European Heart Journal - Cardiovascular Imaging Advance Access published March 3, 2014

European Heart Journal – Cardiovascular Imaging
doi:10.1093/ehjci/jeu022

European multicentre validation study of the accuracy of E/e′ ratio in estimating invasive left ventricular filling pressure: EURO-FILLING study

Maurizio Galderisi[1]*†, Patrizio Lancellotti[2†], Erwan Donal[3], Nuno Cardim[4], Thor Edvardsen[5], Gilbert Habib[6], Julien Magne[2], Gerald Maurer[7], and Bogdan A. Popescu[8]

[1]Department of Translational Medical Sciences, Federico II University Hospital, Naples, Italy; [2]Department of Cardiology, GIGA Cardiovascular Sciences, Heart Valve Clinic, University of Liège Hospital, Belgium; [3]Department of Cardiology, Hospital Pontchaillou-University Medical Center, Rennes, France; [4]Cardiology Department, Hospital da Luz, Lisbon, Portugal; [5]Department of Cardiology, Oslo University Hospital, Norway; [6]Cardiology Department, Hospital La Timone, Marseille, France; [7]Division of Cardiology, Second Department of Medicine, Medical University of Vienna, Austria; and [8]Carol Davila' University of Medicine and Pharmacy—Euroecolab, Institute of Cardiovascular Diseases, Bucharest, Romania

Received 4 October 2013; accepted after revision 19 January 2014

Aims The non-invasive estimation of left ventricular filling pressures (LVFPs) represents a main goal in the clinical setting. Current recommendations encourage the use of pulsed-wave Tissue Doppler for calculating the ratio between the preload-dependent transmitral E velocity and the average of septal and lateral early diastolic velocities (e′) of the mitral annulus. Despite its wide use, real utility of the E/e′ ratio has been recently challenged in patients with either very advanced heart failure or preserved left ventricular (LV) ejection fraction. However, only few studies performed the invasive and non-invasive estimation of LVFP simultaneously. The EURO-FILLING Study will validate the E/e′ ratio (and additional non-invasive estimates) against simultaneously measured LVFP obtained by left heart catheterization in a multicentre study involving reference European echo laboratories collecting a wide population sample size of cardiac patients with and without heart failure.

Methods and results The EURO-FILLING study is a large, prospective observational study in which simultaneous assessment of invasive and non-invasive measurements of LVFP will be acquired in eight reference European centres. Centralized reading of the collected parameters will be performed in a core laboratory. Not only standardized echo Doppler measurements but also novel echo parameters such as LV global longitudinal strain and global atrial strain (obtainable by two-dimensional speckle tracking echocardiography) will be tested for predicting invasive measurements of LVFP.

Conclusions The EURO-FILLING study is expected to provide important information on non-invasive assessment of LVFP and to contribute to the standardization of this assessment in clinical practice.

Keywords Left ventricular filling pressure • Diastolic function • Tissue Doppler • Left atrium • Speckle Tracking Echocardiography

Rationale

Elevated left ventricular (LV) filling pressure (LVFP) is a major determinant of cardiac symptoms and prognosis in patients with chronic heart failure, regardless LV ejection fraction (LVEF).[1,2] The invasive estimation of LVFP may be done either by right heart catheterization which allows to measure pulmonary capillary wedge pressure (PWCP) as an indirect, though accurate, estimate of left atrial pressure[3,4] or by direct sampling of LV cavity during left heart catheterization.[5]

In this view, the non-invasive estimation of LVFP is a main goal in the management of cardiac patients. Non-invasive estimation of LVFP

* Corresponding author: Echocardiography Laboratory, Cardioangiology with CCU, Department of Medical Translational Sciences, Block 1, Federico II University Hospital, V. S. Pansini 5, 80131 Naples, Italy. Tel: +39 (0)81 7464749; fax: +39 (0)81 5466152, Email: mgalderi@unina.it

† M.G. and P.L. equally contributed to the study.

may be obtained by Doppler echocardiography. Current recommendations[6] encourage the use of pulse-wave Tissue Doppler for calculating the ratio between the preload-dependent transmitral E velocity and the average of septal and lateral early diastolic velocities (e′) of the mitral annulus. This parameter correlates with the rate of myocardial relaxation and is relatively independent on pressure flow gradients.[6] In addition to be widely feasible and available, the E/e′ ratio predicts the outcome in the settings of acute myocardial infarction,[7] heart failure,[8] arterial hypertension,[9] and in patients mechanically ventilated in intensive care unit.[10] The E/e′ ratio is currently used in clinical practice also to drive medical therapy and titrate cardiac drugs in patients affected by chronic heart failure.[11]

