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New and old echographic parameters in heart failure

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Echography (ECHO) is a first-line technology for diagnostic evaluation and prognostic stratification of patients with heart failure (HF). Recognizing specific diseases or conditions amenable to specific treatment is a crucial step in the work-up of patients with HF. Left ventricular ejection fraction (EF) measurement, despite its pathophysiological and methodological limitations, is the primary parameter for the HF classification, incorporating forms with reduced, moderately reduced, and preserved ejection fraction. The cardiac filling parameters could characterize the haemodynamic profile of the various forms of HF and guide different clinical therapeutic strategies. Besides the conventional parameters, widely validated by the clinical practice (old parameters), ECHO provides new information on cardiac function (deformation index), which prospectively could refine our phenotypic classification, beyond EF, thus opening new prospects in the pre-clinical identification, and in the selection of the appropriate treatment for HF patients Stemming from the recent technologic improvements, it is possible to analyse conventional parameters with innovative and automatic approaches, which are quickly available, and able to open new perspectives in the treatment of patients with HF.

Introduction

Heart failure (HF) is responsible for high morbidity and mortality with a significant epidemiological burden in the general population (prevalence 1–2%) and progressively increasing after the seventh decade of life (prevalence >10%).[1] Heart failure represents the epiphenomenon of different cardiovascular diseases and is characterized from the pathophysiological point of view by the inability of the heart to maintain an effective and adequate flow to the body's requests without increasing the filling pressure. Early diagnostic recognition and the appropriate selection of the therapeutic strategy are essential to improve the clinical-prognostic course of HF. The clinical examination, although it represents an important element, can prove to be non-conclusive in the presence of ambiguous symptoms or comorbidities and still need to be integrated with instrumental methods for a correct diagnostic classification and an accurate characterization of the HF haemodynamic profile.

Echocardiography (ECHO), due to its informative contribution and the extensive application in the general population, has established itself as a method of crucial importance for the diagnostic evaluation and prognostic stratification of patients with HF. In addition to the conventional and widely validated parameters in clinical practice ('old parameters'), the ECHO, for recent technological advances, provides new information that in perspective can refine the evaluation of cardiac function and open new scenarios in pre-clinical identification and in selecting the appropriate treatment for HF patients.

Conventional echocardiographic parameters ('old') in heart failure

Echocardiography with a transthoracic and, when indicated, transoesophageal approach is essential for identifying, in patients with clinically manifest HF, cardiac pathologies, or conditions amenable to specific treatment.

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Table 1 Conventional echocardiographic parameters in heart failure

ENTITY	METHOD	ABNORMAL VALUES	INTERPRETATION	CAVEAT/PITFALL
LV pump function indices	EF(%) SV(ml)	<55 <35 ml/m2	HFrEF HFmrEF HFpEF Reduced ejection volume	2D limitations, Load dependence Left ventricular outflow area measurement
LV muscle function indices	Dp/Dt (Hg/sec) Tei index	>1200 >0.40	Reduced contractility Reduced global LV performance	MR related, low sensitivity Low applicbility (AF), pseudo.normalization in HFpEF
Cardiac Morphologic Indices (2D)				
LV	EDD (mm),EDV (ml) ESD (mm),ESV(ml) EI (D/L)	>25 mm/m2,>50 ml/m2 15 mm/m2 ,19 ml/m2	Remodling	Foreshortening
LA	LAD (mm),LAV(ml)	>40, >36ml/m2	High intracavitary pressure	Shape complessity
RV	EDD,SAX/LAX	>0,5	Remodeling	
IVC	D (mm)	>20 mm	Venous congestion	
IVS	curvature	flattened	Right pressure oveload	
RA	Volume (ml),IAS	>30, left -curved	High intracavitary pressure	Incomplete visualization
LV filling indices	E wave DT (msec) E/A ratio Em septal (cm/sec) E/Em ratio AR DT (msec)	<150 >2 <8 >15 >300	Restrictive LV filling Increased LV diastolic pressure	Angle dpendence Jet allignment
LA filling indices	PVF S/D ratio PV AR-MV A wave (msec) RAF (cm/sec)	<55% >30 >30	Increased La pressure	

