CONTROVERSY

Is It Still Valid to Measure Ejection Fraction When There Are New Deformation Indexes to Evaluate Ventricular Function?

Agonist

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An echocardiographic study helps in the assessment of systolic and diastolic left ventricular function due to potential clinical implications over the treatment and the prognosis of different heart diseases.

Systolic function depends on three factors: the left ventricular (LV) function, arterial coupling (ventriculoarterial coupling) and blood volume. In the particular case of the left ventricular function, this is determined by the preload, afterload, contractility, heart rate, ventricular geometry and synergy of contraction. The interaction of these factors determines the shortening of longitudinal and circumferential fibers, with the consequent thickness of the ventricular wall and the expulsion of systolic volume (SV). A 14% of fiber shortening produces approximately a 40% of ventricular wall thickness. (1) Therefore, parietal thickness and the reduction of ventricular volume are inversely related; the greater the thickness, the lesser the end-systolic volume with greater SV and vice versa.

Several indexes related to shortening (Tissue Doppler Imaging, strain rate) may be altered in presence of normal ejection fraction (Ef). However, all these indexes are affected by load conditions and ventricular geometry besides contractility. (2, 3)

ASSESSMENT OF SYSTOLIC FUNCTION

Left ventricular systolic properties may be analyzed through indexes which reflect the ventricular performance, ventricular function and contractility. (4) The performance assesses the heart as a pump and it may be estimated from the development of intraventricular pressure, systolic volume or the integration of both through systolic work (pressure x volume). Indexes of ventricular function are referred to the relationship between a performance parameter (SV, systolic work) and the preload (end-diastolic volume or pressure), determining the classical Frank-Starling curves. The term "ventricular function" has been spread in order to include parameters which depend on fiber shortening, such as endocardial and mesoparietal shortening fraction, Ef, longitudinal shortening (M-mode of the lateral mitral annulus or MAPSE), tissue Doppler (S wave), myocardial deformation (strain) and velocity of myocardial deformation (strain rate). Many of these indexes have been wrongly considered as indexes of myocardial contractility, since all of them depend on the preload and afterload, as well as ventricular remodeling and contractility. (5-9) If load conditions, especially afterload, are added to the analysis, these indexes could be used as contractility parameters.

Contractility is referred to the intrinsic property of the fiber or myocardium of contracting itself and it may be assessed through isovolumetric indexes (+dP/dt), of ejection (parietal stress vs. endocardial shortening) or end-systolic function (maximal elastance). +dP/dt depends on acute changes in the preload, afterload and maximal elastance, on chronic changes in volume and ventricular mass. Due to afterload is inversely related to the ventricular ejection, the fact of establishing the appropriate shortening (Ef or shortening fraction) for the afterload level that the LV presents, seems to be the most appropriate way of quantifying contractility. (4) Therefore, a change in a performance or ventricular function parameter may be due to a modification in contractility only if it is not attributed to variations on the preload and afterload.

EJECTION FRACTION VERSUS DEFORMATION INDEXES

Ef is defined as the SV normalized to the end-diastolic volume (EDV):

$$Ef = SV / EDV$$

It may be estimated quantitatively (Simpson's method, area – length or 3D Echo) or visually graduating its decrease qualitatively as mild (till 45%), moderate (45-30%) and severe (< 30%) with appropriate reproducibility. This last mode allows us to obtain the information quickly at the beginning of the study which is not invalidated by a poor acoustic window and it does not require any synchronization with electrocardiography. Besides, parameters allow us to obtain information about the pathophysiology of the studied heart disease: the decrease of Ef with

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normal SV is due to the increase of the EDV which responds to a process of ventricular remodeling (Frank-Starling). If the SV is reduced and the EDV is normal, it should be due to a decrease in contractility (myocarditis or acute ischemia) or a loss of myocytes (acute myocardial infarction). Due to Ef depends on the endocardial motion, it is influenced by the ventricular geometry, especially in concentric hypertrophy, in which the decrease of ventricular volumes exaggerates endocardial motion, so that normal Ef may coexist with decrease contractility. However, a correlation between the decrease in inotropism and longitudinal shortening has not been shown in this group of patients. (5)

