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Recommendations of the European Association of Echocardiography

How to use echo-Doppler in clinical trials: different modalities for different purposes

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The European Association of Echocardiography (EAE) has developed the present recommendations to assist clinical researchers in the design, implementation, and conduction of echocardiographic protocols for clinical trials and to guarantee their quality. Clinical trials should be designed and conducted based on the knowledge of the pathophysiology of the clinical condition studied, the technical characteristics of the echo-Doppler modalities, and the variability of the tested parameters. These procedures are important to choose the most reliable and reproducible techniques and parameters. Quality assurance must be guaranteed by adequate training of peripheral site operators to obtain optimal echo-Doppler data and by using a core laboratory for accurate and reproducible data analysis.

Keywords Echocardiography • Clinical trials • Cardiac chambers • Cardiac haemodynamics • Native valves • Prosthetic valves • Quality control

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Introduction

Echocardiography is widely used in clinical trials to identify epidemiological features, elucidate pathophysiological mechanisms and to assess treatment effectiveness. It is important, therefore, to select the adequate echo-Doppler modality and the parameters to answer the specific clinical questions for which a clinical trial is designed and conducted. In 2004, the American Society of Echocardiography (ASE) proposed recommendations for the appropriate use of echocardiography in clinical trials.[1] This document was followed by a joint effort between the ASE and the European Association of Echocardiography (EAE) to standardize the use of echo-Doppler for cardiac chamber quantification,[2,3] and heart valve function.[4–6] The present document aims at providing recommendations regarding the use of standard and advanced echo-Doppler modalities and helping trial designers, epidemiologists, and clinicians to select the most appropriate modality and parameters to achieve a significant result.

Principles and general remarks

Echocardiography offers several imaging modalities and measurements which can be used in clinical trials. Accuracy (validation against autopsy and/or reference techniques), reliability in the clinical setting, reproducibility, and prognostic value of a given parameter are the characteristics that must be taken into account when the specific end-points of the clinical trial are formulated. In addition, the level of clinical relevance of the chosen echo-Doppler parameter should always be considered. In particular, the variability of changes of a given measurement, even irrespective of the statistical significance of the average values, should be carefully taken into account. For instance, the clinical relevance of

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ejection fraction (EF) changes after a treatment intervention should be analysed considering much more the measurement standard deviations (SDs) than the mere statistical significance of these changes. A significant change of 1–1.5 points in an average EF should not be overemphasized when the inter- and intra-observer variability is higher than 10%.

The recording of echo-Doppler imaging as well as the performance of all the standard measurements obtained with the various ultrasound modalities [M-mode, two-dimensional (2D), and Doppler] shall be performed following recognized rules and conventions.[3,7] The determination of all the standard echo-Doppler measurements should be the result of averaging measurements of at least three heart beats in patients with sinus rhythm and of averaging measurements derived from 10 cardiac cycles (alternatively, from three non-consecutive beats with cycle lengths within 10% and 20% of the average heart rate) in patients with atrial fibrillation (AF).[3,7] In order to minimize the variability of measurements, the use of the same instrumentation is recommended for repeated assessment over time.

Use of echo-Doppler in clinical trials: different modalities for different purposes

There are basically two types of clinical trials in which echocardiography is used. In one type of studies echo-Doppler is used to identify phenotypes/features in order to define a certain study population (on the basis of echo-Doppler parameters). The other type of trial involves echo-Doppler measurements [e.g. chamber volumes, Left ventricular (LV) mass] as primary or secondary endpoints for efficacy and safety purposes. While echo-Doppler parameters are considered acceptable as a proof of concept of treatment in phase II trials, the use of echo-Doppler measures as primary endpoints in phase III studies (for drug registration) remains controversial. Indeed, in this particular case it is necessary to show that a given echo-Doppler parameter is a real surrogate of clinical events. In this view, the prognostic value is not sufficient but should be combined with the demonstration that modifications of the echo-Doppler measurements correspond (better if proportionally) to changes in outcome events. At present, regulatory authorities do not consider echo-Doppler parameters as endpoints in pivotal trials designed to prove efficacy of a drug in several clinical situations such as ischaemic and non-ischaemic heart failure, and systemic arterial hypertension.

However, the role of echocardiography in clinical trials has been changing in the last decade for two main reasons:

- The accuracy of echo-Doppler modalities and measurements does not refer to autopsy data anymore, but to cardiac magnetic resonance (CMR). This is now considered the reference method of non-invasive cardiac imaging. In interventional trials, CMR allows to reduce the sample size of the study population because of the smaller variability of its measurements.
- New echo technologies, mainly three-dimensional echocardiography (3DE) and speckle-tracking echocardiography (STE), have become available and are competitive with CMR in accuracy while being less expensive and more widely available.

Application of echocardiography in trials designed to define a given study population has remained unchanged over the years. When using echo-Doppler parameters as inclusion criteria they can be checked peripherally but an echo core laboratory (ECL) should be preferred. New ultrasound technologies may provide a better quantitative approach, especially in trials using parameters as endpoints, and in some cases are mandatory, such as the measurement of LV volumes by 3DE. However, these new tools may have a high variability and a core laboratory should always be implemented in order to reduce it.

Quantification of cardiac chambers: recommendations for strategies and measurements to increase reproducibility

The quantification of cardiac chamber geometry and function[3] is the most frequent application of echo-Doppler in a clinical trial.[1] The ASE and EAE have reviewed the technical aspects of acquisition and measurements of cardiac chamber by echo-Doppler and established normal reference values.[3,8]

Left ventricular structure and function

LV diameters, wall thickness, and volumes

LV diameters, volumes, and wall thickness have physiopathological, clinical, and prognostic values. *LV diameters* (at end-diastole and end-systole) and wall thickness (at end-diastole) can be obtained from correctly aligned M-mode (better temporal resolution) or direct 2DE (better spatial orientation).[3] M-mode-derived LV diameters allow to estimate accurately the size in ventricles with symmetric geometry and contraction [e.g. arterial hypertension, aortic stenosis (AS)] and have good reproducibility.[9] Comparison of controls and patients in epidemiological studies often requires the use of gender-specific cut-off values, and normalization for body surface area (BSA, m^2) or height (m), in order to define normality and the degree of deviation from it.[3]

The calculation of *LV volumes* is preferable for the determination of LV size and becomes imperative in patients with distorted ventricles and/or wall motion abnormalities [coronary artery disease (CAD) and/or acute myocardial infarction (AMI)].[3] Among the various algorithms used to calculate LV volumes from 2D tomographic views, the biplane method of summation of disks is the most accurate in abnormally shaped ventricles.[3] When compared with CMR, 2DE LV volumes show underestimation[10] and a higher inter-study variability which is statistically significant for LV end-systolic volume (13.7–20.3 vs. 4.4–9.2%, $P < 0.001$).[11] Consequently, a larger study population samples (55–93% larger than using CMR) is needed to demonstrate significant changes in LV size. In patients with suboptimal image cavity delineation, contrast agents can be used intravenously to enhance border delineation, which increases accuracy and reproducibility of LV volumes.[12,13] Semi-automated detection of the LV endocardial borders surface using 3DE data sets of the left ventricle (*Figure 1*) is now available