Despite its wide use, the real utility of the E/e′ ratio has been challenged in some studies, which included patients with either very advanced heart failure[12] or normal LVEF.[13] In the latter condition, the relationship between the E/e′ ratio and PWCP appeared to be highly variable, especially after LVFP manipulation by preload changes.[13] A weak relationship between the E/e′ ratio and left atrial pressure was also found in patients with hypertrophic cardiomyopathy.[14]

Studies supporting[11,15–20] or contradicting[12–14] the concept stating that the E/e′ ratio is a truly accurate estimate of LVFP have common limitation. Indeed, all these studies been performed on relatively small sample size population and were mostly performed in one centre. In addition, only few studies performed simultaneously the invasive and non-invasive estimation of LVFP.[11–13,15–18] This was again performed on relatively small sample size series and primarily using an indirect measurement of LVFP such as PCWP (*Table 1*). The simultaneity of these two assessments remains, however, an important prerequisite in order to avoid the main bias deriving from changes of the haemodynamic conditions (e.g., heart rate, blood pressure, blood volume) possibly occurring in the different moments in which the two exams are performed.

The main aim of the EURO FILLING study is to validate Doppler echocardiographic measurements of the E/e′ ratio—and additionally, other currently used non-invasive estimates of LVFP—against the simultaneous measurement of invasive LVFP, obtained by left heart catheterization in a multicentre study involving reference European echo labs. The study will collect a wide population sample size of cardiac patients with and without heart failure.

The objectives of the EURO FILLING study will be the following:

(1) To assess the accuracy of E/e′ ratio (and additional, currently used non-invasive estimates of LV filling pressure) in estimating LVFP by using e′ average [(septal e′ + lateral e′)/2] in the whole population and according to LVEF values (i.e. ≥50 and <50%).
(2) To investigate the impact of sampling septal e′ and lateral e′ on the accuracy of E/e′ ratio in estimating LVFP in the whole population and according to LVEF values (≥50 and <50%).

Study population

The EURO-FILLING will be a multicentre study involving eight reference centres across Europe, able to recruit consecutive adult patients of both genders undergoing clinically indicated coronary angiography because of ascertained or suspected coronary artery disease. Each laboratory will be requested to recruit patients with and without heart failure (according to the 2012 ESC guidelines),[21] and their history and clinical status at the time of enrolment will be recorded. Each laboratory will be requested to include at least 10 consecutive patients with normal LVEF ejection fraction (≥50%) and 10 consecutive patients with reduced LVEF (<50%).

Exclusion criteria will include more than mild valvular heart disease, valvular prosthesis, mitral annulus calcification, previous myocardial infarction involving basal septum and/or basal lateral wall, atrial fibrillation and severe arrhythmias precluding Doppler analysis, left bundle branch block, any kind of pacemaker, hypertrophic cardiomyopathy, pericardial disease, and inadequate echocardiographic imaging. Patients taking diuretics or vasodilators (nitrates) on the day of the examination will also be excluded, since such drugs could alter loading conditions (even if echo and invasive measurements will be performed simultaneously as per protocol).

Table 1 Main studies which assessed simultaneously E/e′ ratio and invasive left ventricular filling pressures

Authors, journal, and year	Clinical setting	Sample size (*n*)	Tissue Doppler sampling	Invasive parameter	Correlation E/e′ vs. cath
Nagueh SF *et al.*, *J Am Coll Cardiol*, 1997	Patients with and without HF	60	Lateral	PCWP	$r = 0.87$
Nagueh SF *et al.*, *Circulation*, 1998	Patients with ST and HF	100	Lateral	PCWP	$r = 0.86$
Nagueh SF *et al.*, *Circulation*, 1999	HCM patients	35	Lateral	Pre-A pressure	$r = 0.76$
Ommen SR *et al.*, *Circulation*, 2000	HF patients	100	Lateral, septal, Avg	M-LVDP	$r = 0.51$ lateral $r = 0.64$ septal $r = 0.62$ avg
Dokanish H *et al.*, *Circulation*, 2004	ICU patients	50	Avg	PCWP	$r = 0.69$
Mullens S *et al.*, *Circulation*, 2009	HF patients with low EF (≤30%)	106	Lateral, septal, Avg	PCWP	$r = 0.14$ lateral $r = 0.18$ septal $r = 0.18$ avg
Bhella PS *et al.*, *Circ Cardiovasc Imag*, 2011	HF patients with normal EF (>50%)	47	Septal	PCWP	$r^2 = 0.37$
Nagueh SF *Circ Cardiovasc Imag*, 2011	Patients with decompensated HF	79	Average	PCWP	$r = 0.61$

Avg, Average; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICU, intensive care unit; PCWP, pulmonary capillary wedge pressure; M-LVDP, mean left ventricular end-diastolic pressure; ST, sinus tachycardia.

