic algorithms, as well as the spectrum of the heterogeneous HFpEF syndrome. [41] As part of this process, a pathophysiological interpretation of TDI patterns related to distinct patient groups was possible, showing the ability of ML methods to distinguish alterations in diastolic function in the diseased patient groups – more fusion of early and late diastolic curves during exercise with similar heart rates, delayed early diastolic lengthening reflective of relaxation/compliance abnormalities or early vs. late diastolic filling patterns, and increased variability in the onset of atrial contraction and a failure of peak a' wave increase during exercise, suggestive of increased filling pressure. Multi-feature analysis of rest and exercise data, as well as of regional data opposed to only global, resulted in a better disease assessment than analysing the data independently.[42] Unsupervised ML has also been used to combine whole-cycle echo data, specifically LV strain and volume curves, with relevant and heterogeneous clinical variables, to form a meaningful representation of cardiac function in each patient, relating it to therapy response [43]. These methods facilitate the fusion of heterogeneous data, weighing the contribution of each input to the final result, allowing extraction of interpretable physiological patterns from patient data without the influence of potentially incorrect clinical diagnostic labels of borderline patients. [42] Indeed, the most controversial, and also the most interesting contribution of such sophisticated spatiotemporal analysis, might be the way borderline patients are classified, which may not concur with traditional diagnostic labels, potentially reflecting suboptimal capability of diagnostic guidelines. [39,41,43]

Challenges ahead

Besides the time limitations and knowledge requirements, there are other relevant and inherent challenges when integrating complex data in everyday clinical assessment – selection bias of patients in analysis, missing data, embedded noise in imaging data, validation of used algorithms and reproducibility, to name a few. The results of most studies mentioned above are confined to single-center cohorts or cohorts from selected, well-defined populations [36,41,43]. One of the strongholds of ML methods lies in the possibility to incorporate prospective patient data or in testing/validating the algorithms on different datasets [17,44]. Missing patient data, a relevant problem in clinical practice and research, has been previously addressed with the exclusion of patients with incomplete data [35,45], which can heavily bias the conclusions of the analysis. Novel approaches have used data imputation methods to resolve missing clinical parameters[36,43] or velocity curves [39], potentially increasing the utility of complex data integration in a real-life setting. As in any deductive process, the quality of conclusions depends on quality of used information. Complex approaches using imaging data are highly dependent on image quality and reproducibility of measurements. Strain and strain-rate curves are burdened with embedded noise. Here novel approaches can be used as noise filtering techniques [46] – where the most important dimensions/ principal components of data variability capture the major clinically interpretable patterns, whereas, less relevant ones capture the noise. In the future, data extraction (e.g. deformation analysis on available echo images) as well as data preparation (e.g. time alignment), needed for more complete analysis, could be automated [47,48], thus enabling standardization through increased reproducibility. Finally, all novel algorithms are in need of being subjected to stringent validation before incorporation into the clinical environment. A scheme showing the advantages and challenges regarding a more comprehensive data integration are presented in **Figure 5.**

Conclusion

The balance between clinical utility, in the sense of usability and time-efficiency, and overall applicability, in the sense of precision for the patient under investigation, represents the main challenge in the assessment of diastolic (dys)function. The high-reaching aim of personalized medicine that could resolve these tensions may be feasible through a more comprehensive integration of all relevant data – from clinical to whole-cycle echocardiographic data. Complete data integration seems to be a long-lasting goal, the way forward in diastology, and machine learning seems to be one of the tools suited for the challenge. Each successful integration of heterogeneous data to patient assessment offers incremental value to the goal of better understanding complex topics such as diastolic dysfunction or HFpEF. With more comprehensive approaches we can see improved shaping of disease phenotypes and better relation of these phenotypes to underlying pathophysiological processes - which may help affirm diagnostic reasoning, guide treatment options, and reduce limitations related to previously unaddressed confounders. The aim has slowly shifted from strict categorical classifications of disease/health towards the exploration of disease as a continuous spectrum, ranging from health to dysfunction, with the novel goal being personalized positioning of patients into a certain part of this spectrum. Finally, the main clinical value can be harvested from relating newfound distinct phenotypes to long-term patient trajectories, a goal consistently highlighted in contemporary publications. With perpetual proof that traditional approaches to complex problems are not the optimal solution, there is room for a steady and cautious, and inherently very exciting paradigm shift towards novel diagnostic tools and workflows to reach a more personalized, comprehensive and integrated assessment of cardiac function.