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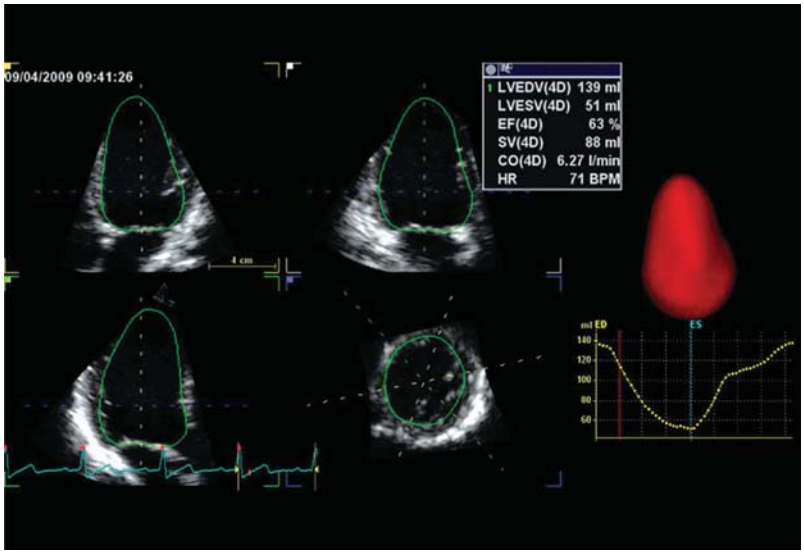

Figure 1 3DE measurement LV volumes using a semi-automatic endocardial detection algorithm. LV endocardial surface is detected both in longitudinal and in transversal planes of the left ventricle in order to develop a dynamic model of the left ventricle that is independent of geometrical assumptions about its shape. Quantitative analysis panel and volume-time plot are provided on the right.

to obtain rapid and accurate volume measurement.[14] Test–retest variability by a separate operator has shown lower underestimation of LV volumes by 3DE than by 2DE when CMR is the reference technique.[15,16] Further concordance of 3DE-derived volumes vs. CMR can be obtained by tracing the endocardium so that it includes trabeculae in the LV cavity.[16]

LV mass

LV mass has been calculated by echocardiography in epidemiological studies and treatment trials dealing with systemic arterial hypertension. LV hypertrophy is an independent predictor of morbidity and mortality in the general population and changes of LV mass induced by anti-hypertensive treatments have been extensively studied. While LV mass measurements (indexed for BSA or height) identify LV hypertrophy, relative wall thickness categorizes LV geometry (concentric or eccentric).[3]

All LV mass calculations/measurements (M-mode, 2DE, 3DE) are based upon the subtraction of LV cavity volume from the volume enclosed by the LV epicardium ('shell' volume) to obtain myocardial volume, which is then multiplied by myocardium specific weight (1.05 g/mL). LV mass calculations can be made using linear primary measurements from 2DE-guided M-mode or direct 2DE views. The ASE formula earlier proposed for estimation of LV mass[3] is considered appropriate for evaluating patients with normal LV geometry but its accuracy is suboptimal [standard error of estimate (SEE) from 29 to 97 g, 95% confidence interval (CI) 57 to 190 g] in comparison with post-mortem LV mass.[17] This calculation has also a large inter-observer variability (SEE, from 28 to 41 g; 95% CI, 55 to 80 g)[17] and a poor inter-study (test–retest) reproducibility, with SDs of the difference between successive measurements from 22 to 40 g (95% CI, 45–78 g).[17] However, in the RES trial (Reliability of M-mode Echocardiographic Studies) (from 16 centres with good expertise for quantitative echo), the probability of proving a true change in LV mass over time for a single-reader difference was a change >18% of the initial value (90% interval of agreement of test–retest between-observer variability = −26 to 30 g).[18] By using anatomically corrected 2DE linear measurements, the reproducibility of LV mass was similar in the ECL of the multicentre PRESERVE (Prospective Randomized Study Evaluating Regression of Ventricular Enlargement) trial: between-study LV mass change of ±35 g (18% of the baseline value) and 17 g, to have a likelihood of being true change >95 and >80%, respectively.[9]

The 2DE method of LV mass calculation is based on the truncated ellipsoid model and area-length formula,[3] relying on myocardial area measurements (=total area − cavity area) at the mid-papillary levels and excluding the papillary muscles in the endocardial tracing. It has been validated against post-mortem measurement. Accuracy (SEE = 31–39 g) and reproducibility are slightly better than calculation derived from linear measurements.

The calculation of LV mass from 3DE removes geometric assumptions regarding LV shape and reduces errors due to foreshortened views[19,20] (*Figure 2*). 3DE-derived LV mass has been validated against post-mortem measurement (concordance = 0.92) and CMR (concordance = 0.91).[21] A much lower LV mass underestimation vs. CMR has been found using 3DE rather than 2DE.[14,21] The very good reproducibility of LV mass with 3DE (intra-observer variability = 7–12.5%)[20,21] could significantly reduce sample size to assess LV mass changes when compared with M-mode/and 2DE and become competitive with CMR.

LV global and regional systolic function

LV global function

The LVEF is the most widely used parameter to assess outcome in epidemiological studies on heart failure, valvular heart diseases, and CAD, and to test treatment effects on cardiac function. The

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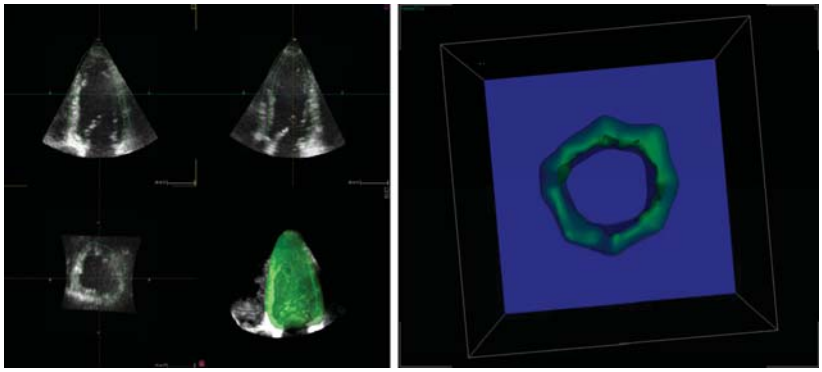

Figure 2 LV mass is measured with 3D by subtracting the LV endocardial volume from the LV epicardial volume (right panel). The myocardial volume that is obtained (left panel in green) is then multiplied by 1.05 g/mL (myocardial specific weight) to obtain LV mass.

reproducibility of 2DE-derived EF has been tested and both ±7% of inter-observer variability[22] and ±5% of test–retest reliability[17] have been reported. Despite the better accuracy of measurement of LV end-systolic and end-diastolic volumes by 3DE, there is no additional value in calculating EF by 3DE because of the constant underestimation of echo-derived LV end-diastolic and end-systolic volumes when compared with CMR.[14,15]

In patients with LV concentric geometry, calculation of *mid-wall fractional shortening*, obtainable by mathematical model from LV diameters and wall thickness at end-diastole and end-systole, has shown prognostic power and can be used to detect alterations of LV systolic function which precede the reduction in EF.[23]

LV longitudinal systolic function is an important component of LV pump function because it contributes to 60% of the stroke volume[24] and its decrease often precedes EF impairment. LV longitudinal systolic function can be quantified by either measuring systolic excursion of the mitral annulus using M-mode or, more simply, myocardial systolic velocity of the mitral annulus (septal, lateral, or average) with pulsed tissue velocity imaging (TVI).[25] Age-specific reference values for mitral annulus TVI have been generated.[26] Longitudinal deformation imaging derived by 2D STE is a more reproducible technique to assess LV longitudinal function, in particular in round-shaped left ventricles where the correct alignment of the Doppler beam to obtain TVI is difficult. However, at present reference values for LV longitudinal systolic function by STE are not available from population studies.