AR, aortic regurgitation; D, diameter; DT, deceleration time; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; EI, eccentricity index; ESD, end-systolic diameter; ESV, end-systolic volume; FAC, fractional area change; IAS, interatrial septum; IVC, inferior vena cava; IVCC, inferior vena cava collapse; IVCCD, inferior vena cava diameter; IVRT, isovolumetric relaxation time; IVS, interventricular septum; LA, left atrium; LAD, left atrial diameter; LAV, left atrial volume; LAX, longitudinal axis; LV, left ventricle; PI, performance index; PVF AR, pulmonary vein flow atrial reverse; PVF, pulmonary vein flow; RA, right atrium; RAF, PVF reverse atrial flow; RV, right ventricle; RVOTvti, right ventricular outflow tract velocity time integral; SAX, short-axis; sIVCF, systolic inferior vena cava flow percentage; sPAP, systolic pulmonary artery; s-TDI, systolic tissue doppler imaging; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitant velocity.

In addition, the ECHO can detect heart disease in the asymptomatic phase allowing the pre-clinical applicability of therapeutic measures in good time in order to limit the onset or progression of HF towards advanced clinical stages.

Table 1 shows the conventional morpho-functional indices that are sufficiently validated by clinical use in HF patients with their respective limitations and interpretative cautions.

Basically, the conventional ECHO parameters are aimed at evaluating the pump function, the filling profile of the left ventricle (LV), and the haemodynamics of the right ventricle (RV).

The ejection fraction (EF) of the LV is the most relevant parameter for the pathophysiological framework and HF prognostic stratification. In accordance with the guidelines, the EF values are used to define forms of HF with pump dysfunction (EF $<$ 40%) [heart failure with reduced ejection fraction (HFrEF)] compared to those with preserved EF ($>$50%) (HFpEF), or intermediate forms with moderate (midrange) pump malfunction (EF 40–49%) (HFmrEF).[2,3] The discriminating levels of EF and the related observations of HF clinical trials are however based on the use of two-dimensional (2D) techniques potentially limited by the geometry of the ventricular cavity and by the accuracy in determining the volumes. It follows that the categorization of the HF can be reliable for extreme values of compromise or of normality of the EF values, while it can be conditioned for the intermediate values by the respective degree of reproducibility of measurement by means of 2D ECHO.

Heart failure with reduced ejection fraction

Patients with HFrEF may have varying degrees of remodelling and reduction of EF, determining differentiated clinical-prognostic profiles. The EF $<$35% value characterizes a subgroup of patients with unfavourable evolution who can benefit, regardless of the degree of clinical impairment, of differentiated interventions in addition to the standard pharmacological treatment. However, systolic dysfunction is not a fixed parameter but, due to a natural clinical course or induced by therapeutic measures, it can present significant directional variations with consequent impact on prognostic recategorization.[4]

The filling indices can characterize the haemodynamic profile of patients with HFrEF for the purpose of prognostic stratification and a targeted therapeutic choice.[5] The most accurate and extensively applied indexes for identifying high values of the LV filling pressure are shown in *Table 1*. The discriminating power of the individual parameters is conditioned by the level of cut-off used and by the respective potential methodological limitations or dependence on the LV load conditions. Below the threshold of high accuracy of the individual indices, an integrated and multiparametric approach is required for estimating an increased LV filling pressure. The haemodynamic profile of the cardiac sections on the right is of extreme clinical-prognostic relevance and can condition the applicability of advanced therapeutic choices.[6] The morpho-functional evaluation of the RV makes use of multiple parameters, albeit with important methodological and applicability limitations, in the context of a very complex cavity geometry. The most used parameters in clinical practice include the analysis of the inferior vena cava (dimensions $>$ 20 mm and reduced inspiratory collapsibility $<$50%) indicative of systemic venous congestion and high right atrial pressure respectively, which can be useful as a guide for choosing and evaluating the effectiveness of medical therapy.

