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Review Article

Updated knowledge and practical implementations of stress echocardiography in ischemic and non-ischemic cardiac diseases: An expert consensus of the Working Group of Echocardiography of the Hellenic Society of Cardiology

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ABSTRACT

Stress echocardiography (SE) is a well established and valid technique, widely used for the diagnostic evaluation of patients with ischemic and nonischemic cardiac diseases. This statement of the Echocardiography Working Group of the Hellenic Society of Cardiology summarizes the consensus of the writing group regarding the applications of SE, based on the expertise of their members and on a critical review of present medical literature. The main objectives of the consensus document include a comprehensive review of SE methodology and training—which focus on the preparation, the protocols used, the analysis of the SE images, and updated, evidence-based knowledge about SE applications on ischemic and nonischemic heart diseases, such as in cardiomyopathies, heart failure, and valvular heart disease.

1. Information about the consensus document

The expert consensus document on stress echocardiography from the Working Group of Echocardiography of the Hellenic Society of Cardiology was written as a uniform text and then submitted for publication in two separate, but integral parts: Part I on the theoretical framework, preparation, performance, and analysis of stress echocardiography and Part II on clinical applications of stress echocardiography on ischemic and nonischemic heart diseases. Part I includes the information about the scope, the methodology of consensus document, and the status of consensus recommendations.

2. Scope of the consensus document

Stress echocardiography (SE) is a well established and valid technique, which is widely used for diagnosis and decision making in ischemic and nonischemic cardiac diseases. This expert consensus statement of the Working Group of Echocardiography of the Hellenic Society of Cardiology summarizes the consensus of the writing group after a critical review of present medical literature on SE and its usage in ischemic and nonischemic cardiac diseases. The main objectives of the present consensus document are the following:

1. Updated, evidence-based knowledge about SE and its applications.
2. A comprehensive review of SE methodology, summarizing its implementations – an issue usually not covered by the guidelines.
3. An assessment of the diagnostic and prognostic value of SE for clinical decisions, intended to improve patient outcomes.
4. Incorporation of the best available evidence into clinical practice and the current standard-of-care, accompanied by practical recommendations.
5. Help researchers identify gaps in the evidence and shed light on what key research questions have yet to be answered.

This task force was set down by the Hellenic Society of Cardiology and included members of the Working Group. The target readers are cardiologists who intend to practice in SE or those who are already involved in SE in daily practice.

3. Methodology of consensus document and status of consensus recommendations

We structured a multilevel procedure of repeated assessment and cross-checks to achieve the maximum degree of consensus. The co-chairs of the Task Force created a list of four chapters and related subchapters/topics, and then, they asked the members of the writing group to perform a thorough, comprehensive literature review till August 2020, using search terms relevant to SE in MEDLINE, EMBASE, and other databases. At the end of almost each subchapter/topic, a keypoints box summarized the recommendations of the whole panel of experts based on the strength of evidence and the level of agreement. Writing group members were asked to weigh the strength of evidence for or against diagnostic and prognostic results ranking the strength of evidence based on the type of studies; R: Randomized trials, O: Observational studies/nonrandomized trials, M: meta-analyses/systematic reviews, E: expert consensus in absent or controversial observational data. Thereby, the level of evidence for consensus statement was graded as follows:

I) Strong evidence: supported by at least one randomized trial or meta-analysis/systematic review and the statement is strongly recommended (“should do” or “are used”).
II) Weak evidence: supported by only observational/nonrandomized trials and the statement is recommended (“may do” or “may be used”).
III) Expert opinion: absent or controversial observational data and consensus between experts about the recommended statement (“may do” or “may be used”). In the latter case, the consensus of this Task Force was achieved after thorough deliberation, which was predominantly based on their clinical experience, and the gap of evidence was underlined. Additional comments from this Task Force about controversial issues are typed in italics within the document. Mostly, the present writing group did not proceed to negative recommendations, because SE is a diagnostic technique and all the related contraindications or limitations of its use had been listed in the related chapter. All created drafts of each chapter were then exchanged between co-chairs and after amendments and homogenization, they were incorporated in a document, which was sent to a body of reviewers along with a list of queries with regard to remaining inconsistencies. The latter body was asked to make a quality control, assess the key points, and reply to queries. After obtaining reviewers' feedback, the last step of reviewing was the final approval/rejection of all created recommendations by all expert members, using an online voting system organized by the co-chairs. The status of agreement for each statement was ranked as: “Strong

consensus" which implicates unanimous agreement between experts; "Consensus" which is defined as nonunanimous, but >70% agreement to reach consensus; and "No consensus" which implicates that <70% agreement and consensus were not reached. The evidence review procedure derived with some modification from the respective procedure was applied in expert consensus documents of the European Heart Rhythm Association[1].

4. Theoretical framework of stress echocardiography

4.1. Introduction-History of stress echocardiography

Supplement.

4.2. Indications

Traditionally, SE has been used for coronary artery disease (CAD) diagnosis[2,3], especially in patients with ECG abnormalities, LBBB, pacemaker, or those unable to perform treadmill stress tests owing to mobility restrictions[4]. SE is the first-line method for ischemia detection because of its low cost, availability, and nonradiation exposure[5]. Through the last decades, physicians have become more familiar with this method and echocardiography technology has been improved, expanding the indications of SE. This method can be used in CAD diagnosis and prognosis, especially after acute coronary syndrome or in myocardial viability assessment[6,7].

Besides CAD, SE has also proven its value in nonischemic cardiac diseases. Exercise stress echocardiography (ESE) may identify increased pulmonary and LV diastolic filling pressures in patients with suspected heart failure with preserved ejection fraction (HFpEF)[8], while dobutamine SE can quantify the LV contractile reserve (CR), a worthy prognostic parameter in cardiomyopathies. Moreover, one of the major applications of SE is the so-called "valve stress echocardiography" that can help in the accurate evaluation of native and prosthetic valve diseases, especially when there is a mismatch between symptoms and disease severity[9–13]. Details are provided in the following sections and all indications are summarized in Table 1.

Keypoint:	Evidence/Studies	Consensus status
The indications for stress echocardiography are not limited in CAD, but they are expanded to a broad spectrum of cardiac diseases by using different stressors and protocols.	Strong R,E[3,4,6,11]	Strong

4.3. Contraindications of stress echocardiography

SE can be performed in a wide variety of patients in a relatively safe way. Absolute and relative contraindications highlight the balance of benefit versus the risk of the test. The absolute and relative contraindications for pharmaceutical stress echocardiography (PSE) or ESE are presented in Table 2[4,7,14–16].

As far as vasodilation (dipyridamole or adenosine) testing is concerned, absolute contraindications include the presence of severe conduction disturbances and bronchopneumonic disease, while resting systolic pressure below 100 mmHg is mentioned as the only relative contraindication[17,18].

Keypoint:	Evidence/Studies	Consensus status
Operators of stress echocardiography should be aware of all relative and absolute contraindications.	Expert opinion E	Strong

4.4. Complications of stress echocardiography and safety issues

Despite the reported safety, rare severe complications have been recorded during SE (Table 3) [19–25]. Previous studies have failed to establish a relationship between DSE-induced ventricular tachycardia and CAD. This carries prognostic significance (reduced survival over follow-up) only when it occurs in the context of impaired LV function[26–29]. Although hypotensive response during exercise has been strongly associated with myocardial ischemia and poor prognosis, hypotension during DSE cannot be considered as a specific indicator of myocardial ischemia[30]. During dobutamine infusion, many patients (12–50%)[4] may experience benign adverse effects, including nausea, flushing, headache, neck/chest pounding, paresthesia, urinary urgency, and dyspnea[31]. Atropine is relatively safe, but owing to its anticholinergic properties, it may cause urinary retention, increased intraocular pressure, delirium, flushing, constipation, delayed gastric emptying, nausea, dry mouth, and weakness.

Keypoints:	Evidence/Studies	Consensus status
Stress echocardiography is a safe method, but complications may occur.	Strong R[19–23,28–30]	Strong
Exercise seems safer than a pharmacologic stress test, possibly because of preselection criteria.	Weak O[27,31]	Consensus

4.5. Training requirements

4.5.1. Training in stress echocardiography

Several international scientific bodies and national societies have released either recommendation documents or guidelines with regard to the application of SE, which include details of training requirements[2,32,33].

The added skills required for scanning the heart under stress conditions undeniably differ from usual studies at rest. Thus, a medical professional should be involved in stress studies only after adequate training and competence in TTE. Interestingly, the interpretation of SE examinations by an incompetent operator undervalues the diagnostic accuracy of the technique[34]. For getting advanced level competence and independence in SE, the European Association of Cardiovascular Imaging (EACVI) recommends trainees to undergo more than 100 SE studies under the supervision of a level III (Entrustable Professional Activity level; EPA level 5) trained expert, in a high-volume laboratory, ideally with the possibility of angiographic confirmation[2,32].

The training document COCATS level 4 task force 5, written by the members of ACC and ASE, recommends for level II competence in SE, interpretation of a minimum of 100 SE studies supervised by a level III trainer, and for level III competency another 100 studies

Table 1
Indications and the related parameters of stress echocardiography in ischemic and nonischemic cardiac diseases[4,5,8,11].

Indications	Type	Parameters
Coronary artery disease		
• CAD diagnosis in intermediate pretest probability (15–85%)	DSE/ESE	WMA assessment (two adjacent segments)
• Acute chest pain (no ECG abnormalities and negative biomarkers) in intermediate risk patients		Impaired CFR (optional)
• CCTA or coronary angiography with moderate stenosis		
• New angina or regular monitoring in previous PCI or CABG patients		
• Risk stratification post myocardial infarction		
Viability assessment and need for revascularization	DSE	Viable/Non-viable myocardium, stunning/hibernating myocardium, scar
Diastolic dysfunction		
HFpEF [Intermediate HFA PEFF score (2-4)]	ESE	E/e' $\geq$ 15, TR Vmax >3.4 m/s
Valvular Heart diseases		
Aortic stenosis (AS)		
1. Severe asymptomatic	ESE	Symptoms, ΔMPG: > 18-20 mmHg, ΔLVEF
2. Symptomatic non-severe	ESE	<5%, PASP $\geq$60 mmHg, abnormal BP response
3. Low-flow/Low gradient	DSE/ESE	ΔMPG: > 20 mmHg AVA$\leq$1 cm^2, MPG at rest and peak, ΔSV
Aortic regurgitation (AR)		
1. Severe asymptomatic	ESE	Symptoms, ΔLVEF <5%
2. Non-severe symptomatic	ESE	PASP elevation, MR severity change
Mitral stenosis (MS)		
1. Moderate/severe, asymptomatic	ESE	Symptoms, PASP elevation
2. Moderate symptomatic	ESE/DSE	Peak MPG >15 mmHg (ESE) or peak MPG > 18 mmHg (DSE), PASP elevation (ESE)
Mitral regurgitation (MR)		
1. Severe asymptomatic	ESE	Symptoms, PASP $\geq$60 mmHg, ΔLVEF <4%, ΔGLS <2%, TAPSE <19 mm (degenerative MR)
2. Moderate symptomatic	ESE	MR increase (ΔEROA $\geq$+13 mm^2, secondary MR) PASP $\geq$ 60 mmHg, ΔLVEF <4%, ΔGLS <2%
Cardiomyopathies		
Hypertrophic cardiomyopathy (non-obstructive)	ESE	LVOTO > 50 mmHg, abnormal BP response
Dilated cardiomyopathy	ESE/DSE	Contractile reserve

BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCTA, coronary computed tomography angiogram; DSE, dobutamine stress echocardiography; EROA, effective regurgitant orifice area; ESE, exercise stress echocardiogram; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; LVOTO, LV outflow track obstruction; MPG, mean pressure gradient; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; SV, stroke volume; TR Vmax, tricuspid regurgitation maximum velocity; WMA, wall motion abnormalities; Δ, change.

Table 2
Absolute and relative contraindications of stress echocardiography (PSE and ESE)[4,7,14–16].

Absolute contraindications
Acute myocardial infarction (within 3 days)
Ongoing unstable angina
Uncontrolled cardiac arrhythmias
Symptomatic severe aortic stenosis (except low-gradient and/or low-flow aortic stenosis)
Uncontrolled or acute heart failure
Acute myocarditis or pericarditis
Severe hypertension >200/110 mmHg at baseline
Hypertensive crisis
Active endocarditis
Inability to exercise (for ESE)
Acute pulmonary embolism
Hypertrophic obstructive cardiomyopathy (for DSE)
No written consent to undergo the stress testing
High-grade AV block (second or third degree)
Intraventricular (recent) thrombus
Previous hypersensitivity/allergy to pharmaceutical agent (for PSE)
Narrow – angle glaucoma (for atropine use)
Pyloric stenosis (for atropine use)
Myasthenia gravis (for atropine use)
Relative contraindications
Uncorrected medical conditions, such as significant anemia, important electrolyte imbalance, and hyperthyroidism
Recent stroke or transient ischemic attack
Recurrent or persistent supraventricular arrhythmias
Obstructive uropathy (for PSE using atropine)
Abdominal aortic aneurysm (for ESE)
Thoracic aortic aneurysm
Intracranial aneurysms

interpreted under supervision. Those studies are required to include not only ischemia assessment, but other indications such as diastolic function, valvular diseases, and viability assessment. For maintenance of competency, it is recommended that operators should interpret at least 100 SE studies annually and participate in continuing medical education.

To achieve an all-around diagnostic approach that enables to address single patient requirements, it is important to gain experience with all types of stressors (pharmacological and exercise). However, as difficulty varies according to patients' characteristics, type of SE, and selected protocol, it is recommended to begin with

Table 3
List of potential major (life-threatening) and minor complications of stress echocardiography[19–25].

Complications	ESE (%)	DSE (%)
Acute myocardial infarction	0.01	0.02
Sustained Ventricular Tachycardia (sVT)	0.05	0.15
Ventricular Fibrillation (VF)	<0.01	0.04
Cardiac rupture	-	0.01
Stroke	0.01	0.01
Syncope	0.01	-
Complete atrio-ventricular block	0.02	-
Death (VF and cardiac rupture)	0.01	0.01
Conduction abnormalities other than complete A-V block	0.04	0.23
Non-sustained ventricular tachycardia	0.25	1-3
Atrial fibrillation/flutter	0.05	0.9
Paroxysmal supraventricular tachycardia (SVT)	0.14	1.3

easier and safer studies, and then progress to the more technically challenging and advanced jeopardy.

4.5.2. Training in contrast echocardiography

Training in contrast echocardiography should include training in composition and safety of microbubble agents, imaging methods, indications and contraindications, and specific scenarios in which contrast is of added value. In the 2017 EACVI recommendations, the following requirements for operators using contrast echocardiography in TTE are provided[35]: (1) participation in courses of contrast echocardiography, (2) basic life support training, (3) supervised performance and interpretation of at least 25 contrast echo studies, and (4) maintenance of competency by performing at least 50 contrast echo studies annually.