LV regional function

The assessment of regional wall function is often performed by visual, semiquantitative analysis (scoring) of both inward endocardial motion and myocardial thickening.[3] A 17-segment model of the left ventricle has been proposed by the American Heart Association in order to obtain a standardized myocardial segmentation and nomenclature for tomographic imaging of the heart that is shared by all imaging modalities (nuclear cardiology, CMR, cardiac computed tomography, positron emission tomography, and coronary angiography). LV segments are identified according to internal anatomical landmarks of the left ventricle, in the standard parasternal (long-axis and short-axis at the mitral, papillary, and apical levels), apical (5-, 4-, 3-, and 2-chamber), and subcostal (long-axis and short-axis) views. Each segment can be visualized in more than a single echocardiographic section and from different approaches for a more reliable and complete evaluation of wall motion. As a rule, segmental wall motion can be definitely assessed when the endocardial contour is clearly visualized for at least 50% of its length. The 17-segment model meets the basic requirements of any reasonable segmentation: it is simple enough to be employed in practice; it has an anatomical basis; segments can be easily identified on the basis of obvious echocardiographic landmarks; there is good correspondence with the distribution of coronary arteries; the model has stood the test of multicentre studies.[27] Accuracy and reproducibility of a *wall motion score* analysis are dependent on the reader's experience. Attempts to quantify segmental LV function have been unsuccessful so far. 2D STE-derived strain rate imaging is very promising[28] because of its technical advantages (absence of tethering effects of adjacent myocardial segments, no angle dependence when compared with TVI). However, experience with this technique is still limited.

How to increase accuracy of LV measurements

Performance recommendations

In order to increase accuracy and reproducibility of 2DE-derived LV volume measurements, LV cavity foreshortening must be avoided by reducing the difference of the LV long axes length in four- and two-chamber views to <10%. LV cavity should be acquired at the lowest possible depth in order to display it on the screen as large as possible and the same field depth should be kept for both four- and two-chamber apical views. Larger than necessary sector width should be avoided in order to preserve spatial resolution.[3] In the case of suboptimal visualization of endocardial borders of more than two LV segments, an i.v. contrast agent can be used to improve endocardial border visualization.[12,13] When using 3DE full-volume, consecutive four-beat ECG-gated subvolumes must be acquired during apnoea and care should be taken to encompass the entire LV cavity in the digital data set without artefacts. After the 3D acquisition, nine-

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slice display mode is mandatory to ensure optimal imaging of the entire LV endocardium at each short-axis level and lack of stitching artefacts.

When performing TVI the longitudinal excursion of the LV wall must be aligned with the Doppler beam. TVI sample volume (<5 mm) must be positioned at ~1 cm away from the septal or lateral insertion sites of the mitral leaflets or 1 cm away within interventricular septum and/or lateral wall myocardium and adjusted to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Both gains and filter settings should be set low. All TVI recordings should be obtained at sweep speed of 50–100 mm/s, in order to improve temporal resolution and the reproducibility of time interval measurements.

Reading recommendations

In order to calculate LV mass by using M-mode or 2DE, the measurement of chamber dimensions and wall thicknesses by using direct 2DE measurements in the parasternal long-axis view must be preferred. This method prevents incorrect alignment of the M-mode cursor which should be perpendicular to both the septum and LV posterior wall.[3] Novel, rapid 3DE LV analysis can be performed by analytic software which provides automatic slicing of LV full-volume data set, manual alignment of the LV central longitudinal axis, LV reference point identification, automated identification of endocardial borders at both end-diastole and end-systole and final data set display. Systematic border verification and manual correction of automated or semiautomated border detection are often required and recommended to increase accuracy of 3DE-derived LV volume measurements.[16] Manual tracing of the endocardial border should be performed outwards the black–white interface in order to include endocardial trabeculations.[15]

Right ventricular structure and function

Right ventricular (RV) function is an important independent predictor of mortality in heart failure, pulmonary arterial hypertension (PAH), and several systemic diseases involving the heart. Because of the complex morphology of the right ventricle no single echo view or imaging plane will provide enough information to adequately evaluate RV structure and function by M-mode or 2DE.[8] RV free wall thickness can be measured in subcostal four-chamber view. All the methods attempted to estimate RV size (diameters, areas, and volumes) are unreliable.[8,29]

Tricuspid annular plane systolic excursion (TAPSE), earlier proposed as an accurate index of RV global systolic function, takes into account that RV shortening occurs mainly along its longitudinal axis. TAPSE has been validated against RV EF obtained by radionuclide angiography. It has an important prognostic role in population studies[30] and its use in clinical trials can be suggested. However, TAPSE does not accurately assess changes in RV systolic function after cardiac surgery. The absence of a post-operative decrease in 3DE-derived RV EF supports in fact the hypothesis that geometrical rather than functional RV changes explain reduction in TAPSE under these circumstances.[31] RV longitudinal function can be quantified also using 2D STE-derived strain or by simple pulsed TVI which allows measuring myocardial systolic velocity (s') at the lateral tricuspid annulus.[32] Age-specific reference values of RV TVI have been generated[33] and its prognostic value has been demonstrated.[34] Recently, semi-automated detection of the RV endocardial surface and volume measurements from 3DE has been validated against CMR,[35] and has been found to be accurate and reproducible for assessing RV EF.[36] This is due to the inclusion of significant important volumes of the RV inflow and outflow tracts, which are missed by 2DE measurements.[29] The possibility to assess RV volumes and EF by 3DE could potentially stimulate clinical research about the prognostic role of the right ventricle in several heart diseases and the effects of treatments on RV structure and function.

How to increase reproducibility of RV measurement

Performance recommendations

When acquiring images for measuring RV wall thickness care must be taken to reduce the gain in order to blunt the signal of the tricuspid tendinous chords and avoid overestimation. M-mode tracings for TAPSE and TVI of tricuspid annulus should be obtained from the apical approach during held end-expiration. Care shall be taken to align M-mode or TVI beam along the direction of tricuspid annulus motion.[3,8] TVI sample volume should be positioned at 1 cm from the insertion site of the tricuspid leaflets or 1 cm away within RV lateral wall and adjusted to cover the longitudinal excursion of the tricuspid annulus both in systole and diastole. When acquiring full-volume RV data sets for 3DE quantification a modified apical approach should be used and consecutive four-beat ECG-gated subvolumes acquired during breathholding. Care should be taken for positioning the right ventricle in the centre of the image sector with optimal visualization of all RV walls and outflow tract throughout the cardiac cycle. Harmonic imaging with adjustment of gain, frequency, depth, and sector size for adequate temporal resolution (>20 volumes/s) should be used for image optimization. Respiratory manoeuvers may be helpful to improve endocardial border visualization. 2D RV multiplane display and 3D RV transversal plane during acquisition and nine-slice display after acquisition can be used for quality check.

Reading recommendations

RV free wall thickness should be measured at the tricuspid valve tendinous chords, where variability is lower.[3] When measuring TAPSE, M-mode should be preferred because of higher temporal resolution.[3] The inclusion of RV outflow tract in the data set is critical for 3DE measurement of RV volumes. When available, the sensitivity setting of the semiautomated endocardial border identification software should be set at 0 in order to allow the software to include trabeculae within RV cavity volume.

Left atrial size and function

The left atrium produces neuro-hormones and exerts three important haemodynamic functions: contractile (15–30% of LV filling), reservoir [collection of pulmonary venous flow (PVF) during ventricular systole] and conduit (blood flow from the left atrium to the ventricle during early diastole). Left atrial (LA) dilation occurs in response to impaired LV filling and as a consequence of mitral valve (MV) disease, LV hypertrophy, AF. In all these conditions, LA volume is a possible surrogate study endpoint in a clinical trial. The prognostic role of LA volume has also been

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well demonstrated.[37] In patients in sinus rhythm, with no history of atrial arrhythmias or heart valve disease, LA volume reflects LV diastolic function and LA pressure.[37]

LA volume

LA size changes occur in all directions and, similarly to the left ventricle, a single dimension (i.e. LA antero-posterior diameter), despite being used for a long time and provided of a prognostic value, is not an accurate representation of actual LA size.[3] The 2DE calculation of LA volume reflects better LA remodelling and has been validated against cine-computerized tomography.[3] LA maximal volume (at LV end-systole) can be measured by using either the area-length or the disc summation method, without significant difference between the two methods.[3] Reference values of LA volume and cut-off values to categorize LA enlargement (mild, moderate, severe) have been established.[3] Although 2D-derived LA volumes show a systematic underestimation vs. 3DE,[38,39] and CMR[40] they have satisfactory intra- and inter-observer variability (mean difference $\pm$ SD = 6 $\pm$ 6 mL and 8 $\pm$ 8 mL, respectively)[41] and can be used in clinical trials.