Procedures

A preliminary comprehensive echo Doppler examination (including the assessment of both LV and right ventricular chambers) will be performed the same day but before (within 1/2h) the invasive and non-invasive assessment of LVFP. Quantification of left ventricle and left atrium geometry and function will be performed by 2-D echocardiography according to ASE-EAE recommendations.[22] Calculation of LVEF will be done by modified Simpson's rule. Tricuspid annular plane systolic excursion will be used as an index of right ventricular systolic function.

Each echocardiographic laboratory will provide simultaneous non-invasive and invasive (left heart catheterization) estimation of LVFP of all the recruited patients. This will be done in the catheterization laboratory, in the same supine body position, immediately before coronary angiography.

Measurements of invasive left ventricular filling pressure

Invasive measurements will be taken by an end-hole catheter which allows the most precise localization of the pressure measurement and avoids any source of error due to catheter positioning.[23] The catheter will be connected with a pressure transducer and inserted into LV chamber passing through the aortic valve in order to measure early LV diastolic pressure, LV end-diastolic pressure (LVEDP), and mean LV diastolic pressure (as the integral of the area under the whole diastolic curve, from the time of mitral valve opening to mitral valve closure) using a simultaneously recorded ECG-derived R wave as a reference. The standardization of frequency response will be at least 15–20 Hz, in order to obtain accurate measurements, in particular of LVEDP. Values of invasive pressures will be calculated as a mean of at least three consecutive cardiac cycles.[5] An accurate zero reference level is a prerequisite for the reliable determination of intra-cardiac pressures. The mid-chest position/level will be preferred as the zero reference point in this study. A recording of the zero reference will be performed immediately before and after the LV pressure measurements. The zero reference sampling will be saved together with the LV pressure data. A core lab placed in Liege (Belgium), blinded to the echocardiographic data, will read all pressure recordings.

Assessment of Doppler-derived left ventricular diastolic function and left ventricular filling pressure

The assessment of Doppler transmitral inflow diastolic filling and pulsed wave Tissue Doppler of the mitral annulus will be performed according to the standardized EAE procedures.[6,24] Additional non-invasive estimation of LVFP will include pulmonary venous flow parameters, pulmonary arterial systolic pressure, and global longitudinal strain (GLS), while the quantification of global left atrial systolic strain will be optional.

Performance recommendations

Transmitral pulsed Doppler will be recorded in the apical four-chamber view. The pulsed Doppler sample volume of LV transmitral inflow will be placed at the tips of mitral leaflets where the velocity amplitude is maximal. When recording pulsed-wave Tissue Doppler velocities of septal and lateral mitral annulus, special attention will be paid to the Doppler spectral gain settings and the velocity scale will be kept at ~20 cm/s above and below the baseline. Minimal angulation (<20°) will be maintained between the ultrasound beam and the direction of cardiac motion during the sampling of each of the mitral annular sites.

Pulmonary venous flow will be recorded according to the ASE/EAE standardized procedures by placing a pulsed Doppler sample volume (2–3 mm) at 0.5 cm into the right upper pulmonary vein for optimal recording of the spectral waveforms.[6]

Two-dimensional speckle tracking echocardiography (STE) of the three apical views of the left ventricle will be acquired by ASE/EAE standardized procedures, achieving appropriate frame rates by the reduction of the number of ultrasound beams in each frame (thereby reducing the spatial resolution and imaging quality) and positioning the focus at an intermediate depth to optimize the images for STE. Sector depth and width will be adjusted to include as little as possible outside the region of interest.[24] Optional recording of apical four- and two-chamber views focused on left atrium will be also acquired in order to estimate global left atrial systolic strain.[25]

Reading recommendations

Measurements of parameters of LV diastolic function and non-invasive LVFP will be done in the core laboratory by independent experienced investigators who will be blinded to the results of invasive haemodynamic data at the time of analysis. Early (E) and atrial (A) peak velocities and their ratio, and E velocity deceleration time will be measured. Using pulsed-wave Tissue Doppler, early diastolic velocities (e′) will be measured at both septal and lateral mitral annulus and averaged as recommended.[4] The ratio of transmitral peak E velocity to peak e′ velocity will be calculated as an estimate of LVFP as the sole measurement of septal (E/e′S), lateral annulus (E/e′L), and by averaging e′ of 2 sites (septal and lateral: E/e′A2) (*Figure 1*).

Measurements of pulmonary venous flow will include peak systolic velocity (S), peak anterograde diastolic velocity (D), the S/D ratio, and the peak retrograde atrial reverse velocity (Ar) (*Figure 2*). The time duration of Ar and the time difference between Ar and transmitral A velocity (Ar − A) will also be calculated.

