INVITED EDITORIAL

Heart Vessels Transplant 2024; 8: 327-31
DOI: 10.24969/hvt.2024.500

Stress echocardiography in daily clinical practice: an update from the European Association of Cardiovascular Imaging

Francesco Loria, Giuseppe Iuliano

Cardio-Thoracic-Vascular Department, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Largo Città d'Ippocrate, 84131 Salerno, Italy

Introduction

Since its introduction in the late '70s (1), stress echocardiography (SE) has become one of the most accurate functional imaging tests for inducible myocardial ischemia (2). Over the years, indications to SE have gone beyond coronary artery disease (CAD) and have included other conditions such as valvular heart diseases, heart failure (HF), and hypertrophic cardiomyopathy (HCM). These changes led to a new consensus statement from the European Association of Cardiovascular Imaging (EACVI)(3) which updates the 2009 SE expert consensus of the European Association of Echocardiography (EAE) (4) and the latest 2016 advice of the American Society of Echocardiography (ASE) in collaboration with the European Association of Cardiovascular Imaging (EACVI) (5). This consensus exposes the need for a paradigm shift in SE to take a step forward from the simple qualitative/visual assessment of regional and global heart function at rest and during stress. There are three main reasons for this shift: declining positivity rate (from >60% in the eighties to the current <10%), inability to capture the multiple sources of ischemic patient vulnerability and easy applicability of the new parameters. Moreover, there are also non-clinical factors that help to reinforce the usability of SE in daily clinical practice: low cost, no radiologic exposure and trivial CO2 emissions (6-8).

Methodology

The general SE protocol includes assessment of symptoms, 12-lead electrocardiographic continuous recording, periodic evaluation of blood pressure and imaging monitoring. Imaging always starts with a resting transthoracic echocardiogram (TTE) study to assess the acoustic quality of the exam, to exclude other reasons that could explain the patient's symptoms (e.g. pericardial effusion in chest pain) and to rule out contraindications to stress testing such as acute myocardial ischemia, aortic dissection, or pulmonary embolism. Each exam should include three components: 2D for regional wall motion (RWM) and left ventricle (LV) volumes, lung ultrasound (LUS) for B-lines, and Doppler for coronary flow velocity reserve (CFVR).

2D: regional wall motion and volumetric analysis

The first step is LV RWM assessment. It is visually evaluated from apical four-, two-, and three-chamber views, and parasternal long- and short axis views. The standard 16- or 17-segment model is recommended with a segmental scoring system ranging from 1 (normal/hyperkinesia) to 4 (dyskinesia, stretching with paradoxical thinning and/or outward motion during systole). The wall motion score index (WMSI) is calculated as the sum of the individual segments' score divided by the number of visualized segments and is 1.0 in normal conditions. A positive score variation (peak WMSI > rest) indicates ischemia; a negative score (peak WMSI < rest) indicates viability or just contractile reserve; an abnormal score (WMSI > 1.0) at rest unchanged at peak stress indicates a fixed or scar response. The biphasic response corresponds to a viable response at a low dose (akinesia or severe hypokinesia becoming normal), followed by an ischemic response at a high dose (normal wall motion becoming hypo-, a-, or dyskinesia).

Measurement of LV volumes during SE is not routinely used in many labs because of the frequent degradation of imaging during stress and time consumption. However, LV volumes provide important prognostic information.

Address for Correspondence: Giuseppe Iuliano, Cardio-Thoracic-Vascular Department, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Heart Tower – Room 807, Largo Città d'Ippocrate, 84131 Salerno, Italy.
E-mail: gi.iuliano93@gmail.com **Phone:** +39 3465335232
Citation: Loria F, Iuliano F. Stress echocardiography in daily clinical practice: an update from the European Association of Cardiovascular Imaging. Heart Vessels Transplant 2024; 8: 327-31. doi: 10.24969/hvt.2024.500
Received: 03.07.2024 **Accepted:** 04.07.2024

The normal response at peak stress is an increase of end-diastolic volume (EDV) (preload reserve) and a reduction of end systolic volume (ESV) (contractile reserve). An increase in LV ESV ≥ 10% from baseline during stress is considered abnormal (4, 9).