From the clinical point of view, Ef is the parameter which is related to the evolution and prognosis of patients with heart failure. This fact presupposes a constant model, with an unimodal curve, in which the gradual decrease of Ef is accompanied by a greater ventricular dilation, remodeling and worsening of the symptoms. Within this hypothesis, those indexes that are early altered (strain rate), even before than Ef, could be very useful. Recent studies, (10) have shown that Ef presents a bimodal distribution, showing two different patterns of ventricular remodeling that represent heart failure with preseved Ef and decreased Ef in patients with heart failure of ischemic and hypertensive origin. Such clinical finding is in accordance with the different response that these two groups have when facing the inhibition of the renin-angiotensin system and they would involve two different phenotypes in patients with heart failure, and with different physiopathological mechanisms. Therefore, in patients with heart failure the determination of the group to which they belong (preserved or decreased Ef) would have greater clinical impact than the detection of subclinical alterations of the ventricular function.

The deformation or strain ($\mathcal{E}$) is the relative change in length (Δl) of a normalized material to its initial length (l_0): (11)

$$\mathcal{E} = \Delta l / l_0$$

The deformation velocity or strain rate (SR) is the first derivative of the strain as regards time:

$$\mathrm{SR} = d\,\mathcal{E} / dt$$

At first, the tissue Doppler was used to assess strain and SR, but then the analysis with 2D Echo was added. In the echocardiography, the ventricular wall presents a speckle pattern with echolucent and echorefractive areas which are formed as a consequence of the interaction among reflected ultrasound waves. When two waves in phase interact, their widths are added (echorefractive area) and when these are out of phase in 180 degrees, they are canceled (echolucent area). The speckle analysis of the ventricular wall allows us to locate natural acoustic markers called speckle patterns or Kernel areas and to follow their movement through a correlation analysis. The geometric position of each marker changes according to the myocardial motion (deformation or strain).

Deformation indexes have the advantage of analyzing the global and regional deformation of the ventricle, as well as their modifications in time which is useful to assess the ventricular synchrony. This requires a good acoustic window and an appropriate sign of ECG to perform its subsequent analysis, since data may not be obtained while the echocardiography is carried out.

SR studies the thickness of the ventricular wall in its different axes (longitudinal, transverse and radial) and torsion, while Ef analyzes the behavior of chamber reduction as a consequence of the thickness; therefore, both processes are intimately related.

To conclude, Ef is the most useful index of ventricular function due to its clinical value to establish the diagnosis, prognosis and assessment of the treatment in most heart diseases. (13) Due to the bimodal curve that patients with heart failure of ischemic and hypertensive origin have, the determination through Ef to which group the patient belongs (preserved or decreased Ef), has greater clinical value than the detection of subclinical alterations of the ventricular function. Ventricular deformation indexes allow us to gain parameters of muscle mechanics in the time domain at regional and global levels which represent a great contribution to the study of ventricular function. This information does not replace Ef due to the aforementioned reasons, but it contributes new quantitative parameters which extend the possibilities of analyzing the left ventricular function.

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BACKGROUND

Ejection fraction assessment (Ef) has been consolidated as an accessible and reliable parameter in the quantification of the ventricular systolic function and it has also shown a huge value in welfare decisions and as a prognostic indicator. However, exceptions to linearity between functional class and Ef are large and they are placed at both sides of their value spectrum. We recognize many examples where Ef seems to be inadequate to give us appropriate information about the ventricular mechanics.

Acute heart failure syndrome with preserved Ef represents an increasing prevalence and its mortality at long-term differs as regards the one observed in patients with depressed Ef. (1)

The recent recognition of severe aortic valve stenosis with low gradient and normal Ef as a clinical entity suggests that most of the cardiologists have considered that if Ef is normal, expulsion parameters will also be normal. However, the diagnostic problem of the low gradient lies in the limited systolic unloading (< 35/ml/beat/m^2), even with preserved Ef. (2) Congestive symptoms in hypertrophic cardiomyopathy have been explained through the classical model of diastolic dysfunction, considering that they represent a normal Ef or even a high one. Finding another noxa model, which may act with hyperfunction and after 300 milliseconds presents severe dysfunction in diastole, is difficult to find.