Author Contributions

Filip Loncaric - Concept/design, Data collection, Data analysis/interpretation, Statistics, Drafting article, Approval of article
Maja Cikes - Concept/design, Critical revision of article, Approval of article
Marta Sitges - Concept/design, Critical revision of article, Approval of article
Bart Bijnens - Concept/design, Critical revision of article, Approval of article

References

1. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: New insights from a combined hemodynamic and Doppler echocardiographic study. Journal of the American College of Cardiology. 1988;12:426–40.

2. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical Utility of Doppler Echocardiography and Tissue Doppler Imaging in the Estimation of Left Ventricular Filling Pressures: A Comparative Simultaneous Doppler-Catheterization Study. Circulation. 2000;102:1788–94.

3. Bahler RC, Martin P. Effects of loading conditions and inotropic state on rapid filling phase of left ventricle. American Journal of Physiology-Heart and Circulatory Physiology. 1985;248:H523–33.

4. Gardin JM, Rohan MK, Davidson DM, Dabestani A, Sklansky M, Garcia R, et al. Doppler Transmitral Flow Velocity Parameters: Relationship between Age, Body Surface Area, Blood Pressure and Gender in Normal Subjects. American Journal of Noninvasive Cardiology. 1987;1:3–10.

5. Thomas JD, Newell JB, Choong CY, Weyman AE. Physical and physiological determinants of transmitral velocity: numerical analysis. American Journal of Physiology-Heart and Circulatory Physiology. 1991;260:H1718–31.

6. Munagala VK, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Association of newer diastolic function parameters with age in healthy subjects: a population-based study. Journal of the American Society of Echocardiography. 2003;16:1049–56.

7. Dumesnil JG, Gaudreault G, Honos GN, Kingma JG Jr. Use of Valsalva maneuver to unmask left ventricular diastolic function abnormalities by Doppler echocardiography in patients with coronary artery disease or systemic hypertension. American Journal of Cardiology. 1991;68:515–9.

8. Kuecherer HF, Kusumoto F, Muhiudeen IA, Cahalan MK, Schiller NB. Pulmonary venous flow patterns by transesophageal pulsed Doppler echocardiography: Relation to parameters of left ventricular systolic and diastolic function. American Heart Journal. 1991;122:1683–93.

9. Yamamoto K, Nishimura RA, Burnett JC, Redfield MM. Assessment of left ventricular end-diastolic pressure by Doppler echocardiography: Contribution of duration of pulmonary venous versus mitral flow velocity curves at atrial contraction. Journal of the American Society of Echocardiography. 1997;10:52–9.

10. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Relation of pulmonary vein to mitral flow velocities by transesophageal Doppler echocardiography. Effect of different loading conditions. Circulation. 1990;81:1488–97.

11. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler Tissue Imaging: A Noninvasive Technique for Evaluation of Left Ventricular Relaxation and Estimation of Filling Pressures. Journal of the American College of Cardiology. 1997;30:1527–33.

12. Popović ZB, Desai MY, Buakhamsri A, Puntawagkoon C, Borowski A, Levine BD, et al. Predictors of mitral annulus early diastolic velocity: impact of long-axis function, ventricular filling pattern, and relaxation. European Heart Journal - Cardiovascular Imaging. 2011;12:818–25.

13. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. Journal of the American Society of Echocardiography. 2009;22:107–33.

14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. 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. Journal of the American Society of Echocardiography. 2016;29:277–314.

15. Sanchis L, Andrea R, Falces C, Poyatos S, Vidal B, Sitges M. Differential Clinical Implications of Current Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. Journal of the American Society of Echocardiography. 2018;31:1203–8.

16. Popović ZB, Sato K, Desai MY. Is universal grading of diastolic function by echocardiography feasible? Cardiovascular Diagnosis and Therapy. 2018;8:18–28.

