Assessment of Systolic and Diastolic Cardiac Function beyond Traditional Markers in Hypertensive Patients. Role of Cardiac Reserve

Natalia PATRASCU
“Carol Davila” University of Medicine and Pharmacy, Cardiology Department, University Emergency Hospital, Bucharest, Romania

ABSTRACT
Background: the mechanical performance of the cardiac pump should be evaluated not only at rest but also in relation to its response to peak stimulation, since the earliest consequence of the cardiac pump capacity in the evolution of heart failure is the decrease of the maximal performance. This can be assessed by measuring the cardiac functional reserve, usually by a physical or a pharmacological stress test combined with echocardiography imaging.

Content and comments: in symptomatic heart failure, the main purpose is to objectively identify the point to which the impairment of the pump function is irreversible. Moreover, there is growing evidence that the functional systolic and diastolic reserve is decreased even in the early, subclinical stages of cardiac dysfunction that exists for example in hypertensive disease and that the decrease seems to be related to the number of the associated cardiovascular risk factors.

Conclusion: thus, better preventive and therapeutic strategies could be established by detecting a reduced functional reserve in this category of patients at high risk of heart failure development, with important public-health implications.

Keywords: functional reserve, stress test with dobutamine, subclinical heart failure, beta-blockers, tissue Doppler imaging, speckle tracking

BACKGROUND
Similarly to other engines, the mechanical cardiac pump performance varies between zero and an intrinsic maximal point, so that it should be evaluated not only at rest but also in relation to its response to peak stimulation. In heart failure there is an impairment of the pump mechanism, the earliest consequence being the decrease of the peak performance. In more advanced stages, the heart becomes incapable of maintaining a normal level of its function even at rest (1).

The remarkable ability of the healthy heart to increase its performance at exercise was at-
ascribed mainly to a direct effect of the beta-adrenergic stimulation for a better contractility. Also, at prolonged exercise, the left ventricle (LV) relaxes faster, with an increase of the stroke volume and a lower end-systolic volume and, as a result, the diastolic filling is markedly increased at exercise, even if the filling time shortens with >60%. The transmirtal gradient at early diastole increases, preventing a raise in left atrial mean pressure during the effort. Thus, both systolic and diastolic LV functions are influenced at normal physical exercise or during the administration of beta-agonist drugs at rest.

In heart failure, there are several abnormal stages in the adrenergic stimulation pathway, including the reduced number of beta-adrenergic receptors and deficiencies of G protein that could be the substrate of the impaired beta-adrenergic amplification of the force-frequency effect observed in this pathology (2).

**Content and comments**

Various techniques have been used to study the LV performance in overt heart failure and/or in the asymptomatic subclinical systolic dysfunction, including the non-invasively dobutamine stress test echocardiography (DSE) which evaluates the contractile reserve, meaning the improvement of the contractile function during the inotropic stimulation (3) or, in other terms, the extent of increase or change in ventricular function that occurs during exercise or pharmacological stress (typically with dobutamine) (4) and defined as the difference between the peak cardiac performance after dobutamine and the baseline resting value (5). The purpose of this test is to identify objectively the point to which the impairment of the pump function is irreversible; thus, the long term outcome of a patient can be assessed.

Traditionally, cardiac systolic performance can be assessed by measuring a conventional echo parameter such as the ejection fraction (EF) (defined as the ratio between stroke volume and end-diastolic volume). However, the detection of early, subclinical myocardial disease is difficult when using the echocardiographic techniques that can evaluate only the global systolic or diastolic function. By comparison to standard echocardiography, with tissue Doppler imaging (TDI) or speckle tracking methods, some more specific parameters can be obtained—such as longitudinal and radial myocardial velocities, strain and strain rate and if these investigations are used in combination with a DSE, myocardial abnormalities, as a response to the stress, can be identified with a higher degree of accuracy (6).

**The principles of pharmacological stress test with dobutamine**

Stress echocardiography is based upon the fundamental causal relationship between the induced myocardial ischemia and the regional wall motion disturbances of the LV. In the presence of a significant, flow-limiting coronary stenosis, the physiological stress increases cardiac rate and contractility that can be maintained by myocardial flow increase. Systolic wall thickening, endocardial excursion and global contractility determine an end-systolic volume decrease (thus, an ejection fraction increase) in comparison to the resting values and the absence of this pattern at stress should be considered an abnormal response.