How to increase accuracy and reproducibility of LA measurement

Performance recommendations

While recording apical views for computing LA volume, care should be taken to maximize base and length of the LA cavity and to avoid cavity foreshortening. In order to check the accuracy of recording, the difference of the two lengths (from the mid-line of the plane of mitral annulus to the opposite superior part of the LA cavity) in apical four-chamber and two-chamber views should be $<$5 mm.

Reading recommendations

When performing LA planimetry for LA volume calculation, the confluences of the pulmonary veins and LA appendage must be excluded from the LA cavity, and the mitral plane drawn as a straight line connecting lateral and septal sides of the mitral annulus.

Quantification of cardiac haemodynamics: recommendations for measurements and strategies to increase reproducibility

Contractility and afterload

Global LV pump function results from the interaction of myocardial contractility, preload (end-diastolic myocardial fibre length), heart rate, and afterload. The ejection phase indices (EF, stroke volume, cardiac output) cannot determine the relative contribution of each of these variables to LV function. Load-dependency of these parameters may induce inaccurate estimation of intrinsic contractility. The most physiological measurement of LV afterload is *end-systolic stress* (*ESS*) [longitudinal (meridional) ESS for longitudinal endocardial fibres and circumferential ESS for mid-wall fibres] but all the attempts to accurately measure it by echocardiography have been disappointing.[42]

Both colour TVI and 2D STE measures of myocardial deformation provide relatively load-independent indices of LV contractility.[43,44] However, colour TVI-derived strain rate imaging is limited by its angle dependency, whereas 2D STE is angle-independent and enables the estimation of longitudinal, radial, and circumferential percent deformation (strain, %) and deformation rate (strain rate, s^{-1}) as well as of LV twisting. Both global longitudinal and circumferential strain have been validated against cardiac CMR in selected populations[44] and are highly feasible and reproducible.[45] Global circumferential strain is a powerful predictor of cardiac events and provides prognostic information additional to EF in acute heart failure.[46] Strain rate appears to be the most robust parameter of myocardial contractility (due to its strong relationship with invasive myocardial elastance)[47] but is less reliable and reproducible than strain, whose afterload dependency has been conversely demonstrated.[48] Global longitudinal strain is a more robust parameters than radial and circumferential strain when different cardiac ultrasound systems are used for examination.[49] The use of STE (in particular longitudinal strain) could be encouraged in clinical trials.

Performance recommendations

Optimal performance of 2DE STE requires the recording of three consecutive cardiac cycles of good quality, at high frame rate (40–80 frames/s) without dual focusing.

Reading recommendations

The off-line assessment of 2D strain is semi-automatic, but when automated tracking does not fit with the visual impression of wall motion, the endocardial borders tracing must be manually adjusted. Most of the wall thickness must be incorporated in the region of interest while avoiding to include the epicardium. End-systole is defined by the aortic valve closure in the apical long-axis view, and therefore this view has always to be analysed first.

Diastolic function and LV filling pressure

A comprehensive evaluation of LV diastolic function cannot be performed solely based on Doppler-derived transmitral inflow patterns (E and A peak velocity, *E*/*A* ratio, E velocity deceleration time), which are sensitive to loading conditions.[50] This precludes the distinction between normal and pseudonormal patterns resulting from elevated LV filling pressure (LVFP).[50] In the clinical setting, the non-invasive estimation of increased LVFP can be done in different ways. They include: the *Valsalva manoeuver* applied to transmitral filling (*E*/*A* ratio fall $\geq$50%); the combination of LV filling with PVF (pulmonary vein atrial reverse velocity duration – transmitral A duration [Ar–A duration] $\geq$30 ms); the combination of LV filling with colour M-mode-derived *velocity flow propagation* [(Vp) (*E*/*Vp* ratio) $\geq$2.5][7] or with *pulsed TVI*-derived early diastolic velocity (e') of the mitral annulus (*E*/e' ratio).[7] The *E*/e' ratio $\geq$15 if using e' of septal site of the mitral annulus or $\geq$13 if using average values of septal and lateral site indicates accurately increased LVFP.[7,51] Since LA volume reflects the cumulative effect of LVFP over time,[7] the detection of LA dilation (LA volume $\geq$34 mL/m^2)

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allows to make a diagnosis when *E*/e' ratio falls within the grey zone (range = 8–15 when using average e').

Feasibility of Doppler measurements

Excellent-quality transmitral flow patterns can be recorded in most patients (94% feasibility), Valsalva manoeuver can be adequately performed in 61% of patients,[51] PVF signals in 73% of patients, and pulsed TVI in 97% of the patients.[51]

Reproducibility of Doppler measurements

The intra- and inter-observer reproducibility of transmitral Doppler is excellent in both cohorts[52,53] and population-based samples,[54] and better for flow velocities (intra- and inter-observer correlations $\geq$0.89) than for time intervals (inter-observer correlations = 0.59–0.96).[54] Test–retest (biological) reproducibility, including pulsed TVI, is equally good in single centre (80% CI of absolute between-study differences ranged from −0.11 to +0.19 for *E*/*A* ratio at tips of MV)[52] and in multicentre settings.[53] The observer reproducibility (limits of agreement: $\pm$11 to $\pm$ 45%)[55] and the test–retest reproducibility of PVF (intra- and inter-observer repeatability coefficients of Ar–A duration = 50 and 57 ms, respectively)[56] are not good enough for being used in clinical trials. The feasibility and reproducibility of *E*/e' ratio should direct the choice of this index in estimating LVFP in clinical trials. Age-specific normal values of pulsed TVI have been generated[26] and *E*/e' ratio is a powerful predictor of survival.[57,58]

How to increase reproducibility of Doppler indices of LV diastolic function

Performance recommendations

The pulsed Doppler sample volume of LV transmitral inflow should be placed at the tips of mitral leaflets where the velocity amplitude is maximal.

Reading recommendations

Care is needed when measuring E velocity deceleration time in patients with sinus tachycardia (overlapping of E and A velocity), by prolonging the slope of E velocity into the A waveform to baseline. For the assessment of global LV diastolic function, it is recommended to measure pulsed TVI signal at both septal and lateral sites of the mitral annulus and possibly use average values of e' velocity to calculate *E*/e' ratio.

Pulmonary arterial pressure and right atrial pressure

Pulmonary arterial pressure reflects underlying pulmonary vascular disease or the response of the pulmonary vascular tree to elevated pressures in the left heart (e.g. left heart failure, valvular heart diseases). Echo-Doppler is commonly used for assessment of pulmonary arterial pressure and it is sufficiently sensitive to clinical changes. Of course, standardization is needed to include Doppler-echo measurements as endpoints in clinical trials on PAH.[59]

Estimation of right-sided pressures

In the absence of pulmonary valvular stenosis, the Doppler estimation of pulmonary arterial systolic pressures (PAPs) has gained importance over standard right-heart catheterization. PAPs can be derived from continuous wave (CW) Doppler sampling of tricuspid regurgitation (TR) jet, using the modified Bernoulli equation: PAPs = 4 V_{TR}^2+ RAP in which V_{TR}, peak velocity of TR jet obtained by CW Doppler and RAP, mean right atrial pressure.[60] RAP can be estimated by recording the diameter of the inferior vena cava while the patient performs a 'sniff' according to standardized methods.[60] The non-invasive estimation of PAPs has been validated against right-heart catheterization, has a recognized prognostic value in various cardiac diseases, and has been applied to assess drug's effects in randomized, placebo-controlled trials. The feasibility of this method is limited in certain settings (only 30% success rate in obstructive pulmonary disease).[60] RV outflow tract velocity systolic time intervals do not provide a reliable alternative since their 95% CI of the estimated PAPs are too wide to be recommended.[60] A further method utilizes the duration of TVI-derived tricuspid annular relaxation time which, normally absent, progressively increases with increasing PAPs[61,62] (values $\geq$40 ms have a negative predictive value for PAH = 100%[62]). This method is feasible in all patients and its use can be considered suitable for clinical trials when TR is not detectable or spectral Doppler cannot be interpreted adequately.