17. Selmeryd J, Henriksen E, Dalen H, Hedberg P. Derivation and Evaluation of Age-Specific Multivariate Reference Regions to Aid in Identification of Abnormal Filling Patterns. JACC: Cardiovascular Imaging. 2018;11:400–8.

18. Shah AM, Claggett B, Kitzman D, Biering-Sørensen T, Jensen JS, Cheng S, et al. Contemporary Assessment of Left Ventricular Diastolic Function in Older Adults: The Atherosclerosis Risk in Communities Study. Circulation. 2017;135:426–39.

19. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliasch G, Cardim N, et al. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. European Heart Journal - Cardiovascular Imaging. 2017;18:961–8.

20. Balaney B, Medvedofsky D, Mediratta A, Singh A, Ciszek B, Kruse E, et al. Invasive Validation of the Echocardiographic Assessment of Left Ventricular Filling Pressures Using the 2016 Diastolic Guidelines:

Head-to-Head Comparison with the 2009 Guidelines. Journal of the American Society of Echocardiography. 2018;31:79–88.

21. Andersen OS, Smiseth OA, Dokainish H, Abudiab MM, Schutt RC, Kumar A, et al. Estimating Left Ventricular Filling Pressure by Echocardiography. Journal of the American College of Cardiology. 2017;69:1937–48.

22. Giannuzzi P, Temporelli PL, Bosimini E, Silva P, Imparato A, Corrà U, et al. Independent and incremental prognostic value of doppler-derived mitral deceleration time of early filling in both symptomatic and asymptomatic patients with left ventricular dysfunction. Journal of the American College of Cardiology. 1996;28:383–90.

23. Dini FL, Michelassi C, Micheli G, Rovai D. Prognostic value of pulmonary venous flow Doppler signal in left ventricular dysfunction: contribution of the difference in duration of pulmonary venous and mitral flow at atrial contraction. Journal of the American College of Cardiology. 2000;36:1295–302.

24. Bella Jonathan N., Palmieri Vittorio, Roman Mary J., Liu Jennifer E., Welty Thomas K., Lee Elisa T., et al. Mitral Ratio of Peak Early to Late Diastolic Filling Velocity as a Predictor of Mortality in Middle-Aged and Elderly Adults. Circulation. 2002;105:1928–33.

25. Troughton RW, Prior DL, Frampton CM, Nash PJ, Pereira JJ, Martin M, et al. Usefulness of Tissue Doppler and Color M-Mode Indexes of Left Ventricular Diastolic Function in Predicting Outcomes in Systolic Left Ventricular Heart Failure (from the ADEPT Study). The American Journal of Cardiology. 2005;96:257–62.

26. Liang H-Y, Cauduro SA, Pellikka PA, Bailey KR, Grossardt BR, Yang EH, et al. Comparison of Usefulness of Echocardiographic Doppler Variables to Left Ventricular End-Diastolic Pressure in Predicting Future Heart Failure Events. American Journal of Cardiology. 2006;97:866–71.

27. Redfield MM, Jacobsen SJ, Burnett J John C, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of Systolic and Diastolic Ventricular Dysfunction in the CommunityAppreciating the Scope of the Heart Failure Epidemic. JAMA. 2003;289:194–202.

28. AlJaroudi Wael, Alraies M. Chadi, Halley Carmel, Rodriguez Leonardo, Grimm Richard A., Thomas James D., et al. Impact of Progression of Diastolic Dysfunction on Mortality in Patients With Normal Ejection Fraction. Circulation. 2012;125:782–8.

29. Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. Mortality Rate in Patients With Diastolic Dysfunction and Normal Systolic Function. Arch Intern Med. 2011;171(12):1082–1087.

30. Somaratne JB, Whalley GA, Gamble GD, Doughty RN. Restrictive Filling Pattern is a Powerful Predictor of Heart Failure Events Postacute Myocardial Infarction and in Established Heart Failure: A Literature-Based Meta-Analysis. Journal of Cardiac Failure. 2007;13:346–52.

31. Bianco CM, Farjo PD, Ghaffar YA, Sengupta PP. Myocardial Mechanics in Patients With Normal LVEF and Diastolic Dysfunction. JACC: Cardiovascular Imaging. 2020;13:258–71.