4.5.3. Certification

SE certification is a process that examines the competency and safety of echocardiographers undertaking this modality. There are only a few certification schemes that may admit criteria of objectiveness in the examination process[36,37]. The most known scheme is that of the British Society of Echocardiography[4]. In the context of the semester training in advanced echocardiographic techniques, the Working Group of Echocardiography of the Hellenic Society of Cardiology recommends trainees to perform more than 100 SE studies (predominantly for the evaluation of ischemia and to a lesser extent for other indications), using various SE modalities, under the supervision of certified experts in high-volume laboratories accredited by local authorities.

4.5.4. Echocardiography laboratory accreditation

Several international periodical updates for the standards and processes for the accreditation of echocardiographic laboratories exist[38]. Staff requirements and all other standards of the SE laboratory infrastructure are presented in the publications released by relevant scientific bodies.

Keypoints:	Evidence/Studies	Consensus status
Competency in performing and interpreting the SE exam requires proficiency in transthoracic echocardiography and training under supervision for at least 100 SE studies.	Expert opinion E	Consensus
Maintenance in competency requires at least interpretation in 100 SE exams annually.	Expert opinion E	Consensus

5. Test preparation, performance, and interpretation

5.1. Staff and lab requirements

SE should always be performed by a team of minimum two individuals: 1) a SE-certified cardiologist who performs and analyses the echocardiographic study, and 2) a trained technician or nurse, responsible for drug administration, haemodynamic/electrocardiographic monitoring and documentation. At least one individual should have a valid certification to provide Advanced Life Support.

Requirements regarding equipment, drugs, and exam room depend on the type of stressor, pharmacology, or exercise. In any circumstance, the set-up must allow the accommodation of a crash team in case of a cardiac arrest scenario. A fully equipped, easily accessible resuscitation trolley and defibrillator must remain on site. Echocardiography machines with SE analysis software, digital acquisition, and storing capabilities are necessary. In case of pharmacological stress, an infusion pump is required, while medically certified treadmills or semisupine/upright bicycles should be used in ESE. A 12-lead continuous ECG monitoring is desirable.

5.2. Drugs

The most common drugs used in SE, along with their recommended doses and the potential side effects are presented in Table 4.

5.3. Patient preparation and informed consent

A patient information leaflet with details about preparation (medication stopping, diet instructions, clothing) may be offered at the time of appointment booking. The patient should fast for 4 h before the ESE. They may also abstain from caffeine products or smoking for the same period before DSE or vasodilating stressors. In case of ischaemia investigation, antianginal medication (i.e., b-blockers, calcium channel blockers, nitrates) may/should be withheld for 4–5 half-times (practically average 48 h) if well tolerated and according to the clinical query, as they have been associated with a lower sensitivity of SE[39].

A written informed consent about the test, including the rational, technique details, potential findings and complications, should be signed by the patient or next of kin as SE is not a risk-free procedure. Following the consent form signing, the patient is cannulated, unless it is deemed unnecessary (e.g., ESE without the use of i.v. agents).

5.4. Comparative evaluation of exam protocols

5.4.1. Exam protocols in ischemic heart disease

There are two main techniques for the evaluation of myocardial ischemia: PSE (frequently using dobutamine) or ESE with either semisupine bicycle or treadmill. In general, ESE is the preferable technique in patients who exercise as it follows the natural stress response. ESE provides functional prognostic information, hemodynamic assessment, and presents a better and more predictable safety profile than PSE. Moreover, treadmill exercise induces a greater magnitude of ischemia than dobutamine-atropine infusion owing to the higher rate-product achieved by exercise.[40]

However, hyperkinesia, as a normal response to stress, is more prominent and concrete in DSE rather than ESE. DSE may exaggerate even small differences in myocardial thickening between segments, because the contractility response to dobutamine is greater because of β1 adrenoceptors stimulation, while high dobutamine dose slightly reduces afterload through β2 adrenoceptors stimulation. Moreover, a normal increase of afterload is observed during ESE and hyperkinesia is less marked at advanced stages. *This Task Force has not drawn a firm conclusion for the comparative efficacy of PSE versus ESE in ischemia detection.*

In case of unavailable exercise facilities and limited exercise tolerance (unfit, elderly patients, mobility restrictions), PSE is the preferred modality over ESE. Finally, the echocardiographic assessment of global and regional myocardial viability is relatively easier during PSE.

5.4.2. Exam protocols in non-ischemic heart diseases

In most cases, semisupine bicycle ESE is appropriate for the continuous evaluation along with workload increment of diastolic function, valvular disease severity, and cardiomyopathies. In addition, PSE application, in the context of nonischemic heart diseases,

Table 4
Drugs intravenously used in stress echocardiography, recommended doses, and potential side effects.

Drug	Dose	Side-effects
Dobutamine	Pump infusion of 5-40 mcg/kg/min as per protocol	Nausea, tremor, palpitations, headache, hypotension, hypertension, chest pain, arrhythmia, myocardial infarction
Atropine	Bolus doses of 0.25 mg up to maximum 2 mg	Tachycardia, palpitations, dry mouth, constipation, mydriasis, nausea, agitation, urinary retention, increased intraocular pressure
Adenosine	Pump infusion of 140 mcg/kg/min over 6 min	Flushing, chest pain, burning sensation, shortness of breath, metallic taste, dizziness, nausea, headache, bradyarrhythmia
Dipyridamole	Pump infusion of 0.56 mg/kg over 4 min, followed after 2 min by 0.28 mg/kg over 2 min	Dizziness, flushing, headache, stomach ache arrhythmia, chest pain, bronchospasm, hypotension
Metoprolol	Bolus doses of 1 mg up to maximum 5 mg	Bradyarrhythmia, hypotension, dizziness
Esmolol hydrochloride	Infusion of 0.5 mg/kg during 1-minute period	Bradyarrhythmia, hypotension, headache
Aminophylline	Bolus dose of 240 mg	Chest discomfort, dizziness, arrhythmia, headache

is limited in low-flow, low-gradient aortic stenosis (LF/LG AS) with reduced ejection fraction, mitral stenosis (when ESE is nonfeasible), and DCM (for CR assessment) (Table 1).

In comparison to PSE, ESE appears to be the most convenient stress modality to assess the functional capacity of participants and hemodynamic changes during stress. Till now, there is no universal consensus on the suggested ESE protocol. Societies of cardiac imaging have generally proposed a stepped protocol on a semisupine bicycle starting at 25 Watts, at ~60 repetitions per minute (rpm), increasing by 25 Watts every 2 min and terminating at 85% of age-predicted maximal heart rate (220—age) or owing to symptoms[1]. The desired duration of a bicycle ESE should range between 6 and 10 min. The workload increments may be adapted to the participant's exercise capacity to achieve a gradual increase in heart rate. ESE may be inconclusive when it is stopped prematurely because of the inability to maintain the right rpm or when it lasts longer and the participant stops owing to leg fatigue before heart rate target achievement. Elderly or patients with a low level of exercise capacity may follow individualized light protocols with lower initial workload (e.g., 10 or 20 Watts) and smaller workload increments (e.g., by 10 Watts)[4,41,42]. Blood pressure monitoring and continuous electrocardiogram recording (preferably 12-leads) is required.

Although many published studies have used treadmill exercise stress test for valvular diseases assessment, bicycle ESE is the preferred method. In the latter case, the operator can continuously assess the haemodynamic behaviour (change of regurgitation or stenosis severity) of the valves and PASP elevation at baseline, low workload, peak exercise, and recovery. In treadmill tests, mostly using classical Bruce protocol, that information is available only at baseline and right after exercise cessation, during early recovery[43]. Thereby, the operator has a very short time to obtain echocardiographic views, before the hemodynamic changes disappear (within 30 s). Hence, the patient may remain standing on the treadmill or may immediately lay down on a bed next to the treadmill machine for postexercise echocardiography. *The present Task Force has not concluded to a specific exam protocol, which should depend on the study indications, the patient's capability to exercise, and the preferred technique*. The main protocols are presented in Fig. 1.

5.5. Images acquisition, analysis, and interpretation

5.5.1. Images acquisition and analysis in ischemic heart disease

Before SE, a full echocardiographic study is necessary when no recent one is available. The following standard group of images should be obtained at baseline, during stress, and at recovery stages of SE, according to the test protocol:

1. Parasternal long axis view.
2. Parasternal short axis view at the level of the papillary muscles.
3. Parasternal short axis view at the level of LV apex.
4. Apical four chamber view.
5. Apical two chamber view.
6. Apical three chamber view (additional value regarding the evaluation of LV apex).

The sequence of views acquisition depends on personal experience, routine practice, and contrast use. Subcostal views might be useful as an alternative in the case of suboptimal standard views. A preset machine protocol for either PSE or ESE is preferable to ensure all images acquisition and to reduce the duration of the study. The acquisition of comparable echocardiographic views at each stage of the study is the most challenging issue of the technique and needs expertise, precision, and quickness. The addition of intermediate stages improves sensitivity and functional assessment of CAD[44]. Technically, some operators suggest the acquisition of more than one cardiac cycle per view, especially in atrial fibrillation, and a second row of views at peak stress to ensure optimal imaging.

Continuous single-lead or preferably 12-leads ECG should be recorded during the procedure. Heart rate (HR) and blood pressure (BP) should be obtained at each stage of the study; especially when symptoms of thoracic pain, dyspnea, or dizziness appear. When b-blockers are used during the recovery stage, the operator should focus on regional rather than global changes in myocardial function[45].

Based on clinical experience, the members of this Task Force encourage the performance of image analysis always after stress test completion, using an appropriate SE software for comparative evaluation of views between stages. The clinical interpretation of global and regional myocardial function is mainly performed, so far by the visual assessment of myocardial wall thickening and inward motion of the endocardium (Table 5).

The following points should be considered for images interpretation of a SE:

A) This Task Force encourages operators to use the term "myocardial thickening abnormalities" instead of "wall motion abnormalities – WMA" as a more accurate index of ischemia. WMA could be pseudo-negative in cases of ischemic segments tethering to the normal proximal ones or

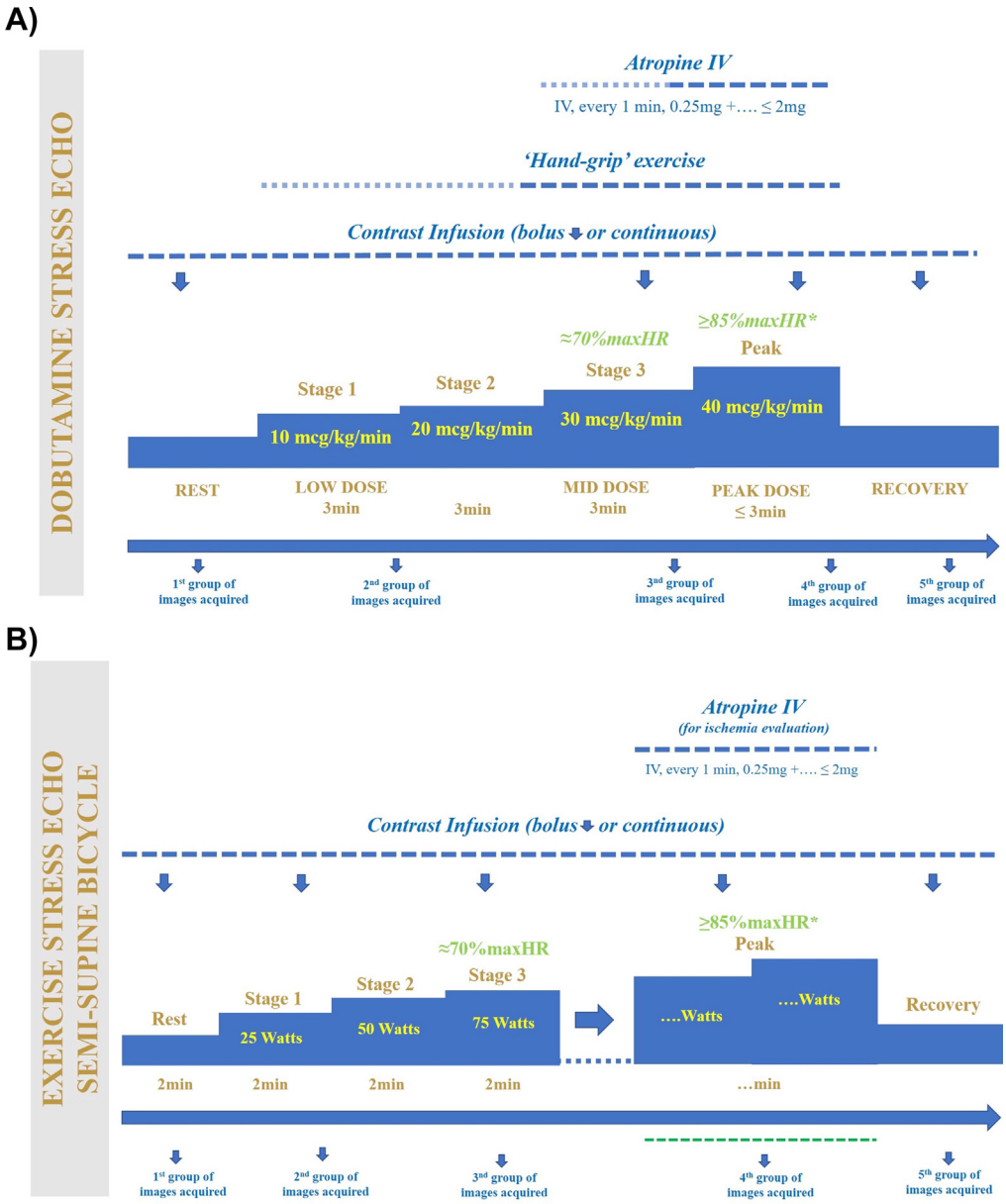

Figure 1. Stress echocardiography protocols. *A) Dobutamine Stress Echocardiography - Evaluation of ischemia.* Blue dotted line: Optional - mainly used, if needed, in the following (arrows) stages. Light blue dotted line: Optional – could be used in the following (arrows) stages. HR, Heart Rate. *B) Exercise Stress Echocardiography/Semi supine bicycle - Evaluation of ischemia.* Blue dotted line: Optional - mainly used, if needed, in the following (arrows) stages. Green dotted line: The time during which the group of images should be acquired. HR, Heart Rate. *C) Exercise Stress Echocardiography/Treadmill - Evaluation of ischemia.* Blue dotted line: Optional - mainly used, if needed, in the following (arrows) stages. Green dotted line: The time during which the group of images should be acquired. HR, Heart Rate. *D) Vasodilator Stress Echo - Evaluation of ischemia.* Blue dotted line: Optional - mainly used, if needed, in the following (arrows) stages. Green dotted line: The time during which the group of images should be acquired. HR, Heart Rate. *E) Dobutamine Stress Echo - Evaluation of Viability ± Ischemia.* Blue dotted line: Optional - mainly used, if needed, in the following (arrows) stages. Green dotted line: The time during which the group of images should be acquired. HR, Heart Rate. *F) Exercise Stress Echo/Semi supine bicycle - Evaluation of Valve disease ± ischemia.* Blue dotted line: Optional - mainly used, if needed, in the following (arrows) stages. Green dotted line: The time during which the group of images should be acquired. HR, Heart Rate or symptoms or positive (ECG-ECHO) for Ischemia.

pseudo-positive in basal inferior and septal segments owing to their tethering to aortomitral fibrous continuity.

