White Paper

Ultrasound CV technologies for heart failure

ESAOTE HEART VESSELS our commitment

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Heart failure (HF) is a leading cause of cardiovascular morbidity and mortality worldwide. It has a prevalence of about 1-2% in the adult population of developed countries, reaching ≥ 10% among people > 70 years of age[1]. More than 1 million people are hospitalized annually for HF, with 5-year mortality rates of approximately 50%[2]. HF diagnosis starts with the evaluation of symptoms, physical examination, and electrocardiogram findings.

Natriuretic peptides represent important diagnostic and prognostic tool in patients with signs of heart failure, but they should always be complemented by echocardiography that provides essential information on left and right ventricle dimensions, myocardial systolic and diastolic function, and intracardiac flow pattern.

Over the last decades, several technological advancements were made in the echocardiographic field, helping us to understand the morpho-functional abnormalities underlying cardiovascular diseases.

Since these technologies are still struggling to enter routine use, this white paper aims to turn the spotlight on some of the new Esaote cardiac ultrasound imaging technologies, highlighting their applications in HF diagnosis, management, and monitoring during cardiac rehabilitation.

Transthoracic echocardiography (TTE), due to its non-invasiveness and safety, is the method of choice for assessing cardiac structure and function for diagnosis, therapeutic decision-making, and therapy monitoring.

As a matter of fact, the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) assigned to standard TTE the highest level of recommendation (Class Ia) and to TDI and 2DSTE the second level (Class IIa) indicating that these newer technologies should be considered in the diagnostic protocol of subjects at risk of developing HF in order to identify myocardial dysfunction at the preclinical stage.

Recommendations for cardiac imaging in patients with suspected or established heart failure

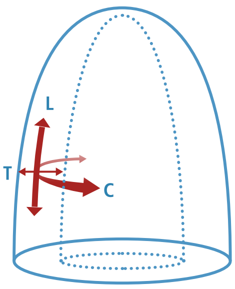
Recommendations	Class[a]	Level[b]
TTE is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of either HFrEF, HFmrEF, or HFpEF.	I	C
TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device (ICD, CRT) treatment recommended for HFrEF.	I	C
TTE is recommended for the assessment of valve disease, right ventricular function, and pulmonary arterial pressure in patients with an already established diagnosis of either HFr, HFmrEf, or HFpEF in order to identify those suitable for correction of valve disease.	I	C
TTE is recommended for the assessment of myocardial structure and function in subjects to be exposed to treatment which potentially can damage myocardium (e.g. chemotherapy).	I	C
Other techniques (including systolic tissue Doppler velocities and deformation indices, i.e. strain and strain rate), should be considered in a TTE protocol in subjects at risk of developing HF in order to identify myocardial dysfunction at the preclinical stage.	IIa	C

LV strain GLS

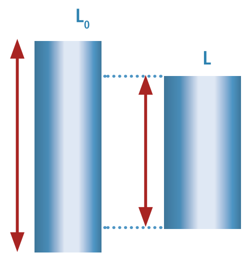
Two-dimensional (2D) speckle-tracking echocardiography (2DSTE) is a gray-scale based, angle-independent technique of myocardial deformation imaging, which allows myocardial contraction and relaxation to be assessed. The myocardial deformation is quantified as strain or strain rate.

Strain is the percentage change in the length of a myocardial segment compared to its resting length; strain rate is the rate at which this deformation takes place, expressed as 1/s. Normally, strain and strain rate have negative values in systole when myocardium shortens, and positive values in diastole when myocardium lengthens.

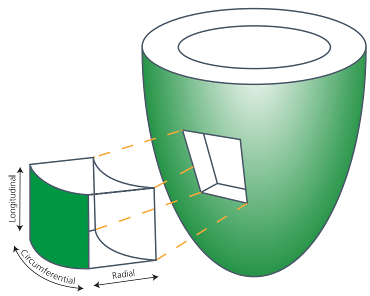
The STE software identifies a number of bright speckles generated by the scatter of the ultrasound beam after its interaction with the myocardium and follows them frame by frame. Then, through an algorithm, it calculates the magnitude of myocardial deformation in each direction and generates strain and strain rate curves.