Stress echocardiography may use as stress factors the exercise (with a treadmill or a bicycle) or pharmacological agents (dobutamine, adenosine, dipiridamol or pacing). Dobutamine is a synthetic catecholamine with positive inotropic and chronotropic effects due to the affinity for beta 1, beta 2 and alpha adrenergic receptors from myocardium and vessels. Because of the various affinities, the cardiovascular effects of dobutamine are dose-dependent, with an increase of contractility from small doses, followed by a progressive tachycardia at larger doses. The final result of these interactions is a combination of an increased contractility and heart rate with an associated myocardial oxygen request and if the coronary reserve is limited, the oxygen request will overcome the offer and ischemia will be induced. By all these mechanisms, a stress test becomes a very useful tool for risk stratification in patients with known or suspected coronary artery disease, previous revascularization or infarction and, importantly, in asymptomatic patients with cardiovascular risk factors (7). In hypertensive disease, for instance, either significant atherosclerotic coronary stenosis or microvascular ischemia can induce such an abnormal response at stress testing.

DSE standard protocol involves the administration of the drug in perfusion, starting with a low dose of 5 mcg/kg/min, with an increment...
after 3 minutes steps to 10, 20, 30 and 40 mcg/kg/min. The use of low doses allows a better assessment of viability and ischemia of segments with resting abnormal wall motion. The end points are the achievement of target heart rate (defined as 85% of the age-predicted maximum heart rate), new or worsening wall-motion abnormalities of moderate degree, significant arrhythmias, hypotension, severe hypertension, and intolerable symptoms (7). Atropine can be used as needed, to obtain the target heart rate for increasing the sensitivity.

Image interpretation by conventional visual assessment analyses the endocardial excursion and wall thickening of the LV segments and also the wall motion timing. Abnormal results are fixed motion impairment, new or worsening motion abnormalities or delayed contraction and/or relaxation, all indicating the presence of ischemia. The visual assessment has, however, an important inter- and intra-observer variability so that new quantitative methods have been developed. TDI provides the measurement of tissue velocities in radial axis for the LV posterior wall and in long axis for the other myocardial regions; displacement, strain and strain rate can be derived consequently. The tissue velocity imaging used for DSE showed accuracy comparable with wall motion assessment in multiple unicentric or multicentric studies (7). For assessing the systolic function, peak systolic myocardial velocities (S) are measured; the functional systolic reserve is calculated as the absolute or percentage increase of the velocities' values from baseline (resting) to peak stress. Similarly, for diastolic function peak early diastolic myocardial velocities are measured (e') and the diastolic functional reserve is calculated as the absolute or percentage increase of the velocities from baseline to peak stress. In the absence of cardiac disease, e' increases to a similar extent to the increase in transmural E flow velocity so that, normally, the E/e' ratio (known as a good marker for estimating the LV filling pressures) remains unchanged at stress test. On the other hand, when diastolic dysfunction exists, the increased left atrial pressure determines an increase in mitral E flow velocity, while myocardial e' remains reduced, given the limited preload effect on it, and the E/e' ratio increases (8).

Strain (measuring myocardial shortening or lengthening) and strain rate (measuring its rate) provide better assessment of myocardial contraction and relaxation than displacement or tissue velocities. However, like all Doppler derived parameters, tissue velocities, strain, and strain rate are influenced by the angle of interrogation so that off-axis apical images may result in calculation errors. Recently introduced 2D echocardiographic methods for assessment of strain and strain rate (speckle tracking echocardiography, STE) eliminate the angle dependency of these Doppler-based techniques (7). In a study published in 2010 by Bansal et al, comparing TDI and STE for prediction of viability at DSE showed that the combination of these two methods with DSE can predict viability, being the most accurate at lower doses stages (9).

The use of STE for stress tests intends to objectify regional myocardial function in an angle independent and site specific manner and allows quantitative assessment of longitudinal, transversal, radial and circumferential strain, which cannot be completely appreciated visually. The combination of circumferential and longitudinal strains with visual wall motion score index (WMSI) results in very high rates of sensitivity. Given this, STE can be particularly useful in asymptomatic patients or patients found to have normal conventional echocardiographic studies. Ng et al used STE to describe myocardial dysfunction in asymptomatic diabetic patients and demonstrated impaired longitudinal systolic and diastolic function. Also, in asymptomatic patients with degenerative mitral regurgitation, Lancelotti et al showed there is a limited contractile reserve as assessed by global longitudinal strain, which predicts postoperative LV dysfunction (10). It is also a technique for quantification of a new parameter, left ventricular torsion (11).