B) The delayed onset of contraction in the early phase of systole (tardokinesis) and the postsystolic contraction may represent potential indexes of myocardial ischemia.

C) LV dilatation and reduction of left ventricular ejection fraction (LVEF) during SE indicates extensive ischemia.

D) Wall motion/thickening assessment is based on a 16- or 17- (LV apex included) segment model. Each segment is scored, according to the following criteria:
   1 Normal wall motion (myocardial thickening >50%).
   2 Hypokinesia (myocardial thickening 10–50%).
   3 Akinesia – severe hypokinesia (myocardial thickening <10%).
   4 Dyskinesia (paradoxical systolic motion – systolic outward stretching).

E) Wall Motion Score Index (WMSI) is calculated by dividing the sum of all segmental scores by the total number of myocardial segments (16 or 17). In normal, nonischemic myocardium, WMSI equals 1.

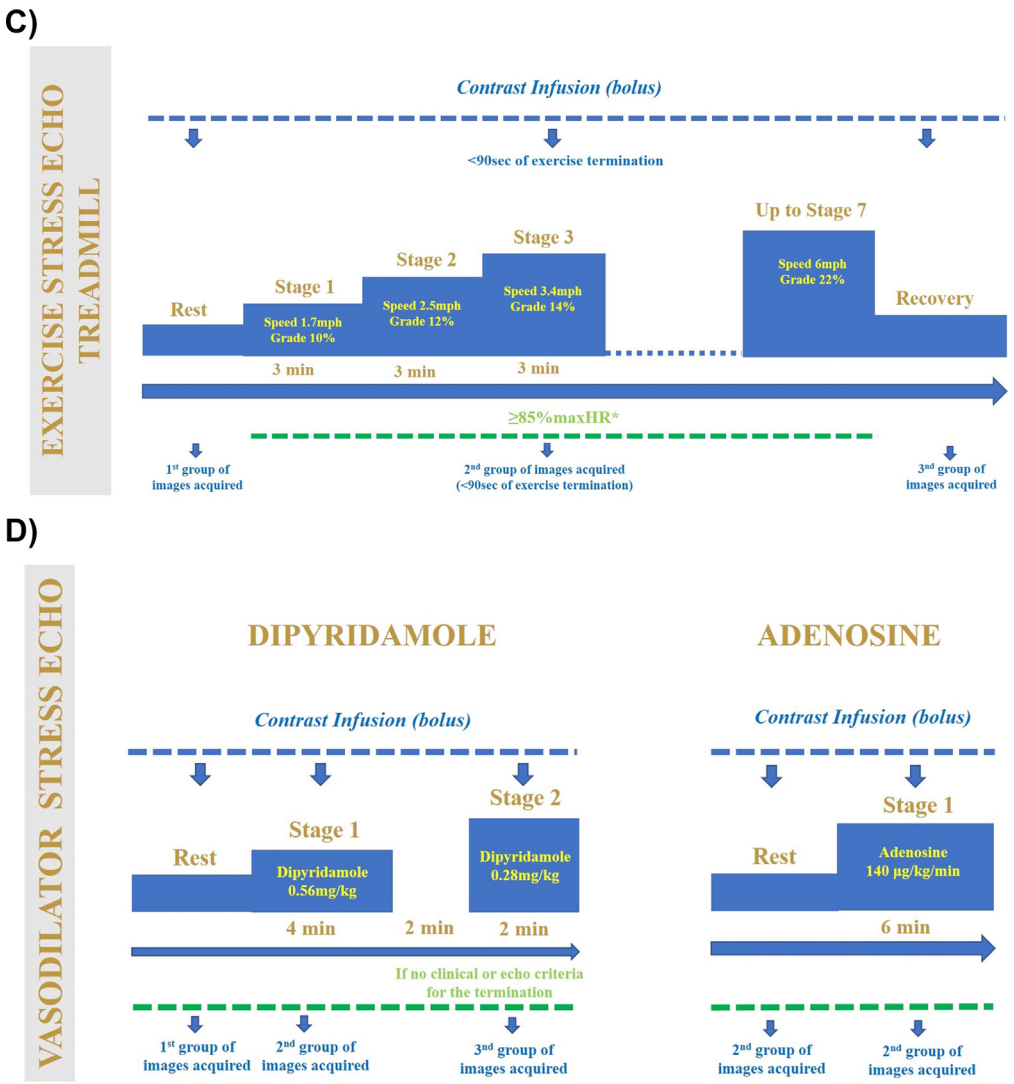

Figure 1. (*continued*).

5.5.2. Images acquisition and analysis in nonischemic heart diseases

The protocol selection and the type of image views in non-ischemic heart diseases should be based on individuals' characteristics, the clinical query, and the operator's experience. Despite the variety of nonischemic heart diseases, preset machine protocols of SE for each type is preferable to ensure protocol completion and reduced study duration. The great advantage of ESE over PSE is the estimation of exercise capacity and hemodynamic changes during a test, which should be always reported based on the following: achieved workload, duration of the test, maximum heart rate, and heart rate changes during or after the test (e.g., a steep rise at early stages or slow drop at recovery). All these parameters should be reported at the end.

Echocardiography during ESE includes the recording of the 2D parasternal and apical LV views for the assessment of WMA, and additionally, the evaluation of some or all of the following parameters, depending on the clinical query: color doppler in aortic, mitral, and tricuspid valve, trans-aortic valve velocity, LV outflow velocity, mitral valve (MV) inflow pattern, mitral and tricuspid annulus tissue Doppler velocities, and maximum values of tricuspid regurgitation velocity (TR Vmax). The aforementioned views and parameters are acquired at baseline and each stage up to recovery during cycling, while only at baseline and at early recovery stage of ESE on treadmill: within 1–2 min after exercise cessation for MV parameters and within 30 s for TR Vmax and other echocardiographic parameters.

Table 5
Interpretation of segmental myocardial thickening response during stress echocardiography applied for myocardial ischemia detection.

Rest	Stress	Interpretation
Normal	Hyperdynamic	Normal (Without significant CAD)
	Hypokinetic/akinetic	Myocardial Ischemia
Hypokinetic	Improved Contractility/ Normal or less hypokinetic	Viable myocardium (Non-transmural infarction, stunned myocardium)
	Improved contractility at early stages and then worsening	Biphasic Response: Viability+ Myocardial ischemia
Akinetic	Akinetic/Dyskinetic	Scar (Transmural Infarction)

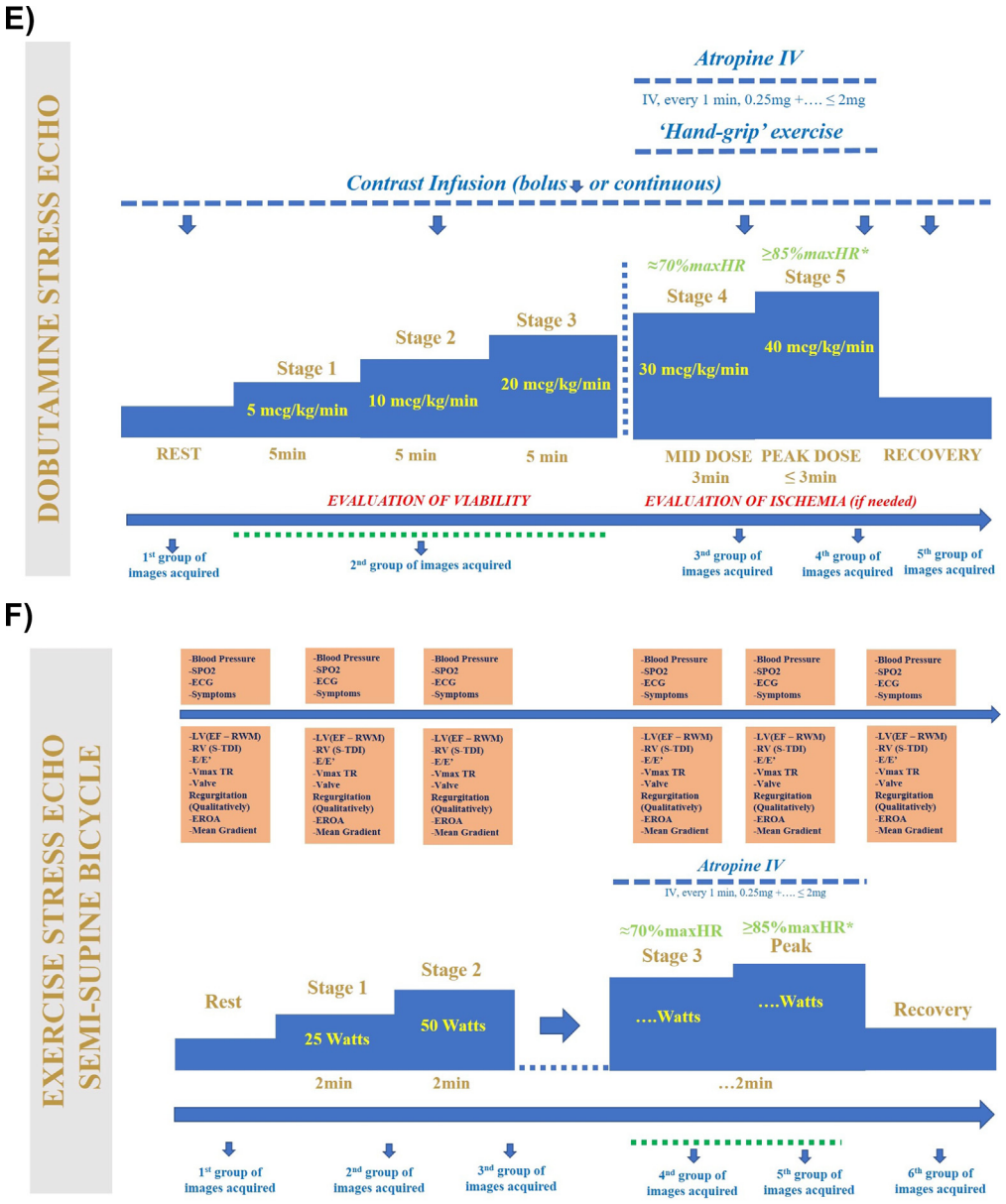

Figure 1. (*continued*).

For diastolic dysfunction diagnosis and heart failure with preserved ejection fraction (HFpEF), the most widely-used echocardiographic parameters are the following: E/e' ratio and TR Vmax, during diastolic stress test echocardiography (DSTE) combined with baseline e' wave.

Nowadays, the assessment of right ventricular function at rest and peak exercise (TR Vmax, tricuspid annular plane systolic excursion - TAPSE, S' wave in Tissue Doppler imaging) has gained increasing interest. It may assist to identify patients with exertional dyspnea, exercise-induced pulmonary hypertension (EIPH), or RV dysfunction, despite normal pulmonary artery systolic pressure (PASP) at rest[46].

Although ESE is a more natural way for a stress test, with many advantages over the PSE, it is technically demanding with several technical and functional factors limiting its utility. From the technical point of view, the operators should be trained on this modality as a separate part of SE training, as they have to get used to suboptimal images in semisupine position, hyperventilation, sweating, and patient's motion during ESE. Participants should be familiarized with bicycle or exercise on a treadmill, and hence, a brief pretest exercise on bicycle or treadmill may be sometimes necessary. In parallel, severe calcification of MV annulus, no or insufficient TR jet, poor exercise capacity owing to mobility restrictions, and inability to measure one or more of the required parameters at maximal exercise, limit the reliability of ESE.

5.6. Criteria for protocol completion

Both PSE and ESE aim to increase the HR above 85% of the maximal, age-predicted heart rate (220 - age)[4]. If the achieved HR is lower than that target, the diagnostic sensitivity for ischemia falls and caution should be taken when interpreting a normal submaximal test[47]. Slight ST depression during DSE may confound the final report when there are not simultaneous echocardiographic findings of ischemia. However, ST elevation or significant ST depression in $\geq$2 contiguous leads should be always reported and considered as an index of ischemia and reason for premature

Table 6
Endpoints of stress echocardiogram[33,48].

Absolute
Achievement of target HR (85% of maximal, age-predicted HR)
Completion of protocol (maximal drug dose) or limiting symptoms (chest pain, fatigue)
Obvious echocardiographic findings of extensive myocardial ischemia
Marked ischemic ECG changes: symptomatic ST elevation > 1 mm (other than aVR or V1) in 12-lead ECG recording
Symptomatic drop in SBP > 10 mmHg from baseline (only in ESE)
Sustained ventricular tachycardia
Central nervous system symptoms (ataxia, pre-syncope)
Relative
New or worsening wall motion abnormalities
LV dilatation and/or new onset of global LV dysfunction
ST depression > 2 mm
New arrhythmia (atrial fibrillation, supraventricular tachycardia, non-sustained ventricular tachycardia
SBP ≥ 220 mmHg or DBP > 110 mmHg
Drop in SBP > 20 mmHg from previous level measurement
Drop in HR > 20% from starting heart rate

HR, heart rate; ECG, electrocardiography; SBP, systolic blood pressure.

termination of SE, independent of symptoms or WMA development. During DSE, acute chest pain accompanied with ST depression, but without WMA may indicate microvascular CAD. Medical complications and other reasons for early termination of the test (endpoints) are listed in Table 6.

5.7. Reporting

A stress echocardiogram report should include.

1. Clinical information and an indication of the study.
   2.Protocol information (stressors used, doses, maximal achieved HR and BP, maximal achieved workload, duration of exercise).
   3.ECG and clinical findings during the rest and stress study (arrhythmias, ischemic ECG changes, symptoms, complications).
   4.Reason for the termination of a test (protocol completion, symptoms, echocardiographic findings, complications).
5. Echocardiographic findings at baseline and during stress test depending on the indication and type of exam (left ventricular systolic function and wall motion evaluation, flow velocities and gradients).

5.8. Image enhancement with contrast agents

Approximately 33% of the patients referred for SE have suboptimal image quality despite the use of harmonic imaging modalities, commonly owing to overweight and/or the presence of pulmonary disease. The use of contrast agents improves the visualization and detection of regional WMA, enhances reader confidence of study interpretation, and improves sensitivity and accuracy for the detection of CAD[29,35]. Although the recommended indication for the use of contrast agents (Table 7) is the suboptimal visualization of the endocardial border of two or more adjacent LV segments, in many echo labs worldwide, contrast agents are used in the majority of SE procedures. Despite initial concerns, the administration of contrast agents is safe even in the case of acute coronary syndromes, or when contrast stress echocardiography (CSE) is performed on children or young adults[49].