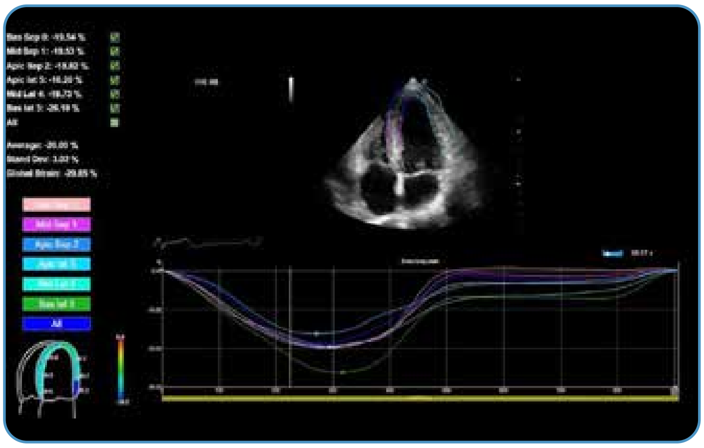
In the heart, the usual directions are longitudinal, transmural, and circumferential as shown to the left.



The cylinder shows strain (compression along its long axis), which can be described as Lagrangian strain from L_0 to L. However, the figure also shows simultaneous thickening or expansion in the two transverse directions.



In systole, there is longitudinal shortening, transmural (Radial) thickening, and circumferential shortening. (J Am Coll Cardiol Img. 2011;4(6):671-679. doi:10.1016/j.jcmg.2011.02.015)



Role of LV strain in HF

STE is able to detect subclinical LV systolic dysfunction in an early stage of HF disease, when LVEF is still normal.

In patients with HF and preserved EF (HFpEF), an isolated impairment of one myocardial layer can be present, compensated by the augmentation of function of the other layers, so that LVEF and overall LV performance remain preserved. For example, in cardiac diseases with involvement of subendocardial fibers, like subendocardial infarction, the reduced longitudinal deformation is compensated by LV hypertrophy and an increase in circumferential strain and twist.

Similarly, in pericardial diseases, which involve the epicardial layer, there is an impairment of twist and circumferential deformation, compensated by the increase of longitudinal mechanics.

A diastolic dysfunction is generally present in HFpEF, due to progressive myocardial fibrosis, impairment of subendocardial function, or damage of twist and untwist mechanisms.

On the other side, patients affected with HF and reduced EF (HFrEF) usually show transmural myocardial involvement (e.g. transmural infarction), with impairment of both longitudinal and circumferential strain, fall in LVEF, and dilatation of LV cavity.

STE adds a prognostic value to the traditional indexes of LV systolic function in both stable and intensive care settings.

Lower GLS values were found to be associated with higher NT-proBNP levels, which is a proven prognostic factor in HFpEF6.

In another recent study, patients with HFpEF and reduced longitudinal systolic strain had significantly lower event-free survival than those with preserved longitudinal strain, whereas LVEF did not predict event-free survival.

GLS showed to be an independent predictor of all-cause mortality also in HFrEF patients.

Moreover, both longitudinal and circumferential strain rate were demonstrated to be independent predictors of death and hospital stay for HF after myocardial infarction (MI).

A low GLS after coronary angioplasty in a population of patients with recent non ST-elevation MI was predictor of negative LV remodeling at follow-up.

STE could also be useful in guiding LV lead placement in patients with HFrEF, ventricular dyssynchrony, and indication to CRT: the ideal place to improve the chance of response would be the one adjacent to the most delayed (determined by time to peak radial strain) but non-scarred (segmental radial strain >10%) LV myocardial segment.

Finally, GLS was found to be a predictor of outcome in patients with advanced aortic stenosis.