The immediate reflection should be: Is our function assessment, from the thickness which represents mainly the radial excursion, enough? Is the ventricular chamber performance the accurate reflex of what happens at the myocardial fiber level? Are global parameters applicable to the segmentary analysis?

When facing these matters, we should analyze new technology contributions in echocardiography which help us to obtain a more complete vision of the ventricular mechanics.

FROM ANATOMY TO FUNCTION

The particular disposition of myocardial muscle fibers: thick, longitudinal and descending in the endocardium, circumferential in the mesocardium and predominantly longitudinal in the epicardium with an opposed direction to the endocardium, allows an ideal mechanics where 15-20% of the decrease in the myocyte length achieves a 40-60% of LV wall thickness and an Ef of 60%. This is obtained at the expense of modifications of each segment in a longitudinal, circumferential and radial sense.

Likewise, contraction is accompanied by a clockwise rotation in basal segments and anti- clockwise rotation at apical level, generating a true torsion along the longitudinal axis of the left ventricle. (3)

Techniques based on Doppler effect, which are applied to the myocardial wall, facilitate the regional analysis of the contraction where we may analyze:

- Excursion (tissue tracking).
- Movement velocity (tissue Doppler).
- Deformation (strain and strain rate)

Tissue Doppler is obtained through filters that eliminate signs of blood flow and this study expresses the velocity and sense of the myocardial movement. Tissue Doppler may be assessed as pulsed Doppler or integrating different myocardial velocities with color tissue Doppler which allows us to assess myocardial velocities and parameters that derive from such velocities. The strain analyzes the deformation suffered by each segment during contraction which is considered negative (shortening) in a longitudinal and circumferential sense and positive in a radial sense (enlargement). The strain rate expresses the velocity of such deformation at different phases of the cardiac cycle. Parameters that depend on the Doppler effect are affected by an interrogation angle, situation that limits the application on apical segments and on the wall of spherical ventricles.

When facing this problem, we have the speckle tracking technique, which from information derived from the recognition and monitoring of acoustic markers in the myocardial wall, may analyze the parietal movement independently of the interrogation angle. 2D strain allows the deformation (longitudinal, radial and circumferential), rotation, torsion and

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detorsion velocity studies.

New dot-matrix transducers allow the capture of the complete left ventricular volume with high resolution, so that the three-dimensional monitoring of acoustic markers may be carried out; the deformation in the aforementioned patterns and in new parameters may be analyzed, as the strain area (circumferential and longitudinal deformation of a certain myocardial area: endocardial or mesocardial one).

CLINICAL APPLICATIONS

The differential diagnosis between athletic heart syndrome and hypertrophic cardiomyopathy is difficult. When doing exercise, the myocardial adaptation achieves a more efficient contraction with great deformation in basal segments of the septum as regards normal people, situation that differs markedly from findings in hypertrophic cardiomyopathy. (4)

Patients with hypertensive heart disease present strain reduction even before the worsening of Ef. (5) This alteration of the longitudinal deformation begins in the basal septum and it enlarges as the patient progresses in functional class. Radial and circumferential deformation and Ef are reduced in FC III and IV.

Hypertrophic cardiomyopathy reduces the deformation especially in the septum and in basal segments, according to the fibrillar disarray and interstitial fibrosis, (6) where 45% of patients with the phenotype present paradoxical systolic stretch of at least one segment. (7) Horizontalization of contraction vectors is observed, in such a way that longitudinal deformation is reduced, circumferential strain increases, there is heterogeneity in the deformation of different segments and apical rotation and torsion are exaggerated. (8)

Torsion is basic to establish, during systole, a load of potential energy in restoration forces. When they are released in diastole, they facilitate suction and quick ventricular filling. (9) The velocity reduction in diastolic detorsion facilitates heart failure even with preserved Ef.