Presently, the role of CSE primarily refers to the diagnosis and prognosis of chronic CAD in adults (Fig. 2). CSE also improves the diagnostic accuracy in special conditions such as the presence of LBBB, right ventricular apex pacing, or left ventricular hypertrophy, which impair the sensitivity and specificity of the SE. Finally, in acute chest pain, it has been demonstrated that CSE is an accurate bedside modality to reclassify the patients in the acute chest pain unit – on top of clinical, laboratory, and ECG data[50]. In the future, CSE may add more information on the pathophysiology of cardiac function, rheological data at rest, and during exercise or pharmacological stress protocols[51,52].

Alternatively, abrupt destruction of contrast microbubbles after applying a high mechanical index impulse and a regional, slow contrast replenishment may uncover coronary microcirculation abnormalities during a steady infusion rate of contrast agent. The so-called myocardial perfusion test provides incremental prognostic information over clinical variables when it is performed[53]. Despite those promising results, its clinical use is still limited in clinical practice, probably because of technical obstacles (e.g., required software and contrast agent pump infusion).

5.9. Assessment of coronary flow reserve

Coronary flow reserve (CFR) is evaluated noninvasively with Doppler echocardiography and is feasible in left anterior descending artery (LAD) in >90% of the patients, whereas in posterior descending artery (PDA) and circumflex artery (Cx) in approximately 50% of the patients[54–58]. The use of contrast agents (e.g., 0.1–05 ml, bolus IV) further improves the feasibility of the method.

The flow in the distal segment of the LAD is detected by color Doppler (Nyquist limit between 10–20 cm/s) from the apical 2 chambers view with a slight angulation of the probe and flow velocity (maximum and average diastolic velocity) is measured by Pulse Wave Doppler. In LAD, maximum diastolic velocity varies between 15–35 cm/s, while the maximum systolic velocity is between 15–20 cm/s at rest[50,52,53]. Reverse diastolic flow at rest that reflects retrograde filling of the artery by collaterals is a very specific marker of coronary occlusion[51]. To calculate the coronary velocity reserve, maximum diastolic velocity in the coronary artery is recorded at rest and after the administration of either adenosine (2 mg bolus or 140 mcg/kg/min continuous infusion over 2–3 min), regadenoson (a single slow bolus), dipyridamole (0.84 mg/kg over 6 min) or dobutamine (usually at 30 mcg/kg/min)[59]. For dobutamine, it is proposed to achieve a 50 bpm increase of HR from baseline or at least 75% of the maximum predicted HR to consider it sufficient in the test for CFR analysis[60]. The measurement should be made in at least 3 cycles and the values should be averaged. The ratio of maximum diastolic velocity during hyperemia to the maximum diastolic velocity at baseline indicates the CFR (Fig. 3). Alternative to

Table 7
Commercially available contrast echo agents at present.

Gas core	Shell	Trade name	Bubble size (μm)
Octafluoropropane	albumin	Optison VR (GE Healthcare, Princeton, NJ, USA)	1-10
Sulfur hexafluoride	lipid	SonoVue (Bracco Imaging S.p.A, Milan, Italy)	1-10
Octafluoropropane	lipid	DefinityVR (Lantheus medical imaging, Billerica,MA,USA)	1-10
Perfluorobutane	lipid	Sonazoid (GE Healthcare, Princeton, NJ, USA)	2-3

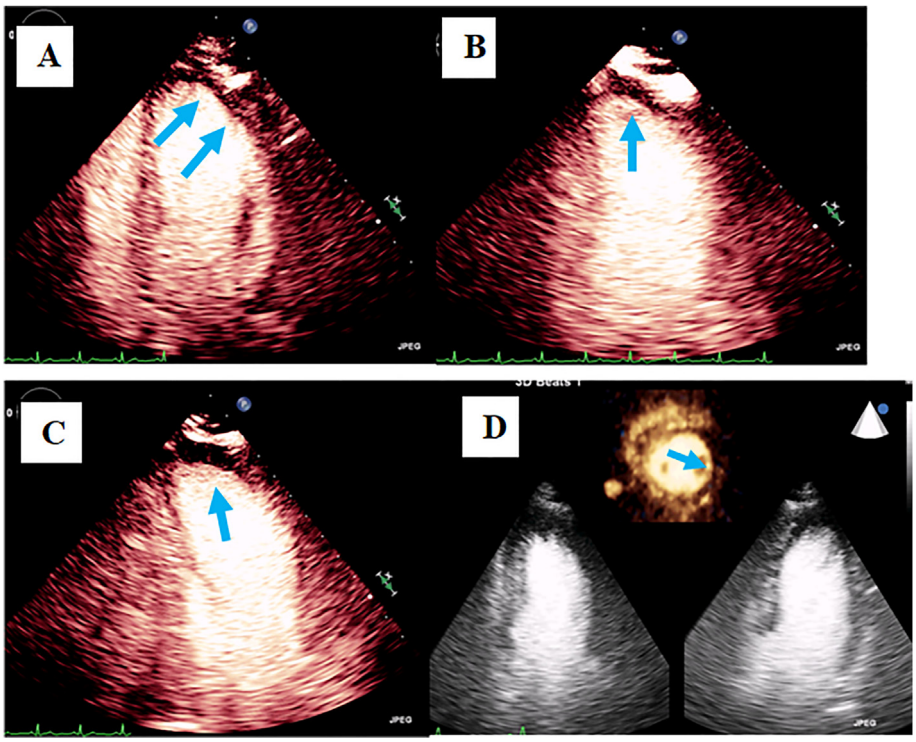

Figure 2. A 65-year-old man with proximal severe LAD stenosis revealed an early extended myocardial ischemic response at the apex and the anterolateral wall (arrows). Four chamber view (4CH), 2CH, 3CH, and 3D data set from the cardiac apex (A,B,C,D), respectively.

maximum values, the operator can calculate the ratio of the means or integrals (VTI) of diastolic velocities[55].

CFR <2 indicates hemodynamically significant coronary stenosis (>70%) or microcirculatory impairment (caused by atherosclerosis, hypertension, diabetes mellitus, cardiac syndrome X, dilated or hypertrophic cardiomyopathy, and aortic stenosis) or a combination of both (Fig. 4). In case of reduced CFR, only coronary angiography without significant coronary artery stenosis may distinguish the impairment in coronary microcirculation.

CFR can be used in combination with SE to get additional information, just before the test, when adenosine is used, or during the test when dobutamine is preferred. There is extensive evidence on the role of CFR in CAD diagnosis and its additive predictive value in DSE[61,62].

Keypoints:	Evidence/Studies	Consensus status
Coronary flow reserve (CFR) provides a well-validated index incorporating both epicardial and microcirculatory contributions.	Strong R[58] O[59,62]	Consensus
CFR may enhance the sensitivity of stress echocardiography.	Weak O[61,62]	Consensus
CFR is mostly obtainable in the left anterior descending artery, while its applicability is very limited in right and left circumflex arteries.	Weak O[54,57]	Strong consensus

5.10. Additive value of 3D-echo in stress echocardiography

Acquiring all necessary images at each stage of SE, mainly at peak stress, is a demanding and time-consuming procedure[63]. Recent advances in transthoracic matrix transducers have led to a fair improvement of 3D image quality[64–66] allowing a fast and simultaneous acquisition of all LV segments by rotating and slicing the volumetric dataset[67].

Achieving high frame rates is of utmost importance in SE for thorough WMA detection. According to the American Society of Echocardiography, ≥20 frames/sec (fps) at rest is required for interpretable and valid images and this frame rate must increase to >30 fps when heart rate exceeds 140 beats/minute[68]. Until recently, high frame rates could be feasible only with multibeat acquisitions, patients' breath-holding, and without arrhythmias. Novel advances in probes and software technology allow single-beat 3D images of the whole LV with more than 30 volumes/sec (volps), albeit with limited spatial resolution[67].

The advantage of 3D-multislice imaging is the visualization of all 17 LV segments in a single view, reduced procedure duration, and the avoidance of apical foreshortening[66]. To improve both spatial and temporal resolution at peak stress, the operator can reduce the image frame rate (higher spatial resolution) and simultaneously record multi beat acquisitions (up to 6 beats) of consecutive electrocardiographically-gated, narrowed subvolumes in the dataset (higher temporal resolution). *Due to the lack of an established imaging protocol of 3D echocardiography during SE for ischemia detection, the present Task Force has proposed a step-by-step approach combining 2D and 3D images acquisition* (Table 8).

5.11. 2D Strain-Speckle tracking Imaging

Speckle tracking echocardiography (STE) has been developed for the assessment of myocardial deformation. The motion of speckles in a certain region of interest is traced frame by frame throughout the cardiac cycle. Lack of angle dependency, high feasibility, and reproducibility are the main advantages of STE. However, relatively low frame rates (50–90 frames/sec) and inter-vendor variability are the main limitations that may compromise the accuracy of strain measurements during SE[33,69].

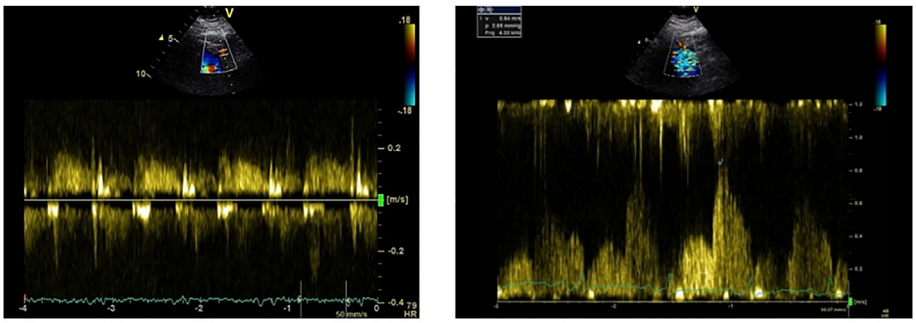

Figure 3. Patient with normal coronary reserve. CFR = 0.86:0.18 m/s = 4.7.

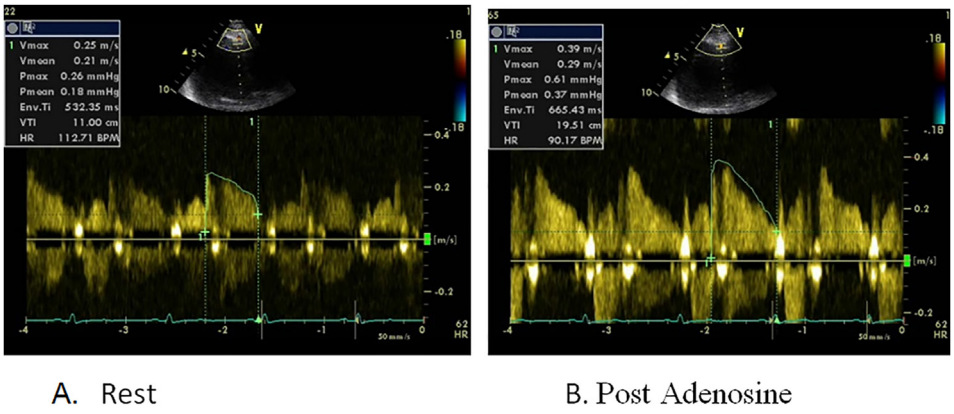

Figure 4. Patient with impaired coronary reserve. CFR = 0.39:0.25 m/s = 1.56.

The ischemic myocardial segments present reduced or lack of systolic longitudinal and circumferential shortening and radial thickening. Since longitudinal subendocardial fibers are affected earlier in the case of myocardial ischemia, a significant reduction in regional and global longitudinal strain from rest to stress has been demonstrated consistent with ischemia[33], even if there is not yet a definite cut-off value. Quantification of GLS at rest and during stress can be displayed in polar maps (bull's eye plots) side by side for direct comparison of strain values (Fig. 5). The main limitations are the GLS reduction during SE, even in normal subjects, owing to changes in loading conditions (reduction of LV preload, increase in systolic pressure) and the inadequate frame rate in the setting of tachycardia[70,71]. Furthermore, the concurrent use of STE and contrast agents is not possible, so far limiting its application in patients with optimal acoustic windows. Post systolic shortening after aortic valve closure is a promising index of myocardial ischemia, but it remains to be proved in SE[72]. Hence, it is still uncertain whether STE might have a complementary role in ischemia or myocardial viability diagnosis[33]. Perhaps, an increase in myocardial strain values during low-dose DSE may provide stronger evidence for myocardial viability[72].

In dilated cardiomyopathy (DCM) with advanced systolic dysfunction, the assessment of CR with SE may stratify cardiovascular risk, response to therapy, and functional recovery[13,73]. GLS changes during SE have added prognostic value to resting GLS and left ventricular ejection fraction (LVEF)[74]. In hypertrophic cardiomyopathy (HCM), impaired CR as expressed by a blunted increase in GLS during ESE may differentiate HCM from other causes of cardiac hypertrophy, such as hypertensive cardiomyopathy or athlete's heart[75]. There are also potential applications of STE in valvular diseases for decision-making[76,77].

Quantification of right ventricular (RV) longitudinal deformation either as global RV strain or strain of RV-free wall is also feasible. This provides additional information about RV function and pulmonary hypertension prognosis over conventional echo markers[33]. Nevertheless, the application of STE in RV pathology is still very limited.

Table 8
The step-by-step approach of a combined 2D and 3D stress echocardiography protocol for ischemia detection.

- Standard 2D views (PLAX, PSAX, 4CH, 2CH, 3CH) followed by real-time 3D views of the LV at each stage (baseline, low-dose, mid-dose, peak-dose, and recovery).
- Multislice technique to obtain the three apical views (4CH, 2CH, 3CH) and short axis views from the apex to LV base.
- Optimization of 3D images: 1) Reduce depth and volume width, focusing only at LV for higher frame rates. 2) Acquisition of 4–6 multibeat, consecutive, electrocardiographically-gated, subvolumes to increase the temporal resolution (>30 fps) during patient's breath-holding. 3) In patients with arrhythmias (e.g., atrial fibrillation), the frame rate can be increased and a single-beat data set can be acquired to avoid stitching artifacts. 4) Prefer contrast agents to increase sensitivity. 5) Use dynamic range at the basal and apical limits of the sector to avoid the interference of the mitral valve and LV outflow track.
- Comparison of 2D and 3D multislice images both at rest and peak stress.

6. Stress echocardiography in ischemic heart disease

6.1. Pathophysiology of ischemia

Supplement.