Even in the absence of inducible RWM abnormalities (RWMA), LV dilation can be a sign of CAD and is associated with unfavorable prognosis (10). Given their important diagnostic and prognostic role, LV volumes and at least one of the derived indices of force should be reported. The most important indices of force are contractile reserve [systolic blood pressure (SBP)/ESV peak to rest ratio], cardiac output [stroke volume×heart rate (HR)], cardiac reserve, cardiac power output (mean arterial pressure×cardiac output/451) and power mass (0.222×cardiac output×mean blood pressure/LV mass). The abnormal values of prognostic significance are an increase of force (or power mass) < 70% with exercise or dobutamine and < 10% for vasodilators (11, 12).

Lung ultrasound (LUS)

LUS at rest and during stress is focused to assess pulmonary congestion mirrored by the presence and number of B-lines, which are hyperechogenic lines that arise from the pleural line, extend towards the edge of the screen and move synchronously with respiration. A four-site scan can be used, including the third intercostal space, symmetrically in the right and left hemithorax, one site from the mid-axillary to the anterior axillary line and another site from the anterior axillary to the midclavicular line. For each site it is assigned a score ranging from 0 (black lung) to 10 (white lung), with a total possible score from 0 (all four sites with 0 individual site scores) to 40 (all four sites with individual site scores of 10).

CFVR imaging: colour-Doppler and pulsed-wave Doppler

CFVR is expressed as the ratio of peak hyperemic to rest maximal diastolic flow velocity; values > 2 are considered normal. The coronary flow velocity (CFV) is measured with pulsed-wave Doppler at the level of the mid-distal portion of the left anterior descending (LAD) artery, visible in the low parasternal long-axis view and/or modified three-chamber view under the guidance of color-Doppler flow mapping and with vendor-specific settings (13). In normal conditions, CFV is biphasic, with a lower peak during systole and a higher peak during diastole, when myocardial extravascular resistance is lower. The typical use of CFVR is during vasodilator stress tests with adenosine or dipyridamole, when the color-Doppler flow signal becomes brighter and larger, so it is easier to assess (success rate >95%). CFVR can be also evaluated with pacing, dobutamine, and semi-supine exercise, but with increasing difficulty and decreasing success rate. A reduced CFVR is a strong predictor of all-cause mortality in chronic coronary syndrome, independent and incremental over resting global longitudinal strain (GLS) (14) and RWMA (15). CFVR has a prognostic value in non-ischemic conditions such as HCM (16), non-ischemic-dilated cardiomyopathy (17) and heart transplant recipients (18).

Stressors

Potential stressors to be used are exercise, dobutamine, a vasodilator (dipyridamole or adenosine), and external pacing in patients with permanent pacemakers. Exercise, with semi-supine exercise as preferred method, is the first line stressor in most cases because it reproduces a physiological stress and is safer. Dobutamine is an adrenergic agonist, which increases myocardial oxygen demand as it happens during exercise; it is used in patients with inability to exercise, to detect myocardial viability and in the evaluation of low flow-low gradient aortic stenosis. Dobutamine is administered in increasing doses up to 40 μg/kg/min in 3-minute steps; atropine with a maximum dose of 1 mg can be used to reach the target HR. Contraindications to dobutamine are resting SBP > 180 mmHg, left ventricular outflow tract gradient > 30 mmHg and serious, recent arrhythmias. Dipyridamole is a vasodilator agent, which reduces myocardial oxygen supply trough vertical and horizontal steal. It is administered with a syringe by hand-protocol in dose of 0.84 mg/kg over 6 minutes, with no need for atropine co-administration or infusion pump. The peak hyperemic and ischemic effect occurs between 1-6 min after the end of the infusion and it lasts several minutes, so its effect is antagonized by the antidote aminophylline, avoiding fast injections since the drug is potentially arrhythmogenic. Adenosine is rarely used since its half-life is only a few seconds. Regadenoson is a relatively new vasodilator agent with a selective agonist action on α2 receptors. It is easily administered as a bolus of 0.4 mg in a 5 mL solution, it has not the undesirable effects of α1, α2B, and α3-receptors stimulation (such as dyspnea, bronchospasm, headache, and flushing), but it is significantly more expensive than dipyridamole and adenosine.