32. Popescu BA, Beladan CC, Popescu AC. Diastolic Function Assessment Revisited. JACC: Cardiovascular Imaging. 2019;12:1162–4.

33. Loncaric F, Nunno L, Mimbrero M, Marciniak M, Fernandes JF, Tirapu L, et al. Basal Ventricular Septal Hypertrophy in Systemic Hypertension. The American Journal of Cardiology [Internet]. 2020; Available from: http://www.sciencedirect.com/science/article/pii/S0002914920301120

34. Baltabaeva A, Marciniak M, Bijnens B, Moggridge J, He FJ, Antonios TF, et al. Regional left ventricular deformation and geometry analysis provides insights in myocardial remodelling in mild to moderate hypertension. European Journal of Echocardiography. 2007;9:501–8.

35. Ahmad T, Lund LH, Rao P, Ghosh R, Warier P, Vaccaro B, et al. Machine Learning Methods Improve Prognostication, Identify Clinically Distinct Phenotypes, and Detect Heterogeneity in Response to Therapy in a Large Cohort of Heart Failure Patients. Journal of the American Heart Association. American Heart Association; 7:e008081.

36. Segar MW, Patel KV, Ayers C, Basit M, Tang WHW, Willett D, et al. Phenomapping of patients with heart failure with preserved ejection fraction using machine learning-based unsupervised cluster analysis. European Journal of Heart Failure. 2020;22:148–58.

37. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, et al. Phenomapping for Novel Classification of Heart Failure With Preserved Ejection Fraction. Circulation. 2015;131:269–79.

38. Hatle L. How to diagnose diastolic heart failure a consensus statement. European Heart Journal. 2007;28:2421–3.

39. Tabassian M, Sunderji I, Erdei T, Sanchez-Martinez S, Degiovanni A, Marino P, et al. Diagnosis of Heart Failure With Preserved Ejection Fraction: Machine Learning of Spatiotemporal Variations in Left Ventricular Deformation. Journal of the American Society of Echocardiography. 2018;31:1272-1284.e9.

40. Cikes M, Sutherland GR, Anderson LJ, Bijnens BH. The role of echocardiographic deformation imaging in hypertrophic myopathies. Nature Reviews Cardiology. 2010;7:384–96.

41. Sanchez-Martinez S, Duchateau N, Erdei T, et al. Machine Learning Analysis of Left Ventricular Function to Characterize Heart Failure With Preserved Ejection Fraction. Circ Cardiovasc Imaging. 2018;11(4):e007138.

42. Sanchez-Martinez S, Duchateau N, Erdei T, Fraser AG, Bijnens BH, Piella G. Characterization of myocardial motion patterns by unsupervised multiple kernel learning. Medical Image Analysis. 2017;35:70–82.

43. Cikes M, Sanchez-Martinez S, Claggett B, Duchateau N, Piella G, Butakoff C, et al. Machine learning-based phenogrouping in heart failure to identify responders to cardiac resynchronization therapy: Machine learning-based approach to patient selection for CRT. European Journal of Heart Failure. 2019;21:74–85.

44. Cikes M., Sanchez Martinez S., Claggett B., Solomon SD., Bijnens B. 4302 Machine-learning integration of complex echocardiographic patterns and clinical parameters from cohorts and trials. Eur Heart J 2019;40(ehz745.0147).

45. Lancaster MC, Salem Omar AM, Narula S, Kulkarni H, Narula J, Sengupta PP. Phenotypic Clustering of Left Ventricular Diastolic Function Parameters. JACC: Cardiovascular Imaging. 2019;12:1149–61.

46. Jolliffe IT. Principal Components in Regression Analysis. In: Jolliffe IT, editor. Principal Component Analysis [Internet]. New York, NY: Springer New York; 1986. p. 129–55.

47. Dey D, Slomka PJ, Leeson P, Comaniciu D, Shrestha S, Sengupta PP, et al. Artificial Intelligence in Cardiovascular Imaging. Journal of the American College of Cardiology. 2019;73:1317–35.