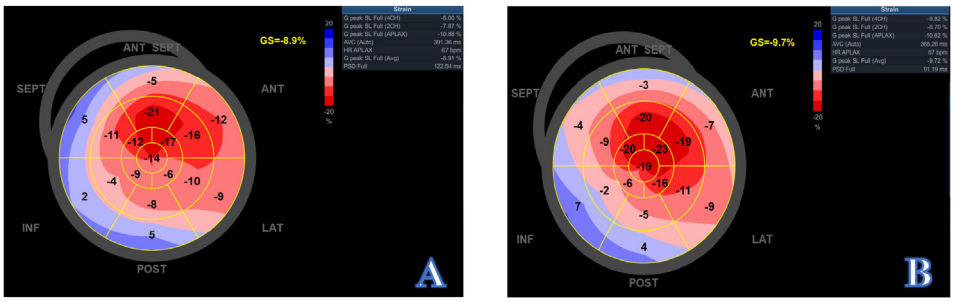

Figure 5. Speckle Tracking Imaging – Longitudinal strain. (A) Ischemic cardiomyopathy in a patient with a history of an extensive inferior-posterior-lateral myocardial infarction (B) No viability is detected during low-dose dobutamine SE.

6.2. Stress echocardiography and nonobstructive coronary arteries

6.2.1. Ischemia with nonobstructive coronary arteries

Over the last decade, an increasing number of patients are observed with evidence of myocardial ischemia with non-obstructive coronary arteries (INOCA). Although there is a debate in the definition of obstructive CAD between guidelines and other published studies[78,79], it is accepted that only lesions more than 50% can produce ischemia. INOCA may be attributed to either the over-sensitivity of present diagnosing methods (i.e., high-sensitive troponin) or a wide variety of pathophysiologic mechanisms. The term INOCA is respectively used as an umbrella definition of these syndromes representing a heterogeneous working diagnosis that requires further elucidation of potential underlying causes[80,81], as follows: atherosclerosis, plaque rupture, coronary dissection, Takotsubo-like syndrome, myocarditis, and thrombophilia disorders[82]. Moreover, in a sizable subgroup of patients, coronary microvascular dysfunction has been proposed as the leading pathophysiology[83]. In micro-vascular disorder, CFR may elucidate the causes of symptoms. In a large observational study in women with persistent angina, 26% showed CFR<2.0 and this was associated with significantly greater physical limitation and disease perception scores on relevant questionnaires[84]. Beyond CFR, the ability of SE to identify microvascular disease remains limited. Other common reasons for INOCA syndrome are coronary vasospasm[85] and underestimation of significant lesions which now can be identified by advanced interventional methods (fractional flow reserve - FFR and optical coherence tomography - OCT).

6.2.2. Management of "false results" in stress echocardiography

With regard to the increasing number of SE performed worldwide, "false-positive" SE may have a less benign prognosis than previously considered. In a retrospective study, patients with "false-positive" WMA had similar long-term outcomes with patients exhibiting true-positive WMA[86]. However, that resounding finding requires further investigation. However, a negative SE for ischemia does not entirely rule out the presence of angiographically obstructive CAD. There are several common technical reasons which lower the sensitivity of the method ("false negative"): 1) low-quality views of the lateral and inferolateral walls when the culprit lesion is located at the territory of Cx artery, 2) patients with suboptimal imaging owing to body habitus, 3) submaximal level of stress, and 4) antianginal treatment[87]. Finally, the diagnosis of a single-vessel disease may become challenging in less severe (50–70%) stenosis[88], where ischemia may not be detected depending on the anatomy of the rest of the vessels supplying the same myocardial wall.

Keypoints:	Evidence/Studies	Consensus status
Detection strategies for INOCA are still scarce. The Task Force did not end up to a consensus about the contribution of SE to INOCA diagnosis.	Expert opinion E	No Consensus
The clinical importance of regional wall motion abnormalities during SE in patients with nonsignificant coronary artery stenosis requires further investigation.	Expert opinion E	Strong consensus

6.3. Accuracy of stress echocardiography and comparison with other imaging modalities

SE has been validated over many years with coronary angiography. A meta-analysis of 55 studies with 3,714 patients demonstrated high sensitivity and specificity of approximately 81% and 84%, respectively[25]. The sensitivity of the method is even higher at left main or multivessel disease, and lower when the culprit lesion is at the circumflex artery. In single-vessel diseases, the sensitivity may be increased with b-blockers use at the end of the test as it interacts with dobutamine β1 receptors, leaving unopposed β2 and primarily α1-adrenergic vasoconstriction[78].

Presently, in addition to SE, the most popularly available diagnostic tests for CAD are stress cardiac MRI (CMR), single-photon computed tomography (SPECT), positron emission tomography (PET), and coronary computed tomography angiogram (CCTA). Except CCTA which provides direct visualization of the coronary tree anatomy, all other techniques aim to functional testing. The diagnostic accuracy of the aforementioned imaging modalities has been derived from a pool of trials, taking into consideration the pretest probability. Table 9 summarizes the diagnostic accuracy of all available tests.

SPECT imaging has been used for ischemia detection over many decades. Its major disadvantage is the radiation exposure and the related risk for cancer development, which reduces its repeatability. SPECT has roughly similar accuracy with DSE, demonstrating superiority on interobserver variability as it is a less operator-dependent method[89]. SE has demonstrated higher accuracy in three-vessel disease than SPECT in which discrimination power is based on perfusion differences between myocardial segments, and so, global ischemia might be missed.

PET is similar to SPECT, with higher accuracy but less validation[90]. Its cost is higher and is also less widely available because of the expensive equipment and difficulties in obtaining adequate radionuclides[91].

Table 9
Comparison of imaging modalities for CAD diagnosis regarding their sensitivity and specificity[97].

Diagnosis of coronary artery disease		
	Sensitivity (%)	Specificity (%)
Exercise ECG	45-50	85-90
Exercise stress Echocardiography	80-85	80-88
Exercise stress SPECT	73-92	63-87
Dobutamine stress Echocardiography	79-83	82-86
Dobutamine stress MRI	79-88	81-91
Vasodilator stress Echocardiography	72-79	92-95
Vasodilator stress SPECT	90-91	75-84
Vasodilator stress MRI	67-94	61-85
Coronary CTA	95-99	64-83
Vasodilator stress PET	81-97	74-91

Stress CMR is the newest diagnostic test that demonstrates PET-superiority on accuracy and shares features from both SPECT and DSE. Dobutamine or vasodilators are the common stressors in S-CMR. However, the use of dobutamine is quite problematic, because of its arrhythmogenic effect and the limited space in the magnet room which makes it unsuitable for successful emergency response. Stress CMR is certainly less operator-dependent compared with SE, with no radiation exposure. Implanted pacemakers and other implantable devices on the left pectoral site or metallic valves cause artifacts with unfavorable effects on the test's accuracy. Despite the high potential of stress CMR, several factors limit its wide usage worldwide, such as the expensive equipment, safety issues, and claustrophobia.

CCTA appears to be the best modality in patients with low pretest likelihood for CAD, no previous diagnosis of CAD, and characteristics associated with good image quality, with the expense of radiation exposure[25]– even if the latter appears to be much lower nowadays (media effective dose 0.63–4.77 mSv)[92]. It is primarily an anatomical, nonfunctional technique with high specificity, which detects subclinical coronary atherosclerosis or rule out anatomically significant CAD[93]. A low coronary calcium burden, referred to as Coronary Artery Calcium Score (CAC Score), demands very low radiation exposure and can almost rule out CAD, as a CAC score of zero is associated with low risk of CAD and coronary events in short-term patients with low pretest probability (e.g., asymptomatic screening setting)[94]. Patients with extensive coronary calcification are less benefited by CCTA as the severity of coronary lesions cannot be accurately measured.

Recently, a combination of CCTA with functional assessment of coronary fractional flow has emerged as a quite promising modality, but requires further investigation[95]. The selection of a diagnostic technique for any given patient to rule-in or rule-out CAD should be based on the optimal pretest probability range for each test and the assumed reference standard[96].

Keypoint:	Evidence/Studies	Consensus status
The selection of the appropriate diagnostic test for ischemia relies primarily upon the local resources, the availability of the test, the clinical judgment, the individual's pretest probability, and the patient's preference.	Strong M[25,90]	Strong consensus

6.4. Ischemic cardiomyopathy-viability assessment

Myocardial viability refers to myocardial segments with preserved metabolic and/or contractile function after prolonged impaired blood supply, which may recover after the restoration of blood flow[98]. Episodes of persistent myocardial ischemia may lead to any of the following three distinct, pathological patterns: myocardial necrosis with a scar; stunning; and hibernating myocardium[99,100]. Viability refers to the latter two patterns.

6.4.1. Protocols, methods, and technical considerations

Dobutamine remains the most widely used inotropic agent, but other agents such as dipyridamole[101], adenosine, or nitroglycerin, and exercise have been also used in viability tests. A low-dose DSE is usually performed (incremental infusion rates of 5, 10, 20 mcg/kg/min every 3–5 min) according to the patient's clinical and hemodynamic status and contractile response. Higher dobutamine infusion rates (up to 40 mcg/kg/min) may be applied for myocardial ischemia detection, after completion of the viability test (Fig. 1E). Withdrawal of beta-blockers is not mandatory before the test, but their presence may reduce the sensitivity of the method[102]. Alternatively, proceeding to high-dose dobutamine infusion may be effective and safe for b-blockers-treated patients. SE with low-dose dipyridamole infusion (0.28 mg/kg over 4 min or 0.56 mg/kg over 4 min)[103] or low-dose adenosine infusion (80, 100, 110 mcg/kg/min at 3 min intervals)[104] for the detection of myocardial viability may be used when dobutamine is not well tolerated or contraindicated. ESE on a supine bicycle[105] with low increments of workload (10–20 W) every 1-2 min stage has also been employed, but it has not gained broad acceptance. Myocardial perfusion imaging has been used to assess microvascular integrity in many studies, exhibiting good results[106,107]; hence, the European Association of Cardiovascular Imaging (EACVI) has adopted it as a particularly useful tool for myocardial viability detection[35]. LV deformation indices (strain or strain rate) have been applied adjunctively during low-dose DSE, showing promising results[108].

6.4.2. Detection of regional myocardial viability

A viable myocardial segment is characterized by initial hypokinesia or akinesia at rest and significant improvement of myocardial thickening during inotropic stimulation, known as the contractile reserve (CR). A regional response to SE is important in CAD patients to address the question of revascularization in the following cases: A) Viable, initially hypokinetic, segments are likely to improve after revascularization as the myocardial wall consists of scar and hibernating myocardium[109]. B) Viable, initially akinetic segments, are less likely to improve after revascularization because SE has high specificity, but lower sensitivity in predicting revascularization efficacy[110]. C) Lack of improvement during low-dose DSE is associated with a low likelihood of functional recovery after revascularization; however, it is not excluded.

The main determinant of viability assessment during SE is the contractility changes of myocardial segments. Remodeled myocardial segments or regions with nontransmural injury exhibit contractility improvement during low-dose DSE protocol[111]. The coexistence of ischemia is another reliable sign of viability. Thereby, the contractility worsening of at least two adjacent segments after initial improvement (biphasic response) has the highest positive predictive value[112], while the worsening of contractility during low-dose DSE protocol in initially hypokinetic myocardial segments indicates both ischemia and increased cardiac mortality[113]. Diagnostic criteria of viability during a DSE study are presented in Table 5, while a diagnostic algorithm is also proposed in Fig. 6.

6.4.3. Quantification of global myocardial viability and criteria for intervention

Some factors may affect the diagnostic accuracy of low-dose DSE to predict revascularization-induced functional recoveries such as the number of viable segments, the protocol, the type of response

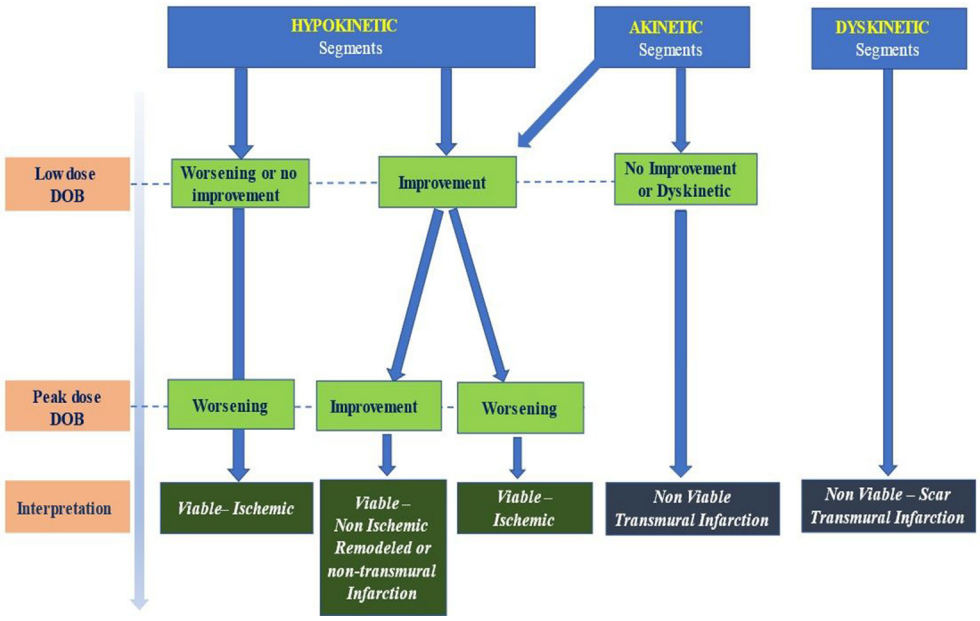

Figure 6. A proposed diagnostic algorithm of viability during a DSE study.

during the test, and the timing of evaluation[100]. *As a general approach of this Task Force, the detection of less than 3 viable myocardial segments in low-dose DSE indicates an insufficient amount of global cardiac viability and justifies exclusion from revascularization.* Previous studies have suggested four dysfunctional segments as the minimum amount of viable myocardium that can induce a 5% increase of EF and a favorable outcome[114]. An increase of WMS >3.5 grades during low-dose DSE has an overall accuracy of 84% for the detection of functional recovery[115]. A combined low- and high-dose DSE protocol has exhibited considerable sensitivity (75–89%) and specificity (68–93%) for the detection of viable segments in both the postinfarction phase[116] and the chronic phase[117], especially when a biphasic response coexists[118]. Dipyridamole infusion protocols have lower diagnostic accuracy[119], whereas low-dose adenosine SE has shown significant diagnostic potential[99]. The addition of contrast agents may improve both sensitivity and specificity of DSE[120].

Compared to other imaging modalities (18FDG-PET, SPECT, CMR), DSE has been documented to have the highest specificity for the detection of viable myocardium[121]. Nuclear techniques have higher negative predictive values of ≥95%[122], while CMR techniques have comparable diagnostic accuracy[123].

Great skepticism was raised when viability assessment as a decision-making tool was challenged in the underpowered HEART study[124] and during the nonrandomized subanalysis of the STICH trial[125]. Although both studies had many limitations, no survival superiority was demonstrated in the revascularization arm over the nonrevascularization in any of them, except in patients with >10% viable myocardium.