The volume overload linked to mitral or aortic regurgitation arises difficulties in the interpretation of the ventricular dysfunction and surgical opportunity of asymptomatic patients. Ef reduction is a late indicator of ventricular dysfunction, considering an inferior level of normality (60%) superior to the one of population free of valvular heart disease. To unmask the subclinical ventricular dysfunction, overcome Ef limitations, which are imposed by load conditions and predict the postoperative worsening of the ventricular function, are important in this group. Lancelotti et al. showed in a group of 70 asymptomatic patients with organic mitral regurgitation that patients that required surgical treatment presented (similar levels of Ef) a minor longitudinal strain in rest and a minor increase of the strain with exercise than the ones that evolved adequately with medical treatment, difference that was more outstanding in patients with postoperative ventricular dysfunction. (10)

Ef assessment, in patients that underwent chemotherapy, is in checking stage. Controls with endomyocardial biopsy show that myocardial damage may be early and they suggest a low sensitivity of Ef for its early detection. Jurcut et al., in a pilot study of liposomal doxorubicin application, detected radial and longitudinal strain modifications in the first cycles of the treatment, without Ef modifications. (11) Ganame et al. studied a pediatric population that had received treatment with anthracycline in a minor dose of 300 mg/m², and although Ef was normal (64 ± 6%), they found that annular velocities and radial and longitudinal strain were reduced and Tei index (global function) was prolonged. (12) We still have to study if these findings justify the early treatment with beta-blockers, ACE inhibitors or anticytotoxics to avoid the irreversible myocardial damage and if deformation parameters should systematically replace the Ef as a method of early detection of cardiotoxicity.

Choy et al. detected, with a 2D strain in rest, those patients with a severe injury of three vessels or the left coronary trunk, with normal Ef and parietal motility, identified by a value of a minor longitudinal strain of -17.8%, with sensitivity and specificity of 79%. (13)

In connection with the post-infarction assessment, the longitudinal strain was more precise than the Ef and end-systolic volume and comparable to the score of parietal motility to predict the size of the myocardial infarction at the beginning of the admission. (14)

2D strain has allowed us to separate the transmural infarction from the subendocardial one, which represents low levels of longitudinal and circumferential strain, correlating with the percentage of late gadolinium captation on cardiac MRI. (15)

Other studies have shown that a great longitudinal strain of -4.5% distinguishes segments with feasible myocardium from those with transmural scar with a sensitivity and a specificity of 81%. (16)

Our group has set out the value of the longitudinal 2D strain for the diagnosis of myocardial ischemia during the procedure with dipyridamole, with great sensitivity than the analysis of parietal motility and comparable with the coronary reserve due to transthoracic Doppler. (17)

Stanton et al. have shown that the 2D strain adds an additional prognostic value to clinical data (age, diabetes and hypertension) in a non-selected series of patients with greater predictive value for survival than the one added to the Ef. A global longitudinal strain of -12% was equivalent to an Ef of 35% for mortality prediction. (18)

Wang et al. analyzed deformation parameters in patients with heart failure and preserved or worsening Ef. Patients with diastolic heart failure presented an Ef similar to controls, with reduction of the longitudinal and radial strain, with preserved circumferential strain and rotation. The longitudinal strain allowed us to separate patients with diastolic heart failure from controls with normal Ef values. In patients with Ef depression, the deformation in three senses was altered and the torsion was significantly reduced. (19)

Dokainish et al. assessed patients with dyspnea and Ef greater than 50%. Patients with LVEDP > 20 mmHg presented minor systolic velocity at mitral ring level, minor strain and systolic strain rate, with Ef values and dp/dt measured in an invasive way similar to patients with LVEDP < 20 mmHg. (20) Deformation parameters were more useful than preejective and ejective ones.

In patients with amyloidosis AL, with normal echocardiography and Ef, the tissue Doppler showed minor strain and strain rate as regards controls. (21)

The differential diagnosis between restrictive cardiomyopathy and constrictive pericarditis is always difficult, and in absence of thickness and evident pericardial calcification depends on the finding of an abnormal respiratory variation in flow velocities that loses specificity in case of an increase of the airway resistance. Patients with constrictive pericarditis present a marked reduction in circumferential deformation and in rotation, limited by the pericardial adhesion, while the reduction of longitudinal strain predominates in restrictive cardiomyopathy. (22)

This superficial description of the application of new echocardiographic techniques suggests that the analysis of myocardial deformation allows us to overcome diagnostic and prognostic limitations of the Ef and to expand our interpretation of the ventricular mechanics.

