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REVIEW ARTICLE

Myocardial inotropic reserve: An old twist that constitutes a reliable index in the modern era of heart failure

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Abstract Current national and international guidelines, including those of the European Society of Cardiology, recognize that the assessment of prognosis should be a part of the standard management for patients with chronic heart failure (CHF). However, these same guidelines recognize the inherent difficulty of this process. A variety of factors contribute to this difficulty, including the varying etiology, frequent co-morbidity and, perhaps most importantly, huge inter-individual variability in the disease progression and outcome. Although CHF is chronic, it is also a condition in which significant proportions of patients experience apparently 'sudden' death, which almost certainly contributes to our difficulty in assessing individual patient prognosis. A useful tool for the risk stratification of heart failure patients is dobutamine stress echocardiography (DSE), which determines the myocardial viability in ischemic cardiomyopathy and myocardial contractile reserve in idiopathic cardiomyopathy.
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1. Introduction

In developed countries, the prevalence of heart failure (HF) approaches 1%–2% of the adult population and increases incrementally to ≥10% among people who are 70 years of age. The use of modern therapy has managed to reduce hospitalizations by 30%–50% and augmented the survival rates of heart failure patients.[1] Nevertheless, the

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assessment of the prognosis of these patients remains controversial; this is mainly due to the course of the disease, which may be rather benign or disrupted by sudden cardiac death.

Echocardiography is a widely used technique and, due to its accessibility, reliability, and low price, it has been extensively used to evaluate HF patients. Ventricular function parameters, asynchrony assessment, and mitral valve insufficiency indexes have been extensively used in the risk stratification of these patients.[2]

However, dobutamine stress echocardiography provides significant additive information for evaluating the prognosis of HF patients. Several studies have shown that the study of the contractile reserve, which is defined as the difference between the peak stress and baseline values of an index of contractile workload, may improve the assessment of the prognosis.[3]

The EF is commonly used to evaluate the left ventricular function. However, this index is influenced by the loading conditions of the left ventricle, and the assessment of the contractility may not be accurate.[2] Other factors, such as mitral valve regurgitation, activation of neuroendocrine adaptation mechanisms and the preload of the left ventricle further attenuate the role of the EF.

During stress echocardiography, an increase in the EF $\geq$5% or change from the baseline EF by $\geq$20% is considered to be a hallmark of the presence of inotropic reserve, which identifies patients with a better prognosis.[3] In dilated cardiomyopathy, another index, the wall motion score, was used to evaluate the myocardial viability. During DSE, a change in the wall motion score index of $\geq$ 0.44 coincided with better the follow up results.[2–5]

2. Implication of inotropic reserve in heart failure

Inotropic reserve is not an innovation. Dobutamine will improve the systolic function of the failing ventricle, revealing the presence of contractile reserve. This characteristic is highly dependent on the integrity of myocardial fibers as well as the density of adrenergic receptors. In heart failure, the catecholamine sensitivity is reduced by abnormalities detected in the β-adrenergic receptor signaling pathway and mainly due to downregulation of β1 adrenergic receptor, which impairs contractility.[4] Alterations in the beta adrenergic receptor/G Protein /adenylyl cyclase pathways are implicated in contractile dysfunction, and their study in humans may be quite complex.[4–5]

Patients with an attenuated response to dobutamine had more irregularities in their sympathetic activity (increased levels of plasma norepinephrine or decreased catecholminergic myocardial tissue) for similar ejection fractions. Apart from the increased levels of plasma norepinephrine, previous studies reported decreased beta-adrenergic receptors as well as altered sarcoplasmic reticulum Ca2-adenosine triphosphatase 2a (SERCA2a) and phospholamban in HF.[5–6] These patients also had reduced levels of molecular markers of contractility, which was indirectly evaluated by measuring the messenger ribonucleic acid obtained by biopsies of the LV.[6] Noninvasive techniques could be used to categorize the intracellular irregularities that influence cardiac contractile dysfunction in the future. These changes, at the molecular level, occur early in the course of HF and could thus be somewhat responsible for left ventricular dysfunction.[6–7]

It is necessary to emphasize the clinical implication of inotropic reserve in the era of systolic heart failure. Skalidis & Parthenakis et al. demonstrated that the presence of regional contractile reserve during low dose DSE is correlated with the regional coronary flow reserve (CFR) in DCM patients.[8] In these patients, changes in the regional coronary flow, as well attenuated coronary flow reserve, are demonstrated. Additionally, these two phenomena are attributed to microvascular dysfunction and coronary structural and functional alterations.

Furthermore, DCM is associated with areas of interstitial and perivascular fibrosis, which contributes in the alterations observed in microcirculation and could explain the paradox of normal coronary flow at baseline and reduced coronary flow at maximal hyperemia, as well as associated with the reduced CFR.[8]

The presence of inotropic reserve in HF patients and systolic dysfunction determines both therapy responders as well as plays a key role in the prognosis patients with a stunned myocardium after an acute infarction and DCM patients.[2] The contractile reserve could recognize patients who respond well to therapy. Ischemic cardiomyopathy could designate the patients who benefit the most from revascularization. In HF with LV dyssynchrony (left bundle branch block and QRS $>$ 120 ms), it could predict a good response to resynchronization therapy using biventricular pacing. Additionally, in HF, it could discriminate the patients who will respond to optimal medical therapy.[9–10]