6.4.4. 2D Strain-speckle tracking imaging in myocardial viability

STE is theoretically useful for the evaluation of myocardial ischemia and viability. GLS at rest echocardiography may be used for the evaluation of the infarcted area in patients with CAD and a cut-off value of −12% has shown a good correlation with CMR in the identification of transmural infarction[126]. However, there is no strong evidence supporting the use of STE in SE for the evaluation of myocardial ischemia and viability. According to a recent meta-analysis[127], deformation imaging during SE has higher sensitivity, but similar diagnostic accuracy with visual assessment of ischemia. The lack of definite cut-off values quantifying WMA till now appears to be the most important limitation of the technique.

Keypoints:	Evidence/Studies	Consensus status
Beginning with low and proceeding to high dose dobutamine infusion protocols may be applied for viability assessment.	Expert opinion E	Consensus
DSE provides prognostic parameters, which may aid the decision-making in candidates for coronary revascularization. However, more data from large-scale, studies with long-term follow-up are required.	Weak O[114–118]	Strong consensus
Further investigation may be needed for the clinical use of strain in the evaluation of myocardial ischemia and viability during SE.	Expert opinion E	Strong consensus

6.5. Stress echocardiography in special conditions

6.5.1. Left bundle branch block

Stress testing can be particularly challenging in this high-risk patient group. The prevalence of CAD among patients with left bundle branch block (LBBB) is increased[128]. Exercise ECG stress test is not an option owing to the presence of baseline ECG abnormalities and myocardial perfusion scintigraphy is limited by the high rate of false-positive results[129]. ESE is a feasible and safe option, found to provide significant prognostic information; however, specificity can be compromised in cases of globally abnormal LV contractile reserve, often resulting in poor specificity[130]. DSE has shown good diagnostic accuracy in LBBB patients with suspected CAD[131,132]. *Contrast agents' infusion with a persistent focus on endocardial wall thickening rather than myocardial excursion is advised by*

this Task Force to further improve accuracy in patients with LBBB[133]. In patients with abnormal rest septal thickening, however, detection of inducible ischemia in the LAD territory may be compromised.

6.5.2. Pacemaker-dependent patients

Pacing SE is an efficient and safe option in pacemaker-dependent patients. External programming is applied, starting with pacing at 100 bpm with increments of 10 bpm every 3 min, until target HR is achieved[134]. Sensitivity is suboptimal, especially in patients with one-vessel disease, as it relies only on HR increase, while contractility increases minimally and blood pressure remains unchanged. *Despite limited published data*[135]*, this Task Force encourages the addition of an adjusted dobutamine infusion protocol to pacing SE to increase sensitivity without compromising specificity.*

6.5.3. Atrial Fibrillation

ESE and DSE are both feasible and accurate in patients with atrial fibrillation, despite the presence of specific challenges, such as unpredictable chronotropic response, beat-to-beat variation, and increased prevalence of arrhythmia, particularly with DSE[136]. Those drawbacks may be overcome by acquiring many cardiac cycles for each view per stage.

Keypoints:	Evidence/Studies	Consensus status
DSE with contrast agents use may be the first in-line method for ischemia detection in patients with LBBB.	Weak O[133]	Consensus
Pacing SE is an efficient option in pacemaker-dependent patients, lacking the inotropic triggering which may compromise its sensitivity. It may be combined with a dobutamine infusion protocol to increase its sensitivity.	Weak O[134,135], E	Consensus
The prognostic value of SE is maintained in patients with atrial fibrillation.	Weak O[136]	Consensus

6.6. Stress echocardiography for risk stratification, prognosis, and preoperative evaluation

6.6.1. Risk stratification and prognosis

SE yields prognostic information for risk stratification of patients with known or suspected ischemic heart disease. The presence of inducible WMA classifies patients' prognoses[25]. Most of the evidence has been derived from data banks of thousands of patients for exercise[137–139], dobutamine[140,141], and dipyridamole testing[142]. Both normal baseline echocardiography and SE confer a benign prognosis and give an annular risk of death of 0.4–0.9%[137]. Thus, in this subgroup of patients, coronary angiography can safely be avoided[79]. Peak WMSI can effectively risk stratifying patients into low- (0.9%/year), intermediate- (3.1%/year), and high-risk (5.2%/year) for cardiac events[143]. Risk stratification may cluster the positive or negative response with clinical parameters (diabetes, renal dysfunction, previous revascularization, and therapy at the time of test), resting echocardiography (global LV function), and additive SE parameters (LV cavity dilatation, CFR)[144]. Peak WMSI >1.7 and baseline EF $\leq$ 45% are independent markers of patients at high risk of an adverse clinical outcome[80]. Most recently, the detection of B-lines during SE appeared with independent prognostic value in a large, multicenter study[145].

6.6.2. Preoperative evaluation

Cardiac complications are the main cause of perioperative mortality. Depending on the risk of the operation (low, intermediate, high) and the patient's clinical risk factors, the overall risk should be stratified preferably with an ESE. The latter assesses at the same time the functional capacity of the patient and the presence of ischemia[146]. When physical exercise is impossible, as in elderly patients undergoing high-risk operations, DSE is the method of choice for preoperative risk assessment with excellent negative predictive value for adverse events, similar to SPECT[3]. Even though the positive predictive value of SE for adverse events is low, ischemia during DSE and a history of congestive heart failure remain the two strongest predictors for major adverse cardiac events[36].

Keypoints:	Evidence/Studies	Consensus status
Stress echocardiography in combination with clinical and resting echocardiographic parameters may provide a valuable tool for pre-operative risk stratification.	Expert opinion E	Strong consensus
The perioperative risk may be adequately assessed by stress echocardiography (preferably exercise stress echocardiography).	Weak O[137–145]	Strong consensus

7. Stress echocardiography in nonischemic cardiac disease

7.1. Diastolic stress test echocardiography (DSTE)

DSTE refers to the use of exercise Doppler echocardiography to assess diastolic function and the increase of left ventricular filling pressure (LVFP) during exercise.

7.1.1. Assessment of diastolic dysfunction

Patients with unexplained resting breathlessness or exertional dyspnea/poor exercise and concomitant risk factors for diastolic dysfunction (older age, hypertension, obesity, diabetes, sedentary lifestyle) should undergo diastolic function and LVFP evaluation. DSTE was firstly proposed as a part of the diagnostic algorithm of diastolic dysfunction in patients with indeterminate diastolic function at rest[147]. Exercise changes in E/e' and maximum values of tricuspid regurgitation velocity (TR Vmax) during DSTE combined with baseline e' wave may set the diagnosis of diastolic dysfunction and elevated LVFP. Nevertheless, other studies have doubted the accuracy of those criteria[148,149]. E/e' is a simple and the most popular index of diastolic dysfunction. Patients with diastolic dysfunction, increase cardiac output during exercise at the expense of increased LVFP. E and e' waves are normally expected to be increased during exercise with the ratio E/e' to be either stable or slightly decreased. Usually, in diastolic dysfunction, E wave significantly increases during exercise, while e' remains unchanged leading to a significant E/e' ratio increase. If there is no significant change in E/e' ratio and the clinical suspicion of diastolic dysfunction persists, the test is considered indeterminate and an invasive hemodynamic test may follow.

7.1.2. Heart failure with preserved ejection fraction (HFpEF) diagnosis

In the most recent recommendations from the Heart Failure Association – based again on expert consensus and not on

adequately powered studies[150]— DSTE was indicated in patients with suspected HFpEF when rest echocardiography and natriuretic peptides do not draw a firm conclusion (intermediate probability - HFA-PEFF Score: 2—4). In this case, the exercise achieved parameters: average E/e' ≥15 which may be accompanied or not by TR Vmax >3.4 m/s, have been proposed as supportive indices of HFpEF, but only after assessing resting functional and morphological echocardiographic indices and natriuretic peptides measurements. Positive DSTE is highly predictive of future HFpEF-related events (admissions, cardiovascular death, worsening NYHA Class, or worsening ejection fraction)[151]. Therefore, it is necessary to incorporate DSTE in a diagnostic algorithm for HFpEF or unexplained dyspnea, accompanied by a complex of echocardiographic and hemodynamic indices.

7.1.3. Other useful findings during DSTE

DSTE can also reveal alternative causes of dyspnea, beyond CAD or valvular diseases, such as dynamic left ventricular outflow obstruction (LVOTO) or chronotropic incompetence. Consequently, DSTE should not only focus on diastolic function parameters, but in parallel, evaluate all the dynamic components of LV function (WMA, valvular diseases, etc), RV function (TR Vmax, tricuspid annular plane systolic excursion - TAPSE, S' wave in Tissue Doppler imaging), the chronotropic and blood pressure response, the achieved workload, and the exercise capacity. Those findings are associated with unfavorable outcomes if combined with elevated LVFP[152].

7.1.4. Limitations of DSTE

In addition to the technical issues compromising ESE analysis (Part I, section 4.5.2), several functional factors limit the utility of DSTE. Concomitant medications with negative inotropic action should be considered, as they may affect the association of E/e' with LVFP[153]. At high heart rates, MV inflow waves and annulus Tissue Doppler velocities are fused, and hence, it is suggested that these velocities are measured at low/intermediate levels of exercise test (HR~100—110bpm). To overcome early fusion caused by an abrupt heart rate increase, the latter parameters may be alternatively assayed within the first 1—2 minutes of early recovery as diastolic abnormalities persist after exercise cessation. In parallel, the aforementioned echocardiographic indices may be affected by several functional/clinical factors such as the following: preload, age, exercise type, and LV hypertrophy[154]. The recommended echocardiographic parameters during DSTE are presented in Table 10.

Keypoints:	Evidence/Studies	Consensus status
DSTE may be indicated in patients with unexplained resting breathlessness, or exertional dyspnea and/or poor exercise capacity with indeterminate diastolic function.	Expert opinion E	Consensus
Diastolic dysfunction may fulfil all the following criteria in DSTE: Peak average E/e' > 14 or peak septal E/e' > 15 and TR Vmax > 2,8 m/s with rest values of septal e' <7 cm/s or lateral e' < 10 cm/s.	Expert opinion E	Consensus
The average E/e' ratio accompanied with or without TR Vmax > 3.4 m/s during DSTE may be recommended for HFpEF diagnosis when there is an intermediate probability, but there is still controversy about its clinical applicability and relevance.	Expert opinion E	Consensus

7.2. Stress echocardiography in aortic regurgitation (AR)

Although aortic valve replacement (AVR) remains the cornerstone of management in symptomatic severe AR, the decision of AVR timing remains challenging when there is a discrepancy between symptoms and AR severity[155]. ESE may be a useful diagnostic tool when there is a discordance between symptoms and AR severity, but it has no role in the assessment of AR severity because tachycardia shortens diastole and AR appears to be less severe.

7.2.1. Asymptomatic patients with severe AR

ESE is strongly recommended to unmask symptoms in so-called asymptomatic patients with severe AR. LV views should be acquired during ESE to detect the CR, defined as >5% increase in LVEF, a good predictor of LV systolic function during conservative follow-up or postoperatively[156,157]. It has been shown that exercise TAPSE <20 mm associate with the need for earlier AVR and may be useful[158]. Despite none of these parameters being included in guidelines for routine clinical use, they could be considered to determine surgical timing in patients otherwise not eligible for AVR[159].

7.2.2. Symptomatic patients with nonsevere AR

In symptomatic patients with nonsevere AR, ESE can identify other causes for symptoms, such as inducible ischemia, diastolic dysfunction, dynamic mitral regurgitation (MR), or pulmonary hypertension. The minimum acquired dataset contains LV views, color flow Doppler for MR, and continuous wave Doppler for TR Vmax measurement.

Keypoints:	Evidence/Studies	Consensus status
In asymptomatic patients with severe AR, ESE may unmask symptoms and determine contractile reserve.	Weak O[156,157]	Consensus
In symptomatic patients with non-severe AR, ESE may identify other cardiac-related, other than AR, reasons for symptoms.	Expert opinion E	Strong Consensus
There is no role for SE to assess AR severity.	Expert opinion E	Consensus

7.3. Stress echocardiography in aortic stenosis (AS)

Severe AS is defined by an aortic valve area (AVA) < 1.0 cm^2, which may be accompanied by trans-aortic peak velocity > 4 m/s and/or a mean aortic valve gradient >40 mmHg. SE plays role in the diagnostic workup of the following three categories of patients with — AS: asymptomatic high-gradient severe AS; "classical" low-flow, low-gradient severe AS (LF/LG AS) with reduced (LVEF); and low-gradient severe AS with preserved LVEF[10,160]. The latter group of patients can be further subdivided into preserved (normal-flow) versus reduced (paradoxical low-flow) stroke volume, using a cut-off value indexed (SVi) of 35 ml/m^2. When a severe AS becomes symptomatic, the rate of death is >50% at 2 years unless a valve replacement is performed[161]. SE may contribute to early recognition of AS-provoked symptoms, differentiating true-severe and pseudo-severe AS[161,162] (Fig. 7).

7.3.1. Asymptomatic patients with high gradient severe AS

A symptom-limited graded exercise test is recommended, and at least 85% of the age-predicted heart rate should be reached in the absence of symptoms. Common bicycle ESE protocol is recommended (Part I, 2.4.2). An abnormal exercise response or

Table 10
Protocol of diastolic stress echocardiography.

Stage	Supine bicycle				Treadmill			
	MV inflow velocities (E and A waves)	Mitral annulus TDI (e' septal & lateral)	TR Vmax	LV views (4-, 2- and 3-CH view)	MV inflow Velocities (E and A waves)	Mitral annulus TDI (e' septal & lateral)	TR Vmax	LV views (4-, 2- and 3-CH view)
Rest	√	√	√	√	√	√	√	√
Each stage	√	√	√	√				
Peak	√	√	√	√				
Early recovery (1-2 min)	√	√		√	√	√		√

TDI, tissue doppler imaging; CH, chamber; TR Vmax, tricuspid regurgitation maximum velocity.