How to increase the accuracy of estimation of right-sided pressures

Performance recommendations

When recording colour-guided CW Doppler of TR, the apical four-chamber view should be optimized in order to obtain the best alignment of the Doppler beam to the regurgitant jet direction and avoid underestimation of the peak velocity systolic gradient. Contrast agents can be used to enhance TR signal when it is faint. Correct alignment of Doppler beam is also needed when recording TVI of the tricuspid annulus. All Doppler recordings, including TVI, should be obtained at held end-expiration.

Reading recommendations

When measuring CW Doppler-derived TR signal, only well-defined envelopes should be used for quantifying the regurgitation peak velocity.

Quantification of native and prosthetic valves: recommendations for measurements and strategies to increase reproducibility

Recommendations for the use of echo-Doppler to assess valve disease have been proposed by ASE and EAE[4–6,63,64]. Morphological characteristics (leaflet thickness and mobility, subvalvular apparatus status, presence and extent of calcifications) are semi-quantitatively analysed and their use cannot be recommended in clinical trials unless for a screening of a study group. Endpoints including changes in LV volumes and mass, EF, and Doppler-derived diastolic indices are suitable for trials studying patients in pre- to post-operative periods or during follow-up. Heart rate and blood pressure at the time of the echo examination

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must be recorded because they may influence the parameters of severity of valve stenosis and regurgitation. In general, it is important to recommend main criteria for severity of valve disease which can become selection criteria in some clinical trials and/or endpoints (= reduction in severity degree) for trialists. The consistency of the different echo-Doppler parameters for quantifying the degree of valve regurgitation and stenosis varies with the type of lesion.

Native valves

Mitral regurgitation

Several methods are used to assess mitral regurgitation (MR) severity.[6,64] *Vena Contracta* (severe MR = width ≥7 mm) is accurate and reproducible for central and eccentric jets although it changes with haemodynamics. *Effective regurgitant orifice area* (*EROA*) (severe MR ≥0.4 cm^2) calculated by the PISA method is reliable although subject to geometric complexities of the regurgitant orifice (more accurate for central jets and for circular orifices). *Regurgitant volume and regurgitant fraction* (a regurgitant volume of 40 mL is consistent with a regurgitant fraction of 40% and with a regurgitant area of 40 mm^2) are limited by the degree of LA pressure and the jet direction (eccentric jets tend to appear smaller than central jets). The ideal approach is to integrate multiple parameters. Quantitation of LA volume should also be obtained in order to provide clues to MR severity and determine necessity and timing of surgery.

Reproducibility

The PISA method is relatively independent of the operator experience and acceptably reproducible: intra-observer variability of PISA radius = 0.2 ± 13.5% (2.8 ± 13.3%), inter-observer variability = 0.1 ± 13.8% (1.7 ± 18.0%) for an aliasing velocity of 27–29 cm/s (41–43 cm/s).[65] Changes ≥2.7 mm of PISA radius would have to occur to achieve 95% CI of a true change in MR severity.[65] Vena contracta has a good reproducibility, which can be further improved by 3DE colour Doppler.[66]

Mitral valve stenosis

2D planimetry of the mitral orifice has a very good correlation with anatomical mitral volume flow (MVA).[4] Its feasibility is, however, limited in the presence of a poor acoustic window and/or distortion of the MV. The latter may be obviated by 3DE-guided MV orifice transverse plane recordings.[4] The overall assessment of mitral stenosis [by transesophageal echocardiography (TEE) when needed] should include components of MV apparatus (Wilkins or Cormier scores). Among functional indices,[4] *PISA* (MVA/CW Doppler-derived maximum velocity of diastolic flow) has limited accuracy because of difficult measurement of the convergence hemisphere. CW Doppler-derived *pressure half time* (PHT) time interval (ms) occurring between maximal early diastolic gradient and time point when the gradient is half of initial value (MVA = 220/PHT)—does not require assumptions about inlet geometry and flow rate, is easily performable, correlates well with invasive MVA but is influenced by confounders (early diastolic mitral pressure gradient, LA compliance, LV diastolic function). *Continuity equation* cannot be used in case of AF or concomitant aortic regurgitation (AR) or MR. CW Doppler-derived *transmitral pressure gradient*, simple and reliable, has good correlation with invasive measurements but is limited by factors influencing transmitral flow rate (heart rate, cardiac output, associated MR). The ideal approach for clinical trials is to integrate planimetry (better by 3DE) with functional parameters. Further measurements include LA volume, systolic pulmonary pressure, RV function, and degree of functional TR.

Reproducibility

The reproducibility of MVA planimetry, low by 2DE, is greatly improved by 3DE, which allows adequate MV reconstruction in the majority of the patients (from 70 to 78% in relation with the quality of the acoustic window) because of improved alignment with the orifice and its perpendicular orientation to the mitral stenosis funnel.[67] PHT has high variability, particularly when gradient and compliance are influenced by important and abrupt changes in transvalvular flow (after balloon commissurotomy, in concomitance with AR). The reproducibility of continuity equation is hampered by the number of measurements increasing the impact of errors.

Aortic valve regurgitation

The quantification of AR remains challenging.[5] *Colour flow jet size* is unreliable. *Vena contracta* (severe AR = width >6 mm) is simple and highly feasible but limited in the presence of multiple jets or jets with irregular shapes. *EROA* (severe AR = EROA ≥0.4 cm^2 and regurgitant volume ≥60 mL) by PISA has lower feasibility than in MR due to difficult measurement of flow convergence radius. *PHT of AR* by CW Doppler (severe AR = PHT <200 ms) has limited accuracy because of the impact of confounding factors such as degree of LV diastolic pressure and chronic LV adaptation to volume overload. The best choice can be obtained by combining multiple Doppler methods, particularly when the jet is eccentric.[68] Additional evaluation of LV size and function can be used because it help to stratify the prognosis.

Reproducibility

The continuous change of the area during diastole and eccentric jets can increase the variability of colour Doppler-based measurements of AR. Also the technical setting of the machines (affecting the jet area and thickness of vena contracta) is an important source of variability and it should be noted to be kept constant in serial studies.