All reported echo-Doppler measurements will be averaged from three cardiac cycles.

Using 2D STE, LV regional (18 segments) strain will be measured and GLS will be obtained by averaging all values of LV regional peak longitudinal strain obtained in each apical view before the aortic valve closure (*Figure 3*) according to the ASE-EAE recommendations.[25] Optional analysis of regional left atrial systolic strain will be performed by using a 12-segment model (6 in apical 4 and 6 in apical 2-chamber views) and QRS onset as the reference point (*Figure 4*). Global atrial strain will be obtained by averaging all values of regional peak atrial strain as recommended.[25]

Statistical analyses

All statistical analysis will be carried out by Julien Magne, the appointed EACVI statistician. Data will be presented as mean

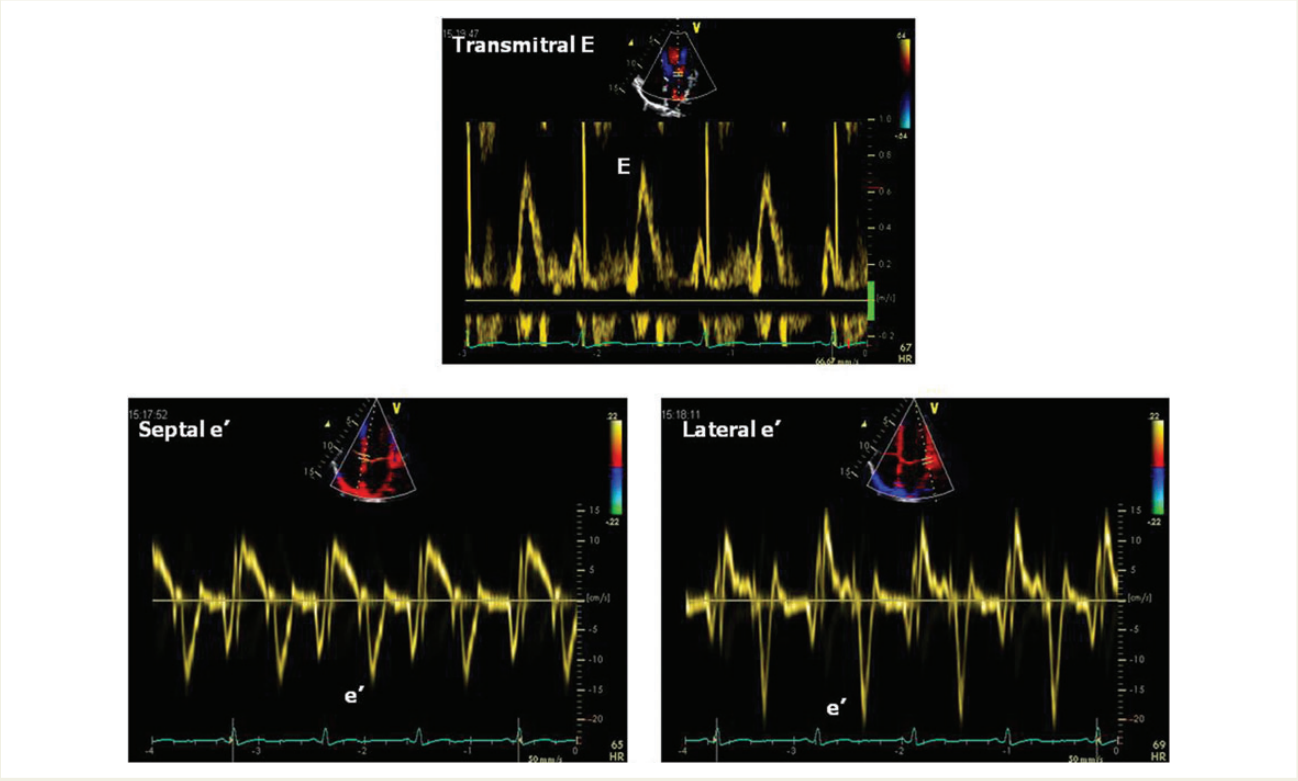

Figure 1: Methodology to calculate the ratio between standard Doppler derived transmitral early diastolic velocity (E) and pulsed Doppler derived early diastolic velocity of the mitral annulus (e′). The e′ velocity can be measured either at the septal site or at the lateral site of the mitral annulus. However, recommendations on LV diastolic function encourage the average of septal and lateral e′ velocities.