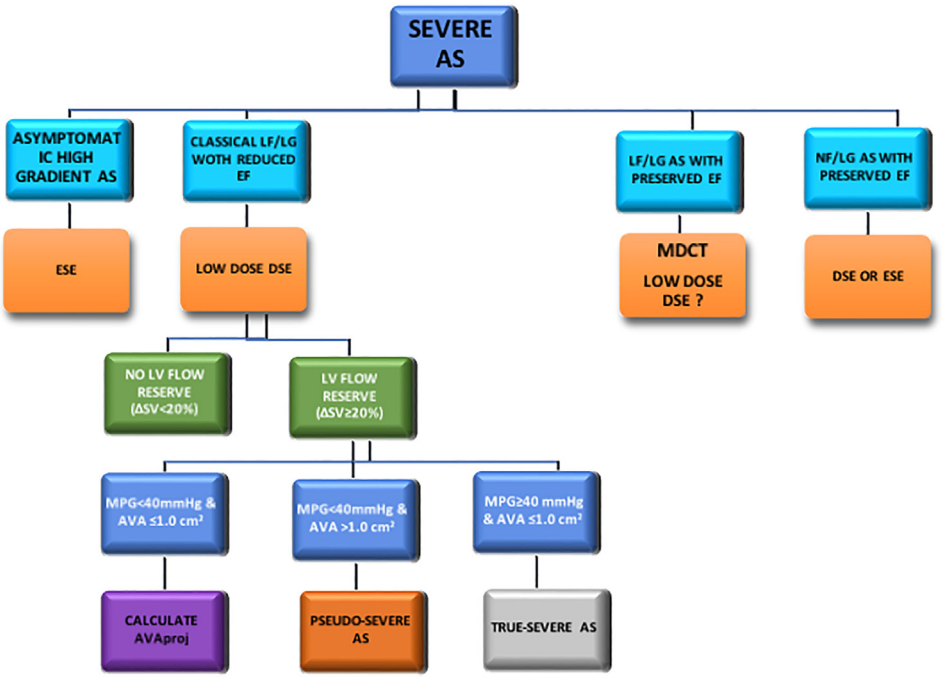

Figure 7. Algorithm for the management of patients with severe aortic stenosis (AS). AVA, aortic valve area; AVAproj, projected aortic valve area; SE, stress echocardiography; DSE, dobutamine stress echocardiography; ESE, exercise stress echocardiography; LF/LG, low-flow, low-gradient; MDCT, multislice computed tomography; .MPG, mean pressure gradient; NF/LG, normal-flow, low-gradient; SV, stroke volume;

echocardiographic findings of poor prognosis during ESE may affect the timing of interventional therapy in patients with severe asymptomatic AS.

- Abnormal exercise response is determined when one of the following occurs[163]:
  - Cardiac-related symptoms (angina, dyspnea, dizziness, syncope, or near syncope).
  - > 2 mm ST-segment depression.
  - Drop or a <20 mmHg increases in systolic BP during exercise.
- ESE indices of poor prognosis in high gradient AS[164]:
  - Aortic valve mean gradient increases by ≥18−a20 mmHg; associated with a 3.8-fold higher risk of cardiac events.
  - PASP increase at >60 mmHg; associated with 2-fold higher risk of a cardiac event at 3-year follow-up.
  - Worsening in LVEF or a slight increase of LVEF <5%.

7.3.2. Classical LF/LG severe AS with reduced ejection fraction

A low-dose DSE can be used to assess LV flow reserve and distinguish pseudo-severe AS from classical LF/LG severe AS[165,166]. The infusion dose of dobutamine starts at 5 μg/kg/min and increases every 5 min by 5 μg/kg/min to a maximum dosage of 20 μg/kg/min. The baseline heart rate should be less than 100 bpm and should increase at least 10 bpm during the procedure. At each stage, the measurements of AVA, stroke volume, and trans-aortic gradient are performed. According to the recommendations of the European and American Association of Echocardiography, a true-severe AS is defined by an increase in maximum velocity over 4 m/s with a valve area <1.0 cm^2 at any time during DSE (Fig. 8)[11]. In contrast, patients having an increase in AVA >1.0 cm^2 without a significant increase in the mean gradient will be classified as having a pseudo-severe AS. The differentiation between true- and pseudo-severe AS remains unclear when there is no LV flow reserve, defined as stroke volume and/or LVEF increase <20% during DSE. Patients with flow reserve in DSE showed lower perioperative mortality than those without[167]. However, other studies from surgical and transcatheter AVR series found no association between flow reserve on DSE and clinical outcomes[168]. For those reasons, the projected AVA at a standardized normal flow rate (Q) (i.e., 250 mL/s) has been suggested as an alternative approach, especially in the absence of contractile reserve, using the formula:

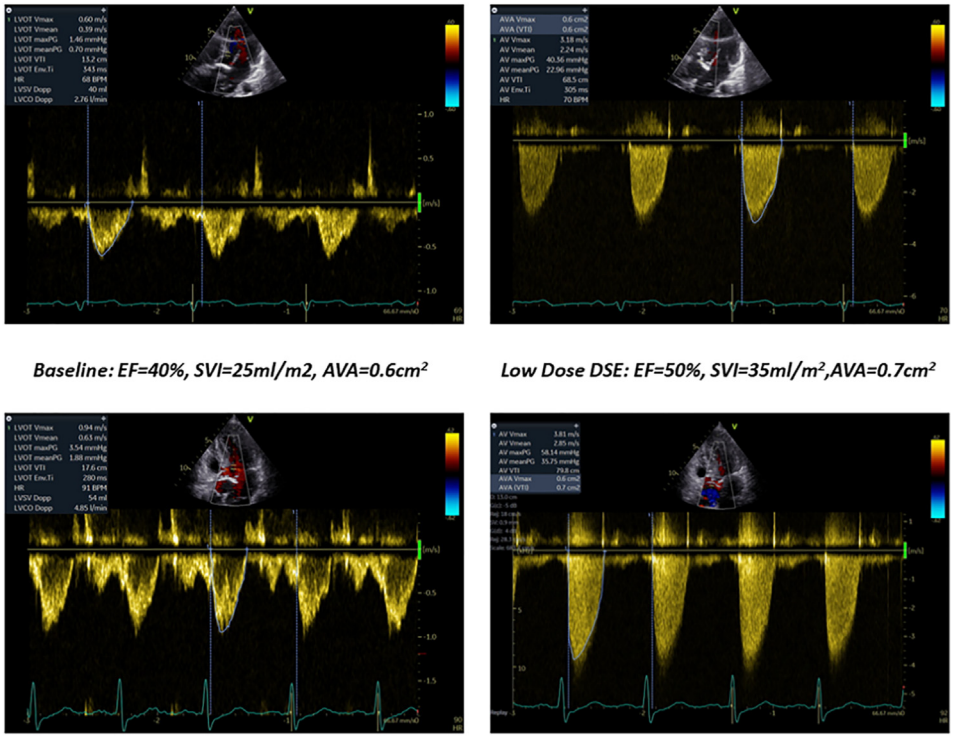

Figure 8. Low-dose dobutamine stress echocardiography in patients with LF/LG severe AS.

Projected AVA = AVArest + (ΔAVA/ΔQ) × (250−Qrest)

where AVArest and Qrest are the AVA and mean transvalvular flow rate measured at rest, and ΔAVA and ΔQ are the changes in AVA and Q during DSE[169–171]. A projected AVA <1.0 cm^2 suggests true-severe stenosis[172].

If the projected AVA cannot be calculated, because there is no ΔQ>20%, the multislice computed tomography (MDCT) may be helpful to further differentiate and detect a severe AS by calculating the grade of calcification (severe AS likely: men≥2000 units, women≥1200 units of Agatston method)[169].

7.3.3. Low-gradient AS with preserved ejection fraction

7.3.3.1. Paradoxical LF/LG severe AS with preserved ejection fraction. Paradoxical LF/LG severe AS with preserved ejection fraction is defined by an AVA <1.0 cm^2, low-flow (SVi <35 ml/m^2), a low-gradient (mean value < 40 mmHg) and LVEF >50%. It has been shown that approximately 1/3 of patients with paradoxical LF/LG severe AS had only pseudo-severe stenosis, thus requiring a different therapeutic approach. Distinguishing true-severe AS from paradoxical LF/LG pseudo-severe AS is much more challenging than in classical LF/LG AS. The application of DSE is questionable, while MDCT may be helpful to detect a severe AS in that case[165].

7.3.3.2. Normal flow, low-gradient (NF/LG) severe AS with preserved ejection fraction. NF/LG severe AS with preserved ejection fraction is defined by an AVA <1.0 cm^2, normal-flow (SVi >35 mL/m^2), a low -gradient (mean value < 40 mmHg), and LVEF >50%. This is usually referred to symptomatic patients with moderate AS and SE aims to determine if there is a coexistent CAD (development of WMA) or a poorly compliant aortic valve. In the latter case, patients with resting trans-aortic mean gradient >35 mmHg and exercise-induced disproportional augmentation of mean gradient (>20 mmHg) should be closely monitored, owing to a higher risk of death and AVR[173].

Keypoints:	Evidence/Studies	Consensus status
ESE in asymptomatic high gradient severe AS may unmask symptoms and determine low exercise capacity associated with poor prognosis.	Weak O[163]	Strong consensus
A low-dose DSE may assess LV flow reserve and distinguish pseudo-severe AS from classical LF/LG true-severe AS.	Weak O[165,167]	Strong consensus
SE may be indicated in an NF/LG to determine a coexistent coronary artery disease or a poorly compliant aortic valve in symptomatic patients with moderate stenosis.	Expert opinion E	Consensus

7.4. Stress echocardiography in mitral stenosis (MS)

SE is being increasingly used to provide diagnostic and prognostic information when there is a discrepancy between symptoms and valve severity in the following cases:

7.4.1. Asymptomatic patients with moderate or severe MS

Small clinical studies have outlined the utility of exercise testing and ESE to unmask underlying symptoms and hemodynamic disorders in otherwise “asymptomatic” patients[174]. An exaggerated rise in left atrial, pulmonary venous, and pulmonary capillary pressures during exercise stimulates the sensation of dyspnea in MS patients. In parallel, the increase in right ventricle afterload limits the expected increase in RV output during ESE and leads to fatigue (achieved heart rate <85% of age-predicted maximum heart rate). ESE provides a more quantitative and objective assessment of those main MS-related symptoms (dyspnea and fatigue) rather than a self-reported, subjective approach. Symptoms onset has been associated with a significant

increase in PASP levels during ESE[175]. PASP may be confounded by physical activity level, age, and gender[176]. A rapid PASP rise at low levels of ESE (≤60W at bicycle testing), in "asymptomatic" patients with significant MS[177] may adequately reclassify them as symptomatic, overcoming the limits of pulmonary circulation changes during exercise. Recently, one of the largest observational studies in asymptomatic patients with significant MS demonstrated the association of higher mortality with lower age/sex-related exercise capacity and exercise-induced PASP level at the end of the treadmill test[178].

7.4.2. Symptomatic patients with moderate MS

The exercise-induced values of both trans-mitral mean pressure gradient and PASP have been proposed to determine intervention need when symptoms are disproportional to MS severity in rest echocardiography[179]. Last AHA guidelines have set an increase in mean gradient to >15 mmHg during ESE, as a cut-off point of hemodynamically significant MS (level of evidence IIbC). However, limited data are available to support that recommendation. An alternative to ESE is DSE with 3-min stages of incremental dose (from 10 mcg/kg/min to 40 mcg/kg/min). DSE takes advantage from its application in patients who are unable to undergo treadmill or bicycle stress test[180,181]. A cut-off value of trans-mitral mean gradient increase to >18 mmHg during dobutamine infusion may identify MS patients at high risk of eventful clinical course without intervention[182]. Notably, the latter study enrolled a cohort with large clinical and echocardiographic variety (symptomatic and asymptomatic patients with MS ranging from mild to severe). Small DSE studies have suggested other indexes of MS severity, but they require further investigation owing to the remaining gap of evidence[183].

Keypoints:	Evidence/Studies	Consensus status
In asymptomatic patients with at least moderate MS, ESE may reclassify the need for intervention in those who develop symptoms or appear with PASP rise (cut off not determined) at an early stage of the exercise test.	Weak - expert opinion O[174,177], E	Consensus
In symptomatic patients with moderate MS (mean gradient: 5 −9 mmHg), an increase in trans-mitral mean gradient to > 18 mmHg (during DSE) or >15 mmHg (during ESE) may indicate earlier intervention with clinical benefits.	Weak O[180,181]	Consensus

7.5. Stress echocardiography in mitral regurgitation (MR)

Recent ESC guidelines (2017) have commented on the potential utility of ESE when there is a mismatch between MR severity and symptoms[10]. However, there is no official recommendation for ESE as part of MR management. The latest ACC/AHA guidelines (2020) recommended exercise testing (level of evidence IIaB) and exercise-induced hemodynamic changes assessment in case of discrepancy between symptoms and primary MR severity[184]. However, specific echocardiographic parameters were not mentioned, while the EIPH was no longer recommended after being part of the 2006 guidelines. Recently, there is a rewarming scientific interest for ESE application in MR patients, which may assist clinical decision-making based on the following parameters:

7.5.1. Symptoms development in asymptomatic patients with moderate or severe MR

The presence of symptoms is one of the most important determinants of mitral valve (MV) surgery decision. It remains a big challenge to reveal MR-related symptoms in patients denying them because they exert self-limited activity to avoid the unpleasant sensation of dyspnea and/or fatigue. Among asymptomatic patients with at least moderate MR, 30−40% appear with masked symptoms and may equally benefit from mitral valve intervention as symptomatic patients. The provocation of symptoms during supine bicycle has been associated with adverse events and the need for MV surgery in patients with MV prolapse (MVP)[185].

7.5.2. Exercise-induced changes in MR severity

Increase in MR severity (defined as ΔEROA ≥ + 10 mm^2 or Δregurgitant volume ≥ +15 ml) may explain the development of symptoms in patients with at least moderate MR[186]. There are several concerns about the validity and variability of EROA and regurgitant volume (RVol) measurements at rest and mainly during ESE[187]. Over the last two decades, since EROA and RVol were proposed, their use for MR quantification during ESE in MVP patients remains limited by research groups other than those initially introduced them[188]. The exaggerated mitral annulus motion and the eccentric jets mostly observed in MVP may further attenuate the accuracy of EROA and RVol calculations. That is more profound at high heart rates during ESE, leading to controversial results[189]. Conversely, the application of EROA and RVol indexes is more feasible in secondary MR[190]. In such a small cohort of mostly (~90%) symptomatic patients, a large increase of MR severity (ΔEROA ≥+13 mm^2) during supine bicycle, among others, was the most important determinant of survival in pharmaceutical-treated patients. Notably, half of them had mild functional MR. In a larger, well-organized study, the MR severity during semisupine, bicycle ESE exerted prognostic value in patients with heart failure − with reduced ejection fraction and secondary MR[191]. Another echocardiographic index of secondary MR severity is the MR jet area. Although it is a semiquantitative index that requires high frame rate echocardiography, it is easily obtainable and representative in optimal views.