Aortic valve stenosis

Aortic valve area (AVA) *planimetry* with 2DE is often unreliable or inaccurate (calcification shadows and reverberation limit the orifice identification). Doppler is therefore the standard mean to assess AS severity. Doppler parameters include jet peak velocity, mean transaortic gradient, and effective AVA calculated using the continuity equation.[4] *AS jet velocity* across the valve (severe AS = peak jet velocity >4 m/s) and *mean transaortic pressure gradient* (severe AS ≥ 40 mmHg) are accurate but dependent on the flow through the valve. In studies comparing native aortic valve velocities with valve prostheses, peak velocities should be the preferred option. *AVA by continuity equation* requires three measurements: AS jet velocity time integral (VTI) by CW Doppler,

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LV outflow tract (LVOT) diameter for calculation of a cross-sectional area, which is assumed to be circular, and LVOT time velocity integral of systolic velocity recorded with PW Doppler. The use of continuity equation should be recommended since it is clinically validated, reliable for decision-making and much more predictive of outcome than the anatomic AVA. Additional, prognostically validated, parameters include extent of leaflet calcification,[4,69] rate of increase in transaortic velocity and of decrease of AVA over time,[69] LV end-systolic diameter, and degree of LV hypertrophy.[4] When compared with invasively determined AVA, AVA calculated by including 3DE stroke volume in continuity equation is more accurate and reproducible than the conventional continuity equation based on measurement of LVOT diameter.[70]

Reproducibility

The reproducibility of continuity equation is limited because of the variability of its three components. AS jet and velocity time integral have a very low intra- and inter-observer variability (~3–4%), while the measurement variability for LVOT diameter is 5–8%, a range that, when squared for the calculation of cross-sectional area, becomes the greatest potential source of error.[4]

How to increase the reproducibility of echo-Doppler measurements of valvular diseases

Performance recommendations

Colour flow of valve regurgitation must be recorded by high resolution, zoomed view of supravalvular region for visualizing the three components of regurgitant jets: flow convergence, vena contracta, and jet regurgitant area. The vena contracta must be imaged for the largest obtainable proximal jet size and the operator should search in multiple planes perpendicular to the commissural line. To estimate the extent of regurgitant jets, the colour scale shall be set at 50–60 cm/s or at the highest limit allowed by the machine and the colour gain set step by step just below the threshold of colour noise artefacts. In the PISA method, the aliasing velocity has to be set between 15 and 40 cm/s. To obtain accurate transvalvular gradients, great care should be put to align the Doppler sound beam as parallel as possible to the flow (guided by both 2DE image and sound). To avoid underestimation of measured velocities, multiple approaches should be routinely attempted (apical, right parasternal, and suprasternal) to ensure recording of the maximal AS jet velocity. LVOT view has to be recorded in the zoom mode, avoiding foreshortening of the structure. LVOT velocity tracing should be recorded immediately below the aortic annulus by adjusting the ultrasound beam and choosing the acoustic window that provides the highest velocity signal.[4] The 2DE recordings for valve planimetry should be obtained from zoomed images using cine-loop mode, in order to select the proper timing in the cardiac cycle and better delineate valve orifice and leaflet tips. The gain setting should be adjusted to visualize the whole contour of the valve orifice in order to reduce technique variability. In serial studies, the same machine and main machine settings should be maintained.

Reading recommendations

When measuring CW Doppler-derived velocities, only well-defined envelopes should be used for quantifying velocities. LVOT diameter should be measured at early systole by the leading edge to leading edge method[3] at the hinge point of aortic cusps.

Prosthetic valves

In addition to thorough 2DE assessment, Doppler is the only suitable technique for providing objective and reproducible measurements of prosthetic valves haemodynamics.[71] The general principles for evaluating prosthetic valve function are similar to those of native valve stenosis. All valve prostheses are more or less inherently stenotic and higher velocities and pressure gradients are recorded when compared with native valves.[71] All mechanical valves have a functional mild leakage to avoid thrombosis and occluder stuck. Colour Doppler may show the regurgitant jet but has limited accuracy for quantifying it. Therefore, CW Doppler, combined with other markers, e.g. LV volumes and function, should be the right choice to assess the severity of regurgitation. TEE is frequently needed for assessing prosthetic valves, particularly mitral prostheses.[71]

Similar to native valves, the parameters recommended for an aortic prosthesis include mean transvalvular gradient, peak transvalvular velocity, peak LV outflow velocity and their ratio (=Doppler velocity index), and the effective orifice area (EOA) derived by the continuity equation as well as the presence and severity of prosthetic and para-prosthetic regurgitations.[71] The estimation of the pressure gradient always requires the application of the complete Bernoulli equation since the valve has no restrictive orifice and trans-prosthetic velocity is not so high as in native AS.[71]

The parameters recommended for mitral prostheses are peak transvalvular velocity, velocity-time integral of transvalvular velocity, mean transvalvular gradient, and the extent of prosthetic/para-prosthetic regurgitations.[71] Calculation of EOA by PHT is not valid in normofunctioning mitral prostheses because the orifice is no longer stenotic and PHT depends on heart rate, stroke volume, LV and LA compliance, and initial LA pressure. In clinical trials on prosthetic valves additional echo endpoints should include changes in LV mass, systolic, and diastolic function.[71]

How to increase the reproducibility of measurements of prosthetic valve function

The same recommendations for native valve assessment are valid for prosthetic valves. Multiple probe angulations and the use of off-axis views may be needed for optimal imaging and Doppler recording. To avoid under- or over-estimation of haemodynamic changes in serial examinations, heart rate, and cardiac rhythm have to be recorded, in particular for mitral and tricuspid prostheses, as the mean gradient is dependent on the diastolic filling period. The use of the same echo machine for serial studies is needed to assess haemodynamic changes of prostethic valves over time.

Quality control in clinical trials

Echo-Doppler parameters, which are accurate and reproducible, can be considered to support or refute the hypothesis/objective for which a trial has been designed. This also allows to reduce the sample size needed of patients included in trial.

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Quality control is of paramount importance to reduce variability among laboratories and operators and must be run by using appropriate procedures for data acquisition, storage, and interpretation. Several approaches involving investigators/operators equipment and training can be used. The role of ECLs is very important in controlling the quality and hence limiting the inter- and intra-observer variability of peripheral centres involved in the study. *Table 1* summarizes the 10 main points to ensure quality control in clinical trials.

Step 1: Definition of the imaging protocol

Echo-Doppler parameters to be included in a study protocol will be chosen taking into account their *accuracy* (mainly by validation with a reference imaging modality such as CMR), *reliability*, *reading variability* (intra- and inter-observer), *biological variability* (*day-to-day* or *test–retest*) and *instrumentation variability* (*machine-to-machine*).

Strict criteria for echo imaging acquisition (e.g. echo views, machine settings), review and storage (e.g. CD-ROM or DVD, non-DICOM format) at the participating peripheral centres, data preparation and collection, labelling, and missing data documentation should be clearly stated by the ECLs in an image review chart in order to ensure standardization and followed by each peripheral centre participating in the study.

Before starting the trial, it is important to validate the quality of recordings obtained by each peripheral centre. This is fundamental for the following reasons: (i) it will spare researchers from collecting data that cannot be utilized properly due to poor image quality or improper data acquisition, adding an unnecessary burden to patient and study costs; (ii) it will prevent unreliable measurements from being entered in the central database of the study, thereby preserving the value of the entire study.

Table 1 Top-ten procedures recommended from EAE for quality control of clinical trials.

1. To choose the ECLs on the basis of the head and team experience in both ultrasound technique and clinical trial planning and performance
2. To involve the head and the ECLs in the study design
3. To standardize 'hands on' training of echocardiographers either onsite or at centralized meeting before starting the clinical trial
4. To monitor echocardiographers of the peripheral sites for technical quality (acquisition, storage, and processing) of their echo studies
5. To overview quality of the study acquisition at peripheral sites with the head of the core laboratory
6. To minimize the number of readers in ECLs in order to improve reproducibility of measurements
7. To check the reader variability of ECLs by periodical joint reading sessions with the head
8. To maintain an optimal level of communication between ECLs and peripheral sites throughout the time course of the study
9. To maintain an optimal level of communication between ECLs and both study sponsor and steering committee throughout the time course of the study
10. To involve head and investigators of both ECLs and peripheral sites in data analysis, presentation, and publication

ECLs, Echocardiographic core laboratories.

Step 2: Quality assurance

Quality assurance (QA) is needed to minimize the imaging acquisition or reading variability existing in any trial using echo. Adherence to an accurate QA plan will reduce the amount of missing data and provides confidence in the final results of a given clinical trial. QA should be carried out at two levels: (i) at the clinical peripheral sites where data are collected; (ii) at the ECLs where data are analysed.