Numerous factors (arrhythmias, mitral insufficiency, and loading conditions), however, can affect the accuracy of the filling indices especially in terms of specificity. In particular, atrial fibrillation represents the most common condition that can invalidate the applicability and predictive power of the functional and cardiac filling indices.

Echocardiography plays a key role in the evaluation of patients with potentially reversible LV dysfunction after specific interventions. In patients with coronary artery disease, the ECHO can identify the akinetic myocardial areas, through the measurement of the wall thickness ($>$5 mm) and the demonstration of contractile reserve, signs of vitality predictive of functional recovery after coronary revascularization. The identification of contraction asynchrony for delayed electrical activation from left bundle branch block can provide an important guide to the appropriate selection of candidates who can benefit from electrical resynchronization therapy (CRT). The presence at the level of the interventricular septum of 'flash' (expression of early electrical activation), with subsequent 'stretch' (following the delay of the postero-lateral wall) revealed a high predictive value of the effectiveness of CRT.[7]

Heart failure with preserved systolic pump function

The diagnosis of HFpEF represents an important diagnostic challenge in relation to the low specificity of symptoms and frequent comorbidity as a possible alternative cause of the apparent clinical picture of HF. The picture of HFpEF is to be traced from the pathophysiological point of view to a reduction in cardiac output associated with an increase in filling pressure despite a preserved EF. The diagnostic pathway of HFpEF must therefore be aimed at recognizing heart disease characterized primarily by an increased filling pressure due to myocardial or LV chamber stiffness, associated with inadequate cardiac output despite preserved EF values (in percentage relation with a ventricular volume of small size). Echocardiography is the first-line diagnostic modality for the recognition of structural heart disease characterized by increased wall thickness secondary to pressure overload or myocardial diseases (primary or due to the involvement in systemic diseases). Due to the increased filling pressure, patients with HFpEF may develop a reduced pre-load reserve which makes the LV intolerant to increased or previously tolerated post-load values, with the development of pump dysfunction and reduction of the EF (condition of 'after-load mismatch'). It follows that HFpEF can veer towards stable forms of HFrEF due to progression of the underlying disease or present fluctuations of HFrEF due to the onset of trigger factors capable of reducing the pre-load reserve LV (e.g. Tachycardia, high blood pressure). Patients with a clinical history of HF, although presenting a normal EF value at the time of clinical observation, may experience concomitant and transient pump dysfunction during the onset of symptoms. The diagnosis of HFpEF can therefore be accepted from the nosologic point of view after excluding factors capable of outlining fluctuating pictures of LV dysfunction. Coronary artery disease represents the most common condition that can lead to transient pictures of decompensation or 'flash' pulmonary oedema due to ischaemia and related systolic dysfunction with functional mitral insufficiency. The active search for inducible myocardial ischaemia therefore represents an essential element to define, through the exclusion of coronary artery disease, the diagnosis of isolated HFpEF.

In analogy with what is described for the HFrEF frameworks, the characterization of the haemodynamic profile through the filling parameters is a crucial factor in the work-up of patients with HFpEF, not only for diagnostic purposes but also for prognostic stratification and guide to an appropriate treatment. Filling indices can characterize forms of advanced decompensation with restrictive haemodynamic patterns, severe pulmonary hypertension, and related systemic venous congestion. In view of the limited diastolic reserve, the filling indices can guide clinical practice in optimizing the pre-load to avoid reducing the flow from excessive subtraction of blood volume or, conversely, conditions of disproportionate volume with venous (systemic or pulmonary) congestion and possible onset of systolic dysfunction due to after-load mismatch.