Finally, digital data acquisition and the possibilities of off-line analysis, reviewing multiple cardiac frames at rest and at different stages of stress simplified the method, increased its accuracy and decreased the inter-observer variability.

The impaired functional reserve in hypertensive patients and interactions with other risk factors

LV subendocardial function is governed by the longitudinal myocardial fibers, whereas the radial function is mainly due to the mid-wall circumferential fibers (12). In hypertensive patients, the microvascular ischemia and fibrosis
lead first to subendocardial dysfunction. When LV hypertrophy (LVH) is already present, the impairment of both systolic and diastolic function is even more pronounced, since LVH is associated with a reduction of the coronary flow reserve, by endothelial dysfunction, the narrowing of the small arteries, rarefaction of microcirculation especially on the subendocardial level and the perivascular fibrosis. This subendocardial dysfunction is also related to an increase in conduit arterial stiffness that can contribute to myocardial ischemia by an impaired ventricular-arterial coupling (13).

Evidence about the impaired LV functional reserve in hypertensive patients with LVH come even from 1989 when Tubau et al measured the increase of EF and of the systolic blood pressure/end-systolic volume index ratio and found that both parameter’s variations were reduced (P<0.05) after exercise, meaning the presence of an abnormal ventricular function response to exercise in those patients (14).

Henein et al. showed that in patients with heart failure with preserved ejection fraction (HF-PEF) due to hypertension, even if resting EF is normal, there are reduced systolic function reserves that limit their exercise capacity. Patients were tested by resting and peak exercise echocardiography (conventional, with TDI and speckle tracking techniques). It was found that, in comparison to normal subjects, at peak stress, EF and global longitudinal strain rate failed to increase (15).

The assessment of the subendocardial function by measuring the longitudinal shortening is a sensitive marker of an early, subclinical left ventricle dysfunction determined by arterial hypertension and the accuracy of the method can be increased by measuring the systolic functional reserve during a DSE (16). It was showed that beta-adrenergic stimulation by dobutamine unmasks subtle impairment of myocardial functional reserve in hypertensive subjects with normal parameters at rest which is related mainly to increase in LV relative wall thickness (17). In a study that assessed the LV function (by standard echocardiography and DSE with TDI imaging) in 35 asymptomatic hypertensive patients with LVH compared with a similar age-matched number of normal subjects, we showed that both at rest and at peak stress longitudinal velocities, as well as systolic functional reserve were lower in the hypertensive group (p <0.001 and p <0.01 respectively); the radial systolic functional reserve increased compensatory but without statistical significance (18).

The implications of performing a stress test in hypertensive subjects with LVH and no symptoms at rest are to identify patients at higher risk to develop heart failure. Moreover, a stress test can make a differential diagnosis between detection of coronary heart disease as a cause of ischemic reduction of contractile reserve opposed to its reduction related to hypertrophy and fibrosis in hypertensive patients. In case of diagnosing ischemia, the assessment of wall motion abnormalities, both visual or by measuring myocardial velocities on TDI, is often completed by symptoms and/or ECG signs registered during the test or the recovery time. It has to be mentioned that detection of ischemia by standard visual interpretation is rather difficult in patients with concentric remodeling and global hyperkinesia, making segmental abnormal wall motion more difficult to assess (7). However, the method is a useful tool for differentiation between these two conditions for a better selection of patients suitable to be explored and/or treated more invasively by coronary angiography and revascularization.

Apart from hypertension, other cardiovascular risk factors that contribute to atherosclerosis also predict clinical heart failure and there are some evidences about the way they affect myocardial function and, moreover, that the cardiac function impairment can be related to the number of risk factors existing for each patient. Vinereanu et al studied the regional ventricular function at rest and during DSE in asymptomatic type 2 diabetic patients with no evidence of coronary heart disease and showed that they had a lower longitudinal systolic functional reserve. The radial systolic velocities were higher, which explained the preservation of the ejection fraction (EF) (16). Also, there are many data showing that obesity, smoking or dyslipidemia, as major cardiovascular risk factors for atherosclerosis and coronary events, are related by different mechanism to an impairment of systolic and/or diastolic function but specific studies concerning the cardiac reserve status are insufficient (19-21).

In an attempt to test the hypothesis that subclinical myocardial dysfunction in asymptomatic subjects is associated to the number of major cardiovascular risk factors, Vinereanu et al. measured regional LV function at rest and
during DSE in 246 subjects, analyzed in five groups according to the presence of six important risk factors. It was found that longitudinal systolic functional reserve decreased proportionally with the number of risk factors while the radial functional reserve was increased in the group having >3 risk factors. These changes provide new targets for preclinical diagnosis and for monitoring responses to preventive strategies (22,23).