Contraindications to vasodilator agents are asthma or phylline therapy, bradyarrhythmia and resting SBP < 80 mmHg. Pacing can be an option in patients with a permanent pacemaker; in this case, it is necessary to use external programming with 10 beats increase every 30 seconds (4).

Ultrasound echo-contrast echocardiography

Ultrasound contrast agents (UCAs) consist of microbubbles that are about the size of a red blood cell and have similar rheology. UCAs emanate non-linear signals that are distinct from those generated by myocardial tissue, thus making easier the interpretation of RWMA when ≥ 2 contiguous segments cannot be adequately visualized by standard TTE. Moreover, UCAs enable a better analysis of LV volumes, enhance the Doppler signal in the LAD for CFVR study and the tricuspid regurgitant velocity signal for the estimation of pulmonary artery systolic pressure (PASP). Another more advanced and more technically challenging application of UCAs is the study of myocardial perfusion. It is based on the concept that UCAs can be cleared from the myocardium by a transient increase in the mechanical index called flash imaging, following which the myocardium should normally replenish in 5 seconds. Perfusion is assessed at the end of systole in the three apical

views and it requires the administration of a bolus of UCAs during peak bicycle, dobutamine or vasodilator stress. A qualitative score can be used to grade myocardial perfusion; this score ranges from 0 (no opacification even after 10 seconds) to 2 (homogenous opacification occurring within 5 seconds of flash imaging).

The ABCDE protocol

A systematic approach is crucial to standardize the execution of SE and, in this perspective, ABCDE protocol should always be used. It consists of a five steps protocol which includes the assessment of RWM (step A), B-lines (step B), LV contractile reserve (step C), Doppler-based assessment of CFVR in LAD (step D) and HR ratio (HRR) (step E) (19). The HRR is the ratio of peak HR to basal HR; the normal values are > 1.80 for exercise or dobutamine and >1.22 for dipyridamole. A reduced HRR is a strong predictor of mortality in chronic coronary syndromes, independent and incremental over RWMA (20-22).

Since indications to SE have gone beyond CAD, other additional useful parameters can be included in the ABCDE protocol, namely mitral regurgitation (step F), dynamic LV or transvalvular obstructive gradient (step G), pulmonary hemodynamics (step P), and right ventricle function (step R). Left atrial volume changes (step L for left atrium) can also be assessed; an abnormal response is characterized by an excessive left atrial dilation during stress (Δ variation from rest to stress > 8 mL/m2), with a reduction or subnormal increase in global peak atrial longitudinal strain. It should be emphasized that patient-specific protocols should be adopted according to the specific clinical question.

Indications and accuracy

CAD is still the most frequent indication to SE due to its high diagnostic accuracy (80-90%) in predicting obstructive epicardial CAD (4, 23). False negative response (significant CAD despite no RWMA) occurs more often in case of submaximal stress, in patients taking anti-ischemic drugs at the time of testing and in limited forms of single-vessel disease, above all ischemia confined to left circumflex territory. Stress-induced RWMA in the absence of significant CAD ('false positive response') are rare, often due to epicardial coronary artery vasospasm or hidden cardiomyopathy and is associated with worse prognosis (4, 24, 25). According to current guidelines, SE is recommended as initial test in intermediate-high risk symptomatic patient, and as second test in doubtful cases after inconclusive coronary computed tomography angiography (26); it can be also prescribed in patients with known CAD and stable angina despite optimal medical therapy, for risk stratification in suspected or known CAD (26), before high-risk elective non-cardiac surgery in patients with poor functional capacity and a high likelihood or known CAD (27) and in patients with HF with reduced ejection fraction (HFrEF) and CAD for assessment of ischemia and viability (28). SE is also an option to detect inducible myocardial ischemia in coronary anomalies, transposition of the great arteries post-switch operation (29) and Kawasaki disease (30).