48. Knackstedt C, Bekkers SCAM, Schummers G, Schreckenberg M, Muraru D, Badano LP, et al. Fully Automated Versus Standard Tracking of Left Ventricular Ejection Fraction and Longitudinal Strain: The FAST-EFs Multicenter Study. Journal of the American College of Cardiology. 2015;66:1456–66.

Figures

Figure 1

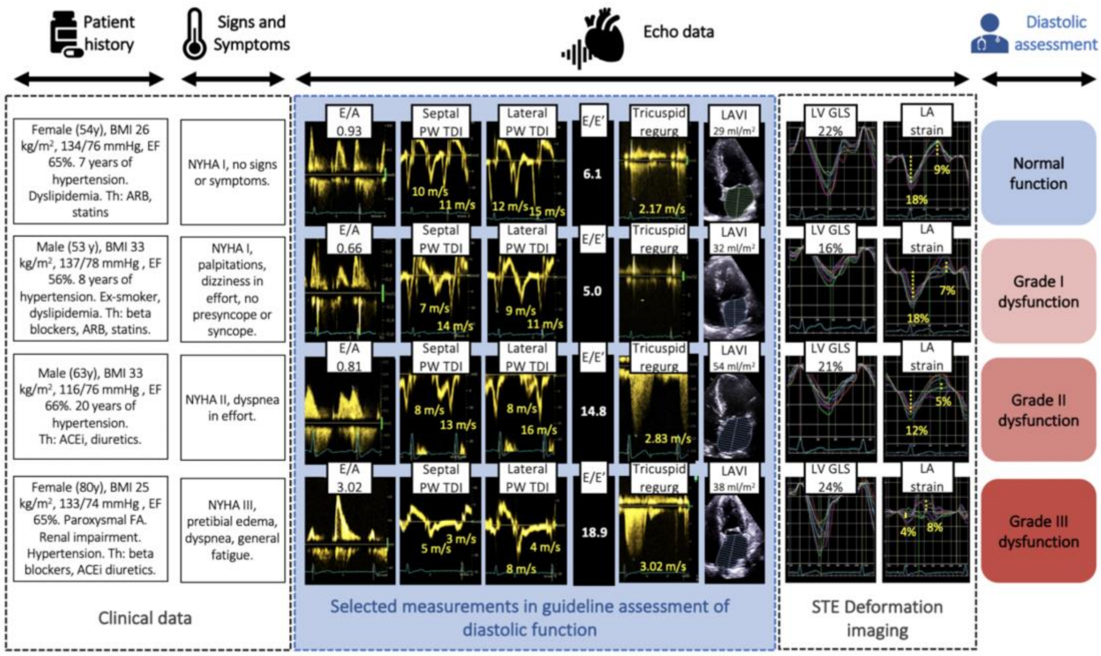

Figure 2

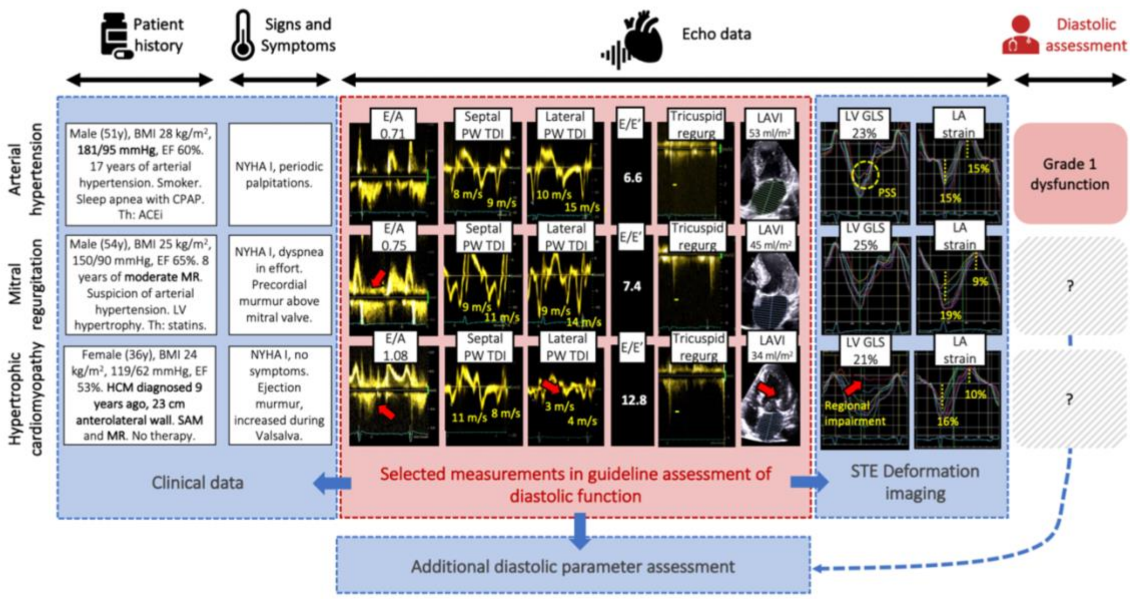

Figure 3

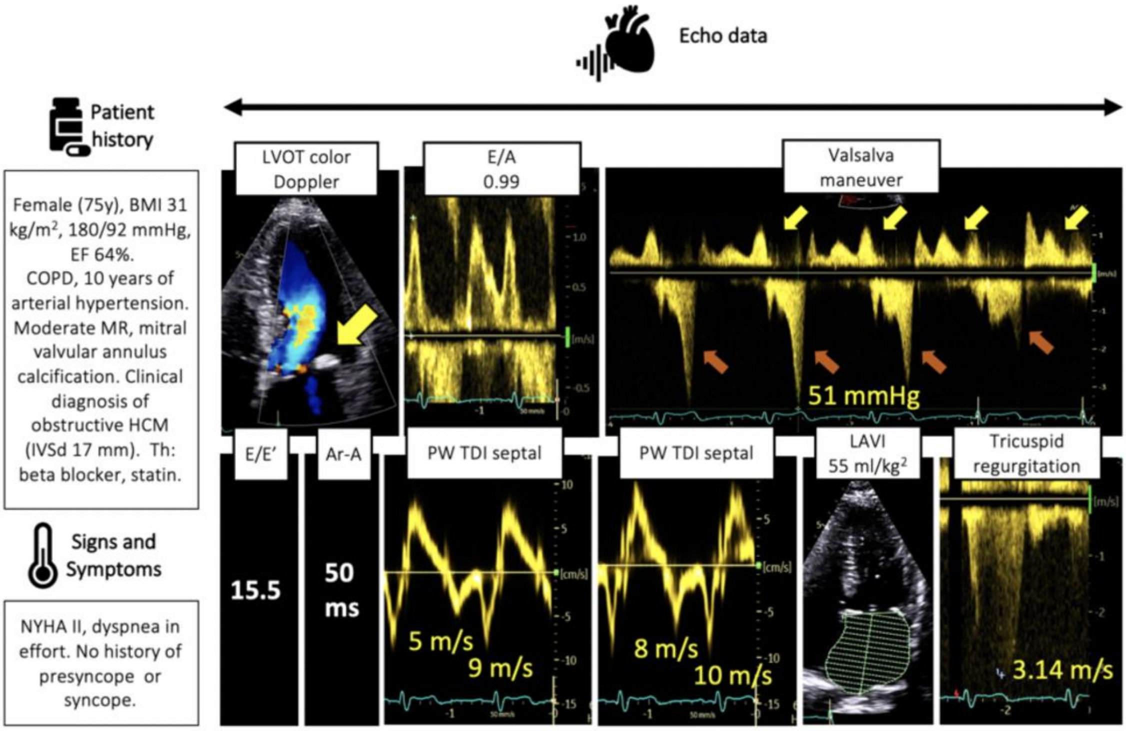