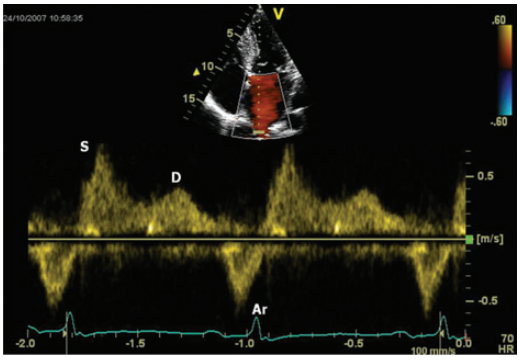

Figure 2: Methodology of measurement of pulmonary venous flow velocity. Pulmonary venous flow pattern obtained by pulsed Doppler sample volume at 0.5 cm into the right upper pulmonary vein. AR, atrial reverse velocity; D, early diastolic velocity; S, systolic peak velocity.

value ± SD. The relationship between invasive and non-invasive parameters will be assessed using linear regression. Multiple linear regression analysis will be performed to identify the independent contributors of invasive LVFP in the whole population, as well as according to the LVEF values (≥50 and <50%). Concordance of invasive measurements and non-invasive estimates of LVFP will be assessed using the Bland–Altman analysis. Receiving operating characteristic curves will be constructed and the area under the curves determined for the prediction of LVEDP ≥15 (pathologic cut-off point) and ≥18 mm Hg (prognostic cut-off point). Sensitivity, specificity, positive predictive value, and negative predictive value predicting LVEDP ≥15 and ≥18 mm Hg will be calculated for various cut-off values of each non-invasive parameters (including the predefined ratio). In addition, the independent predictor of LVEDP ≥15 and ≥18 mm Hg will be identified using logistic regression. The null hypothesis will be rejected at $P \leq 0.05$.

Quality control of the study

Each peripheral echocardiographic laboratory will follow the standard operational procedures recommended by principal investigators (PI) and core laboratory in terms of data imaging acquisition, data storage, and data processing.

The core laboratory will be organized to ensure the quality control of echo Doppler exams performed in peripheral echocardiographic laboratories and optimize reading procedures in order to limit the inter- and intra-observer variability of measurements. Internal reproducibility of core laboratory will be checked (the Bland & Altman test; interclass correlation coefficient, inter-rater agreement: kappa) on a limited data set of invasive and non-invasive LVFP. Continuous links will be kept between core laboratory and PI during the overall study duration period.