Tissue Doppler Imaging

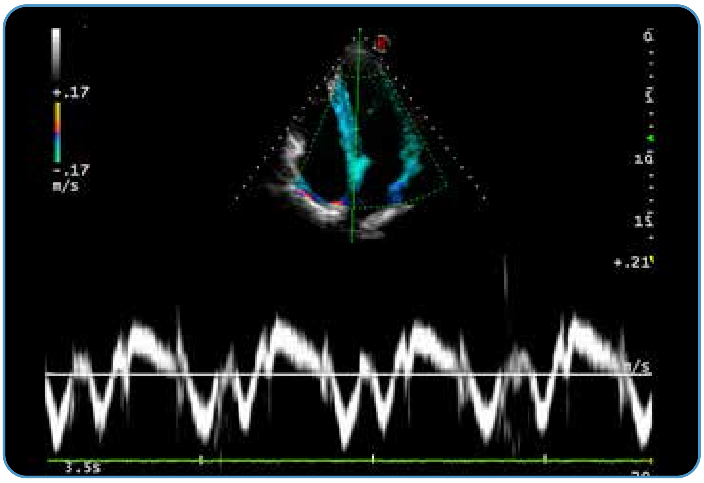
Tissue Doppler imaging (TDI) is an echocardiographic technique which allows myocardial velocities to be measured using Doppler principles. TDI can be performed in 3 different modalities: pulsed wave (PW), color, and 3D mode.

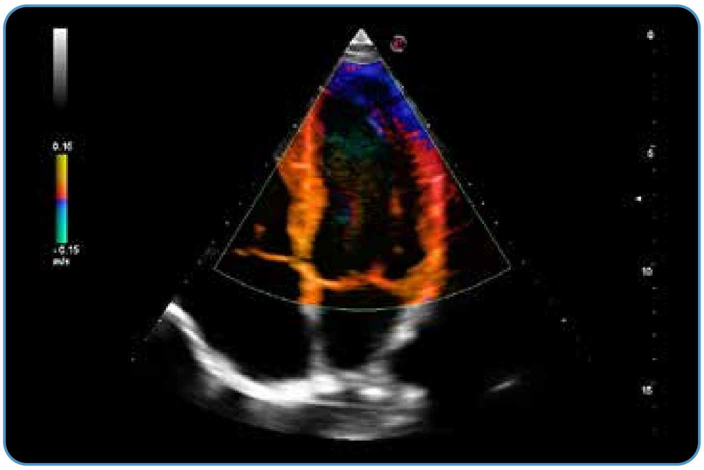
PW TDI measures the instantaneous regional myocardial peak velocities. A sample volume of 5-7 mm is placed in the ventricular myocardium, adjacent to the mitral annulus, in apical views, in order to obtain longitudinal movement of mitral annulus, which is a good surrogate for LV longitudinal contraction and relaxation. PW TDI has high temporal resolution but doesn't permit the simultaneous analysis of more myocardial segments.

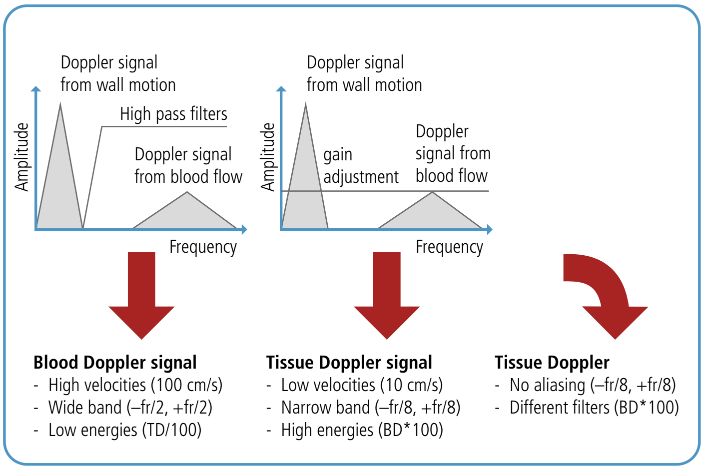
With color TDI, a color-coded box is superimposed on gray-scale 2D or M-mode images, indicating myocardium direction and velocity. Color TDI has higher spatial resolution, it allows simultaneous interrogation of several myocardial segments included in the color box, but it needs offline quantification of myocardial velocities. Offline velocities obtained by color TDI are approximately 20-25% lower than those obtained from PW TDI.