Non-ischemic indications for SE include HF with preserved ejection fraction (HFpEF) to assess increase in E/e' ratio or pulmonary hypertension (28), valvular heart diseases such as mitral stenosis, mitral regurgitation, low flow-low gradient aortic stenosis to evaluate increase in severity or exercise-induced pulmonary hypertension (31, 32) and HCM to identify left ventricular outflow tract obstruction (33, 34).

SE can also be used in congenital heart disease for gradients estimation; specifically, it is recommended in case of changes in clinical status or for routine surveillance every 2–5 years in asymptomatic unrepaired or every 12 months in asymptomatic repaired patients for subaortic stenosis, aortic coarctation and repaired tetralogy of Fallot (35).

Prognosis

The assessment of RWMA, alone, is not effective for risk stratification, above all in specific subsets of population. For example, reduced CFVR, LV contractile reserve, and HRR show independent value in predicting outcomes in diabetic patients even without inducible RWMA (36). The assessment of patient vulnerability is better achieved with the ABCDE protocol. Each abnormal step can be assigned a score of 1 so a normal response has a score of 0 and a completely abnormal response has a score of 5. This score has a strong prognostic impact with an annual all-cause mortality ranging from 0.4% (score 0) to 2.7% (score 5) (23). This approach also allows clinicians to better understand patient's vulnerability and to optimize therapy.

Conclusions

SE is no longer simply based on the assessment of RWMA but is a multiparametric examination with numerous applications, which go beyond CAD. The ability to evaluate numerous parameters in a single exam makes it a first-line functional imaging test with a high accuracy and a strong prognostic impact. Low cost, lack of exposure to ionizing radiation and absence of CO2 emissions are other important advantages of SE in the era of sustainability.

Peer-review: Internal

Conflict of interest: None to declare

Authorship: F.L. and G.I. equally contributed to the preparation for manuscript, and fulfilled authorship criteria

Acknowledgements and funding: None to declare

Statement on A.I.-assisted technologies use: We declare that we did not use AI-assisted technologies in preparation of this manuscript

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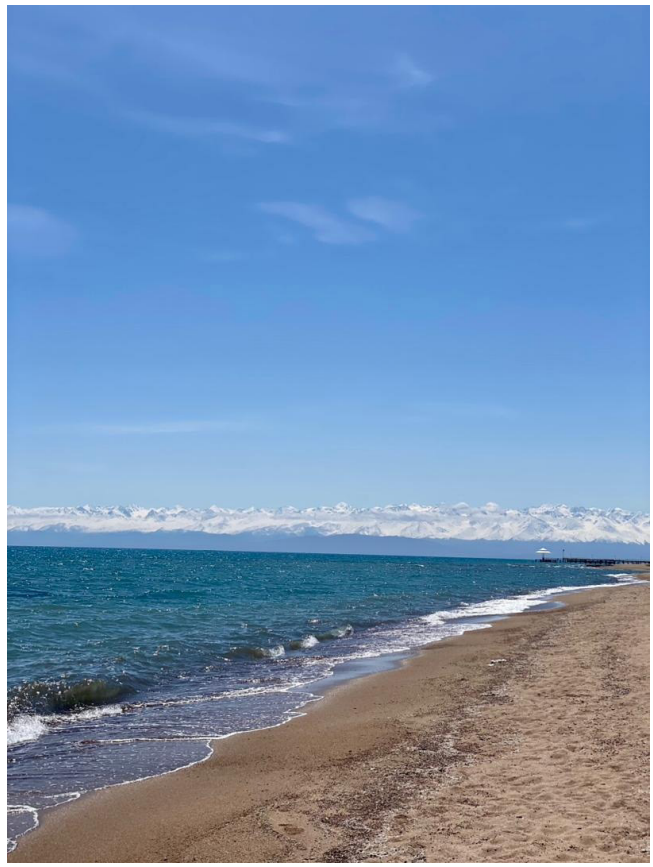

Issyk-Kul - a pearl between mountains, June 2024. Marjan Aikimbaeva, Bishkek, Kyrgyzstan