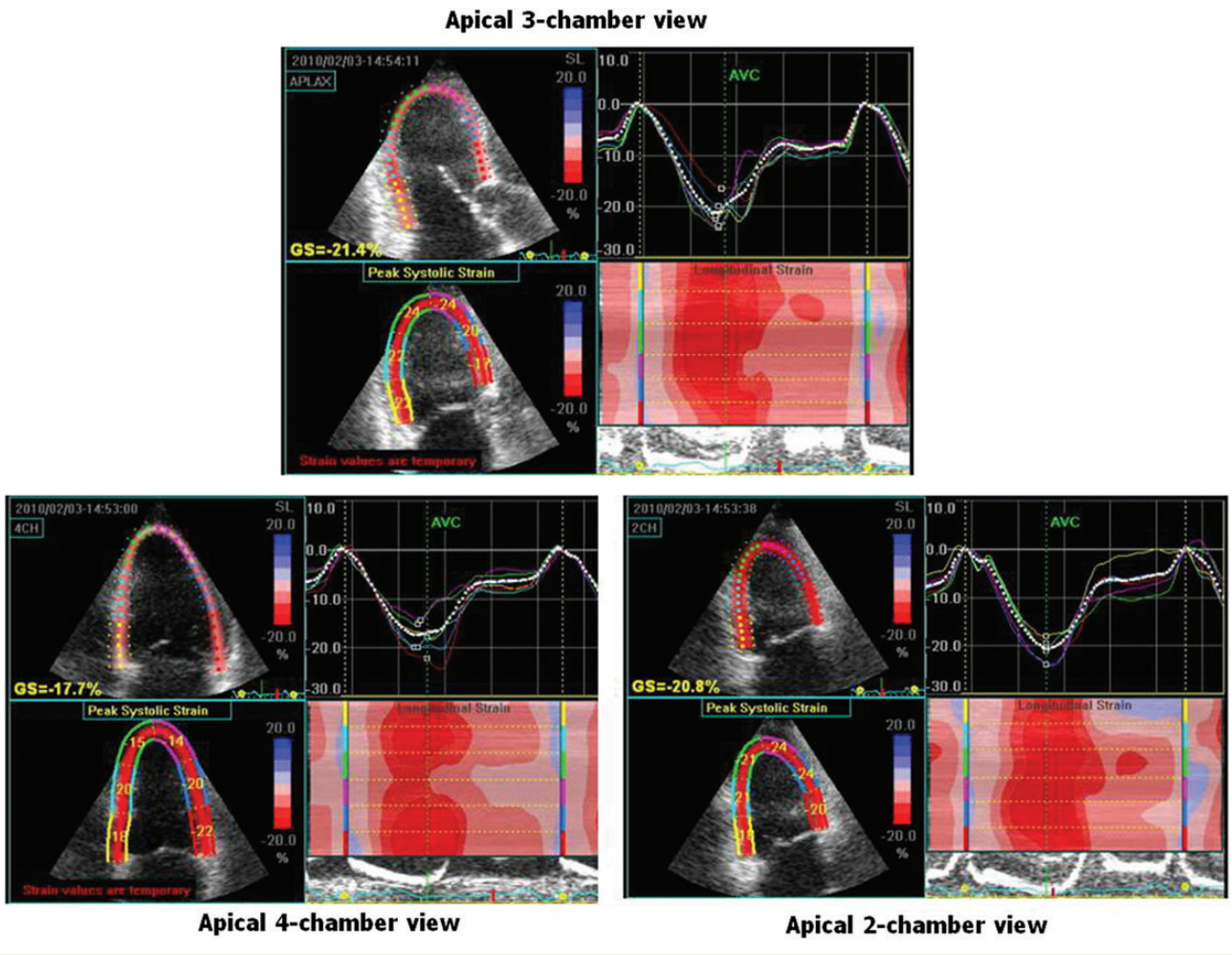

Figure 3: Speckle tracking echocardiography (STE)-derived left ventricular (LV) longitudinal strain during cardiac cycle in the three apical views. In the left section of each view colour representation of STE on 2-D imaging (upper) and quantitation of peak regional strain values (normally negative) referring to six myocardial regions. In the right upper section of each view regional colour systolic curves of systolic strain while dotted white line corresponds to average strain (GLS). In the right lower section qualitative colour M-mode strain representation referring to the six consecutive myocardial segments: at the bottom LV basal right segments (red colour) of each view, at the central part LV apex, at the top LV basal left segments (yellow colour) of each view; red and pink colours refer to systolic deformation.

Ethical Committee

The EURO-FILLING study will be conducted according to the rules for research in human subjects. Protection of privacy with regards to processing of individual data will be ensured. The institutional ethical committees of the participating centres will approve the project. All patients will give their written informed consent.

Discussion

Non-invasive estimation of LVFP is critically important in the clinical setting in relation to its diagnostic and prognostic implications and also in order to manage heart failure patients with appropriate cardiac therapy and timing.[1–11] Despite being largely applied in the current practice and encouraged by echocardiographic recommendations,[6] the use of E/e′ ratio remains controversial in heart failure patients with either normal or depressed LVEF.[11–18] A main weak point of this debate depends on the fact that only few studies performed a simultaneous assessment of the E/e′ ratio (or other non-invasive estimate) and invasively measured LVFP, on a relatively small sample size population.[11–13,15–20]

The EURO-FILLING study aims to establish associations between simultaneously determined invasive and non-invasive measurements of LVFP in a large population of consecutive patients undergoing cardiac catheterization because of suspected or ascertained coronary artery disease. The EURO-FILLING study will be the largest prospective study to explore this issue in patients with both normal and reduced LVEF by a multicentre approach which will involve reference EACVI echocardiographic laboratories across Europe. Not only the E/e′ ratio but also the other currently used diastolic parameters (e.g. mitral inflow derived E velocity deceleration time, Ar-A time duration difference, pulmonary arterial systolic pressure) will be