With 3D TDI, a color-coded TDI is applied to the triplane apical view (simultaneous acquisition of 4-, 2-, and 3-chamber view). Velocity analysis is performed offline. 3D TDI also allows LV volumes and EF to be calculated.

PW TDI represents the cardiac cycle throughout 3 waveforms: systolic myocardial velocity (S') above the baseline; early diastolic myocardial relaxation velocity (e') below the baseline; late diastolic myocardial velocity associated with atrial contraction (a') below the baseline.







Role of LV strain in HF

LV systolic impairment as measured by TDI was found in patients with HFpEF and LV hypertrophy.

TDI proved to be a promising technique in LV diastolic function evaluation. Nowadays, TDI assessment of LV diastolic function always accompanies the traditional echocardiographic indexes based on Doppler patterns of mitral inflow, since it is less load dependent.

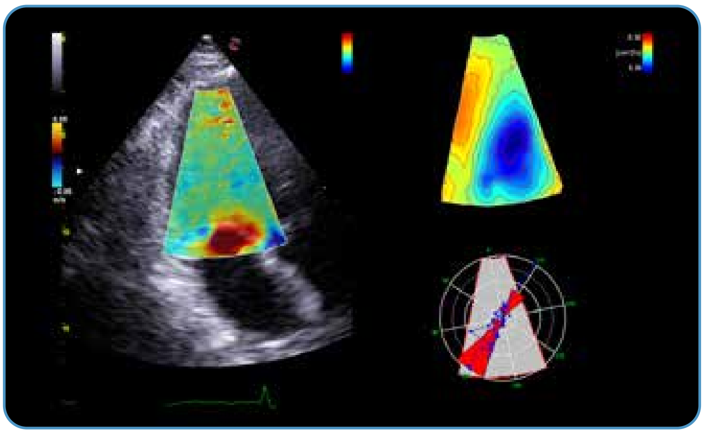
Moreover, E/e’ ratio has proved to be a useful tool in estimating LV filling pressures. An elevated E/e’ ratio (> 15) is a predictor of poor outcome in both HFrEF and HFpEF. However, some other conditions such as LV hypertrophy, left bundle branch block, atrial fibrillation, extensive calcifications of the mitral annulus, and constrictive pericarditis, may lead to underestimation of e’ and overestimation of the E/e’ ratio. Importantly, demographic parameters should always be considered in a LV filling pressure evaluation, since a strong linear positive correlation between age and E/e’ ratio was found in healthy individuals.

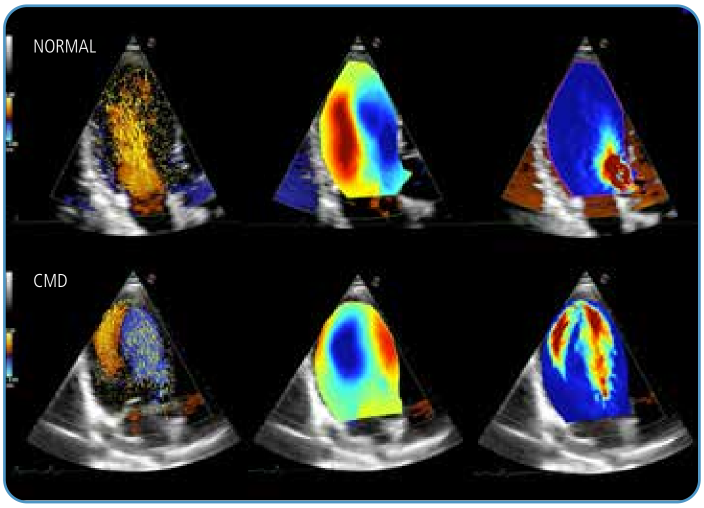
Color Doppler flow mapping

Analysis of intracardiac flows represents another way to approach the study of LV function. In normal conditions, during diastole, when blood flow enters the LV from the LA, it gives rise to the formation of two vortices, which rotate around a virtual axis, storing kinetic energy: a main, anterior vortex which rotates clockwise, and a secondary, posterior vortex which rotates counterclockwise. The main vortex determinant is the natural asymmetric geometry of the mitral valve apparatus (the anterior leaflet is longer than the posterior, and the mitral valve orifice is eccentric as compared with the LV axis).