The size of the left atrium (LA) represents an important morphological index for the diagnostic recognition and the clinical-therapeutic management of patients with HFpEF.[8] The LA enlargement constitutes an independent prognostic parameter in the heart diseases with HFpEF and is associated with a high risk of atrial fibrillation. The evaluation by stress-ECHO of the onset of pulmonary hypertension represents a modality of high clinical efficacy to evaluate the LA reserve in heart diseases potentially responsible for HFpEF.

Heart failure with moderate reduction of ejection fraction

The phenotype with moderate reduction of EF can represent an important methodological challenge with regard to echocardiographic reproducibility in determining the volumes underlying the EF measurement. The separation of the subgroups with HFmrEF based on an EF interval of about 10% (EF 40–49%) can still fall within the confidence

Table 2 Innovative parameters in heart failure

ENTITY	METHOD	Strength	Limitations
LV and RV ejection indices ejection Fraction stroke volume **LA** size election	3D analysis	Full volume analysis Fore-shortening elimination Shape indepedent Simultaneous regional assessment	Stich artifacts Non applicable in arthythmic patients Less-than-optimal resolution
LV myocardial deformation	2D-Speckle Tracking	Not angle dependent High resolution Torsional mechanics analysis	Non-simultaneous multiview assessment Out-palne motion
Strain Strain rate Rotation Twist Torsion **RV myocardial deformation** Strain **LA deformation** Strain	3D-Speckle Tracking	Not angle dependent Torsional mechanical analysis Simulatneous multiview assessment	Less-tahn-optimal resolution
Automated assessment LV ejection indices LA ejection indices	Automated Speckle Tracking	Fast measurement Not shape dependence Beat to beat analysis No stich artifacts Modifiable endocardial setting Low test-re test variability	Not applicable in unusual LV shape and extreme LA size

LA, left atrium; LV, left ventricle; RV, right ventricle.

limits of the measurement variation even in the presence of an optimal measurement reproducibility (5%). The frequent presence of coronary artery disease can induce in these patient's important fluctuations of EF or evolution towards full-blown forms of HFrEF.

New parameters in heart failure

The EF, although it represents an index of high clinical impact, is influenced, for the same level of myocardial contractility, by the loading conditions (pre- and after-loading) and is not synonymous with LV systolic function. Cardiac function presupposes a complex structural organization of the myocardial fibres which, by virtue of their distribution and the respective contraction sequence, are responsible for the physiological alternation of contraction-relaxation aimed at maintaining an adequate cardiac output without increasing the filling pressure. The distribution of myocardial fibres determines an articulated three-dimensional (3D) contraction function characterized by a longitudinal-circumferential shortening component and a radial thickening component. The EF according to a cardiac pump function model, although expressing the overall ejection of the LV, is substantially determined by the circumferential deformation of the myocardial fibres and is not representative of the other two components (longitudinal and radial) of the contractile function. This can result in functional dissociation states characterized by a preserved circumferential component responsible for normal EF values despite a compromise of the longitudinal or radial component. The use of strain and speckle tracking techniques (*Table 2*) has recently opened new frontiers in the evaluation of cardiac function through myocardial deformation indices,[9-12] capable of identifying conditions of contractile dysfunction in the pre-clinical phase and in the presence of preserved EF following the maintenance of the circumferential myocardial function or favourable loading conditions (e.g. patients with mitral insufficiency).

Although conditioned by a relatively low spatial-temporal resolution, the use of 3D techniques allows to overcome some of the methodological limits of the evaluation of the deformation indices with 2D techniques (angle-dependence, multiple non-simultaneous scans). In order to overcome the barriers related to the need for off-line and 'time-consuming' processing, automatic systems for the immediate processing of the deformation indices have been introduced for applicability in clinical practice. Among the deformation indices, the longitudinal strain has gained increasing clinical application in order to identify contractile dysfunction in the presence of preserved EF values (*Figure 1*).