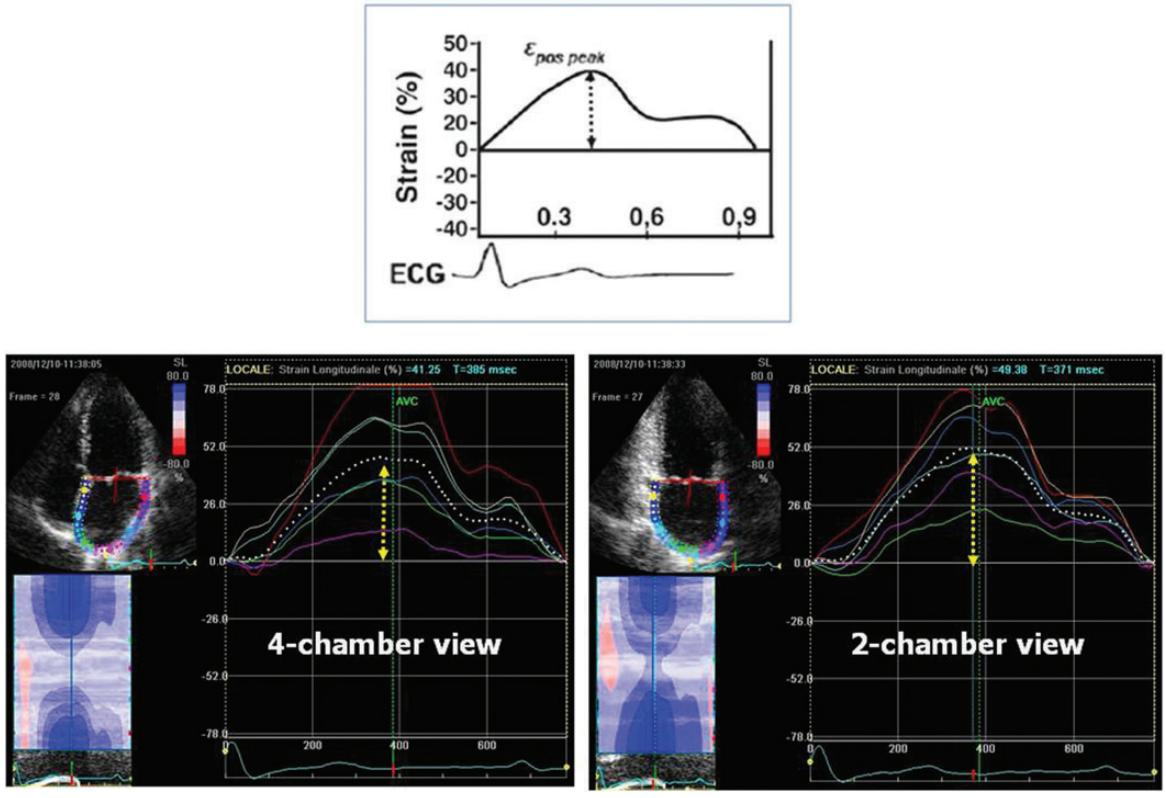

Figure 4: Speckle tracking echocardiography-derived left atrial systolic strain during cardiac cycle in two apical chamber views. Determination of 12 regions, six in apical four-chamber view and six in apical two-chamber view by the use of ECG-derived QRS complex as a reference point and measurement of the positive peak left atrial longitudinal strain.

tested against measurements obtained simultaneously by left heart catheterization. Also measurements derived by new advanced echocardiographic technologies (e.g. LV GLS and global left atrial systolic strain) will be investigated in order to provide a comprehensive assessment of non-invasive LVFP. Of interest, preliminary results have demonstrated the ability of left atrial systolic strain in predicting invasive LVFP.[26] In this regards, no information is available for GLS while preliminary data have been obtained with global diastolic strain rate.[27,28]

Notably, the quality assurance of the EURO FILLING study will be guaranteed by adequately trained operators of reference peripheral sites but also by using a dedicated core laboratory with personnel having considerable technical skills and experience in research projects. The core laboratory will verify the exams obtained in the peripheral centres in terms of completeness, adherence to the acquisition protocol, and data quality. It will also provide valuable determination of invasive and non-invasive measurements according to the standardized procedures.[23]

Limitations

The use of an end-hole catheter for measuring invasive LVFP can be considered a limitation of this project. Micromanometer-tipped catheters provide globally more accurate pressures also in inexperienced haemodynamic laboratories. Unfortunately, they are expensive and also associated with higher risk of embolus. Conversely, end-hole catheters can be standardized (zeroing) from the level of the heart in each patient as an absolute pressure reference.

Conclusions

The EURO-FILLING study will test the accuracy of the E/e′ ratio and other echocardiographic Doppler measurements in predicting invasively determined LVFP. The strength of the study will be the simultaneous assessment of invasive and non-invasive measurements, the involvement of reference centres across Europe, and the use of a dedicated core laboratory which will validate the obtained measurements.

Conflict of interest: B.A.P. has received research support and lecture honoraria from General Electric Healthcare.

Funding

The EURO-FILLING Study is supported by Servier in the form of an unrestricted educational grant. Sponsor funding has in no way influenced the contents and management of the study.

References

1. Stevenson LW, Tillisch JH, Hamilton M, Luu M, Chelimsky-Fallick C, Moriguchi J *et al.* Importance of hemodynamic response to therapy in predicting survival with ejection