Even if phase-contrast magnetic resonance imaging is the gold standard for measuring blood velocities in heart cavities, some echocardiographic techniques have been developed in order to visualize intracardiac flow, including the color Doppler flow mapping (CDFM). The HyperDoppler software by Esaote S.p.A is a recent CDFM based technology that provides different possibilities for representing intracardiac flow data:
- a flow velocity vector map where velocity vectors are displayed as arrows superimposed on the traditional color Doppler flow images, which can be followed frame by frame;
- a circulation parametric map where vortices are represented as compacted regions in blue (clockwise rotation) or in red (counterclockwise rotation);
- a kinetic energy map where the highest level of kinetic energy is depicted in red.

Normally, intracardiac vortices are visualized on apical long-axis.





Role of CDFM in HF

The LV vortex formation is the result of an optimal interaction between LV chamber geometry, morphology of the mitral valve apparatus, and the normal electrical conduction system, which allows the harmonic contraction of the cardiac walls.

If one of these elements is altered, the LV vortex formation is affected too. In DCM, during diastole, there is a single vortex located in the center of the LV that is larger, rounder, and more persistent than in normal subjects, with a greater amount of kinetic energy.

Kinetic energy dissipation is higher in healthy subjects than in patients with DCM or MI and impaired LVEF and stroke volume.

Finally, larger infarctions are associated with a more severe alteration in LV intracavitary blood flow dynamics.

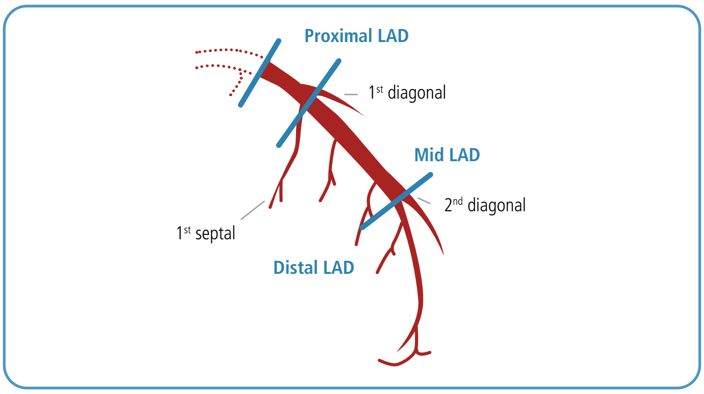
Preliminary data reported the prognostic value of vortex properties in patients with HF.