The hypothesis of the reversal of functional reserve impairment under treatment with new generation beta-blockers

Although many drugs are highly effective in lowering blood pressure, the optimal treatment for preventing progression to heart failure in arterial hypertension is still uncertain. Beta-blockers, a class of drugs with well-established indications and benefits for both hypertension and heart failure seem to show different in-class pharmacological properties with different consequences on the cardiovascular hemodynamics.

Beta-blockers have, at first appearance, two opposite effects: firstly, on a short term, a tendency of decreasing the EF by pharmacological withdrawal of the adrenergic support; secondly, on long term, by biologically improving the myocyte and the chamber function, a tendency of increasing the EF. If the contractile reserve is reduced, the inotropic negative effects of adrenergic pharmacological withdrawal prevail and EF can fall. Conversely, at patients with a preserved contractile reserve, the biological improvement of function overcomes the negative inotropic effect. A sub-study of the BEST trial (the Beta-Blocker Evaluation of Survival Trial) proposed to assess the myocardial contractile reserve by DSE as a possible predictor of improvement of the EF with beta-blockade in patients with heart failure. 79 patients with advanced (NYHA III/IV class) were examined by stress test before the initiation of treatment with bucindolol with the measurement of contractile reserve by WMSI and, after 3 months of treatment, the EF was assessed by gated radionuclide scan. It was found a direct relationship between the contractile reserve and improvement of EF with bucindolol therapy ($r=-0.72$, $P<0.0001$) and WMSI was the most significant multivariate predictor of change in LVEF ($p<0.0002$). These results suggest that the absence of contractile reserve, when the contractile units have been replaced by interstitial fibrous tissue predicts a lack of improvement of the ventricular function. The distinction between responders and non-responders is important, since the decrease of the EF by the adrenergic withdrawal, if not counterbalanced by the biological improvement of the contractile function, can lead to a net decrease of the EF, thereby a worse long-term outcome and even a raise in mortality with beta-blockers therapy (as it happened in this trial with bucindolol). On the other hand, in patients with contractile reserve the benefit of early using beta-blockers on the hemodynamic response is, however, warranted (24) so that measuring this parameter before initiating beta-blocker therapy seems to be important.

Vinereanu et al. studied the effects of 6 months beta-blocker therapy on the cardiac function, including the contractile reserve, in much earlier stages of subclinical systolic and diastolic longitudinal dysfunction in hypertensive patients with LVH and without coronary heart disease, comparing metoprolol were compared with a newer generation beta-blocker with additional vasodilation properties - nebivolol. After the treatment period, neither EF nor the contractile longitudinal reserve changed significantly, although the ejection time, the displacement, the flow propagation velocity and the early diastolic longitudinal velocities increased, all significantly only for nebivolol (25). The results could be explained by the short following period or by the cumulative impact of many other cardiovascular risk factors associated in this group. However, the results highlight the importance of detecting the decrease of the functional reserve in hypertensive patients (nowadays more than 1 billion worldwide - thus, a major public-health issue) and, also, the value of beta-blockade therapy for progression to overt heart failure.

CONCLUSION

The newest generation of drugs, which have additional vasodilation properties, may play a beneficial role, especially for the early stages of HF-PEF and the study of functional reserve is a valuable instrument for the judgment of the potential reversibility of cardiac dysfunction and, by that, for choosing and monitoring the optimal therapy.
REFERENCES

3. Lee HH, Dávila-Román VG, Ludbrook et al. – The concept of ventricular reserve in heart failure and pulmonary hypertension: an old metric that brings us one step closer in our quest for prediction. Curr Opin Cardiol 2011; 26:123-131
5. Haddad F, Vrtovec B, Ashley EA, et al. – Cardiac Pumping Capability
7. Lee HH, Dávila-Román VG, Ludbrook et al. – The concept of ventricular reserve in heart failure and pulmonary hypertension: an old metric that brings us one step closer in our quest for prediction. Curr Opin Cardiol 2011; 26:123-131
8. Francis GS, Desai MYJ – Contractile Reserve: Are We Beginning to Understand It? Am Coll Cardiol Img 2008; 1:727-728
11. Haddad F, Vrtovec B, Ashley EA, et al. – Cardiac Pumping Capability