The selection of *peripheral centres* is important and could be also performed on the basis of EAE accreditation standards.[72] Each peripheral centre should follow the recommended standard operational procedures in terms of data imaging acquisition (modalities and operational modes, scanner settings, data sets to be recorded), data storage (data format, procedure set to transfer recordings and data to the ECLs), and data processing (software tools used to extract any given measurement and parameter). After case registration in the database, a study-specific ID should be generated in order to anonymize the images (de-identification procedure). For this anonymization, dedicated software should be developed implementing basic standard DICOM operations.

The imaging study protocol might contain centre-specific items since some aspects may depend on local logistics or technology and specify the minimum requirements for the echo machines used for the trial. Yearly evaluation of electronic calibration of the machines and transducer decay should be performed since it may be sources of measurement errors.

The ECLs should verify the data obtained in the peripheral centres in terms of data format, completeness, adherence to the acquisition protocol, and data quality. All data will be subsequently analysed and recommendations will be made to the peripheral centres on how their acquisitions might be optimized. If such recommendations have to be made, a new round of data acquisition/analysis will be started until the final formal approval by ECLs. The facilities of ECLs will also need validation to guarantee appropriate extraction of echo parameters and data sent from the different centres should be analysed three times in order to determine the reproducibility of the measurement. The values obtained by this procedure will be compared with what has been reported in the specific literature. If reproducibility is significantly lower from previously published values, the reasons for discrepancies should be sought (e.g. use of different software tools, different acquisition protocols, different reading procedure, insufficient training of the analyser), and solved.

Step 3: Echo core laboratories implementation

ECLs distribution and implementation is critical for the use of echocardiography in clinical trials. *Figure 3* summarizes the ECLs based system for the QA process. The role of ECLs is highly variable in relation to the specific use of echocardiography in a trial, mainly depending on whether the echo-Doppler data will

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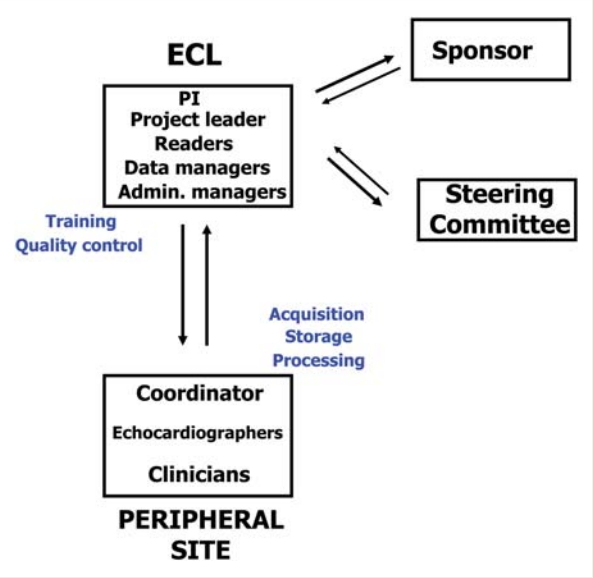

Figure 3 Structure and workflow of ECLs based quality assurance system.

contribute or not to a primary or secondary efficacy or safety endpoint. In any case, the core laboratory will have the responsibility of establishing the imaging protocol and standardizing image acquisition processes and analysis (e.g. definition of suboptimal or unreadable echo imaging, choice of measurements and parameters, decisions regarding number of cardiac cycles to be averaged for measurements) by a proper review chart, organizing and performing education and training programmes of both echocardiographers of the peripheral centres involved in the data acquisition and internal readers of the same core laboratory, as well as managing images and data. It is important for the ECLs to interact with the trial leadership and steering committee and to be fully involved in the study design, in order to optimize technical advantages and limits of a given tool and/or parameter and participate in the choice of the most appropriate and reproducible measurements, in the selection of patients and eligibility criteria for study entry, in the sample size calculations and in the type of blinding (e.g. site, time) if any. The ECLs should encourage and assist transmissions of studies and monitor potential deficiencies in data acquisition and analysis.

The main goal of ECLs is to ensure the best data accuracy by reducing measurement variability. This will prevent any limit resulting from the reading in peripheral centres, and in particular due to insufficient expertise in that required for a specific trial. In this view, the *central reading* of ECLs should involve a practical minimum number of readers with excellent experience, unlike in the peripheral centres where the readers are multiple and can have unverified experience. To further minimize reader variability, inter-reader variability of ECLs should be monitored inside periodically. Obviously, the ECLs cannot eradicate all the sources of variability but it can ensure that acquisition and measurement errors are controlled and do not occur randomly.[73] ECLs will also control and guarantee the data protection in the peripheral centres.

The personnel of the ECLs should include a head, assisted by a project leader able to ensure reading quality, by a team of readers, and operators who are responsible for the data handling and whenever possible, of biostatistics (employed on sample size calculation, statistical methods, and analyses). All personnel should have considerable experience in research projects. Both the head and the project leader are expected to interact closely with the sponsor and other collaborators such as the steering committee and data coordinators of peripheral centres involved in the trial. While general features of ECLs need to be guaranteed, the structural organization of each core laboratory should be maximally flexible, depending on the specific characteristics of the clinical trial.

ECLs should be available in showing its own work efficiency, including procedure, processes, equipment and calibration of echocardiographic instrumentation, staff member training and accuracy of echo-Doppler measurement and data interpretation, according to recently published ASE recommendations.[74]

Application of echocardiography in clinical trials: recommendations for appropriate use

Figure 4 describes the flow diagram to select the optimal echo-Doppler modality and measurement for a specific trial. *Table 2* summarizes the main characteristics (validation, feasibility, reproducibility, prognostic value) of the main echo-Doppler parameters and *Table 3* describes the primary and secondary echo-Doppler EAE recommended endpoints for specific clinical trials.

Arterial hypertension

Studies on regression of LV hypertrophy should involve echo laboratories that are very confident with 3DE. When compared with 2DE, 3DE calculation of LV mass has similar reproducibility to CMR and can be used to reduce sample size and trial cost. The assessment of LV diastolic function in hypertensive trials should involve at least the combination of parameters of LV filling pattern (*E*/*A* ratio and E velocity deceleration time), pulsed TVI-derived measurements of the mitral annulus, and LA volume calculation.

Heart failure

Over the past 30 years, ultrasound imaging has been used for participant selection in several multicenter trials, reduced EF and LV enlargement being the primary entry criteria to assess subsequent outcome. However, only few studies have evaluated LV remodelling during the follow-up period. Based on modern knowledge of echo-Doppler indices, clinical trials dealing with heart failure should combine LV volume and EF calculation with the quantification of more subtle parameters, e.g. pulsed TVI-derived systolic velocities of the mitral annulus or 2D STE-derived longitudinal strain. In recent years some trials have also used echocardiography to assess patients with heart failure with preserved (=normal) EF. These patients can have some degree of LV diastolic dysfunction. When planning studies on heart failure with preserved EF, normal EF should be appropriately classified (values at least