In particular, the assessment of the regional distribution of the degree of impairment of the strain can contribute to the recognition of myocardial pathologies with

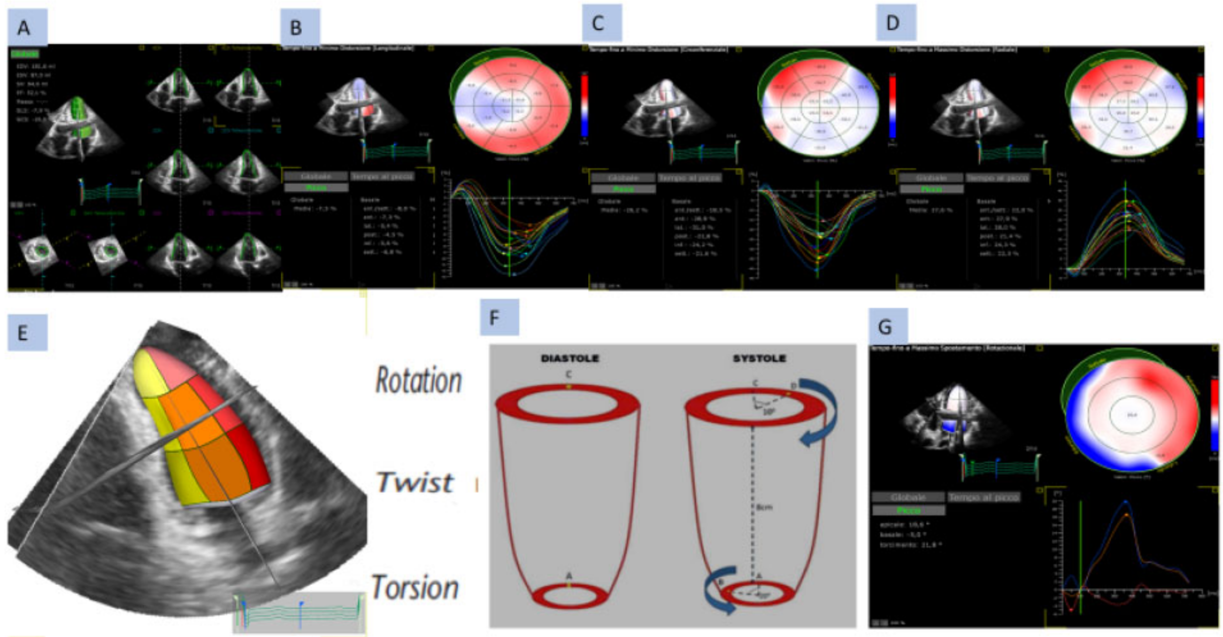

Figure 1 Three-dimensional speckle tracking transthoracic echocardiography. Measurement of longitudinal, circumferential, radial strain (*A-D*), and rotational mechanic indices (rotation, twist, and torsion) (*E-G*).

hypertrophy phenocopies, such as amyloidosis cardiomyopathy, characterized by an important reduction of the strain in the middle-basal segments while sparing the apical regions ('Apical sparing'). Other useful information for the characterization of cardiac contractile function include the rotation, torsion, and 'twist' indices that can be derived by 3D speckle techniques. In subjects with heart disease, an exasperation of the base–apex gradient of the rotation with high twist values is observed, potentially useful for the pathophysiological classification and identification, in the pre-clinical phase, of the genetic or acquired conditions that may evolve towards clinically established forms of HF with or without compromising the EF.

Role of strain indices in the phenotype of heart failure

Although extensive validations with population studies do not yet exist, using the myocardial deformation indices we can envisage new HF phenotypes beyond the EF values.