fraction less than or equal to 20% secondary to ischemic or non ischemic dilated cardiomyopathy. *Am J Cardiol* 1990;**66**:348–1354.
2. Steimle AE, Stevenson LW, Fonarow GC, Hamilton MA, Moriguchi JD. Prediction of improvement in recent onset cardiomyopathy after referral for heart transplantation. *J Am Coll Cardiol* 1994;**23**:553–9.
3. Swan HJ, Ganz W. Measurement of right atrial and pulmonary arterial pressures and cardiac output: clinical application of hemodynamic monitoring. *Adv Intern Med* 1982; **27**:453–73.
4. Sharkey SW. Beyond the wedge: clinical physiology and the Swan-Ganz catheter. *Am J Med* 1987;**83**:111–22.
5. Salem R, Denault AY, Couture P, Bélisle S, Fortier A, Guertin MC *et al.* Left ventricular end-diastolic pressure is a predictor of mortality in cardiac surgery independently of left ventricular ejection fraction. *Br J Anaest* 2006;**97**:292–7.
6. 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. *Eur J Echocardiogr* 2009;**10**:165–93.
7. Hillis GS, Møller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR *et al.* Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction. *J Am Coll Cardiol* 2004;**43**:360–7.
8. Bruch C, Rothenburger M, Gotzmann M, Sindermann J, Scheld HH, Breithardt G *et al.* Risk stratification in chronic heart failure: independent and incremental prognostic value of echocardiography and brain natriuretic peptide and its N-terminal fragment. *J Am Soc Echocardiogr* 2006;**19**:522–8.
9. Sharp AS, Tapp RJ, Thom SA, Francis DP, Hughes AD, Stanton AV *et al.* ASCOT Investigators. Tissue Doppler E/e′ ratio is a powerful predictor of primary cardiac events in a hypertensive population: an ASCOT substudy. *Eur Heart J* 2010;**31**: 747–52.
10. Combes A, Arnoult F, Trouillet JL. Tissue Doppler imaging estimation of pulmonary artery occlusion pressure in ICU patients. *Intensive Care Med* 2004;**30**:75–81.
11. Dokainish H, Zoghbi WA, Lakkis NM, Al-Bakshy F, Dhir M, Quinones MA *et al.* Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. *Circulation* 2004;**109**:2432–9.
12. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation* 2009;**119**:162–70.
13. Bhella PS, Pacini EL, Prasad A, Hastings JL, Adams-Huet B, Thomas JD *et al.* Echocardiographic indices do not reliably track changes in left-sided filling pressure in healthy subjects or patients with heart failure with preserved ejection fraction. *Circ Cardiovasc Imaging* 2011;**4**:482–9.
14. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. *Circulation* 2007;**116**:2702–98.
15. 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 pressure. *J Am Coll Cardiol* 1997;**30**:1527–33.
16. Nagueh SF, Mikati I, Kopelen HA, Middleton K, Quinones MA, Zoghbi W. Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of Tissue Doppler Imaging. *Circulation* 1998;**98**:1644–50.
17. Nagueh SF, Lakkis NM, Middleton K, Spencer WH, Zoghbi WA, Quinones MA. Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. *Circulation* 1999;**99**:254–61.
18. 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.
19. Galderisi M, Rapacciuolo A, Esposito R, Versiero M, Schiano-Lomoriello V, Santoro C *et al.* Site-dependency of the E/e' ratio in predicting invasive left ventricular filling pressure in patients with suspected or ascertained coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2013;**14**:555–61.
20. Nagueh SF, Bhatt R, Vivo RP, Krim SR, Sarvari SI, Russell K *et al.* Echocardiographic evaluation of hemodynamics in patients with decompensated systolic heart failure. *Circ Cardiovasc Imaging* 2011;**4**:220–7.
21. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K *et al.* for ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–847.
22. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA *et al.* American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;**7**:79–108.
23. Courtois M, Kovacs SJ Jr, Ludbrook PA. Transmitral pressure flow velocity-gradients in the left ventricle during diastole. *Circulation* 1988;**78**:661–71.
24. Galderisi M, Henein MY, D'hooge J, Sicari R, Badano LP, Zamorano JL *et al.* European Association of Echocardiography. Recommendations of the European Association of Echocardiography: how to use echo-Doppler in clinical trials: different modalities for different purposes. *Eur J Echocardiogr* 2011;**12**:339–53.
25. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G *et al.* Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr* 2011;**12**:167–205.
26. Cameli M, Lisi M, Mondillo S, Padeletti M, Ballo P, Tisioulpas C *et al.* Left atrial longitudinal strain by speckle tracking echocardiography correlates well with left ventricular filling pressure in patients with heart failure. *Cardiovasc Ultrasound* 2010;**8**:14.
27. Wang J, Khoury DS, Thohan V, Torre-Amione G, Nagueh SF. Global diastolic strain rate for the assessment of left ventricular relaxation and filling pressures. *Circulation* 2007;**115**:1376–83.
28. Kasner M, Gaub R, Sinning D, Westermann D, Steendijk P, Hoffmann W *et al.* Global strain rate imaging for the estimation of diastolic function in HFNEF compared with pressure-volume analysis. *Eur J Echocardiogr* 2010;**9**:743–51.