Furthermore, both the NYHA functional class and exercise tolerance of patients are correlated with the inotropic reserve. Individuals with impaired inotropic reserve have reduced exercise capacity, abnormal systolic and diastolic function and higher BNP levels. Parthenakis et al. manage to demonstrate that alterations in the NT-pro BNP that occur in response to dobutamine administration are correlated to improvement in the contractile function of the left ventricle and may be considered an independent factor for predicting the contractile reserve in DCM patients.[11] During DSE, the mean septal and lateral systolic velocities of the mitral annulus were determined at rest as well as at peak exercise. Patients who had reduced global longitudinal systolic function during DSE (lower peak systolic velocity of the mitral annulus change) had diastolic dysfunction that was manifested by a higher rate of restrictive transmitral flow pattern and higher filling pressures evaluated by E/e'. These patients also had a reduced exercise tolerance.[12]

3. Left ventricular viability

In ischemic patients with LV dysfunction and a viable myocardium, the presence of inotropic reserve during DSE discriminates reversible defects from irreversible damage. Reversibility predicts recovery of function, prevention of remodeling and reduced symptoms and mortality in chronic HF patients.[13–14]

As a result, low dose dobutamine echocardiography is a noninvasive method that can be used for detecting viable

myocardium with a sensitivity of 84% and specificity of 81 %.[15] Amelioration of wall motion and thickening are compatible with a viable, but jeopardized, myocardium. If ≥4 viable segments are detected, this could predict reversible myocardial damage and revascularization would alter the contractility.[13–15]

Nevertheless, the presence of viable myocardium is not always followed by LVEF improvement after revascularization. This phenomenon can be explained by LV remodeling and dilation.[13–15] Patients with an ESV > 140 ml do not show improvement of the contractile state after revascularization. Schinkel et al showed that patients with higher end systolic volumes responded the least to revascularization and their systolic function was not improved. Left ventricular enlargement, remodeling and fibrosis impede functional recovery. However, in the presence of a viable myocardium, tissue perfusion restoration will improve the prognosis.[13–15]

The role of low-dose dobutamine MRI (Dob-MRI) in assessing the inotropic reserve has been extensively reviewed. An end diastolic wall thickness of ≥5.5 mm and demonstration of dobutamine provoked systolic wall thickening of >1 mm are the definitions of myocardial viability. The sensitivity of Dob-MRI reaches 88% and its specificity is 87%, allowing for a better endocardial study and reducing the chance of poor quality images.[16]

4. Inotropic reserve as a predictor in cardiac resynchronization therapy

Patients in the advanced stage of HF, apart from optimal medical therapy, seem to respond well to resynchronization therapy (CRT). The presence of wide QRS complex will identify the candidates for CRT therapy as well as, more recently, the presence of LV mechanical dyssynchrony, which is evaluated by the novel modalities of strain imaging and tissue Doppler. Several studies have stated that LV dyssynchrony could predict more accurately CRT responders than the QRS duration.[17]

At rest, LV dyssynchrony seems to be an insufficient predictive factor. Controversy arises from the incidence of individual differences between LV synchronicity at rest and exercise without provoked ischemia. Patients who demonstrated LV dyssynchrony during exercise showed poor exercise tolerance that was mainly due to a reduced LV stroke volume and increased mitral regurgitation. These patients are likely to be CRT therapy responders. On the other hand, CRT may not be beneficial in patients who do not show dyssynchronization during exercise.[18]

Low dose dobutamine stress echocardiography has recently been used to evaluate CRT therapy. The presence of inotropic reserve correlates with both global and regional contractile function refinement in ischemic and non-ischemic cardiomyopathy. A recent study showed that inotropic reserve was present in 78% of CRT responders, whereas LV dyssynchrony did not show any difference between responders and non-responders.[18–20]

The presence of contractile reserve plays an important role in the prognosis of patients with HF. More specifically, detection of the global and LV lead target site inotropic reserve may help identify patients with a higher augmentation of forward stroke volume. An amelioration of the EF by ≥ 6.7% and of local strain by ≥ 2% could predict CRT responders. However, in the advanced stages, the extent of fibrosis and ventricular remodeling may modify conduction and contraction in such way that constitutes an obstacle for biventricular pacing.[18–20]

5. Implication of inotropic reserve in HF with a preserved ejection fraction

The pathophysiology of heart failure with preserved EF (HFpEF) is not well known and patients are characterized by a poor exercise capacity. During low-dose DSE, the EF in these patients does not increase and, therefore, the inotropic reserve, which depends on the EF change, decreases.[21] Possible causes of this phenomenon are abnormalities of the β-adrenergic receptor the density or of the signaling pathway, failure to increase cardiomyocyte calcium cycling, and a defective response of myofilaments to increased calcium cycling. During stress, the end systolic volume fails to decrease, demonstrating that there is a systolic element in this diastolic disorder.[21]

Furthermore, DSE revealed a reduced diastolic reserve and augmentation of the LV end diastolic pressure that was provoked by stress, leading to reduced exercise tolerance. There is an inverse correlation of the 6-minute distance walk and parameters of diastolic function at rest and exercise.[21] In HFpEF patients during stress, the E/e' ratio and LV end diastolic pressure were increased as a result of impaired LV relaxation. Controls did not have the same response. The distance walked and E/e' ratio showed a negative correlation at rest and with stress in HFpEF patients.[22] Therefore, patients with preserved heart failure present with a lack of diastolic reserve that is crucial for maintaining exercise tolerance.[22]

Finally, a recent study showed that the inotropic reserve of the right ventricle can be accepted as an increase in the systolic pulmonary pressure > 30 mmHg with dobutamine stress echocardiography and color tissue Doppler imaging, which is of high clinical and prognostic relevance in pulmonary hypertension patients.[23]

6. Conclusions

A useful tool for the risk stratification of heart failure patients is dobutamine stress echocardiography (DSE), which can be used for assessing the myocardial viability in ischemic myocardiopathy and the inotropic reserve in dilated cardiomyopathy. The contractile reserve contributes to the identification of CRT responders and is implicated in the HFpEF study. This reserve is a parameter that plays a central role in the modern era of heart failure.

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