- HF with prevalent longitudinal myocardial dysfunction: many cardiopathies induce, in the early stages, a dysfunction of the sub-endocardial layer which can cause an alteration of the longitudinal function with normal EF values due to the compensatory effect of parietal hypertrophy and the contractile reserve of the epicardial layer. Although the finding of alterations in the filling indices indicative of the increase in intracavitary pressure would lead, for the preserved pump function (EF $>$ 50%), towards the diagnosis of 'diastolic decompensation', the HFpEF frameworks actually underlie a reduction in the longitudinal deformation and a related reduction of the relaxation function as an epiphenomenon of a primary alteration of the 'systolic function'.
- HF with transmural dysfunction: the involvement of the whole myocardial thickness can be consequent to the progressive extension of the anomalies of the sub-endocardial layer towards the epicardial one with a proportional reduction of the pump function due to the lack of compensation of the circumferential fibres and evolution towards forms of HFrEF. Conversely, pathological processes with transmural involvement, as in the case of myocardial infarction, can lead to an LV pump dysfunction typical of HFrEF in relation to the extent of the damage.
- HF with prevalent circumferential dysfunction: some cardiac diseases, such as those involving the pericardium, tend to involve the subepicardial layer. The involvement of the subepicardial layer determine the alteration of the circumferential function and of the twist mechanism of the left ventricle, while maintaining the systolic pump function as a compensation for the preserved longitudinal function derived from the subendocardial fibres. The alteration of the circumferential function also occurs in cases of myocarditis, as demonstrated by the altered enhancement observed with MRI. In these cases, both described forms of heart failure can occur with preserved and reduced EF.
- HF with prevalent or isolated atrial dysfunction: LA impairment may represent the phenotype of concomitant or even early cardiomyopathies compared to LV impairment and is an important target for specific