Figure 4

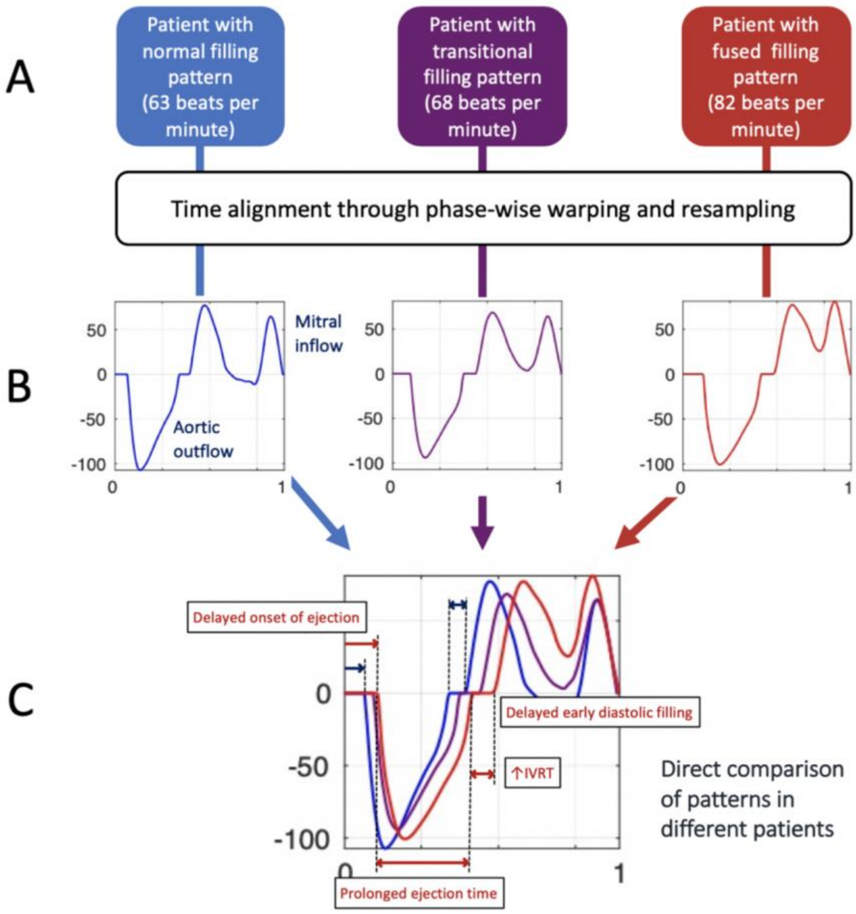

Figure 5

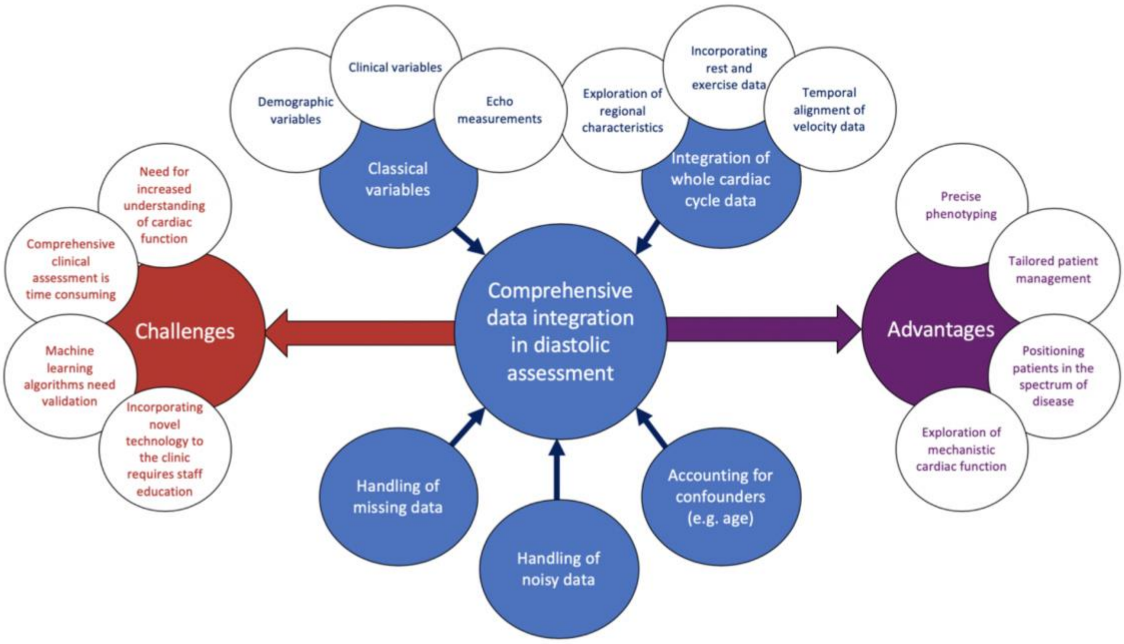
Clinical variables
Demographic variables
Echo measurements
Classical variables
Incorporating rest and exercise data
Exploration of regional characteristics
Temporal alignment of velocity data
Integration of whole cardiac cycle data
Need for increased understanding of cardiac function
Comprehensive clinical assessment is time consuming
Challenges
Machine learning algorithms need validation
Incorporating novel technology to the clinic requires staff education
Comprehensive data integration in diastolic assessment
Precise phenotyping
Tailored patient management
Advantages
Positioning patients in the spectrum of disease
Exploration of mechanistic cardiac function
Handling of missing data
Handling of noisy data
Accounting for confounders (e.g. age)