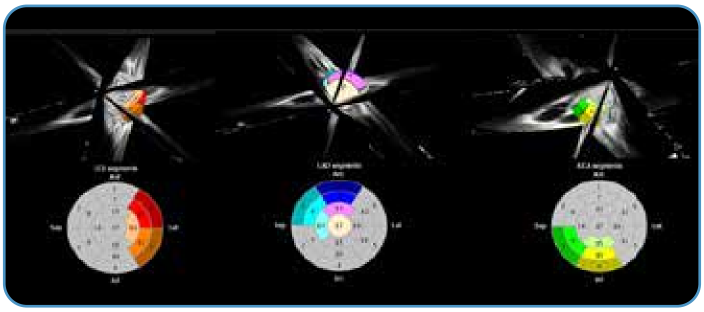
Coronary flow reserve

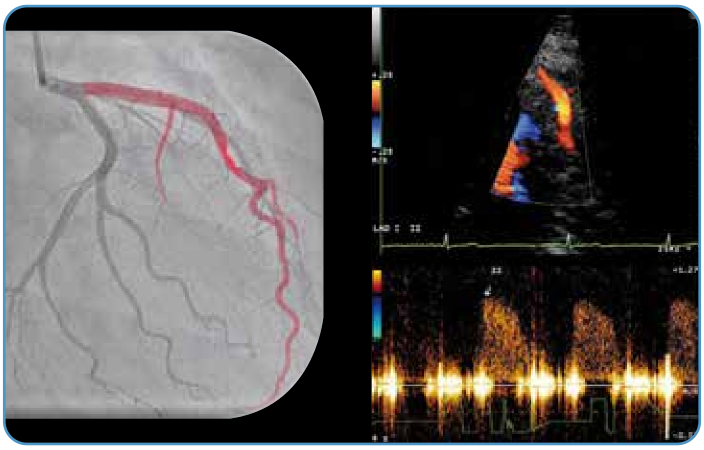
The left anterior descending (LAD) coronary blood flow velocity (CBFV) profile can be recorded by PW Doppler, either with transesophageal echocardiography (TEE), sampling the proximal LAD tract, or with TTE, exploring the mid-distal LAD tract. The success rates in measuring CBFV of posterior interventricular artery (PIA) and left circumflex artery (LCA) recently increased thanks to the advancement in ultrasonic technology.

CBVF by PW Doppler is represented by a biphasic wave, with a lower peak during systole and a higher peak during diastole, for the effect of myocardial contraction.

The most used parameter in the evaluation of coronary flow reserve (CFR) is peak diastolic flow, because it is easy to measure, reproducible, and has a closer correlation with CRF measured by Doppler flow wire and PET. The LAD peak diastolic flow is obtained from a modified apical 2-chamber view, where the transthoracic probe is slightly moved upward and medially, with a little counterclockwise rotation and medial angulation of the probe.
CFR is the ratio of peak diastolic flow during maximal vasodilation induced by Dipyidamole, and baseline peak diastolic flow. CFR feasibility of LAD is very high, reaching 98%, and the use of contrast is rarely needed, when the Doppler signal is not appropriate.







Role of CFR in HF

Current guidelines recommend the use of exercise stress echocardiography (ESE) in patients with unexplained dyspnea. ESE was recently reshaped with the ABCDE protocol: A for asynergy, B for thoracic ultrasound B-lines, C for contractile reserve, D for Doppler-based CFR (in LAD), and E for EKG-based heart rate reserve (HRR, defined as peak/rest HR < 1.62). The ABCDE protocol is therefore useful for documenting the cardiac origin of dyspnoea with a comprehensive assessment focused not only on ischemia (A) but also pulmonary congestion (B), myocardial scar or necrosis (C), coronary microvascular dysfunction (D) or chronotropic incompetence (E)

In a population of patients with arterial hypertension and preserved LVEF, the combination of abnormal CFR and LV GLS was associated with a higher rate of hospitalization for HF, proving that markers of subclinical microvascular and myocardial dysfunction can be used to refine hypertensive HF risk assessment.

A reduced CFR was found in patients with non-ischemic DCM, and identifies a subset of patients at higher risk of spontaneous events, such as death and worsening of clinical status.

Several factors may contribute to CFR reduction in DCM patients, such as LV hypertrophy and pressure overload, impaired endothelium dependent vascular relaxation, vascular wall structural abnormalities, and chronically elevated LA pressure. The presence of left bundle branch block (LBBB) in DCM population was associated with more reduced CFR and more impaired myocardial contractile reserve assessed during dipyridamole stress echocardiography, due to the delay in the mechanical activation of the LV and the subsequent interventricular asynchrony.

Recently, the assessment of CFR on TTE has been proposed as a method to detect cardiac allograft macro- and micro- vasculopathy in heart transplant. Indeed, CFR was shown to be very sensitive in detecting cardiac allograft vasculopathy, and increases the diagnostic accuracy of dobutamine stress echocardiography