The incorporation of the speckle tracking, which allows a quick and efficient study of the different ways of strain and rotation, has allowed us to transfer the concept of deformation from the experimental laboratory to assistential studies and in a near future they will be routine in the daily clinical practice.

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AGONIST'S REPLY

I coincide with the appreciations that Dr. Darú states about the usefulness of the ejection fraction (Ef) and its prognostic value. However, the lack of linearity between Ef and functional capacity (FC, NYHA) is interpreted as a weakness. The functional capacity expressed by dyspnea (NYHA) in the heart failure (HF) is determined by the degree of diastolic dysfunction not by the systolic one; that is why to observe a patient with dilated cardiomyopathy and an Ef of 25% in FC-I with a diastolic filling pattern (prolonged relaxation) and a hypertensive patient with concentric hypertrophy, an Ef of 60% in FC-III and IV with restrictive or pseudonormal pattern is expectable. As I mentioned in the first part, patients with HF and preserved or diminished Ef represent two different phenotypes as regards the response of the renin-angiotensin system and ventricular geometrical patterns.

Besides, with an appropriate treatment, patients with a diminished Ef may present inverse remodeling and those with preserved Ef do not, that is why there are doubts: if "linearity" between a parameter of systolic function and the FC would be useful in the clinical practice, beyond the logical interest of deepening into the knowledge of cardiac mechanics.

A point to emphasize is that most of the aforementioned works, in which new technologies are applied, have a reference to Ef in the title: HF with preserved Ef, low-flow aortic stenosis and preserved Ef, indication of cardiac defibrillator in patients with Ef < 35% which points out the validity of Ef and the need of incorporating it in order to define groups of patients with different presentation or clinical evolution. Some works point out early alterations in the strain as regards Ef. In some of these works, the strain was inversely related to the end-systolic stress (Kosmala) and with systolic pressure (Dokainish) which emphasizes the afterload dependency that any index has to assess fiber shortening.

Therefore, such finding does not necessarily indicate diminished contractility. Diminished "muscle function" does not necessarily presage diminished contractility.

A significant contribution from new indexes is the early detection of systolic dysfunction in the treatment with chemotherapy and in mitral regurgitation, since it would have therapeutic implications independently of the Ef value.

As a conclusion, I wish to express that Ef still has validity to assess the ventricular function and in a near future deformation indexes, which add prognostic value, will be put together in clinical scenes.

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ANTAGONIST'S REPLY

The assessment of ejection fraction (Ef) presents undeniable merits, with easy availability and a huge diagnostic and prognostic value.

Its determination is held to various mistakes. Some of them are technical and they have a difficulty in the inappropriate alignment of echocardiographic views which, on the other hand, are not orthogonal and they assume geometrical models that are sometimes inappropriate.

Part of these limitations may be overcome using 3D echo-planar or 3D full volume views, with excellent correlation with volumes and Ef obtained with magnetic resonance, without the underestimation suffered by the 2D Echo.

The subjective assessment is not acceptable and Ef should always be quantified using available measurement protocols in all the equipments.

Beyond technical aspects, Ef presents limitations in the interpretation of the function, since, as Dr. Migliore states, its dependency from the endocardial movement explains the obtaining of normal values with diminished contractility in patients with ventricular hypertrophy, volume overload and other pathologies.

We coincide in load influences in deformation parameters and in Ef, but we insist that the advance with high assistential value that these new technologies provide is mainly the incorporation of the concept of deformation that facilitates a deeper interpretation of ventricular mechanics and allows us to carry out global, regional, objective and reproducible quantifications.

Ef has an undeniable clinical value; probably we may not replace it. However, we should know its various limitations and reinterpret the myocardial function considering, in such cases, new deformation parameters.

The implication of the longitudinal strain is early in many usual pathological conditions and it precedes the Ef alteration. If our thinking mechanism is limited to the Ef, we may lose the option of an early diagnosis. New parameters facilitate a more comprehensive understanding of the physiopathology that will allow us a more efficient therapeutics. They help us to see in a better way where we look.

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