Figure descriptions

Figure 1 Diastolic assessment using the 2016 guidelines

(*Rows*) Four hypertensive patients with varying degrees of diastolic dysfunction. (*Columns from left to right*) The patient history, signs and symptoms, recommended echocardiographic parameters, and diastolic grades assessed using the 2016 guidelines [14]. Diastolic dysfunction can be assessed in a straightforward way using the four echocardiographic parameters proposed by the guidelines. The grade of dysfunction concurs with the associated clinical picture.

(*BMI – body mass index, EF - ejection fraction, DM – diabetes mellitus, ARB - Angiotensin II receptor blocker, ACEi - Angiotensin-converting-enzyme inhibitors, FA- atrial fibrillation, PW TDI – pulsed wave tissue Doppler imaging, LAVI – left atrial volume indexed to body surface area, LV GLS – left ventricular global longitudinal strain, STE – speckle-tracking echocardiography*)

Figure 2 Challenges of diastolic assessment using the 2016 guidelines

(*Rows*) Three patients with various pathologies: arterial hypertension, moderate mitral insufficiency and hypertrophic cardiomyopathy. Patient history lays out the framework for interpreting related echocardiographic findings. Important echo findings are marked in yellow and red. Further discussion can be found in the text.

(*abbreviations same as in Figure 1, CPAP – continuous positive airway pressure, MR – mitral regurgitation, SAM – systolic anterior motion of the anterior leaflet, PSS – post-systolic shortening)*

Figure 3 An example of data integration in the assessments of a complex patient

A female with long-standing arterial hypertension and clinically diagnosed obstructive hypertrophic cardiomyopathy. The posterior part of the mitral annulus is calcified, moderate mitral regurgitation is present, and the basal septum is hypertrophied, measuring 17 mm. All of the latter influence traditional interpretation of diastolic parameters. Additional investigation is needed. The patient had elevated blood pressure at assessment, which can influence findings. The obstruction is highest in the midventricular region, with the gradient reaching 51 mmHg during the Valsalva manoeuvre. During Valsalva, the inversal of the pseudo-normal mitral inflow can be noted. The E/E' ratio indicates elevated filling pressure, supported by the difference in the timings of the pulmonary vein and mitral inflow A wave duration, LA is enlargement and tricuspid regurgitation velocity.

(*abbreviations same as in Figure 1, COPD – chronic obstructive pulmonary disease)*

Figure 4 A scheme showing the utility of temporally aligning velocity traces

(A) Temporal non-correspondence of the velocity traces can be due to inter-subject differences in heart rate and in the timing of cardiac phases. (B) Temporal alignment can be used to express velocity traces within a common temporal reference. (C) Temporally aligned velocity traces can be directly compared between patients enabling the assessment of the onset and duration of cardiac phases. A later onset of systolic LV ejection, and a prolonged LV ejection and isovolumic relaxation time can be seen in the patient on the right. This concurs with the delayed and reduced peak aortic velocity and the fusions of the early and late diastolic filling.

Figure 5 An overview of data a more comprehensive approach to data integration

A scheme showing the advantages and challenges of a more comprehensive data integration.