7.5.3. Exercise-induced pulmonary hypertension (EIPH)

The measurement of TR Vmax and thereby the calculation of PASP is quite challenging during ESE. A rise of PASP to ≥60 mmHg may independently predict symptoms appearance in asymptomatic patients with degenerative or secondary MR[192]. PASP has already been evaluated as an ESE outcome to explain the exercise intolerance or the out of proportion exertional dyspnea in many left-heart diseases[193,194]. Echocardiographic and invasive measures of PASP have shown high agreement in asymptomatic patients with moderate to severe MR undergoing semisupine bicycle ESE[195]. Nevertheless, several flow-dependent confounders (body weight, age, gender, and physical activity status) and the absence of clearly defined cut-off values at exercise (e.g., peak PASP values vs PASP change) further complicates the EIPH interpretation[196]. A steep increase of PASP at low levels of exercise followed by a further small incline − instead of a gradual, continuous increase up to peak exercise − may easily distinguish patients with truly abnormal test. Recently, a small study reported the early development of EIPH (PASP >50 mmHg) at low workload of ESE (up to 50 watts) as prognostic factor of clinical deterioration in patients with asymptomatic, moderate, primary MR, proposing the 'rule 50-50'[197] (Fig. 9). *Despite limited available data, this Task Force suggests that an early rise of PASP may identify patients with significant MR-related symptoms.*

7.5.4. Tricuspid annular plane systolic excursion (TAPSE)

The development of RV dysfunction during ESE, defined as TAPSE <19 mm, may add further prognostic value in asymptomatic patients with degenerative MR[198].

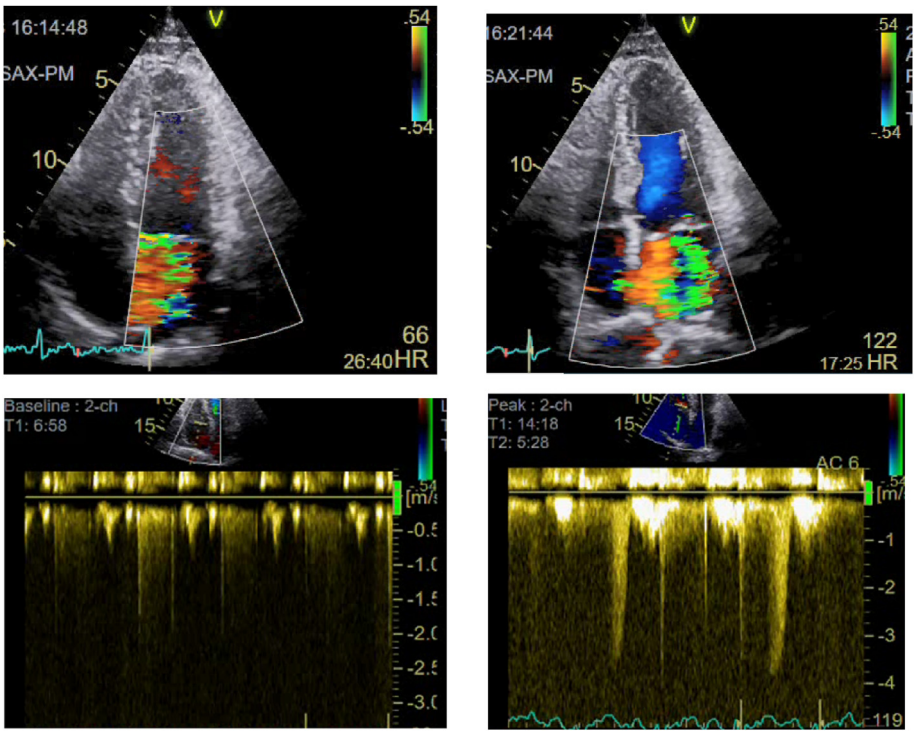

Figure 9. Exercise stress echocardiography in an asymptomatic patient with moderate to severe MR and normal PASP at baseline. Semiquantitative assessment of MR regurgitation, using MR jet area, and detection of exercise-induced pulmonary hypertension at early peak accompanied by severe dyspnea.

7.5.5. Contractile reserve (CR)

It describes the ability of LV to increase cardiac output to meet the metabolic requirements during exercise. A reduced CR [<4% increase of LVEF or <2% increase of global longitudinal strain (GLS) during exercise] is not uncommon in chronic moderate or severe MR and may be independent of LV function at rest[199]. The absence of CR, assessed during exercise testing by GLS change or to a lesser extent by LVEF change, indicates poor prognosis in patients following either MV surgery or medical therapy[76,200]—that effect was independent of resting echocardiographic parameters. In clinical practice, GLS can be obtained only at low levels of exercise, when the heart rate allows an adequate frame rate.

Keypoints:	Evidence/Studies	Consensus status
In asymptomatic patients with moderate or severe MR, the development of symptoms during exercise tests may re-classify the need for intervention.	Weak O[184]	Strong consensus
In patients with either primary or secondary MR, the rise of PASP ($\geq$ 60 mmHg) especially at early stage, the absence of contractile reserve [<4% increase of LV ejection fraction (LVEF) or <2% increase of GLS] and the RV dysfunction (TAPSE <19 mm) (only in degenerative MR) during ESE implicate poor prognosis independent of symptoms.	Weak O[199,200,202]	Consensus
Large increase of MR severity (ΔEROA $\geq$+13 mm^2) in patients with secondary MR is a marker of mortality in non-surgical treated patients.	Weak O[190]	Consensus

7.6. Stress echocardiography in multivalvular or mixed valvular heart disease

Multivalvular heart disease (MuVD) – the combination of stenotic or regurgitant lesions on different cardiac valves, and mixed valvular heart disease, i.e., the coexistence of stenotic and regurgitant lesions on the same valve – are commonly observed in clinical practice[201,202]. The clinical effect of MuVD depends on a complex interplay of pathophysiological factors, combining the severity of each individual valve lesion, loading conditions, and ventricular compensation[201]. *The opinion of this Task Force is that a meticulous transthoracic or even transoesophageal echocardiography should precede the SE to distinguish the structural from the functional element of abnormalities in each valve.* Owing to the lack of strong data, the technical difficulties in the accurate assessment of each valve during stress, and the hemodynamic interplays between valvular pathologies, SE is rarely used in this population (only in 1.5% of such patients in the recent Euro Heart Survey study). It is mainly indicated in patients with MuVD and symptoms disproportionate to resting haemodynamic status or in "asymptomatic" patients with severe valvular disease to uncover symptoms or an abnormal haemodynamic response[195]. Bicycle ESE is the preferred method in this setting, as it allows continuous assessment of multiple valves.

In symptomatic patients with nonsevere, mixed aortic or mitral valve disease, ESE may uncover a significant increase of either regurgitation severity or mean transvalvular gradient. Those findings combined with symptoms, PASP increase, or ventricular decompensation may guide treatment[203] (Fig. 10).

Occasionally, in paradoxical LF/LG severe AS, the reduced forward left ventricular stroke volume might be caused by significant, concomitant MS, MR, or TR[204]. In this setting, judicious use of bicycle ESE or low-dose DSE may assist to discern true-severe AS from pseudo-severe AS[205].

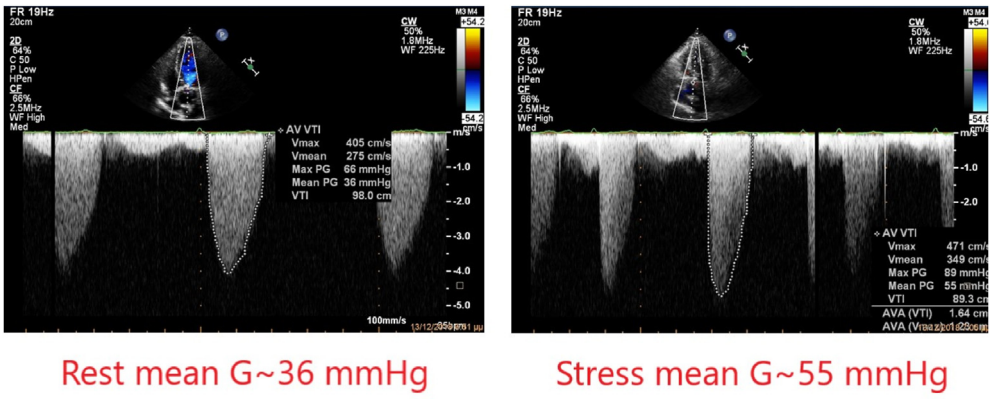

Figure 10. Mildly symptomatic 56-y-old obese male patient with mixed moderate aortic valve disease underwent ESE. At rest, transvalvular gradient (mean gradient~36 mmHg) moderately increased with normal left ventricular ejection fraction (LVEF). At moderate workload, the patient complained of shortness of breath accompanied by a significant increase in transvalvular gradient (mean G~55 mmHg) and a decrease in LVEF<50%).

Keypoint:	Evidence/Studies	Consensus status
After meticulous echocardiographic evaluation of all valves, ESE may assist to uncover symptoms or to assess hemodynamic changes in each valve (stenosis or regurgitation) in patients with either multivalvular or mixed valvular diseases.	Expert opinion E	Strong consensus

7.7. Stress echocardiography in prosthetic valves

SE aims to assess the prosthetic or repaired valve hemodynamic changes during exercise when increased flow through the valve has been achieved and to correlate findings with the patient's symptoms. SE also allows the detection of new regional WMA, suggestive of myocardial ischemia, or exercise-induced MR. The preferred modality is graded bicycle or treadmill SE, which mimics physiological exercise, with DSE reserved for patients with severe symptoms and/or unable to exercise[173].

The main indications for performing SE in such patients are: 1) the presence of symptoms with mildly-moderately increased mean gradients at rest (i.e., 20–40 mmHg in the aortic position or 5–10 mmHg in the mitral position for prosthetic valves and >3 mmHg for mitral valve repair) and 2) "asymptomatic" (truly or claiming) patients with moderate to severe increased gradients at rest[178]. Although not supported by strong evidence, a disproportionate increase in mean trans-valvular gradient either during exercise (i.e., >20 mmHg for aortic prostheses or >10–12 mmHg for mitral prostheses) or at peak exercise (i.e., absolute value > 15–18 mmHg for mitral prostheses) suggests severe prosthesis stenosis or significant patient-prosthesis mismatch. The clinical relevance of those findings is further underpinned by concomitant symptoms and rise of PASP ≥60 mmHg, in the absence of new WMA[206–208]. Of note, although an increase in mean gradient is used for clinical decision making, the index that has been shown to correlate best with at least medium-term prognosis is peak exercise PASP, likely owing to the stronger longitudinal impact of the stenotic lesion on pulmonary circulation and right ventricular performance as compared to gradients[178].

In patients after mitral valve repair with increased mean gradient (>3 mmHg) at rest, it has been proposed that mean transmitral gradient at ≥7 mmHg with concomitant peak exercise PASP ≥ 50 mmHg suggests the presence of functional mitral stenosis. Firm data that support such a recommendation are lacking[209–211]. Interestingly, a recent study in a small population of asymptomatic patients after mitral valve repair showed that more than 50% of the patients had a mean transvalvular gradient >15 mmHg during ESE, questioning the above-used threshold for clinical decision making. However, none of the participants reached a PASP >60 mmHg during exercise; again emphasizing the importance of routine measurement of this parameter during ESE[212].

Keypoint:	Evidence/Studies	Consensus status
ESE may be a useful tool to assess symptoms and uncover hemodynamic changes in prosthetic valves in patients with a discrepancy between symptoms and valvular disease severity (stenosis or regurgitation).	Expert opinion E	Strong consensus

7.8. Stress echocardiography in cardiomyopathies

Stress echocardiography (SE) has been extensively studied in the diagnosis, evaluation of treatment, and prognosis in cardiomyopathies, mainly HCM and DCM, and is increasingly applied in clinical practice.

7.8.1. Dilated cardiomyopathy (DCM)

PSE with either dobutamine or dipyridamole has been most often used in DCM to assess CR. DSE can be used to discriminate ischemic from nonischemic etiology of DCM, albeit with low sensitivity[213,214], and to detect early disease in cardiotoxicity-related and other forms of cardiomyopathy[215,216]. However, there is no consensus on the optimal dobutamine protocol and various doses between 10 and 40 μg/kg/min have been proposed in various studies, with higher doses more likely to reduce false-negative results at the expense of potentially higher risk of arrhythmias[217].

Alternatively, ESE may be used to provide additional information, such as PASP and diastolic function assessment.

The presence of CR in DCM patients with depressed cardiac function at rest is associated with decreased mortality, heart failure hospitalizations, lower need for cardiac transplantation, and better response to heart failure treatment or cardiac resynchronization therapy[218,219]. Interestingly, despite the prognostic value of this

parameter, there is little agreement on how to define CR in DCM. Most trials have assessed a change in the WMSI with cutoffs between 0.15 and 0.44[220,221], while an improvement in LVEF between 2 and 10% has been reported as an index of CR in other studies[222–224]. Of note, different protocols were used in each trial leading to different cutoffs. Furthermore, ESE may enable the differentiation of athletes with dilated LV and low normal LVEF from patients with DCM. A significant improvement in contractile reserve during physical exertion, suggests a physiological response[225].

7.8.2. Hypertrophic cardiomyopathy (HCM)

ESE is widely used in HCM to assess inducible left ventricular outflow tract obstruction (LVOTO) in symptomatic patients with resting LVOTO < 50 mmHg. ESE in standing, sitting, or semisupine position is recommended in the ESC and AHA/ACC guidelines on HCM, when resting echocardiography with bedside provocation maneuvers fails to induce LVOT gradient ≥50 mmHg (class of recommendation IB)[226]. Upright treadmill ESE may be the preferred method as it is more likely to yield significant LVOT gradients ≥50 mmHg[227]. A symptoms-limited test protocol is applied with the endpoint being the achievement of LVOT gradient ≥50 mmHg. DSE is not recommended considering the low specificity and isoproterenol is reserved for use in the cath lab or theatre during septal myectomy[228]. Amyl nitrite may be used in patients who cannot exercise[229]. ESE can be also useful in asymptomatic patients with LVOT gradients <50 mmHg at rest – to guide lifestyle and treatment decisions, such as exercise recommendation and medication (Class of recommendation IIb-C). Up to 9% of HCM patients may develop WMA on ESE in the absence of CAD and this is an independent predictor of cardiac death and events such as cardiac transplantation[230,231]. In specific subgroups of HCM patients, WMA during SE may reach up to 50% of patients; hence, SE is not recommended for the detection of ischemia in HCM[232].

Keypoints:	Evidence/Studies	Consensus status
SE may be recommended to detect ischemia in DCM (weak evidence), but it is not recommended for the same reason in HCM patients.	Weak O[213,214]	Consensus
The absence of contractile reserve during SE is associated with worse clinical outcomes in patients with DCM.	Strong M[218]	Strong consensus
ESE may be useful to detect provocable LVOTO in patients with HCM and no significant resting LVOT gradient at rest.	Weak O[227]	Consensus

8. Summary

SE remains an operator-dependent technique with unambiguous high prognostic value in ischemic cardiac disease. It has multiple additional applications in a wide variety of nonischemic cardiac diseases, such as valvular diseases and cardiomyopathies. Till now, the small sample size, the diversity in protocols, and the absence of prognostic data have limited its wide performance, despite the promising potentiality in nonischemic cardiac diseases. This Task Force concluded with a consensus statement to summarize the evidence-based role of SE, practical recommendations for SE application, and forthcoming advances of dynamic echocardiography.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hjc.2021.07.006.

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