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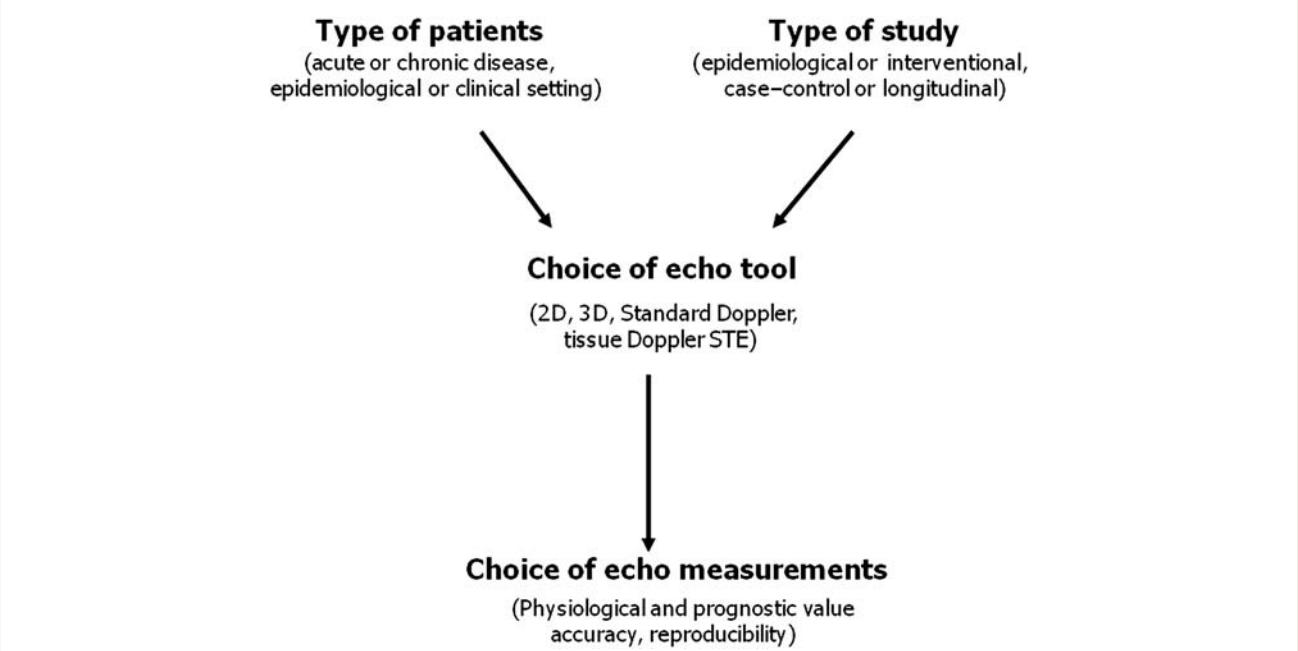

Figure 4 Flow diagram regarding the optimal echo tool and parameters for a specific clinical trial.

Table 2 Characteristics of the main echo and Doppler measurements to be taken into account for their use in clinical trials according to the body of evidence of current literature

Measurement	Accuracy	Feasibility	Reproducibility	Prognostic value
2D/M-mode LV diameters	Fair	Good	Excellent	Fair
2D LV volumes	Poor	Good	Good	Good
3D LV volumes	Excellent	Good	Good	Not demonstrated
M-mode LV mass	Poor	Fair	Poor	Excellent
3D LV mass	Excellent	Fair	Excellent	Not demonstrated
2D EF	Good	Good	Good	Excellent
3D EF	Excellent	Good	Excellent	Not demonstrated
TAPSE	Good	Good	Good	Good
2D LA volume	Fair	Good	Good	Good
E velocity DT	Good	Good	Good	Good
E/*E*a ratio	Good	Excellent	Good	Good
PAPs	Good	Fair	Good	Good
MR ERO (PISA)	Fair	Fair	Fair	Good
MR V. contracta	Fair	Fair	Fair	Not demonstrated
2D MVA	Poor	Poor	Poor	Not demonstrated
3D MVA	Good	Fair	Good	Not demonstrated
MS PHT	Good	Good	Good	Not demonstrated
2D AVA	Poor	Poor	Poor	Not demonstrated
AS continuity equation	Good	Fair	Fair	Good

A, transmitral A velocity; AS, aortic stenosis; AVA, aortic valve area; DT, deceleration time; EF, ejection fraction; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; PAPS, pulmonary arterial systolic pressure; PHT, pressure half time; PISA, proximal isovelocity surface area; TAPSE, tricuspid annular plane systolic excursion.

>50%) and serial assessment of Doppler diastolic indices (including at least pulsed TVI of the mitral annulus in order to obtain a non-invasive estimation of LVFP) identified as possible endpoints.

Myocardial infarction

Based on the recognized prognostic value of post-AMI LV remodelling, several clinical trials have assessed the ability of drug categories

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Table 3 Doppler echocardiographic variables and indices suggested as possible primary and secondary echo endpoints suggested from EAE in specific settings of clinical trials

Disease	Primary echo endpoints	Secondary echo endpoints
Arterial hypertension	LV mass	RWT, MFS, *E*/e' ratio, LA volume, GLS
Systolic heart failure	2D/3D LVEF, DT, PAPs	*E*/e' ratio, MR severity, TAPSE
Heart failure with normal EF	*E*/e' ratio, LA volume	GLS, PAPs
Acute myocardial infarction	2D/3D LVEF, DT, *E*/e' ratio, GLS	LA volume, TAPSE, 3D RVEF
Atrial fibrillation and stroke	*E*/e' ratio, LA volume	LAA flow velocities, MR severity
Cardiac toxicity of chemotherapy	2D/3D LVEF, *E*/e' ratio, GLS	TAPSE, 3D RVEF

2D, two-dimensional; 3D, three-dimensional; DT, deceleration time of E velocity; *E*/e' ratio, ratio of transmitral E velocity to tissue Doppler-derived early diastolic velocity of the mitral annulus; GLS, global longitudinal strain by speckle-tracking echocardiography; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; LVEF, LV ejection fraction; MFS, mid-wall fractional shortening; MR, mitral regurgitation; PAPs, pulmonary arterial systolic pressure; RV, right ventricular; RWT, relative wall thickness; RVEF, right ventricular EF; TAPSE, tricuspid annular plane systolic excursion.

to reverse this remodelling and improve short- and long-term outcome. Again, only few of these studies have evaluated the changes of echo-Doppler parameters over time. Current AMI trials should require sequential quantitation of EF, LV, and LA volumes, LV sphericity (sphericity index), functional MR, Doppler diastolic indices including at least transmitral E velocity deceleration time, pulsed TVI of the mitral annulus and PAPs. Global longitudinal strain, whose prognostic value has been recently shown in patients with AMI,[75] can be appropriately proposed in clinical trials. Stress echo, whose EAE recommendations have recently been published,[76] can be used in trials involving AMI and CAD.

Atrial fibrillation and stroke

Based on epidemiological evidence that LA enlargement is an independent predictor of AF and stroke, clinical trials dealing with these issues should provide accurate estimation of LA volume and Doppler-derived diastolic indices. Causes of embolic stroke include non-valvular AF, LV dysfunction, rheumatic valvular disease, prosthetic valves, and patent foramen ovale, all conditions in which echocardiography is diagnostic. In several stroke and AF trials, TEE plays a pivotal role in detecting LA appendage thrombi and low flow velocities ($<$20 cm/s), and/or spontaneous echo contrast. Peripheral centres and ECLs should aim to reduce variability in the detection of source of emboli (differentiation of appendage thrombus from artefacts such as sludge, pectinate muscles, and pulmonary vein limbs).

Cardiac toxicity of chemotherapy

Acute and late cardiac toxicity of chemotherapy is diagnosed and monitored by echocardiography. Most oncological trials use the sole EF determination as an entry criterion as well as a follow-up marker for explaining cardiac symptoms and signs. Prospective trials should include more comprehensive assessment of LV function (e.g. by using STE and/or TVI), Doppler-derived diastolic function, valve dysfunction, and pericardial diseases.

Conclusions

Echocardiography is a valuable tool for assessing disease effects and treatment outcome on cardiac structure and function in clinical trials. However, since it is an operator-dependent technique, difference in variability of measurements may lead to collection of inaccurate data. To prevent this, clinical trials should be designed and developed on the basis of a thorough knowledge of physio-pathological, prognostic, and technical characteristics of echo-Doppler techniques and parameters, choosing the most performable and reproducible. QA should be guaranteed and implemented by adequate training processes of peripheral centres and appropriate interpretation of data, by a central core laboratory.

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