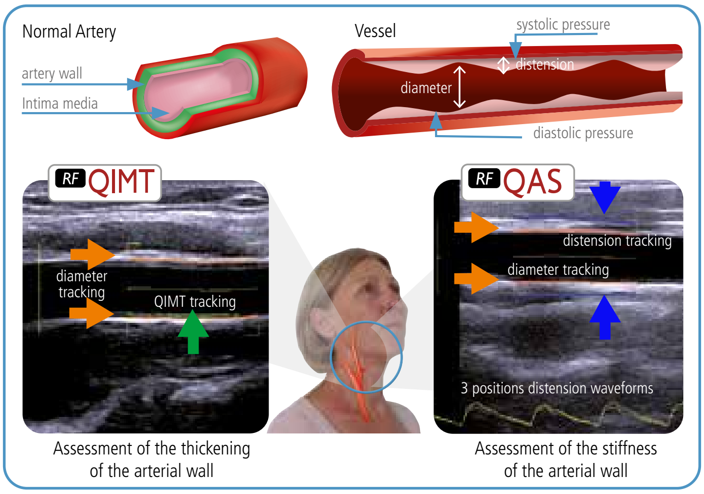
Arterial stiffness

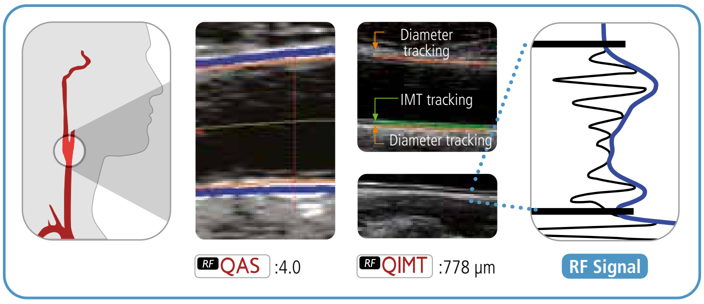
Vascular aging in large arteries is characterized by structural and functional changes, such as intima-media thickening and "stiffening".

Arterial wall thickening is considered a very early marker of atherosclerotic processes.

Arterial stiffening, that is the vessel wall's tendency to resist deformation generated by systolic blood pressure during the cardiac cycle, is mainly due to degenerative and calcified processes.

The recently introduced radiofrequency (RF) data technology allows to measure arterial intima-media wall thickness (IMT) and stiffness RFQIMT and RFQAS respectively -Esaote). All measurements are taken in a selected area of common carotid artery. The blood vessel wall stiffness is expressed in pulse wave velocity (PWV) in m/s, and is obtained from the brachial blood pressure and the accurate measurements of vessel diameter and distension (change in diameter). For both IMT and stiffness the operator gets real-time feedback on measurement quality via quality indicators overlaid on the ultrasound image. This real time feedback gives the operator the possibility to optimize his probe position, in order to obtain a scan plane perpendicular to the wall of the common carotid artery.





Role of arterial thickness and stiffness in HF

Vascular intima-media thickening and stiffening are correlated to cardiovascular morbidity and mortality. Arterial stiffness plays an important role in systolic blood pressure (BP) and pulse pressure (systolic BP – diastolic BP) increase. Moreover, it can contribute to LV concentric remodeling and hypertrophy, impaired myocardial perfusion, and other structural changes in LV that underlie systolic and diastolic dysfunction.

The role of Arterial stiffness in development of HF is still debated. Several studies demonstrated the relationship between arterial compliance and LV diastolic dysfunction, proving that arterial stiffness could play a key role in the development of diastolic HF. This relationship is particularly important in hypertensive women, who have a higher prevalence of diastolic dysfunction than men.

Markers of arterial stiffness have been found to be independent predictors of outcome in patients affected by HFrEF. In the EPHESUS study, performed on patients with HFrEF following MI, it was shown that an increased aortic stiffness, assessed by PWV, was associated with a negative prognosis and significantly contributed to cardiovascular death. Similarly, increased PWV has been shown to be a risk factor for hospitalization and cardiovascular mortality in stable patients with HFpEF.