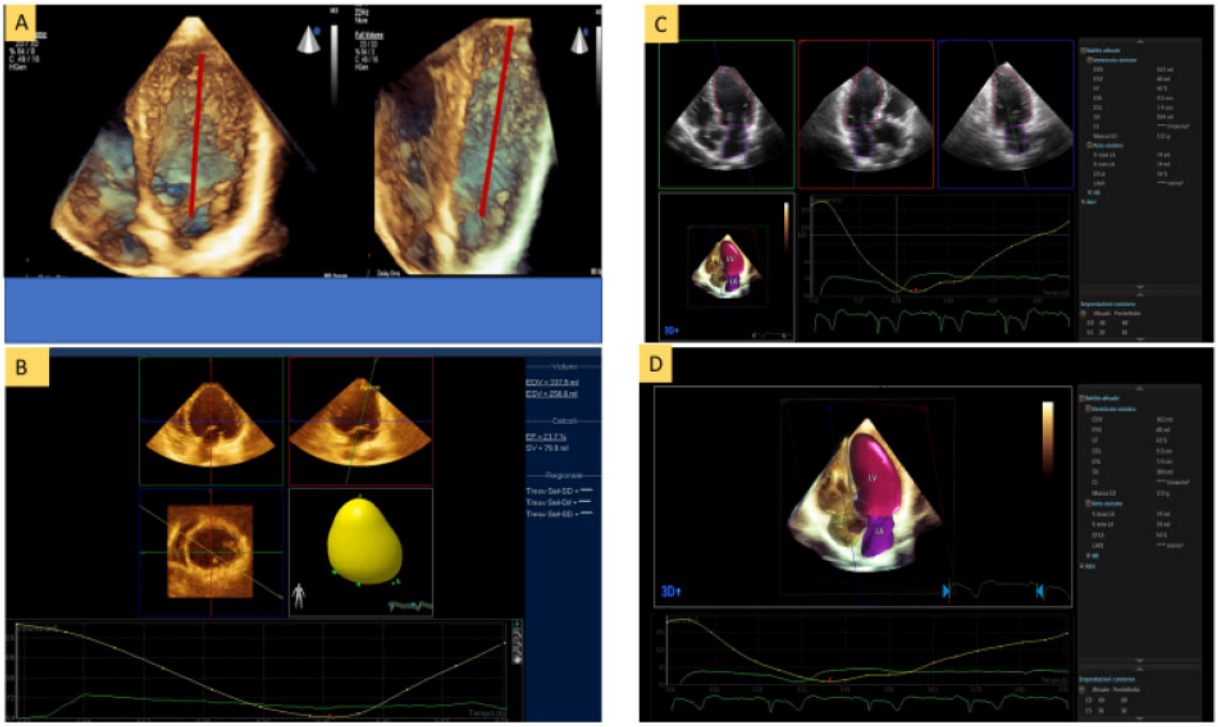

Figure 2 (*A* and *B*) Left ventricular ejection fraction measurement with three-dimensional transthoracic echocardiography. (*C* and *D*) Measurement of left ventricular ejection fraction, stroke volume, and left atrial volume changes using an automated speckle tracking method.

therapeutic strategies. The analysis of LA deformation indices can identify HFpEF frameworks without evidence of impairment of cardiac filling indices that can underlie an autonomous or early LA impairment ('atrial myopathy') regardless of LV dysfunction.[13]

Fluid dynamics parameters

In addition to the cardiac function parameters according to the muscle-pump models, it is possible, by processing the intracavitary flow rate, after injection of sonicated contrast medium, to derive left intraventricular fluid dynamics indices. The preservation of a normal whirling is intended to dissipate energy in order to reduce the transmission by the blood column of high intracavitary stress and allow physiological ejection without high filling pressure. The loss of whirling can provide an index of the haemodynamic burden of heart disease and represent an early signal of cavitary remodeling.[14]

'Old parameters' that can be analysed with new techniques

The EF represents the 'gate-keeper' for the nosologic definition of the HF and the primary Endpoint of the related clinical-therapeutic strategies. The ECHO 3D techniques of recent and increasing diffusion in clinical practice allow to overcome the limits of the 2D approach in the volume and EF determination, providing an acquisition of the entire volume of the LV without the drawbacks of the incomplete visualization of the long axis, with better accuracy and reproducibility. However, potential limits remain due to the need to acquire multiple beats in order to increase the accuracy of the images and allow the applicability of quantitative processing systems. Consequently, there is a risk of acquisitions that cannot be analysed for the presence of artefacts ('stitch artefacts') or of arrhythmias (atrial fibrillation or frequent extrasystole). The 3D ECHO with the application of dedicated processing systems also allows to determine an accurate assessment of the volumes and the EF of the right ventricle, otherwise unreliable if carried out with 2D techniques, with an acceptable degree of concordance with the values measured with CMR. Finally, the use of 3D techniques proves to be extremely useful for measuring the volume of LA, overcoming the limits of 2D-ECHO techniques relating to the complexity of the chamber geometry. A new three-dimensional imaging method is the automatic and instantaneous calculation of volumes and EF by means of the speckle-tracking signal without any need for cavity geometry.[15] An advantage of the automatic measurement system is represented by the possibility of modulating the setting for identification and inclusion of the endocardial border in the determination of volumes in order to reproduce the CMR methodology and increase the degree of concordance between the two methods. The values can be calculated beat by beat allowing to overcome the limitations of conventional 3D ECHO in patients with arrhythmia from atrial fibrillation (*Figure 2*).

The use of automatic systems has the important advantage of providing measurements of cardiac output without the need to determine the area of the LV outflow tract, potentially limited in the presence of complex geometries even with the conventional 3D approach. The determination of systolic blood flow can be of significant clinical impact to define the haemodynamic profile of patients with

HF and to explain the frequent paradoxical inconsistencies between clinical condition and EF values. In addition to the ventricular volumes, the automatic evaluation systems allow to measure the volumetric variations of the LA regardless of the chamber geometry assumptions. The rapid application of automatic heart size measurement systems opens up new perspectives for extending knowledge in the field of HF.

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