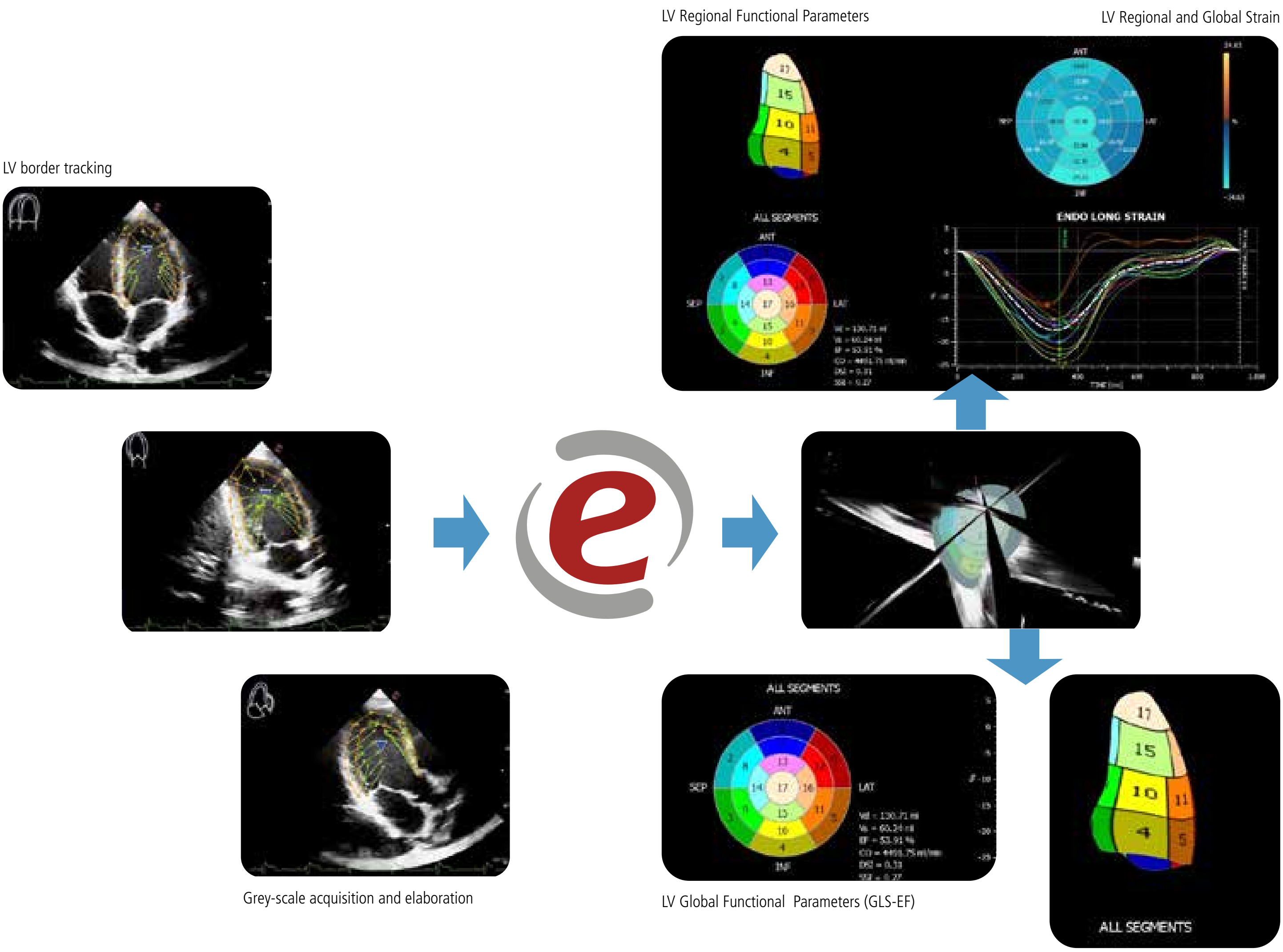
Conclusions

Standard echocardiography is the most widely used imaging modality for the assessment of patients affected by HF with both reduced and preserved EF, for its unmatched ability to combine safety and ease of application with depth of diagnostic and prognostic information.

The newer ultrasound technologies provide valuable insights concerning the pathogenesis of HF, elucidating distinct patterns of myocardial, vascular, and microcirculatory dysfunction and mechanisms associated with progression from subclinical stage to overt HF

All the echocardiographic technologies mentioned above have the advantage of being safe, noninvasive, with a good price-performance ratio, and able to be performed at the bedside.

These technological advancements promise to further expand the role of echocardiography as the modality of choice in HF diagnosis, management, and monitoring after cardiac rehabilitation.



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